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Sedation, Analgesia and Respiratory Drive in Mechanically Ventilated Adults

An overview of the cardiovascular and respiratory effects of sedative agents commonly used in the ICU, emerging concepts of mechanical ventilation induced injury to the respiratory muscles and evolving concepts for sedation monitoring and sedation minimisation to achieve the goal of expeditious liberation from mechanical ventilation.

prescription of sedatives and analgesics should be with a targeted approach to manage the components of pain, agitation, delirium, immobility and sleep precisely (Devlin et al. 2018). In this review we will discuss the cardiovascular and respiratory effects of sedative agents commonly used in the ICU. We will then describe emerging concepts of mechanical ventilation induced injury to the respiratory muscles, and in particular the diaphragm. Finally, we will explore evolving concepts for sedation monitoring and sedation minimisation to achieve the goal of expeditious liberation from mechanical ventilation.

Cardiovascular Effects of Sedation

Sedatives have important cardiovascular effects. An understanding of the physiologic effects of each agent is important, to tailor the sedation strategy to the patient based on their physiologic state and minimise harms (Table 1).

Opioids are μ receptor agonists used for analgesia, but at higher doses can be used for sedation. This class of drug reduces sympathetic tone, and therefore can cause a reduction in both blood pressure and heart rate (Darrouj et al. 2009).

Benzodiazepines are gamma-aminobutyric acid (GABA) agonists and are used for induction and maintenance of sedation.

Although generally considered safe from a cardiac perspective, benzodiazepines can cause a mild reduction in blood pressure and have mild negative inotropic effects (Darrouj et al. 2009; Zakaria et al. 2018). The major limiting factor in their use is the risk of potentiating delirium (Arumugam et al. 2017). The mechanism of action of propofol is similar. While its effect on heart rate is neutral, the effects on blood pressure can be haemodynamically and clinically significant. Like benzodiazepines, propofol has a mild negative inotropic effect. However, unlike benzodiazepines, propofol also decreases systemic vascular resistance and causes venodilation, decreasing left ventricular preload (Zakaria et al. 2018; de Wit et al. 2016). The hypotensive effect can be exacerbated in those with heart disease, therefore, it is generally avoided in those with cardiogenic shock (Zakaria et al. 2018). Etomidate, another GABA agonist, which is used for induction of anaesthesia, has a net neutral effect on haemodynamics, however, it can potentiate adrenal insufficiency and lead to hypotension through this mechanism (Thompson et al. 2014).

Ketamine, an N-methyl-D-aspartate receptor antagonist, causes a dose dependent increase in sympathetic tone. As such, it may increase heart rate, blood pressure,

The Use of Sedation in Mechanically Ventilated Adults in the ICU

Mechanical ventilation is the most widely used form of life support employed worldwide (Pham et al. 2017), and consequently sedatives and analgesics are among the most commonly prescribed medications in the intensive care unit (ICU) (Luz et al. 2022). In fact, in the course of an ICU admission, over 90% of patients will be prescribed analgo-sedation (Patel et al. 2013). The use of sedatives in the ICU represents a delicate balance. On one hand these medications are used for pain, anxiolysis and ventilator synchrony, but expose patients to the significant adverse effects including delirium, nosocomial infections, and increased mortality (Devlin et al. 2018; Shehabi et al. 2012). Contemporary epidemiological analysis suggests that, despite a recommendation against using continuous infusions of benzodiazepines for sedation, midazolam is the most commonly used agent for sedation, with fentanyl the most common opioid (Luz et al. 2022). The

and cardiac output. In critically ill patients, however, particularly those with cardiac dysfunction, the haemodynamic response to ketamine is less predictable, and the net result may be a drop in cardiac output (Zakaria et al. 2018).

Dexmedetomidine, an alpha-2 receptor agonist, provides light sedation without respiratory suppression, making it an attractive option in mechanically ventilated patients. However, its use is associated with hypotension, bradycardia and asystole. Those with acute decompensated heart failure may be at higher risk of these adverse events (Adie et al. 2021).

