Firmer footing for ventilating and monitoring the injured lung

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The acute respiratory distress syndrome (ARDS) is widely considered the signature problem of critical care. From the outset, it was understood not to be a lung disease but rather, a life-threatening clinical condition provoked by diverse stimuli (1). The description of this problem as a syndrome was justified by the assumption that these diverse etiologies could be managed clinically by a unified approach. To this point, that naïve assumption has proven flawed. Critical care investigators and physicians have learned from laboratory experimentation and clinical observation that the pathobiology of ARDS changes rapidly over hours and days and varies significantly in its nature (2,3) as well as severity from individual to individual. Furthermore, patients with ARDS often have multiple concomitant medically and surgically related disorders that further complicate treatment selection and often confound the interpretation of effects from ARDS-specific interventions. Soon after its initial description it also became clear that the disease course is influenced not only by such idiosyncratic disease co-factors but also by the life support measures we apply (4). It follows that wise selection and application of treatment requires consideration of the timing and intensity of any proposed intervention, such as mechanical ventilation.

Interactive links tie together diagnosis, monitoring and appropriate treatment. While acknowledging these complexities, we continue to seek easy—even stereotyped— answers to our clinical questions regarding this knotty problem that require minimal thought (5,6). Unfortunately, but in retrospect not surprisingly, clinical trials testing dichotomous therapeutic alternatives without sufficient mechanistic underpinnings have repeatedly disappointed us (7-9). What now seems to be lacking at the clinician-patient interface is guidance from in-depth understanding of the underlying mechanisms responsible for the clinical manifestations we must confront at the bedside and valid anticipation of the likely consequences of our interventions.

In the June 2018 issue of the *American Journal of Respiratory and Critical Care Medicine*, Maiolo and colleagues provided needed insight into the interrelationships among pathoanatomy, pathophysiology, ventilatory management and important outcomes (10). That elegant scientific study utilized to good effect certain sophisticated analytical computed tomography (CT) methods that are unavailable to practicing clinicians. That work revealed connections among measurable variables and underlying pathophysiology that are highly relevant to everyday decision-making.

Since its original description, ARDS has been recognized to originate in generalized inflammatory lung edema caused by increased vascular permeability and breakdown of the normal alveolar-capillary membrane (1). Whether initiated by pneumonia, sepsis, trauma or immunoreactions, an abrupt onset, diffuse infiltrates compatible with non-cardiogenic edema, refractory hypoxemia and 'stiff', low compliance lungs were seen as instrumental to its pathogenesis. Shortly afterward it was understood that high capillary permeability should prioritize avoidance of unnecessary elevations of hydrostatic forces (11,12). Over the years (and in part as a response to the need for clinical trial enrollment) the pathophysiology-driven underpinnings of ARDS recognition were gradually set aside in favor of more expedient alternatives. 'Multi-lobar'

infiltrates took the place of 'diffuse' infiltrates, and bedside criteria for mechanical properties disappeared from the official definition of ARDS, as the emphasis on hypoxemia took precedence (13). The original term 'refractory hypoxemia' was applied to a wide range of PaO_2/FiO_2 ratios without regard for such modulating factors such as body positioning and strength of hypoxic vasoconstriction, and initially without specification of PEEP level or durability of impaired oxygen exchange. The original concept of 'abrupt' onset devolved into hypoxemia whose cause may have begun as long as a week earlier (12,14). Consequently, the label of ARDS has been broadly assigned in clinical practice and some clinical trials to processes that promote hypoxemia of varying severity, some of which spare broad lung regions, occur against a chronically hypoxemic background, ignore the effects of position and PEEP, and therefore involve relatively flexible and minimally damaged lungs of questionable permeability. [One such condition might be exemplified by massive obesity ventilated in the supine position without elevation of adequate end-expiratory pressure (15)].

In recognition of such shortcomings and the need for improved specificity, the 'official' criteria for determining ARDS (primarily for clinical trials and secondarily for practice) were modestly modified and the oxygenation-defined categories and severity thresholds reassigned in 2012 (14). Understandably, effort was expended to keep the newer definition compatible with the old one (13). For reasons of feasibility and marginality of added diagnostic benefit, measures of disordered lung mechanics remained unspecified, despite their relevance to lung stiffness and clear importance to a valid prescription of safe ventilatory support. Generalized high permeability edema remained the conceptual cornerstone of the underlying pathophysiology of the earliest stage of this disorder, with severity of ARDS and impaired oxygen exchange paralleling its appearance and resolution (14).

