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NARRATIVE REVIEW

Respiratory drive in the acute respiratory distress syndrome: pathophysiology, monitoring, and therapeutic interventions

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Abstract

Neural respiratory drive, i.e., the activity of respiratory centres controlling breathing, is an overlooked physiologic variable which affects the pathophysiology and the clinical outcome of acute respiratory distress syndrome (ARDS). Spontaneous breathing may offer multiple physiologic benefits in these patients, including decreased need for sedation, preserved diaphragm activity and improved cardiovascular function. However, excessive effort to breathe due to high respiratory drive may lead to patient self-inflicted lung injury (P-SILI), even in the absence of mechanical ventilation. In the present review, we focus on the physiological and clinical implications of control of respiratory drive in ARDS patients. We summarize the main determinants of neural respiratory drive and the mechanisms involved in its potentiation, in health and ARDS. We also describe potential and pitfalls of the available bedside methods for drive assessment and explore classical and more "futuristic" interventions to control drive in ARDS patients.

Determinants of respiratory drive

Healthy subjects

Breathing is generated by the rhythmic discharge of groups of neurons located in the brainstem which produces a neural signal directed to respiratory muscles to generate inspiratory effort and tidal breathing [1, 2]. In humans, the activity of the respiratory centres requires a tonic excitatory input that derives from two sources: a chemosensory or "automatic" input and a descending or "behavioural" input.

The *chemosensory input* is a feedback reflex mediated by afferents from central and peripheral chemoreceptors aimed at minimizing fluctuations of the partial pressure of arterial carbon dioxide ($PaCO_2$) and pH and correcting hypoxemia. Central chemoreceptors, located in the ventral surface of the medulla oblongata, regulate the ventilatory response to stabilize CO_2: an increase in $PaCO_2$, by decreasing the pH of cerebrospinal fluid, leads to a linear increase in minute ventilation until steady-state is achieved after a few minutes [3]. The peripheral chemoreceptors, located in the carotid bodies, stimulate breathing by modifying the sensitivity and threshold of the central chemoreceptors, specifically providing faster and more intense responses to modifications in $PaCO_2$ and pH and to hypoxemia [3–5].

The *descending input* is a feed-forward pathway from cortical brain centres and is responsible for adaptive changes of breathing pattern during complex activities, such as physical exercise and mental tasks [6, 7]. Both the chemosensory and the central input are active in awake healthy subjects [8, 9]. Indeed, artificially induced hypocapnia (e.g., through mechanical ventilation) does not abolish respiratory drive [9]. In addition, the respiratory rhythm is modulated by signals from the limbic system, which alters the breathing pattern in response to cognitive and emotional factors, including pain and anxiety [10].

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In physiological studies, the response of the subject to raised $PaCO_2$ level is assessed by measuring the increase in minute ventilation. In this context, two curves exist: the "brain curve", that describes the minute ventilation requested by the neural respiratory drive for a given $PaCO_2$; and the "ventilation curve", that describes the actual minute ventilation of the subject for a given $PaCO_2$. In health, the brain curve coincides with the ventilation curve. The levels of $PaCO_2$ and the corresponding minute ventilation show a linear correlation, the slope of which represents the "brain" respiratory drive [11]. The actual point of equilibrium will lie at the intersection between this neural drive and the metabolic hyperbola, which, instead, is the relationship between ventilation and the resultant $PaCO_2$ for a given level of metabolic CO_2 production and dead space [11, 12] (Fig. 1a).

Acute respiratory distress syndrome

The brain curve, the ventilation curve and the metabolic hyperbola are all potentially modified in ARDS: increased dead space and metabolic CO_2 production shift the metabolic hyperbola upward, meaning that $PaCO_2$ is higher than normal for a given minute ventilation [11]; the slopes and the position of the brain curve and the ventilation curve are altered in opposite directions (Fig. 1b).

