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VIEWPOINT

Looking beyond macroventilatory parameters and rethinking ventilator-induced lung injury

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CRITICAL REAPPRAISAL OF VENTILATOR–LUNG INTERACTIONS

Clinicians recognize that although mechanical ventilation is a necessary tool in managing critically ill patients that develop acute respiratory distress syndrome (ARDS), it can simultaneously induce (16) and propagate injury in the lung it is meant to support (12, 40). The mechanism of this ventilator induced lung injury (VILI) is thought to be related to dynamic strain and cyclic alveolar collapse and reopening (16, 22, 34, 50); however, an all-encompassing single mechanism for VILI remains elusive.

Current ventilator management strategies are guided primarily by macroparameters measured at the level of the ventilator [plateau pressure (Pplat), tidal volume (Vt), and positive end expiratory pressure (PEEP)] and are assumed to be key drivers for propagating or limiting lung injury during mechanical ventilation. These "macroventilatory" settings reflect values applied to and averaged across the whole lung and thus may not be accurate regional indicators of the lung's microenvironment: alveoli and alveolar ducts. The results of the 2000 ARDSnet (1) study established the macroventilation settings using low Vt and limiting Pplat. These results have not, however, been replicated in subsequent clinical studies (25, 46), in part because few clinicians adhere strictly to the low Vt guidelines set forth (3). We also postulate that these macroventilator parameters are too insensitive to accurately and consistently determine the pathophysiologic impact of mechanical ventilation on the pulmonary parenchyma. Without deconstructing and understanding how the mechanical breath impacts the pulmonary microenvironment, reducing VILI and ARDS mortality will be a difficult and inconsistent task.

LIMITATIONS OF CURRENT PROTECTIVE VENTILATION

Conceptually, the lung is often illustrated by a single compartment balloon model in which reducing stress (airway pressure and Vt) reduces volumetric distortion and strain in the balloon wall. This approach, however, is an oversimplification of the complex geometry of the finely partitioned, interdependent, and four-dimensional behavior of the human lung at the level of the microenvironment (22). The balloon model also does not account for lung heterogeneity, a hallmark of ARDS, as collapsed or edema-filled alveoli generate regional stress, inducing strain on the neighboring open alveoli (29, 36).

Mead et al. (24) determined that there is a 13% increase in stress in nonuniform alveoli compared with a uniform system. The magnitude of the stress increase is dependent on several factors, including the number and degree of collapsed alveoli, alveolar surface tension and edema, and location of the alveoli (peripheral vs. central and proximity to a duct). Thus, in lungs with regional inhomogeneity, a delivered Vt will not distribute evenly across the lung parenchyma but will preferentially distribute to areas of higher compliance (9, 54). This mechanical stress causes nonuniform stretch of the epithelial cells that alters the function and signaling of the cells (44, 51). This, in turn, can injure cells and cause apoptosis (43) and alter surfactant secretion (51) and permeability (8).

These regions of stress-rising alveoli concentrate strain, reaching levels up to quadruple that of global strain (20, 35). These unstable zones serve as a propagation point for lung injury (41) as they result in amplified strain on the adjacent open alveoli (24), leading to additional inflammation (2) and alveolar cell membrane rupture (2, 49).

Although it is well understood that heterogeneity exists at the macroscale (9), it is inferred that there is also alveolar heterogeneity resulting from low lung volume and edema (23). In a study of alveolar behaviors using laser-scanning confocal technique, Namati et al. (28) determined that there are three distinct types of alveoli, further compounding regional alveolar heterogeneity. These include alveoli that distend with tidal inflation, those that do not, and those that collapse at expiration (28). This is magnified in the setting of lung injury with loss of surfactant function and with higher rates of derecruitment (23). While stabilizing and promoting alveolar homogeneity is of critical importance, there are no direct methods of assessing alveolar micromechanics (37).

Human and experimental data suggest that excessive tissue strain may occur even when using low "tracheal Vt" (volume measured by the ventilator at the level of the trachea) if the