Volatile anaesthetics are an attractive option in situations of drug shortages and also have a favourable respiratory profile. Volatile anaesthetics decrease blood pressure in a dose-dependent fashion through peripheral vasodilation. This may cause a reflex tachycardia, though the compensatory response may be blunted and insufficient to maintain cardiac output. Volatiles also have a negative inotropic effect. These anaesthetics may also predispose to both brady- and tachyarrhythmias (Jerath et al. 2020).

The Control of Breathing

Respiratory drive, the efferent output of the respiratory centre, is responsible for carbon dioxide (CO_2) homeostasis. Central and peripheral chemoreceptors respond to deviations from the CO_2 setpoint and provide feedback to the respiratory centre, either increasing or decreasing alveolar ventilation. Hypoxaemia and cortical inputs modulate the intensity of this respiratory drive response (Spinelli et al. 2020). The duration of the inspiratory effort is also influenced by pulmonary mechanoreceptors. When activated by lung inflation, they inhibit chemoreceptors at the respiratory centre and help terminate an inspiration cycle (Spinelli et al. 2020), a reflex known as Hering-Breuer. Ventilatory effort, the clinical counterpart of respiratory drive, depends on the integrity of the inspiratory flow-generation pathway (Vaporidi et al. 2020). A given respiratory drive might result in very different efforts depending on the respiratory muscle strength or the diaphragmatic conformation. For example,

some patients with emphysema and flattening of the diaphragm have respiratory drives out of proportion to their ability to generate inspiratory pressure. Conversely, some conditions are associated with respiratory drives higher than their metabolic demand would require. In situations such as delirium and altered pulmonary mechanoreceptors, excessive ventilatory efforts can lead to hyperventilation and, possibly, patient self-inflicted lung (P-SILI) or respiratory muscle injury (Brochard et al. 2016).

We can illustrate the disruption of the inspiratory flow-generation pathway in an example of two patients. Patient A has an appropriate respiratory drive response and a normal-high CO_2 . This patient is recovering from acute illness with low respiratory system compliance and concordance of their brain-ventilation curve (Vaporidi et al. 2020). If they have preserved respiratory muscle strength, this could result in strong inspiratory effort. In this scenario, the issue is not respiratory drive *per se* but rather the adaptation of the brain-ventilation curve to a new condition. Patient B has an inappropriate respiratory drive response and a low CO_2 . Patient B is also recovering from acute illness but has a dissociation between what the brain is expecting ventilation to be and what the muscles can provide (Vaporidi et al. 2020). Such a dissociation may stimulate the respiratory drive, which in turn overwhelms lung-protective reflexes (e.g., Hering-Breuer) and results in a PaCO_2 lower than that required by acid-base homeostasis. Thus, patient B might generate high tidal volumes and a high respiratory rate that ultimately promotes further lung injury and inflammation.

Sedation and the Control of Breathing

All commonly used sedative and analgesic agents in the ICU will affect the drive to breathe (Table 1). A targeted strategy to maintain a safe level of respiratory effort might be an optimal way to balance the risk of respiratory muscle quiescence and excessive respiratory efforts (Sklar et al. 2021; Goligher et al. 2020a; Goligher et al. 2018a; Goligher et al. 2020b). Opioids are currently recommended by clinical practice guidelines as the first agent to

