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WHAT'S NEW IN INTENSIVE CARE

Is my patient's respiratory drive (too) high?

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What "drives" the respiratory drive?

The intensity of the neural stimulus to breathe is called "respiratory drive" [1] and plays a major role in acute respiratory failure before, during, and after mechanical ventilation. Respiratory drive modulates inspiratory effort (the pressure generated by the respiratory muscles) according to metabolic needs through various feedback control mechanisms. It primarily responds to chemical inputs from the central and peripheral chemoreceptors. Additional stimuli arise from mechanoreceptors and vagal inputs (from chest wall, respiratory muscles, airways, and lungs) [1]. The control of breathing is also influenced by behavioral factors and activities (talking, swallowing, exercise), pain (e.g., post-operative patients), temperature, and inflammatory chemokines (e.g., during endotoxemia). Brainstem inflammation may also directly influence the control of breathing [2]. Patients with acute respiratory failure may exhibit high respiratory drive due to deranged gas exchange, high metabolic demands, and/or intense mechanical stimuli. Respiratory drive may also be increased, modified, or even suppressed by acute neurological insults such as stroke or traumatic brain injury.

Why is an excessive respiratory drive bad for my patient?

For many reasons summarized in Fig. 1, a high respiratory drive may lead to lung or diaphragm injury in patients under mechanical ventilation.

High respiratory drive leads to vigorous inspiratory efforts that result in globally or regionally excessive lung distension due to an inhomogeneous distribution of stress and strain [3]. During acute respiratory failure in patients under mechanical ventilation, and in non-intubated patients, excessive respiratory drive can overwhelm lung-protective reflexes (e.g., Hering–Breuer reflex) that aim to limit lung volume, leading to lung injury and inflammation. The consequent deterioration in lung mechanics and gas exchange amplify the potent stimulus to breathe, generating a vicious circle of worsening injury (a mechanism recently termed "patient self-inflicted lung injury", P-SILI) [3]. Excessive respiratory drive can also cause double-triggering and breath-stacking in assist-control modes [4], resulting in higher tidal volumes and injurious lung stress.

High respiratory drive may also contribute to diaphragm weakness in acute respiratory failure. Vigorous inspiratory efforts can cause load-induced injury when diaphragm muscle tissue is sensitized to mechanical stress by systemic inflammation [5]. Eccentric (lengthening) contractions during expiratory braking or during patient–ventilator dyssynchrony may be particularly injurious. Recent data suggest that load-induced injury might result in prolonged mechanical ventilation and ICU stay [6].

During weaning, excessive respiratory drive and elevated ventilatory demands increases dyspnea and can lead to weaning failure and/or extubation failure. Activation of the accessory respiratory muscles is strongly associated with the degree of dyspnea in mechanically ventilated patients [7]. Furthermore, ventilated patients with elevated respiratory drive may experience dyspnea ("air hunger") particularly when the flow delivery is insufficient ("flow starvation"); such dyspnea can cause anxiety and agitation and may contribute to post-ICU psychological symptoms [8, 9].

How do I diagnose an excessive respiratory drive?

Respiratory drive is sometimes assessed through the respiratory rate. Breathing frequency, however, depends on