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"baby lung" surface area is too small to accommodate the applied stress (17, 22, 45). The tracheal Vt does not indicate where or how much of that Vt is being distributed to different regions of the lung and does not necessarily reflect the tidal distension of individual alveoli (17, 42, 45). This was demonstrated in an animal study using in vivo microscopy, in which a low tracheal Vt of 6 ml/kg (macroventilation) was applied and the alveolar Vt (microventilation) was found to vary with changes in PEEP, with significantly higher alveolar Vt and microstrain when PEEP <10 cmH_2O (22). However, in a fully open lung with recruited and homogenous alveoli, a large tracheal Vt (12 ml/kg) resulted in the lowest alveolar Vt and microstrain (Fig. 1) (22). The lung specific elastance and tissue stress directly mediates the degree of tissue strain, which itself is determined by the surface area available to accommodate the force of the mechanical breath (7). The lung specific elastance is modulated by a combination of alveolar surface tension and the degree of alveolar wall crumpling (32). Thus, in a collapsed lung with a lower alveolar surface area available to accommodate the mechanical breath, there is greater stress and strain on the alveoli and alveolar ducts. Follow-up efficacy studies in animals corroborated these findings, in which a traditionally accepted lung-protective approach with targeted macroventilatory parameters (e.g., low Vt and limited Pplat) was compared against a microventilatory approach focused on maintaining alveolar homogeneity and stability. The traditional lung-protective (macroventilatory) approach led to an increased incidence of VILI compared with the microventilatory approach, which had higher Vt and Pplat (21) but lower alveolar Vt and microstrain (22).

Despite many clinical trials and research investigating "treatment" of established ARDS, the results have been largely negative and overall mortality remains unacceptably high (3, 33). Although formally defining ARDS has been important for standardization (4), it has led to ARDS being viewed as a binary construct: it is either present or not (38), when in fact it is a "syndrome" that may be categorized by etiology (pulmonary vs. extrapulmonary) (30), severity or progression (15), responsiveness to treatment (6), or patient pheno/genotype (47). Despite the differences in these subgroups, most clinical trials of ARDS analyze all patients cumulatively (1, 5, 14, 25, 26, 46, 52). Therefore, strict adherence to rigid macroventilatory guidelines based on prior clinical trials of heterogeneous patient populations may not be adequate when treating the individual patient (18, 47, 48). Instead, an understanding of the impact of mechanical ventilation on the microenvironment may be the only parameter universal to all patients.

Understanding the effect a given mechanical breath has on the individual alveoli is of critical importance to recognize the degree of stress to which the alveolus is exposed. The majority of what is known about alveolar micromechanics is based on in vivo and in vitro models (27, 31, 44), but there are no direct methods of assessing the microenvironment in humans in real time. Although there is limited knowledge of alveolar micromechanics (37), it is at the level of the alveolus where the critical physiology unfolds, where injury can be most pronounced, and where gas exchange occurs. Thus greater physiologic understanding of alveolar micromechanics and translation with complex physiological reasoning and directed research is indicated (2).