In ARDS, pulmonary interstitial and alveolar edema result in increased intra-pulmonary shunt and dead space, and decreased functional lung size due to alveolar collapse (the so-called "baby lung") [13]. Systemic

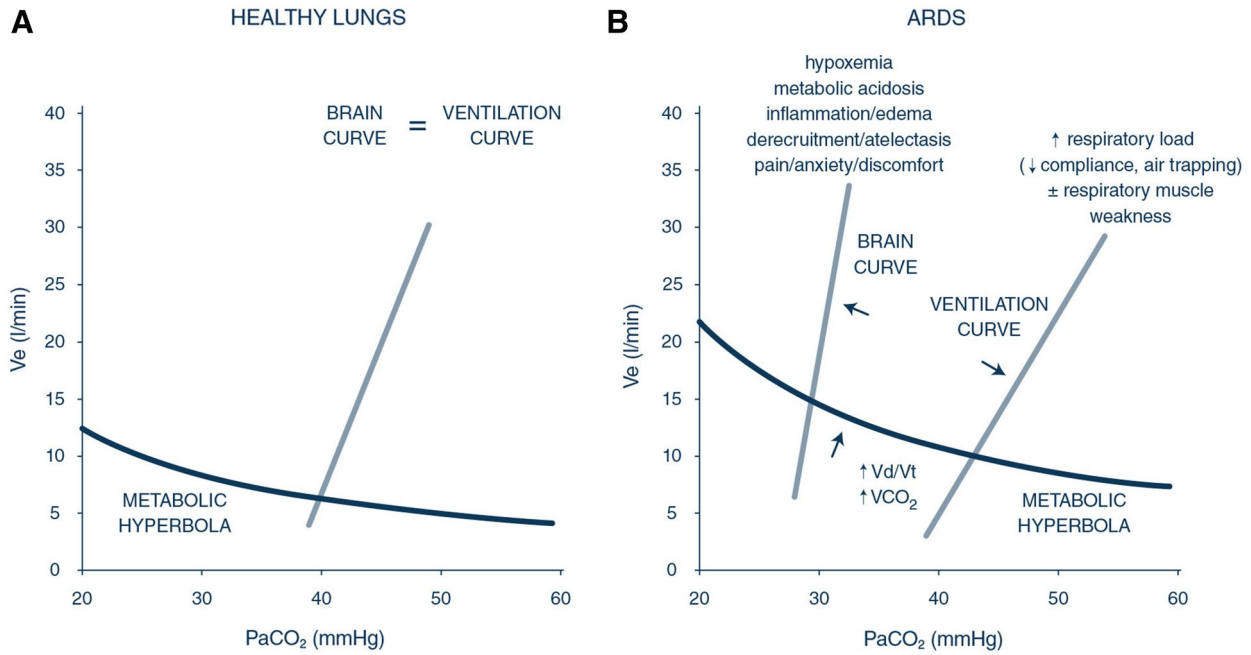

Fig. 1 Metabolic hyperbola, brain and ventilation curves in health and ARDS. The metabolic hyperbola is the relationship between ventilation and the resultant $PaCO_2$ for a given level of metabolic CO_2 production and dead space. Increased dead space or CO_2 production will shift the hyperbola up. The ventilation curve describes the actual effect of changing $PaCO_2$ on resultant minute ventilation. ARDS can shift the ventilation curve to the right (lower minute ventilation despite higher $PaCO_2$) due to increased respiratory load and muscle weakness. Finally, the brain curve (also known as the "controller curve", "CO_2 sensitivity curve" or "ventilation gain curve") describes the minute ventilation theoretically requested by the neural respiratory drive for a given $PaCO_2$. During ARDS, this is shifted to the left (higher minute ventilation despite lower $PaCO_2$) due to multiple concomitant pathologic conditions, including acidosis, inflammation and others. **a** In health, brain and ventilation curves overlap and the ventilation response (i.e., the change in minute ventilation induced by a change in $PaCO_2$) reflects the neural respiratory drive. The metabolic hyperbola is obtained assuming a dead space of 0.3 and a metabolic CO_2 production (VCO_2) of 200 ml/min. Brain and ventilation curves are overlapping and are calculated assuming at $PaCO_2$ of 39.5 mmHg, a ventilation of 6.5 l/min, linearly increasing to 30 l/min at a $PaCO_2$ of 49 mmHg. **b** In ARDS, the metabolic hyperbola is shifted upward due to increase of dead space (0.5) and VCO_2 (250 ml/min). The listed factors cause the brain and ventilation curves to be shifted in opposite directions and diverge. Please, note that a single ARDS patient will be characterized by both curves at the same time: the brain curve will correspond to the theoretical ventilation/$PaCO_2$ correlation desired by the neural respiratory drive, while the ventilation curve will be the actual ventilation/$PaCO_2$ correlation measured by spirometer and blood gas analysis. Brain and ventilation curves are calculated assuming a ventilation of 6.5 l/min at 28 mmHg $PaCO_2$ (increasing to 30 l/min at 33 mmHg $PaCO_2$) and a ventilation of 5 l/min at 40 mmHg $PaCO_2$ (increasing to 25 l/min at 52 mmHg $PaCO_2$), respectively