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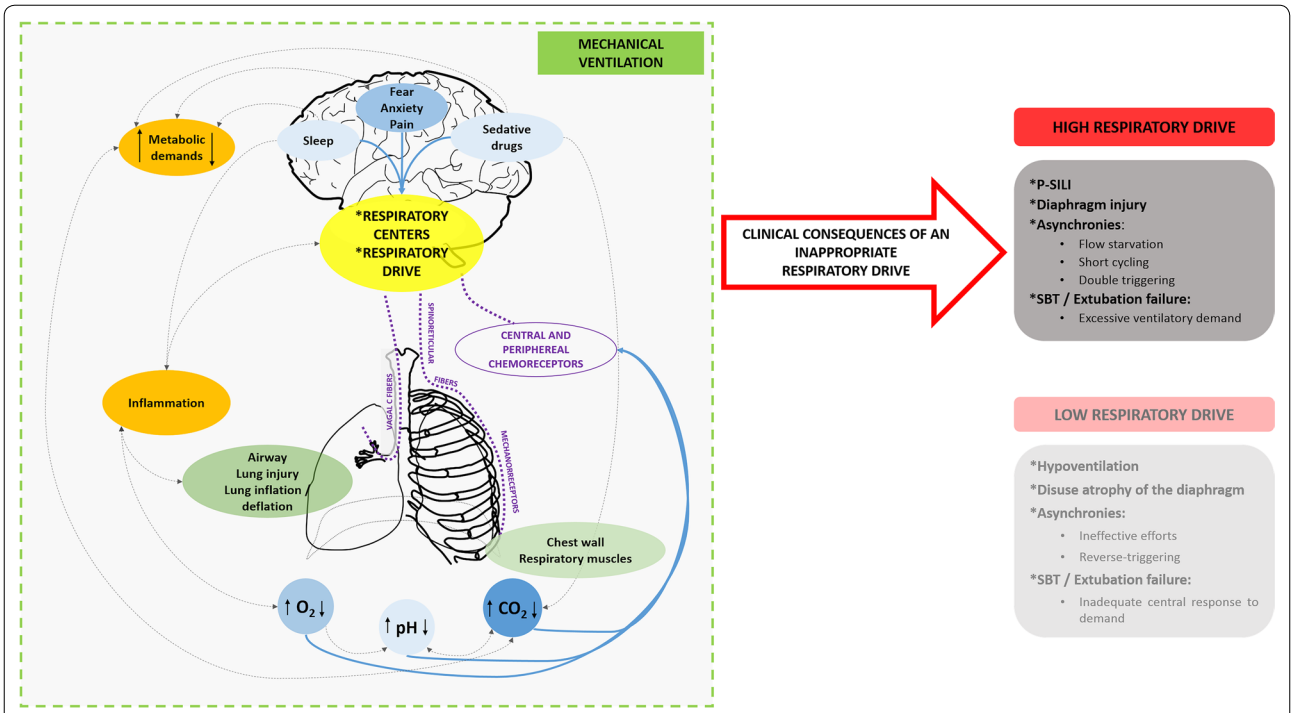

Fig. 1 Physiological mechanisms controlling respiratory drive and clinical consequences of inappropriate respiratory drive during acute respiratory failure. Respiratory centers in the brainstem send inputs to the respiratory muscle that generate ventilation. The main feedback signals include CO_2 tension, acid/base status (pH), and oxygenation. Additional signals modify the respiratory drive either directly, by acting on other variables, or indirectly, by modifying the response of the servomechanism. Colored arrows represent the main determinants and gray lines represent more complex interactions. Some determinants arise from upper neural structures and others arise directly from the airway, chest wall, lung parenchyma, or respiratory muscles. Signals from the airways and lung parenchyma are conducted via vagal C fibers. Mechanoreceptors in muscle spindles, tendons, and joints are conducted through the spinoreticular pathway. Mechanical ventilation can influence all these mechanisms substantially. On the right, the consequences of an inappropriately high and low respiratory drive during mechanical ventilation are listed. P-SILI: patient self-inflicted lung injury; SBT: spontaneous breathing trial

respiratory mechanics and other factors [10] such that it does not reliably reflect respiratory drive or effort. It is also influenced by the level of pressure support: under pressure support, respiratory rate can decrease independently from respiratory drive when mechanical insufflation is prolonged into the patient's neural expiration (i.e., when the ventilator cycling is delayed) [11]. Some patients may also have high inspiratory effort in the absence of tachypnea.