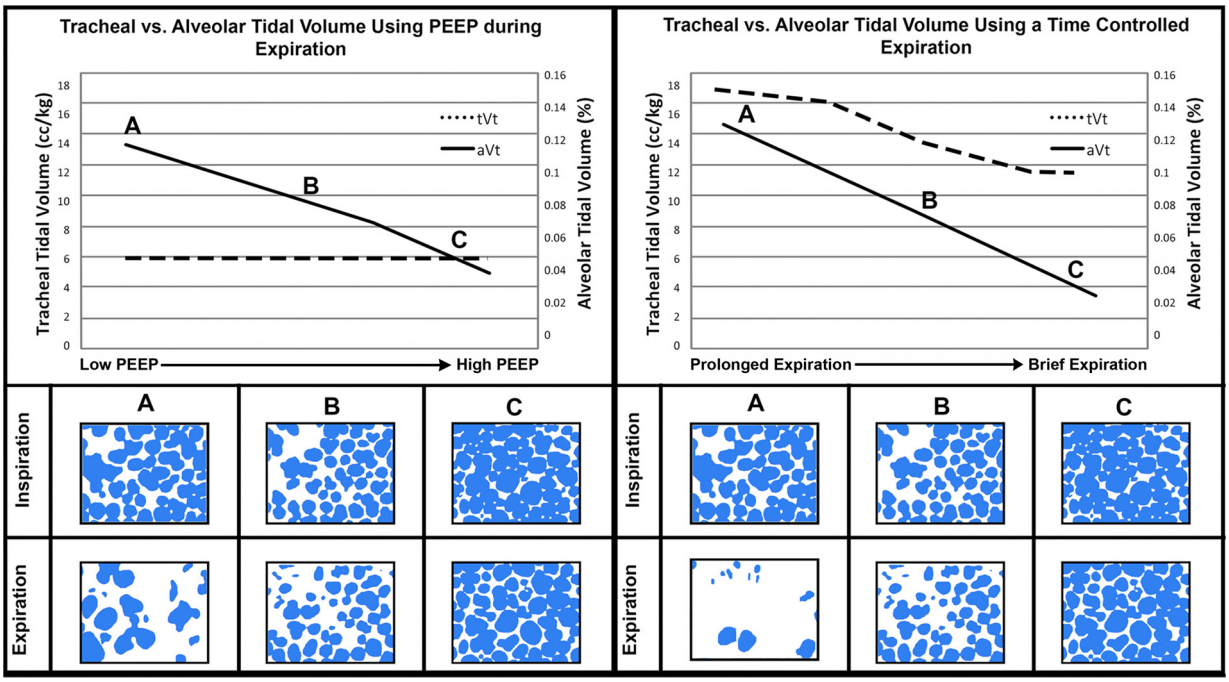

Fig. 1. Comparison of tracheal tidal volume (tVt; tidal volume measured at the level of the ventilator) vs. alveolar tidal volume (aVt; measured by an air space analysis of alveoli visualized with an in vivo microscope). As the PEEP increases (*left*), there are a greater number of open alveoli available to accommodate the tracheal tidal volume. Thus the alveolar tidal volume decreases with increasing PEEP though the tracheal tidal volume remains constant. Using a time-controlled mode (*right*), a shorter expiratory duration leads to improved alveolar stability and decreased end-expiratory alveolar collapse. Despite relatively large tracheal tidal volumes, there are lower alveolar tidal volumes with shorter expiratory times as the tVt are being distributed across a greater number of open, homogenous alveoli. [Representation not based on data but adapted, with permission, from Kollisch-Singule et al. (22).]

EVIDENCE FOR NONLINEAR RELATIONSHIP IN THE CIRCULATION: A PARALLEL CONCEPT

The need to understand how macrosettings impact the microenvironment is evident in both the circulation and ventilation systems. The Surviving Sepsis Guidelines recommend maintaining mean arterial pressure (MAP) above 65 mmHg (11), although there is no clear evidence that this pressure will increase capillary perfusion nor that the same MAP would be effective for all patients (39). Just as the optimal PEEP required to recruit and stabilize alveoli for an individual patient remains ambiguous, the MAP threshold optimal for recruiting and maintaining perfused capillaries is also unknown. For instance, Zakaria et al. (53) demonstrated that intestinal perfusion varied considerably despite maintaining a consistent MAP in a hemorrhagic shock model.

In ARDS, one of the goals of mechanical ventilation is to provide enough alveolar surface area to allow for adequate gas exchange. This is analogous to sepsis, where the goal of resuscitation is to restore the microcirculation to optimize tissue perfusion, particularly in the setting of high metabolic demand (10). Similar to the lung's heterogeneous reduction in functional alveolar surface area available for gas exchange that characterized ARDS, microvascular derangements in sepsis are often associated with a heterogeneous reduction in capillary surface area, which often persists despite targeting macrocirculatory parameters, such as MAP or cardiac output (CO) (10).

Ideal microcirculation involves distribution of CO across open, perfused capillaries to satiate tissue needs; however, the reality is that CO will preferentially distribute to the microcirculation of least resistance regardless of metabolic demand. This is not unlike the microenvironment of the respiratory system, where a delivered Vt will be distributed preferentially across the distal airspaces with lower resistance and more compliant alveoli in a heterogeneous lung. Targeting a macrocirculatory parameter such as MAP with the use of vasoconstrictors can potentially exacerbate tissue hypoperfusion in patients with inadequate intravascular volume by reducing blood flow (13). Just as reducing the CO will decrease microcirculation, reducing Pplat or Vt may paradoxically redistribute stress in the microenvironment resulting in increased dynamic strain in the more compliant lung regions.

CONCLUSIONS

It is essential to understand the impact of a mechanical breath on the "microenvironment," by calibrating the effect of the "macroventilator settings" with the dynamic changes to the alveoli and alveolar ducts. This concept is analogous to macrocirculatory hemodynamic parameters that clinicians routinely use for assessing tissue perfusion when the critical physiology is occurring in the microenvironment of the capillary network. We propose that just as macrocirculatory parameters are poorly correlated with tissue microcirculation and prognosis, macroventilator parameters are likewise poorly correlated with alveolar and alveolar duct microventilation and ultimately outcome (13, 19).

Understanding of the impact of mechanical ventilation on the lung is currently restricted by our reliance on and acceptance of macroventilator parameters to guide patient treatment. Rather than treating the ventilator and macroventilator parameters, a series of physiologic studies are needed that link anatomical, physiological, biochemical, and computational methods so that we may target the microenvironment as the end point of lung resuscitation.

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AUTHOR CONTRIBUTIONS

M.C.K.S., J.S., and L.A.G. prepared figures; M.C.K.-S. drafted manuscript; M.C.K.S., S.V.J., P.L.A., J.S., L.A.G., J.V., D.D.B., L.G., G.F.N., and N.M.H. edited and revised manuscript; M.C.K.-S., S.V.J., P.L.A., J.S., L.A.G., J.V., D.D.B., L.G., G.F.N., and N.M.H. approved final version of manuscript.

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