inflammation is common and extra-pulmonary organ dysfunction frequently develops (Fig. 2).

Impairment of gas exchange leads to an increase in chemosensory input. Increase in $PaCO_2$, promoted by high dead space, induces a linear increase in respiratory drive through both central and peripheral chemoreceptors [14, 15]. On the other hand, the ventilatory response following severe hypoxemia typical of ARDS is not linear but hyperbolic [11]. Peripheral chemoreceptors, which are relatively insensitive at mild hypoxemia, increase the neural respiratory drive in response to more severe hypoxemia, mainly by enhancing the ventilatory response to CO_2 when the partial pressure of arterial oxygen (PaO_2) falls below 60–70 mmHg. This effect can be potentiated by concomitant hypercapnia. Metabolic acidosis, which frequently complicates ARDS because of shock or acute kidney injury, stimulates both peripheral and central chemoreceptors [16].

In addition, ARDS might be associated with alterations of neural respiratory drive induced by mechanisms specifically associated with lung inflammation and altered mechanics. In awake spontaneously breathing rats, ARDS induces an increase in respiratory rate occurring before impairment of gas exchange. Hypoxic ventilatory response is also exaggerated due to a sensitization of peripheral chemoreceptors [17]. Local and systemic inflammation are hallmarks of ARDS [18], and pulmonary C-fibers sensitive to inflammatory mediators (including histamine, bradykinin and prostaglandins) are consistently activated in lung edema [19] and experimental acute lung injury [20]. Vagal afferents from these lung chemoreceptors can modulate the breathing pattern through a central reflex pathway [21]. The consequence of vagal activation is an increase in respiratory rate with a decrease in tidal volume, i.e., rapid shallow breathing [22, 23], possibly through vagally mediated release of cytokines in the brainstem [24].

The lung also contains mechanoreceptors: slowly adapting receptors (SARs) are stretch receptors activated by lung inflation that inhibit central chemoreceptors in

