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WHAT'S NEW IN INTENSIVE CARE MEDICINE

Lung-protective sedation: moving toward a new paradigm of precision sedation

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Lung-protective ventilation (LPV) has primarily focused on limiting lung injury (VILI) secondary to overdistension and collapse [1]. Deep sedation is often required for tolerance of LPV and the inherent discomfort of permissive hypercapnia and low tidal volumes [2]. Patient self-induced lung injury (P-SILI) is postulated to occur during spontaneous breathing secondary to high respiratory efforts, lung stress and strain [3]. While still remaining theoretical in terms of clinical impact, prevention of P-SILI may also require sedation to remove or reduce the intensity of efforts. Furthermore patient–ventilator dyssynchrony has been associated with worsened outcomes [4], and sedation is frequently increased in response. While deep sedation might help achieve ventilation targets thought to be lung protective, escalating sedation may have myriad adverse potential consequences, including hypotension, delirium, delayed wake-up, drug-specific toxicities (e.g., propofol infusion syndrome), impeded early mobility, and diaphragm disuse atrophy, collectively contributing to prolongation of mechanical ventilation and increased mortality [5, 6].

Our current understanding of sedation and lung injury remains limited, with data suggesting that arousal level poorly correlates with markers of patient effort [7], and some potentially injurious dyssynchrony may actually be exacerbated by deeper sedation [8]. Additionally, sedatives are titrated based on scales that assess arousal, not the level of synchrony or respiratory effort. Even with similar arousal, the impact on synchrony and respiratory drive may be widely variable between sedative agents [9] and between individual patients. Current practices treat sedation independently from ventilation, when ideally sedation and mechanical ventilation are not dissociable and should be managed together [10], although the optimal approach to modulating respiratory drive/effort with sedation is unknown. While the initial objective should always be to treat the underlying illness and to optimize mechanical ventilation, the interplay with sedation appears to be highly important and underexplored.

It is time for a new paradigm of personalized sedation, what we call "lung-protective sedation", using sedatives to target synchrony in some patients, facilitating safe levels of dyssynchrony and patient effort, balancing the risk/benefit of sedation and avoiding treatment of the lungs at the expense of the rest of the patient (Supplemental Fig. 1). These strategies should prevent reacting to dyssynchrony and spontaneous efforts without optimization of mechanical ventilation, or understanding its cause(s), with treatment depending on the patients' unique illness. Implementation of lung-protective sedation will require improving our monitoring techniques for sedation beyond the current limited scales, while minimizing oversedation and paralysis, and we propose the following (Table 1).

Improved monitoring tools and determination of safe levels of effort and dyssynchrony

The Richmond Assessment Sedation Scale (RASS), Riker Sedation–Agitation Scale (SAS) and Ramsay Scale represent the most commonly used and studied scales, and were designed to assess the level of arousal, not patient–ventilator interaction or respiratory drive. Sedation depth does not consistently correspond with ventilator synchrony; some forms of dyssynchrony increase with lower scores [8] suggesting that deeper sedation is often

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Table 1 Current paradigms compared with the proposed lung-protective sedation paradigm

	Current paradigm	Lung-protective sedation paradigm
Sedation monitoring	Sedation scales dissociated from mechanical ventilation Markers of arousal NOT drive or effort RASS SAS Ramsay GCS Other scales	New scales based upon patient respiratory drive and effort Candidate scales include: **$P_{0.1}$** *Pro*: noninvasive, generalizable, integrated into many vents. *Con*: measure of drive and not effort **P_{occ}** *Pro*: easily performed at the bedside, better measure of effort than p0.1, generalizable. *Con*: requires breath hold measurement **P_{mus}** *Pro*: a direct measure of inspiratory muscle pressure. *Con*: requires esophageal manometry so less generalizable **PTP** *Pro*: a measure of muscle pressure integrated over time. Does not require volume generation *Con*: requires esophageal manometry so less generalizable **WOB** *Pro*: actual measure of patient generated energy. *Con*: requires volume change, so does not count ineffective efforts, requires esophageal manometry so less generalizable **Campbell diagram** *Pro*: pressure–volume loops of the chest wall used for dyssynchrony phenotyping and measurement of Pmus and WOB. *Con*: specialty training to understand and requires esophageal manometry **Dyssynchrony Indices** *Pro*: may be a good way to combine different forms of dyssynchrony. *Con*: not all forms of dyssynchrony are the same risk for injury, and the ideal index remains unknown
Impact of specific sedatives on mechanisms of lung protection	Unknown at this time	Impact of sedative and analgesics choices are individualized to the unique characteristics of the patient, which may include: Removal vs preservation of spontaneous efforts Attenuation of spontaneous efforts Attenuation of injurious patient–ventilator dyssynchrony Decreased inflammation
Target or "safety" thresholds	Target sedation depth poor marker for impact on patient effort and synchrony Poor relationship between depth of arousal (RASS, SAS scores…) and markers of effort and synchrony No set or predetermined arousal goal levels	Threshold safety levels identified Threshold frequency of spontaneous breathing when trying to make patients fully passive (needs to be better defined) Thresholds of patient effort/drive when allowing spontaneous breathing (for example $P_{0.1}$ with less effort than – 3.5 to 4.0 cmH_2O) Thresholds of dyssynchrony
Patient targeted strategies	Current paradigms have no consistent approach Many clinicians may attempt to personalize their approach, albeit with little data to direct care	Modifiable and adjustable strategies depending on the patient clinical status Severity of illness parameters to use will need clarification, but could be based upon respiratory system mechanics, gas exchange of severity of illness indices for example Targeted passive breathing in some patients (removal of all spontaneous breathing): potentially in sicker and more acutely ill patients Tolerance of spontaneous breathing but at non-injurious levels in some patients: potentially in less sick patients or in patient who are being weaned Identification of dyssynchrony phenotypes and frequencies that may be injurious in specific patient populations