To be sure, there is a justified rationale for focusing primarily on hypoxemia that is not easily responsive to inspired oxygen, as this abnormality drives many clinical decisions regarding the nature [prone positioning, extracorporeal membrane oxygenation (ECMO)] and intensity [positive end-expiratory pressure (PEEP)] of management interventions. Unfortunately, unlike PaO_2 and FiO_2, non-hydrostatic lung edema—a key surrogate marker of the severity of lung damage and indicator of the likely response to elevating mean airway pressure—cannot be directly assessed at the bedside. The simplest windows through which edema (and consequently severity of lung injury) may be inferred are hypoxemia normalized to inspired oxygen fraction (PaO_2/FIO_2 ratio) and diffuse bilateral X-ray densities (16). These signatures are only loosely associated with low respiratory system compliance and increased alveolar dead space, two key generative variables for VILI that obligate high tidal driving pressures and increased ventilation requirements.

One attraction of the 'Berlin' definition may be the introduction of the "severe ARDS" category assigned to a PaO_2/FiO_2 ratio lower than 100 mmHg (14). This numerical value accurately represents what was considered in the initial description of ARDS to be "refractory hypoxemia" because it corresponds to a right-to-left shunt of about 30%, a level that precludes the restoration of PaO_2 to 100 mmHg even when ventilating with pure oxygen. But the Berlin-specified 'moderate' range (PaO_2/FiO_2 =100–200 at PEEP 5 cmH_2O) may include shunt fractions over a very wide span, depending on FiO_2 [20–60% in the Maiolo study (10)]. Problems also arise with the Berlin definition relating to the imprecision of the PaO_2/FiO_2 ratio in assessing the extent of lung edema if measured at unspecified PEEP higher than 5 cmH_2O. Indeed, PEEP may attenuate hypoxemia and distort the relationship between PaO_2/FIO_2 ratio and the amount of edema estimated by quantitative CT scans (16,17). Radiographic densities also fail to reliably correspond to the extent of edema, as they may arise due to different underlying pathologies (consolidation, edema, or collapse) that in turn are associated with differing responses to changes of airway pressure. In other words, the current diagnostic criteria used in clinical trials do not adequately reflect crucial domains of the underlying pathology and pathophysiology (14). In concept, this deficiency is quite important, as knowledge of tissue condition and behavior should be central to rational selection of therapies and tracking of clinical progress.

ARDS therapies may be classified in a number of useful ways. One four-pronged categorization is: preventive; pharmacological; adjunctive; and ventilatory (18). This classification, though reasonable and justified, is rather inert, as it does not yield piercing insight into mechanistic rationale. With bedside management in mind, an alternative and perhaps preferable approach, therefore, might be to classify therapies based on the ARDS disease mechanism that they target: etiology, pathogenesis, or symptoms (10,19). Following this taxonomy, etiological therapy is directed toward reversal and resolution of the root-cause stimulus giving rise to the ARDS. As an example,

antibiotics might be considered "etiological therapy" for sepsis-induced ARDS. Actual curing of the disease leading to ARDS is of paramount importance, as the underlying etiologic disease operating in conjunction with age and co-morbidity accounts for the major fraction of ARDS mortality (20). In the absence of effective etiologic treatment, even the best lung protective approach will have inconsequential impact. Therefore, randomized clinical trials investigating the possible advantages of non-curative treatments (e.g., ventilatory strategy) on mortality must be large enough to allow any associated mortality signal to emerge, and randomization should carefully allocate patients in an equal distribution of key comorbidities and potentially contributory but non-targeted variables within the dichotomous limbs of the study design. More practically and perhaps more logically, such studies should consider alternative end points that selectively reflect ARDS disease modification, with the understanding that such end points may be less directly related to mortality.

Pathogenic therapy, the second mechanism-targeting class of treatment, is directed at the process that leads to the clinical manifestations of lung injury. For example, immuno-pharmacologic therapies may intend to reduce ARDS-associated inflammation and vascular leak but do not address the underlying cause of acute lung injury. They continue to be deployed in practice with such intent and variable success.

Although inconsistently helpful in achieving the downstream endpoint of reducing mortality, corticosteroids administered in the appropriate stage if illness have been shown promising in some recent clinical trials (21,22).