use for an analgesic based approach to facilitate mechanical ventilation (Devlin et al. 2018). Opioids have been associated with less patient-ventilator dyssynchrony and so may be a desirable first agent (Goligher et al. 2020b). Propofol and benzodiazepines both cause respiratory depression, principally by reducing the amplitude of respiratory effort (Goligher et al. 2020b; Vaschetto et al. 2014). Given the shorter half-life and lower delirigenic potential of propofol it is preferred over benzodiazepine-based sedation strategies. Dexmedetomidine and ketamine are attractive agents for use in mechanically ventilated patients. Unlike other agents, they provide sedation, anxiolysis (ketamine may cause rebound agitation), and analgesia with more limited occurrences of respiratory depression (Goligher et al. 2020b; Belleville et al. 1992; Martinez et al. 1985). Finally, inhalational sedation with volatile anaesthetic agents offers a potential alternative for controlling respiratory effort. At doses that would be typically used in the ICU setting, these agents promote spontaneous breathing with elevated respiratory rates and relatively maintained to reduced tidal volumes (Jerath et al. 2020). This breathing pattern may theoretically potentiate safe spontaneous breathing. Further research is required to more specifically study the impact of sedative agents and the control of breathing and how to monitor and titrate sedation to physiological parameters (Sklar et al. 2021; Goligher et al. 2020b).

Ventilator Induced Diaphragm Dysfunction

Protective mechanical ventilation is a life-saving therapy for patients with and without acute respiratory distress syndrome (ARDS). In addition to gas exchange improvement, mechanical ventilation may help restore blood flow to vital organs, improve oxygenation, and reverse muscle fatigue. Conversely, mechanical ventilation may have adverse effects both to the lungs and diaphragm. While the mechanisms of ventilator-induced lung injury have been extensively studied, only recently the focus has turned towards the effects of mechanical ventilation on the diaphragm

Drug class	Mechanism of Action	Blood pressure	Heart rate	Respiratory rate	Tidal volume	Comments
Propofol	GABA receptor agonist	↓	↓/↔	↓	↓	Hypotensive effects may be exacerbated in those with cardiac dysfunction. Avoid use in cardiogenic shock.
Opioids	μ receptor agonist	↓	↓	↓	↓	Often used in combination with other agents, potentiating their haemodynamic effects.
Benzodiazepines	GABA receptor agonist	Mild ↓	↔	↓/↔/↑	↓	Not recommended by current guidelines for continuous infusion due to risk of delirium. Respiratory effects are dose dependent, with higher doses increasing risk of respiratory depression.
Ketamine	NMDA receptor antagonist	↓/↔/↑	↑/↔	↔	↔	Haemodynamic effects depend on overall volume status, sympathetic tone
Dexmedetomidine - bolus	α2 receptor agonist	↑	↓	↔	↔	Initial bolus can cause hypertension due to stimulation of peripheral vasoconstrictor receptors.
Dexmedetomidine - no bolus	α2 receptor agonist	↓	↓	↔	↔	A third of patients still experience significant bradycardia without a bolus
Etomidate	GABA receptor agonist	↔/↓	↔	↔	↔	Used for induction of anaesthesia, risk of adrenal insufficiency and resultant hypotension.
Volatiles	GABA receptor agonist, AMPA and NMDA receptor antagonist	↓	↑	↓/↑	↓	Decrease in tidal volume may be compensated for by an increase in respiratory rate.

Table 1. Physiological effects of sedation

GABA = gamma-aminobutyric acid, NMDA = N-methyl-D-aspartate, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

and other respiratory muscles.

Vassilakopoulos and Petrof (2004) defined ventilator-induced diaphragmatic dysfunction (VIDD) as a loss of diaphragmatic force-generating capacity that is specifically related to the use of mechanical ventilation. The biological mechanisms of VIDD is not in the scope of this review. Yet, it is important to mention that mechanical ventilation per se does not cause VIDD (Goligher et al. 2018b); in fact, ventilatory settings leading to under-assistance or over-assistance, inappropriate PEEP titration leading to excessive diaphragm shortening, and poor patient-ventilator synchronicity are all related to diaphragm dysfunction (Goligher et al. 2018b). Due to the fact that diaphragm dysfunction may be associated not solely with ventilatory settings

but also with other causes such as sepsis, systemic inflammation, and trauma, experts have recently proposed the term critical illness-associated diaphragm weakness (Dres et al. 2017).