RASS denotes Richmond Agitation and Sedation Scale, *SAS* the Riker Sedation–Agitation Scale, *GCS* the Glasgow Coma Scale, $P_{0.1}$ the occlusion pressure generated in the initial 100 ms of an inspiration measured by the ventilator, P_{occ} the occlusion pressure measured during an expiratory breath hold, P_{mus} the inspiratory muscle pressure measured by esophageal manometry, *PTP* the pressure–time product measured by esophageal manometry, and *WOB* the work of breathing

not lung protective, and there was no relationship found between sedation scores and inspiratory effort [7]. We propose that direct measures of synchrony and effort, which may also reflect comfort, would be improved tools for titration of sedation in addition to the currently applied metrics of arousal.

The occlusion pressure during an inspiratory effort in the initial 100 ms ($P_{0.1}$) represents an intriguing measure of drive which has been proposed to estimate effort and predict subsequent decompensation [11]. Many ventilators allow for continuous measurement of this value [11], making it a potential target for sedation titration. The expiratory occlusion pressure (P_{occ}) also represents a potential noninvasive target to measure effort and lung distending pressures and evaluate dyssynchrony [12]. Esophageal pressure (P_{es}) estimation facilitates measurement of respiratory muscle pressure (P_{musc}), work of breathing, the pressure–time product, change in P_{es} over the initial 100 ms, and maximal P_{es} deviation during inspiration, all of which might be good markers of inspiratory effort and drive. These objective measures represent potential targets for monitoring and titration of lung-protective sedation to reduce harm from both insufficient and excessive efforts [13], but precisely what thresholds correspond to clinically important safety/injury signals is not well characterized. Additionally, specific phenotypes of dyssynchrony, the frequency of events and the amplitude of efforts [14] will need to be defined as part of a lung-protective sedation strategy with the development of scales targeting dyssynchrony.

Impact of specific agents on effort and dyssynchrony

Opioids, benzodiazepines, dexmedetomidine, and propofol represent the most commonly used agents during mechanical ventilation. All may lead to suppression of respiratory drive; however, each has variable impact on effort and dyssynchrony, sometimes without predictable effect [9]. Additionally, whereas the presumed mechanism of lung protection for most sedatives is by reducing VILI and P-SILI through achieving synchrony and limiting injurious efforts, inhaled sedation may provide bronchodilation, be rapidly titratable and may directly attenuate lung parenchymal inflammation [15] making them intriguing adjuvants.

Individualization of targets

The application of lung-protective sedation should not entail a single prescriptive approach for every patient and should be adjusted based upon the unique characteristics of the patient. Although clinicians may differentiate the goals based upon clinical characteristics, we currently lack a clear framework and an evidence-based approach to tell us which patient should be fully passive, which patient should be allowed to breathe spontaneously and the characteristics of the patient which might make dyssynchrony more or less injurious. As such, the final and most important aspect of lung-protective sedation is determining in whom and when during the course of illness lung-protective sedation strategies shift.

The concept of lung-protective sedation represents an important paradigm shift, recognizing the inherent link between optimization of mechanical ventilation, sedation and lung injury. This will involve relying not just on instruments that assess arousal and comfort, but also weighing the role of sedatives to attenuate injurious patient–ventilator interactions and regulate "safe" levels of effort, choosing the "right" sedative depending on the clinical scenario and determining the optimal approach depending on the unique patient characteristics. While the development of these strategies may appear ambitious and challenging, they represent a critically important goal to optimize patient care while balancing the potential benefits and harms from sedatives.

Supplementary Information
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