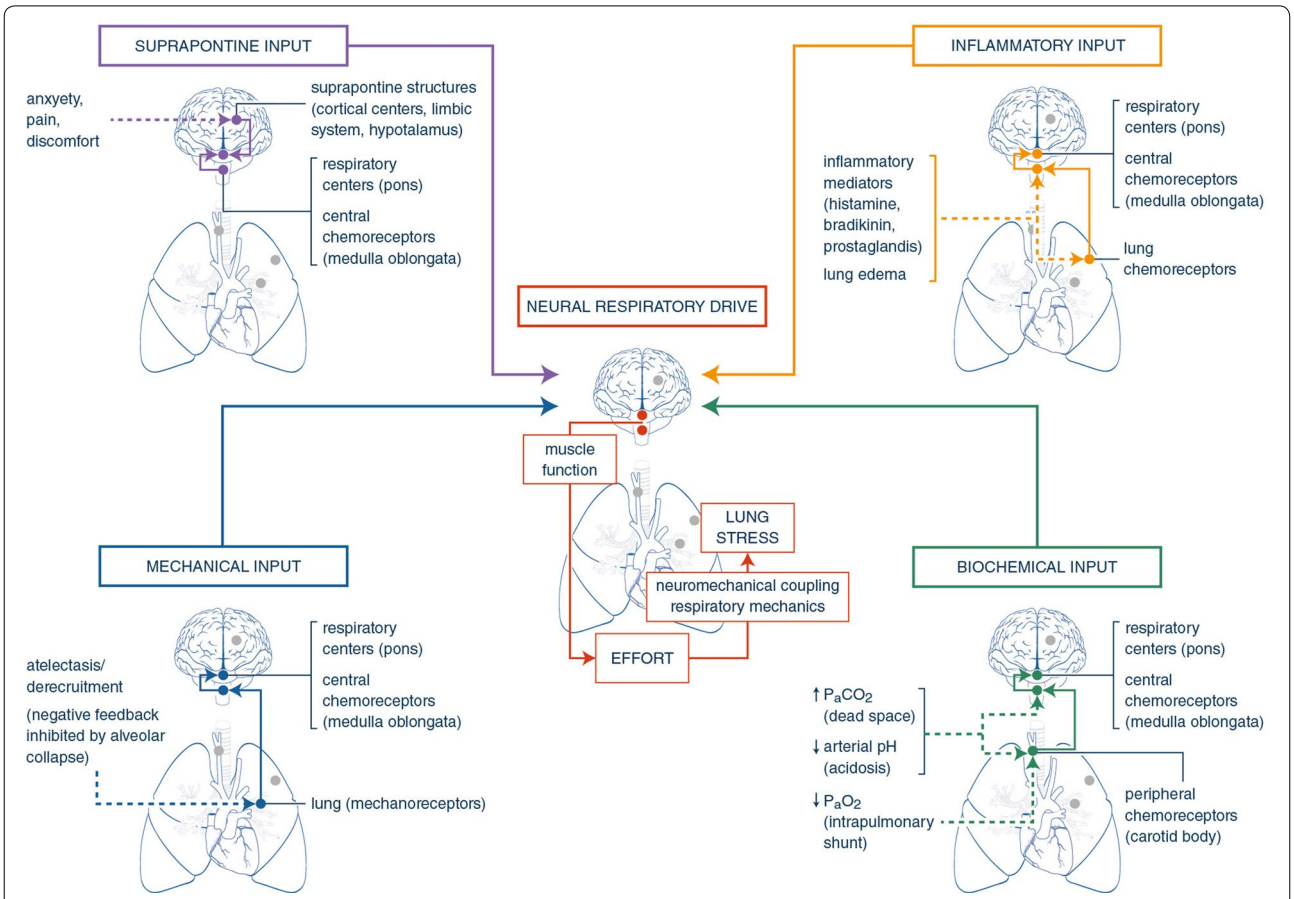

Fig. 2 Schematic representation of control of respiratory drive in ARDS. The figure shows the key triggers of respiratory drive and the anatomic targets where these triggers exert their effects. In the centre, the descending cascade from neural respiratory drive to breathing effort and lung stress is represented, together with the main factors that may cause a dissociation between drive and effort (i.e., muscle function) and between drive, effort and lung stress (i.e., neuromechanical coupling and respiratory mechanics)