Symptomatic therapy, the third and broadest mechanism-targeting class of treatment, is applied in response to the symptoms or consequences of established ARDS, which if unopposed may prove lethal (such as severely compromise to gas exchange). When carefully and thoughtfully applied such 'reactive' therapies (e.g., mechanical ventilation or extracorporeal membrane oxygenation) offer vital life support but themselves carry hazards. At best they only delay long enough to allow recovery from illness and healing of the lung. It is in this latter symptomatic category of ARDS treatments that clinical decision making requires the greatest mastery of pathophysiology, wise judgment, and close monitoring of the relevant variables. Our inability to track the fundamental responses of the lung itself to alterations of life support (such as tissue strain as a function of PEEP level, for example) has led to decades of imprecise management and heated debate among advocates and detractors of these interventions. In establishing closer links between bedside observations and making helpful inferences regarding underlying lung status, the work of Maiolo (10) would appear to have brought us closer to rational ventilatory management.

In the ARDS context, symptomatic therapeutics primarily address the deleterious effects of edema on gas exchange, providing vital assistance until the underlying condition begins to resolve. Regarding ventilatory support, risks of promoting lung damage (e.g., VILI) are weighed against the common objective of assuring adequate gas exchange. This damage is collectively referred to as ventilator-induced lung injury (VILI) and primarily consists of (I) excessive inflation or ventilation (volutrauma); (II) cyclic opening and closing of pulmonary units (atelectrauma); (III) maldistribution of stress and strain with stress focusing at the interface within pulmonary units of different elasticity (lung inhomogeneity); and (IV) intensity, frequency, and duration of tidal cycling (mechanical power) (23,24). Of these, only the latter can be directly assessed by clinicians. The damaging stresses and strains of adverse patterns of mechanical ventilation are influenced not only by plateau pressure and driving pressure, but also by the stress amplifiers of viscoelastance, lung unit drop-out, and mechanical heterogeneity (25). In seeking to avoid VILI, these parameters would be desirable to quantify, but capability to detect and directly measure them is currently lacking. Indeed, many aspects of importance to decisions relevant to the ventilatory support of ARDS cannot be directly measured. In the research setting, however, interrogatory CT analysis allows quantitative determination of both aerated and total lung volumes and of the lung's weight, micro-level heterogeneity, recruitability and regional mechanical properties (16). Were it routinely available at the bedside, such capability would help immeasurably in tracking disease progress as well as in the determination of what to expect when airway pressures and volumes are manipulated in accordance with a given ventilation strategy.

Although this quixotic clinical goal of fully assessing the microanatomy and microphysiology of the patient's lung injury in real time is not currently achievable, data on 227 ARDS patients provided by Maiolo and colleagues help establish actionable links between what we can actually measure and track and those that ideally we would like to know in order to make well-informed ventilatory decisions (10). This admirably detailed paper provided a wealth of anatomical and physiological data addressing issues such as those related to the extent of stress focusing,

mechanical heterogeneity, and the complex impact of PEEP. Correlations established in this analysis suggest that an interim response to our need for prescribing ventilation according to tissue characteristics may be deceptively simple. By dividing the Berlin-classified 'moderate' severity group (PaO$_2$/FiO$_2$ ratio of 100–200 mmHg) at the mid-point cutoff value of 150 mmHg, the authors found that value to represent a useful threshold which demarcated cohorts with distinct anatomical features and requirements. The 150 threshold was a rational choice, as prior work by that group had demonstrated that lung edema—the *de facto* marker of ARDS severity—escalated impressively at lower values of that parameter (16). Moreover, the mortality benefit of prone positioning in ARDS had been shown by others to be confined to that lower range (26). An incidental advantage of breaking the ARDS sample into four categories of oxygenation abnormality (mild, mild-moderate, moderate-severe, and severe) rather than following the Berlin-simplified version (mild, moderate and severe), was the allocation of approximately equal numbers of patients among those four labeling bins.

