Hypoxemia has been a defining feature of acute respiratory distress syndrome (ARDS) since its first description by Ashbaugh and colleagues in 1967 (1). In successive consensus definitions, severity of hypoxemia has been used as the principal variable for stratification of lung injury severity (2,3). Treatment strategies for ARDS often have been applied through this lens, with more severe hypoxemia used to guide initiation and termination of ARDS therapies in research and clinical practice (4).

Reliance on oxygenation as a primary guide for ARDS therapy warrants scrutiny. Conceptually, hypoxemia is a biomarker of lung injury but not clearly on the causal pathway to mortality: refractory hypoxemia occurs in a minority of deaths with ARDS in modern intensive care (5). By contrast, ventilation-induced lung injury (VILI) unequivocally is linked causally to ARDS mortality (6,7), making respiratory mechanics a logical focus for prognostication and guiding therapy.

Past experiences in clinical trials support this framing. Higher positive end-expiratory pressure (PEEP) often improves the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO₂/FiO₂) (8,9), but trials comparing empirical higher versus lower PEEP have not revealed a survival benefit (10,11). In the ARDS Network tidal volume trial (6), survival improved with lower tidal volumes despite worsening of PaO₂/FiO₂ over the first several days. While prone positioning improved survival in the PROSEVA trial (12), a reanalysis of trial data found no correlation between improvement in gas exchange and survival among patients who underwent proning (13).

The work by van Meenen and colleagues, published recently in this journal (14), lends further caution against using gas exchange to gauge early response to ARDS therapy. In a substudy of 90 ARDS patients from the MARS Consortium cohort, PaO₂/FiO₂ improved in 90% of patients following the first session of prone positioning. However, proning-associated change in PaO₂/FiO₂ was not predictive of survival. Pulmonary dead space fraction and airway driving pressure decreased in 66% and 56% of patients, respectively, but only improved driving pressure was predictive of survival.

These findings are consistent with current understanding of the probable mechanism of survival benefit with prone positioning, protection against VILI. In patients with ARDS, proning appears to improve survival only when used concomitantly with low tidal volumes (15). In both healthy individuals and patients with ARDS, prone positioning redistributes mechanical forces to yield more homogeneous lung aeration (16), thereby attenuating stress concentration that otherwise may contribute to VILI (17). Based on geometric modeling of CT data, this more homogeneous redistribution likely occurs from conformational shape matching of the lungs to the chest cavity with proning, during which resultant forces act to oppose gravitational effects on the lungs (18,19).

Why would proning optimize human lung mechanics?
Less heterogeneous regional lung strain in prone position may be an example of vestigial physiology. Most mammalian species are quadrupeds that amble in the prone position. Per evolutionary biology, an optimally designed respiratory mechanical system therefore should minimize lung stress and strain and maximize gas exchange efficiency when the body is prone (20). Likely for the same reason, pulmonary blood flow and ventilation-perfusion matching also are optimized in prone position (21).

The association of driving pressure change with survival, found by van Meenen and colleagues (14), is intriguing but should be interpreted cautiously. Driving pressure is a reasonable bedside marker of global overdistension lung injury risk (22), and a decrease in driving pressure may signify less VILI. However, proning acts primarily to homogenize regional mechanics with relatively little effect on global lung density. Thus, proning-associated decrease in driving pressure may not sufficiently identify all patients who experience less VILI with proning. Perhaps for this reason, the predictive value of driving pressure in their study was underwhelming. The authors appropriately advise against use of proning-associated change in driving pressure for prognostication.

The question of how to identify early a favorable response to prone positioning remains elusive. For ARDS patients with refractory hypoxemia, there is an obvious role for proning to improve oxygenation irrespective of VILI attenuation. For patients without refractory hypoxemia, for whom the benefit of proning is to attenuate VILI, there is no reliable short-term marker (23). Bedside visualization of regional mechanics, such as with lung electrical impedance tomography (24,25), could help gauge early lung-protective response with proning and warrants future investigation. Until more definitive data are available, the best approach would seem that employed by PROSEVA: prone for at least 16 hours per day until gas exchange improves sufficiently to permit weaning ventilator support to minimal settings while supine. Short-term oxygenation and dead space improvement without substantial ventilator weaning should not be used as markers of therapeutic efficacy (13,14).

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None.

**Footnote**

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**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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