rats (for example during the Hering-Breuer reflex), terminating inspiration. Although the Hering-Breuer reflex might be inhibited by the behavioural control of breathing in awake humans [25], decreased inhibitory input from these mechanoreceptors in the atelectatic lung could promote a further increase in inspiratory effort in ARDS. Indeed, the activation of mechanoreceptors appears to decrease as ARDS develops [20], while it is increased by increasing positive end-expiratory pressure (PEEP) [26], probably through stabilized lung recruitment. This could be one of the mechanisms by which high PEEP decreases spontaneous respiratory effort in ARDS [27]. Stimulation of the respiratory centres through each of these mechanisms increases the slope—and shift to the left—of the brain curve. Decreases in lung and chest wall compliance increase the elastic load and can alter the neuro-mechanical coupling between effort and diaphragmatic excursion. The result is a decreased slope of the ventilation curve and an increase in $PaCO_2$, which induces a stimulation of neural respiratory drive and a dissociation between brain and ventilation curves (Fig. 3).

Pain, anxiety and discomfort are common in ARDS patients and all can influence drive. Emotional responses may affect the brain curve independent of a patient's metabolic demands: anxiety and fear act through the forebrain, limbic and cortical structures and the hypothalamus, processing information from the external environment and directly stimulating spinal respiratory motor neurons [10, 28]. Pain affects the respiratory drive through both behavioural responses and a direct reflex on medullary respiratory centres [28]. On the other hand, the use of sedatives might decrease the neural respiratory drive [29].

Poor patient–ventilator interaction is another determinant of drive in subjects with ARDS on mechanical ventilation. Dyssynchronies might increase the respiratory drive because they cause discomfort and increased respiratory load [30]. Mismatch between the timing and duration of mechanical inflation and the neural inspiratory time prevents effective unloading of the respiratory muscles during assisted ventilation. Moreover, air trapping, which may occur during protective ventilation in ARDS due to the high respiratory rate, could cause additional inspiratory load and delayed trigger, both of which can increase drive.

Of note, the more severe the lung injury, the higher the inspiratory effort reflecting increased activation of neural respiratory drive [31].

How to assess respiratory drive at the bedside

A fundamental difference between ARDS patients and healthy subjects is that ventilatory response may not (and usually does not) mirror the respiratory drive [11]. The alterations in neuromuscular function (muscle weakness) and respiratory mechanics (atelectasis and increased lung and chest wall elastance) generate a discrepancy between the activity of the respiratory centres