Somewhat surprisingly, degrees of anatomically determined-edema and severity were not as well correlated over this 'Berlin-moderate' range with the mechanical characteristics that are justifiably believed instrumental to a 'lung protective' approach: minute ventilation, lung compliance and driving pressure. In other words, those oxygenation factors that demarcate disease severity over this moderate range—which includes the majority of all ARDS patients—may be more sensitive to changes in lung status than are the mechanical characteristics we currently regulate to influence it. For example, driving pressure was little different among all sub-categories. That observation, of course, does *not* mean that disease severity has little bearing on dynamic mechanical characteristics or that driving pressure is not important to outcome (27). Tissue recruitable over the airway pressure range of 5–45 cmH$_2$O—and presumed risk for atelectrauma—increased with severity and edema. Furthermore, in order to maintain adequate ventilation, minute ventilation and mechanical power relative to aerating capacity were considerably higher in those most severely affected, despite the acceptance of higher PaCO$_2$ and lower pH (10).

Two other intriguing observations of this study included an unexpected *increase* of mechanical heterogeneity when airway pressure was elevated to high values and the disconnect between severity of lung damage and mortality. On average, the percentage of tissue recruited

over the span of 5–45 cmH$_2$O did not exceed 16% in any severity subcategory. Though a small amount atelectatic (and potentially recruitable) tissue may have remained closed at even higher pressures, the observed increase in heterogeneity and the deleterious effects of heterogeneity-associated 'stress risers' in response to elevating airway pressures should prompt re-thinking of the aggressive 'open lung' approach (28).

No mortality difference was observed between the higher and lower severity groupings within the two severity sectors of the moderate range, despite the clearly worsened anatomical and physiological lung properties of the former (10). Dating from the landmark ARDSnet clinical trial (ARMA) that demonstrated a survival advantage for low tidal volumes (20), the tacit assumption has been made that the link between ventilator settings and mortality risk is the VILI that they cause or avoid. The data of the current paper that fail to show a signal indicating an association between severity of tissue damage to observed mortality, however, would seem to call that generally accepted premise into serious question.

If severity of lung damage due to VILI does drive the observed mortality differences observed among ventilating approaches, what explains that causal link? In truth, we simply do not know the mechanistic connection. Because we can compensate for the lung's primary function of gas exchange (especially in centers where ECMO is available), patients only infrequently die because of inability to oxygenate or ventilate (Do patients die with or from ARDS and why?). If one or more humoral mediators released from the damaged lung (rather than poor oxygen exchange) is responsible for remote organ failures, we have not yet firmly identified them (29). Furthermore, the culpability of deleterious *neural* lung-brain 'crosstalk' that promotes vital organ dysfunction has been posited but not confirmed (30). This uncertainty does not necessarily mean that the causal sequence: 'strategy-VILI-mortality' is a paradigm that should be discarded; one could certainly envision some impairment of vital organ adaptation below our current clinical detection radar or a subtle limitation of reparative processes via an as yet undiscovered humoral or neural influence initiated by VILI or the strategy that led to it.

One other intriguing possibility relates to the proclivity to impaired perfusion, right ventricular afterload and cardiovascular output inadequacy imposed by positive pressure ventilation. In response to adverse cardiovascular signs, we apply symptomatic countermeasures in the friendly but dangerous guise of aggressive fluid administration

and vasopressors that may carry serious problems of their own (31). While ample attention has been given to the determinants of stroke volume associated with elevations of PEEP and mean airway pressure (preload, contractility and afterload), less well recognized is the consistent finding that the heart rate response to the stresses of raised airway pressure is severely blunted (32). Delicate microcirculatory controls that are key to adequately directing the available cardiac output to where it is most needed is compromised by disease, drugs, and perhaps by ventilation-associated autonomic dysregulation (33). Although symptomatic therapies such as lung protective ventilation may influence the trajectory of progress and may profitably buy time for repair, thwarting eventual mortality almost certainly depends primarily on success of etiologic therapies that allow adaptation and healing.

Even after a half century, our current understanding and bedside management of the 'umbrella' syndrome that we label ARDS must still be considered rudimentary. With regard to this problem we are still at the stage of reactive medicine and largely symptomatic treatment insofar as we do not apply individualized therapy with detailed knowledge of the tissue responses we perceive from our relatively crude clinical tools. In this we lag far behind the fields of cardiovascular medicine and oncology, whose modern practices pinpoint and grade their diagnoses at a much more granular level (34). By using elegant scientific methods to reveal important associations of what we can easily measure with the anatomic and physiologic properties of the acutely injured lung, Maiolo and colleagues (10) have brought intensivists one step closer to rational ventilatory management and precision medicine for our signature problem of ARDS.

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Footnote

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