One of the most common ways to assess diaphragm function in critically-ill patients under mechanical ventilation is to measure diaphragm thickness with an ultrasound (Goligher et al. 2015a). Several studies had already associated diaphragm atrophy with mechanical ventilation in selected patients when Goligher et al. (2015b) described the evolution of diaphragmatic thickness over time in more than one-hundred patients admitted to three academic intensive care units. In the first week of ventilation, 44% of patients had decreased diaphragm thickness, 44% had

unchanged, and only 12% had increased. Later, the same authors published a study (Goligher et al. 2018a) where they assessed diaphragm thickness in 191 patients and associated decreased diaphragm thickness with lower probability of liberation from ventilation (adjusted hazard ratio, 0.69; 95% CI 0.54-0.87), prolonged ICU admission (adjusted duration ratio, 1.71; 95% CI 1.29-2.27), and higher risk of complications (adjusted odds ratio, 3.00; 95% CI 1.34-6.72). In a secondary analysis, Sklar et al. (2020) assessed diaphragm thickness in 193 patients and concluded that low baseline diaphragm muscle mass was associated with delayed liberation from mechanical ventilation (adjusted hazard ratio for liberation 0.51; 95% CI, 0.36-0.74), higher risk of acute

respiratory failure (adjusted odds ratio, 1.77; 95% CI 1.20-2.61 per 0.5-mm decrement), prolonged weaning (adjusted odds ratio, 2.30; 95% CI 1.42-3.74), and higher in-hospital mortality (adjusted odds ratio, 1.47; 95% CI 1.00-2.16 per 0.5-mm decrement). Finally, a study with 940 patient-days suggested that changes in diaphragm may (partially) mediate the relationship between respiratory effort and duration of ventilation in ICU survivors ($p=0.04$), risk of complication of acute respiratory failure ($p=0.04$), and length of ICU stay in ICU survivors ($p=0.02$) (Goligher et al. 2018b).

There are yet other tools to assess diaphragm weakness that are not operator-dependent (Supinski et al. 2018). Demoule et al. (2013) used the twitch tracheal pressure (Ptr, stim) in response to bilateral phrenic nerve stimulation to evaluate the diaphragm in eighty-five patients. The authors concluded that diaphragm weakness, defined as Ptr, stim < 11 cmH₂O, was present in 64% of patients admitted to the ICU and was associated with poor prognosis. In another prospective study, diaphragm weakness, also measured with

Ptr, stim on ICU admission and every 48-72h thereafter, was observed in 79% of patients under mechanical ventilation for more than five days (Demoule et al. 2016). Moreover, Supinsky et al. (2016) compared transdiaphragmatic pressure after bilateral twitch simulation with airway pressure during a 30-second inspiratory occlusion in sixty patients and found that both measurements were profoundly reduced in mechanically ventilated patients.

It is adequate to state that diaphragm weakness is a concern that must be addressed in all mechanically ventilated patients. Moreover, it is necessary to gently treat not only the lungs but also the diaphragm. Therefore, a panel of experts recently published a conceptual framework proposing strategies to reduce diaphragm weakness while maintaining lung protective ventilation (Goligher et al. 2020a). **Figure 1** summarises available recommendations of lung and diaphragm protective ventilation together with the latest recommendations, from the ATS/ESICM/SCCM, for mechanically ventilated patients with ARDS (Fan et al. 2017).