To date, there is no direct measure of the central respiratory center's activity. However, if spontaneous breathing is preserved, respiratory center output can be assessed simply and non-invasively in mechanically ventilated patients by measuring the airway occlusion pressure or $P_{0.1}$, i.e., the pressure developed in the occluded airway 100 ms after the onset of an inspiratory effort [12]. It was first described more than 40 years ago [13] and is now available on most modern ventilators. $P_{0.1}$ is independent of respiratory mechanics and the patient's reaction and is, importantly, unaffected by respiratory muscle weakness. Breath-to-breath variability of $P_{0.1}$ is considerable but the average of 3–4 values represents a reliable index of the patient's drive.

Respiratory drive may also be inferred from measurements of inspiratory effort, despite maximal inspiratory effort being undoubtedly affected by muscle weakness. Severe muscle weakness may result in some discrepancy between drive and effort. Inspiratory effort can be directly measured using esophageal manometry to quantify the pressure–time product per minute (PTP) or the work of breathing (WOB) of the respiratory muscles [14]. It can be employed at the bedside with relative ease, but many clinicians are unfamiliar with the technique. Inspiratory effort can be estimated non-invasively by diaphragm ultrasound. Diaphragm thickening during inspiration (quantified by the thickening fraction, TFdi) reflects diaphragm shortening during contractile activation. TFdi is correlated with PTP [15] and electrical activity of the crural diaphragm (EAdi). Because of inter-observer and intraobserver variability, specific training is required. Additionally, respiratory drive may also affect

expiratory effort, which is more difficult to quantify as it requires intra-abdominal pressure measurement.

Electromyography is a more technically challenging technique for monitoring respiratory muscle activity but measurement of EAdi is now available by using one type of ventilator (Maquet®, SERVO-i or SERVO-u). EAdi signals are acquired by placing a specialized nasogastric catheter fitted with electrodes. These signals can be employed to estimate respiratory drive and inspiratory effort. The signal amplitude range can vary considerably between individuals and it is difficult to establish the reference range.

Finally, to assess for the presence of "air hunger" [9], it may be useful to directly query patients about dyspnea and respiratory discomfort if they are sufficiently interactive.

How much respiratory drive is too much?

The optimal target range for respiratory drive and inspiratory effort during mechanical ventilation is uncertain. In healthy subjects breathing at rest, $P_{0.1}$ varies between 0.5 and 1.5 cmH_2O [1], WOB ranges from 2.4 to 7.5 J/min and from 0.2 to 0.9 J/L [14], PTP is approximately 86 ± 21 cmH_2O s/min [16], and TFdi is approximately 20 ± 15% [17]. Higher levels of respiratory drive and inspiratory effort can theoretically put the patients at risk.

Patients successfully liberated from mechanical ventilation could represent an appropriate range of target values for patients under assisted ventilation. The upper threshold of effort in patients that succeed in a trial of spontaneous breathing on a T-piece is a PTP of 200 cmH_2O s/min. Rittayamai et al. [18] recently found that a $P_{0.1}$ higher than 3.5 cmH_2O can diagnose patients above that threshold with a sensitivity of 92% and a specificity of 89%.

Goligher et al. [6] demonstrated that an intermediate range of inspiratory effort (TFdi 15–30%) is associated with the shortest duration of mechanical ventilation. Targeting this range of inspiratory effort might therefore prevent injury to the lung and diaphragm due to high respiratory drive. However, the upper safe limit of respiratory drive to prevent diaphragm and lung injury in an individual patient may also vary with maximal diaphragm strength, the severity and type of lung injury (i.e., the presence of solid-like lung behavior) [19], the degree of systemic inflammation [5], the available blood flow to the respiratory muscles, and the effect of respiratory muscle oxygen consumption on oxygen delivery to the other vital organs.

On the whole, the available evidence suggests that excessive respiratory drive should be avoided whenever possible but optimal strategies for manipulating drive and inspiratory effort need to be tested.

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Compliance with ethical standards

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