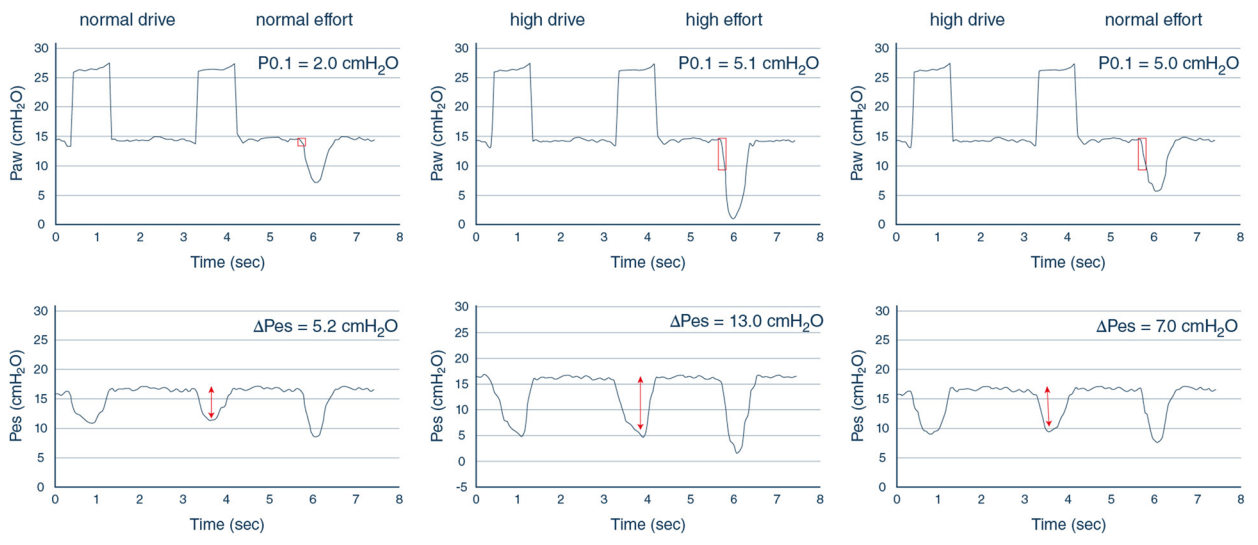

Fig. 3 Potential dissociation between neural respiratory drive ($P_{0.1}$) and respiratory effort (P_{es}) under pathologic conditions. The figure shows simulated identical waveforms for airway pressure (P_{aw}) during supported breaths but with different simulated oesophageal pressure (P_{es}) waveforms. $P_{0.1}$ (i.e., the negative airway pressure generated by occlusion occurring during the first 0.1 s of an inspiration) reflects the intensity of neural respiratory drive. Oesophageal pressure swings (ΔP_{es}) allow quantification of respiratory effort. However, in patients with high chest wall elastance, ΔP_{es} underestimates effort. In the presence of muscular weakness, high drive may be associated with "normal" or even low effort (right panel)

and the resulting motor output. When the intensity of the signal from the brain to the muscles and to the lung is dampened by these alterations, the force of contraction of respiratory muscles and the changes in intrathoracic pressure, flow and volume underestimate the neural drive. Therefore, clinical surrogates of respiratory drive may be conveniently categorized according to their "distance" from the respiratory centres (Table 1). First, neural output (i.e., electrical activity of the diaphragm); second, breathing effort, assessed by changes in pressure induced by the respiratory muscles (i.e., swings in pleural pressure or $P_{0.1}$); and, third, ventilatory response, reflected by the tidal volume and respiratory rate (breathing pattern).

Neural output

The electrical activity of the crural diaphragm (EAdi) reflects the phrenic nerve activity and hence the neural output of the respiratory centres to the diaphragm, provided that neuromuscular transmission and muscle excitability are intact. Eadi may be recorded using an oesophageal catheter with multiple electrodes and it represents the "closest" surrogate of neural respiratory drive available in clinical practice [32]. Because of high inter-individual variability, it is difficult to provide references for absolute values of EAdi [33]. However, trends in EAdi allow the tracking of changes in neural output in individual patients [34]. EAdi is also increased in the presence of low muscle strength [35] and the ratio of actual EAdi to maximum EAdi measured during an occlusion may provide an accurate estimate of the patient neural respiratory drive and effort to breathe [33]. The ratio between tidal volume (V_t) and EAdi represents the neuroventilatory efficiency of the diaphragm [36]: a low V_t/EAdi ratio, either due to diaphragm dysfunction or to compromised respiratory mechanics, indicates dissociation between neural respiratory drive and ventilatory response. EAdi monitoring only assesses the activity of the diaphragm. However, recruitment of accessory inspiratory [37] and expiratory [38, 39] muscles is a strong indicator of increased neural respiratory drive due to a mismatch between the respiratory load and the muscle capacity with decreased expiratory time. Surface electromyography of extra-diaphragmatic respiratory muscles could, therefore, integrate the EAdi for a complete assessment of neural respiratory drive [40].