Approaches to Treat or Reduce Diaphragm Weakness

Extracorporeal CO₂ removal: There is an increased awareness towards preventing diaphragm weakness as it is associated with adverse effects. Conversely, an increased respiratory drive may result in strong inspiratory efforts and ultimately hold deleterious effects in patients on spontaneous breathing. A study evaluated the response to CO₂ removal on eleven spontaneous breathing sheep with healthy and injured lungs (Langer et al. 2014). While CO₂ removal in sheep with healthy lungs successfully reduced minute ventilation (reduction in %, 84 ± 14 , $P < 0.001$), some sheep with injured lungs did not, despite a high percentage of CO₂ removal. The authors concluded that the individual response could differ regardless of similar clinical conditions. In line with these findings, Mauri et al. (2016) conducted a proof-of-concept randomised, crossover protocol in eight spontaneously breathing ARDS patients undergoing veno-venous extracorporeal membrane oxygenation (ECMO). The authors assessed the respiratory drive in different sweep settings and

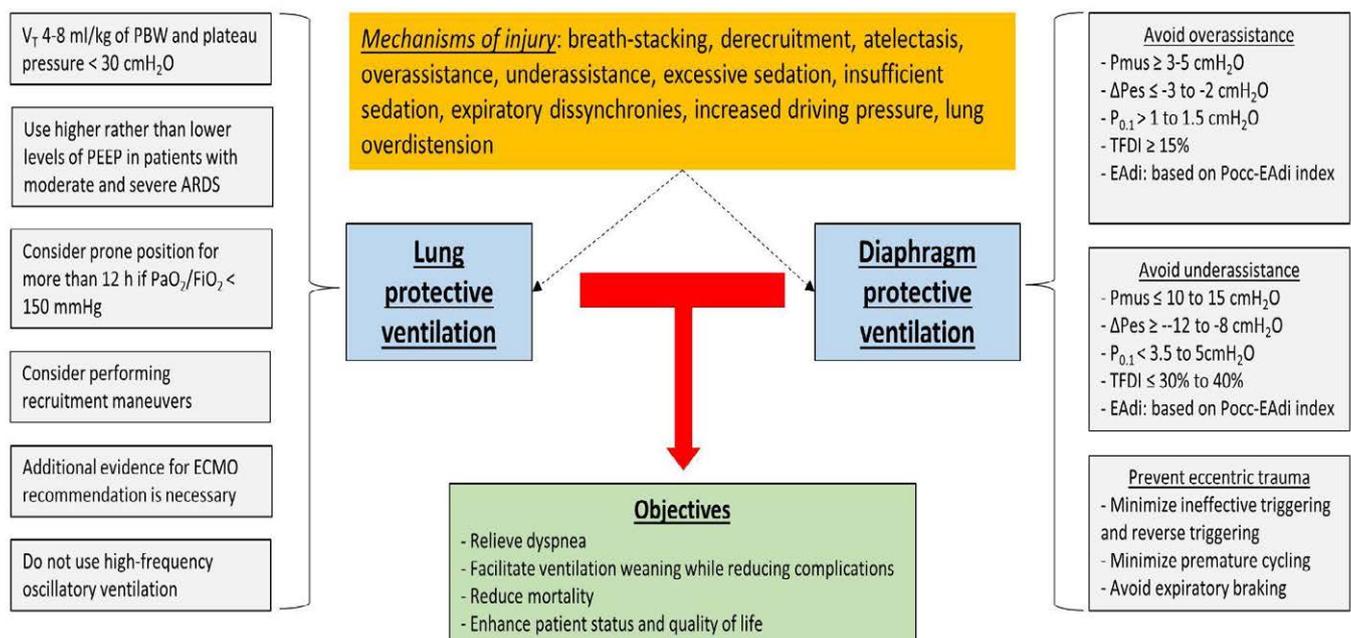


Figure 1. Contemporary recommendations for protective lung ventilation of ARDS patients and for lung- and diaphragm-protective ventilation

found that the amount of extracorporeal carbon dioxide removal directly may influence spontaneous breathing. Respiratory variables such as $p_{0.1}$, electrical activity of the diaphragm, muscular pressure, pressure time product, and peak transpulmonary pressure were inversely related to carbon dioxide extraction ($p < 0.001$ for all): the higher the extraction rate, the lower those variables. It may be possible to assume that extracorporeal CO_2 removal might be an alternative in patients who are likely to develop P-SILI. However, this strategy may be limited to specialised centres and may be associated with increased costs and workload.

