4. Giannoni A, Emdin M, Bramanti F, Iudice G, Francis DP, Barsotti A, *et al.* Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. *J Am Coll Cardiol* 2009;53:1975–1980.
5. Teran FA, Richerson GB. 5-HT neurons and central CO2 chemoreception. In: Müller CP, Cunningham KA, editors. Handbook of the behavioral neurobiology of serotonin, second edition. London: Elsevier; 2020. pp. 377–391.
6. Giannoni A, Borrelli C, Mirizzi G, Richerson GB, Emdin M, Passino C. Benefit of buspirone on chemoreflex and central apnoeas in heart failure: a randomized controlled crossover trial. *Eur J Heart Fail* 2021;23:312–320.

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Reply to Borrelli *et al.*

From the Authors:

We thank the authors for calling attention to an important recent study on examining the use of pharmacotherapy with buspirone in patients with central sleep apnea related to heart failure with reduced ejection fraction (1) in our recent statement (2). As noted, the study found important decreases in chemoreflex sensitivity to carbon dioxide without changes in sensitivity to oxygen. These findings lend support to emerging evidence that central chemoreceptors play an important role in the pathogenesis of central sleep apnea in those with heart failure and stand in contrast to the traditional view that peripheral chemoreceptors are the sole important drivers in this context (3). Although the reductions in the apnea–hypopnea index in this study were modest, this work provides a foundation for much needed novel clinical investigations in addition to clarifying relevant underlying neurobiology. ■

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References

1. Giannoni A, Borrelli C, Mirizzi G, Richerson GB, Emdin M, Passino C. Benefit of buspirone on chemoreflex and central apnoeas in heart failure: a randomized controlled crossover trial. *Eur J Heart Fail* 2021;23:312–320.
2. Orr JE, Ayappa I, Eckert DJ, Feldman JL, Jackson CL, Javaheri S, *et al.* Research priorities for patients with heart failure and central sleep apnea. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021;203:e11–e24.
3. Toledo C, Andrade DC, Lucero C, Schultz HD, Marcus N, Retamal M, *et al.* Contribution of peripheral and central chemoreceptors to sympatho-excitation in heart failure. *J Physiol* 2017;595:43–51.

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The 4DPRR Index and Mechanical Power: A Step Ahead or Four Steps Backward?

To the Editor:

We read with interest the manuscript by Costa and colleagues (1) showing that the combination of driving pressure and respiratory rate is significantly associated with mortality in patients with acute respiratory distress syndrome. Their analysis suggests that a simplified composite variable (driving pressure multiplied by four plus respiratory rate [4DPRR]) is as informative as the more comprehensive equation of mechanical power. Although we are delighted to see that respiratory rate, long neglected, has finally been considered (better late than never) as an essential determinant of ventilator-induced lung injury (VILI), we believe that some conceptual and methodological considerations need to be highlighted.

First, it is essential to make a clear distinction between a parsimonious epidemiological model that includes ventilatory variables associated with mortality and the more VILI-relevant *physical* concept of total energy transferred during mechanical ventilation—expressed as mechanical power (2). Regarding the latter, all elements of the ventilator's settings, including positive end-expiratory pressure (PEEP), should be included because all contribute to the total mechanical energy (3). Mechanical power is not intended to be the "unifying theoretical explanation" of VILI, but it is a more physiological way to summarize the physical contributions of the ventilator settings expressed in meaningful and understandable physical units (J/min) (2).

Although 4DPRR may help estimate the average trade-off between driving pressure and respiratory rate under purely theoretical isocapnic conditions, it is a population-associated statistical measure based entirely on the effect size derived from a mediation analysis; it does not describe a physical quantity or encapsulate total mechanical energy. Indeed, its 4:1 ratio may not apply under all conditions (e.g., when PEEP achieves lung

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recruitment, increases lung homogeneity, or alters dead space). The mechanical effects of PEEP on mortality hazard may be more complex. Indeed, although PEEP's effect on total lung stress and strain will depend on multiple factors (e.g., baseline compliance, recruitability, and lung homogeneity), its amount is not indifferent to the outcome because PEEP can influence driving pressure (for a given V_T) and dead space (and can indirectly influence the respiratory rate) as well as acting independently as a key component of the total mechanical energy delivered.

The relevance of PEEP in determining total stress and strain of the respiratory system is, in one sense, intuitive: omitting PEEP from a calculation of energy would imply that applying 30 cm H_2O of PEEP to an individual patient adds no risk of VILI or other adverse outcomes. On the contrary, it is clear from the univariate, population-based models presented by Costa and colleagues (1) that PEEP, the static elastic component of mechanical power and of total power, impacts mortality with an effect size of similar magnitude as respiratory rate and driving pressure. There are not sufficient data available to fully elucidate the effect of PEEP on outcome, but there is already evidence—some from the same authors—that mechanical power is associated to outcome in the same populations (4).

Second, the simplicity of the bedside calculation of 4DPRR is not superior to the simplicity of the bedside calculation of mechanical power through simplified formulas (5). In addition, the 4DPRR formulation obscures the conceptual understanding of the delivered mechanical energy. Therefore, we argue that moving from the physical and physiological model of mechanical power to a contrived expression based on statistical models devoid of direct physical meaning may be a retrograde step. ■

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References

1. Costa ELV, Slutsky AS, Brochard LJ, Brower R, Serpa-Neto A, Cavalcanti AB, *et al.* Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021; 204:303–311.
2. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, *et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–1575.
3. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, *et al.* Positive end-expiratory pressure and mechanical power. *Anesthesiology* 2019; 130:119–130.
4. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, *et al.*; PROVE Network Investigators. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med* 2018;44: 1914–1922.
5. Chiumello D, Gotti M, Guanziroli M, Formenti P, Umbrello M, Pasticci I, *et al.* Bedside calculation of mechanical power during volume- and pressure-controlled mechanical ventilation. *Crit Care* 2020;24:417.

Reply to Camporota *et al.*

From the Authors:

We appreciate the authors' interest in our work (1). Let us start by emphasizing what we agree on: Driving pressure and respiratory rate are important determinants of ventilator-induced lung injury (VILI). Irrespective of whether we reach an agreement on other issues below, this is a good take-home message. Now let us examine the points on which we diverge.

Based on physical and pathophysiological principles detailed below, we do not think that the elastic, static energy related to positive end-expiratory pressure (PEEP) should be included in the power computation, nor should the energy dissipated in the airways. Indeed, one of the goals of our study was to assess the role of the individual mechanical power components on mortality (1). We clearly demonstrated that the only component of power associated with outcome was the elastic, dynamic component related to driving pressure (*see* Figure 1 in Reference 1); the elastic static component (i.e., PEEP) and the resistive power (related to flow and airway resistance) had essentially a zero contribution to outcome.

Why should this be? PEEP can impact patient outcome through multiple mechanisms. PEEP, however, expands the lungs only once—when applied—and this expansion is sustained throughout the ventilatory support unless PEEP is changed. This single expansion can be tolerated by the lungs or can be excessive. In addition, there may be some further expansion if there is recruitment, but this is not linked to respiratory rate. Thus, it does not make sense to include PEEP in the

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