Partial neuromuscular blockade: Instead of modulating the respiratory drive, there are novel alternatives that dissociate respiratory drive output and inspiratory effort. Doorduyn et al. (2017) proposed partial neuromuscular blockade in patients under invasive mechanical ventilation. The authors successfully titrated a rocuronium infusion to reduce tidal volume and other respiratory variables to lung-protective thresholds. Despite promising physiology, this strategy still has limitations: (1) it requires careful titration of the infusion, which may ultimately increase the workload of healthcare professionals; and (2) patients need to be under deep sedation. Therefore, while it may reduce the probability of P-SILI, a continuous infusion of low-dose rocuronium is likely associated with worse patient-centred outcomes, including those related to deep sedation, as previously described.

Phrenic nerve block: Recently, Pereira et al. (2022) published a translational study

where they bilaterally administered lidocaine perineurally to the phrenic nerve. An animal model of six pigs with ARDS and nine patients with acute lung injury were included. In pigs and humans, bilateral phrenic nerve block was associated with decreased driving pressure, electrical activity of the diaphragm, oesophageal pressure swing, tidal volume, and peak transpulmonary pressure ($p < 0.05$ for all). Furthermore, there was a decrease in pendelluft in four pigs, from nearly 8% to 0% of tidal volume. Although the authors administered lidocaine a single time, it may be possible to insert a perineural catheter and titrate an infusion of local anaesthetic to partially suppress phrenic nerve activity. In this scenario, it would be possible to reduce complications associated with both deep sedation and neuromuscular blocking agents. Yet, the consequences of phrenic nerve block on accessory respiratory muscles have not been assessed and this approach requires training to appropriately identify cervical structures with ultrasound.

Transvenous phrenic nerve stimulation and inspiratory muscle training:

If prolonged deep sedation and invasive mechanical ventilation are needed to maintain mechanical ventilation under protective thresholds, transvenous phrenic nerve stimulation and inspiratory muscle training may be alternatives to facilitate ventilation weaning and improve patient outcomes. Reynolds et al. (2017) tested transvenous phrenic nerve pacing therapy in 18 sedated and ventilated pig divided in three groups: (1) pigs with pacing on alternate breaths, (2) pigs similarly sedated and ventilated but without pacing, and (3)

never-paced control animals. There was a significant decline in diaphragm thickness in group 3 but not in group 1 (0.84 [IQR 0.78–0.89] vs. 1.10 [IQR 1.02–1.24]; $P = 0.001$). In the largest trial on transvenous phrenic nerve stimulation, Dres et al. (2022) randomised 102 patients to bilateral phrenic stimulation and standard of care. There were no differences in the incidence of successful weaning (82% in the treatment group vs. 64% in the control group, $P = 0.59$) and mechanical ventilation days (12.7 ± 9.9 in the treatment groups vs. 14.1 ± 10.8 in the control group, $P = 0.50$). In spite of the negative patient-centred outcomes, the difference in maximal inspiratory pressure (95% CI 11.8 [5–19], $P = 0.001$) should warrant further studies on the topic.

Conclusion

Sedation in the ICU is common, but its interaction with the critically ill, mechanically ventilated patient is complex and incompletely understood. The use of sedative agents requires knowledge and appreciation of both cardiovascular and respiratory effects to mitigate the risks of adverse events while employing them safely to achieve their desired actions. Monitoring of sedation is evolving and ongoing research is currently being conducted to better understand the interaction between the patient and the ventilator. Over-sedation can precipitate diaphragm injury and modern ventilatory strategies should be implemented not only to facilitate lung, but also diaphragm protective ventilation.

Conflict of Interest

None. ■

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