Breathing effort

Indices based on the pressure developed by the respiratory muscles, such as oesophageal pressure swings (ΔP_{es}) and respiratory muscle pressure (P_{mus}), allow reliable quantification of inspiratory effort determined by the neural respiratory drive [41]. Even though ΔP_{es} at increasing PEEP levels did not correlate with changes in the electrical activity of the diaphragm in ARDS patients in one study [27], driving transpulmonary pressure during active inspiration largely depends on ΔP_{es} in presence of high respiratory effort and could be quite difficult to predict when monitoring only the airway pressure [42]. The pressure generated by the respiratory muscles (P_{mus}) is computed as the difference between the static recoil pressure of the chest wall and ΔP_{es}. P_{mus} values higher than 10 cmH_2O might indicate high effort [43]. The negative airway pressure generated by occlusion occurring during the first 0.1 s of an inspiration, known as $P_{0.1}$, is commonly used as an index of respiratory drive [44]. In healthy subjects, $P_{0.1}$ varies between 0.5 and 1.5 cmH_2O. $P_{0.1}$ values consistently above 3–4 cmH_2O indicate high neural respiratory drive and high work of breathing [45, 46]. $P_{0.1}$ depends on the integrity of neuromuscular transmission. However, as compared with other indices based on breathing effort, it is not affected by moderate reductions of respiratory muscle strength, therefore, representing a reliable index of respiratory drive even in patients with muscular weakness [47].

Breathing pattern

Interpretation of the breathing pattern as a surrogate for respiratory drive is challenging in ARDS patients. In healthy subjects, increases in ventilatory demand are met by initial increases in V_t with constant inspiratory time (T_i), resulting in high mean inspiratory flow (V_t/T_i), that reflects high drive [48–50]. Similarly, high V_t (and high V_t/T_i) in spontaneously breathing patients with ARDS suggest dangerous increases in respiratory drive both during noninvasive [51] and invasive mechanical ventilation [52]. Increased respiratory rate occurs only when respiratory drive is three to four times higher than normal and it is detected by an increased ratio of T_i and total breath duration (T_i/T_{tot}) [49, 50]. However, decreased respiratory compliance [53] and muscular weakness may limit the increase in V_t in ARDS [54]. Increased neural respiratory drive could then lead to early increases in respiratory rate with decreased T_i [55] and the rapid shallow breathing index (respiratory rate divided by tidal volume) [56] might indicate high drive with unsatisfied ventilatory demand.

Finally, high respiratory drive due to mechanical load or metabolic demand results in a reduction of the physiologic variability of breathing [57].

As a "gold standard" for clinical evaluation of respiratory drive is lacking, multilevel assessment might be the most informative approach. While measurements closer to the brain centres more reliably reflect the neural drive, downstream parameters (namely the amplitude and the rate of changes in lung volume and pressure that result in ventilation) provide information about the magnitude of

Table 1 Monitoring tools for respiratory drive

Parameter[a]	Physiological level	Monitoring tool	Advantages	Limitations
EAdi	Neural output	Oesophageal catheter with electrodes	Close to neural drive [32]; tracks changes in neural drive (due to changes in diaphragm function, respiratory mechanics or ventilatory assistance) [34, 35]	Inter-individual variability [33]; assesses only diaphragm activity; available only on one type of ventilator [32]
Electromyography	Neural output	Surface electrodes	Assessment of the activity of diaphragm and extra-diaphragmatic muscles	Technically demanding; not routinely available
P0.1	Breathing effort	Ventilator	Automatic measurement available on some ventilators; not affected by respiratory mechanics [44] and moderate muscle weakness [47]; good correlation with work of breathing [44]	Breath-to-breath variability; indirect measure in some ventilators; accuracy of absolute values varies according to the ventilator mode
Dyspnea	Neural output and breathing effort	Guided questions, visual scales, clinical assessment (e.g., Respiratory Distress Observation Scale)	Comprehensive parameter; may reflect the distance between brain and ventilation curve [59, 62]	Relies on patient collaboration and ability to communicate; affected by emotional and cognitive factors (pain, anxiety, delirium, etc.) [59]
Oesophageal pressure swings	Breathing effort	Oesophageal manometry	Estimates contributions of extra-diaphragmatic muscles [41]	Insensitive to the effort required to expand the chest wall; affected by muscle function [41]
Pmus	Breathing effort	Oesophageal manometry	Best indicator of effort, well correlated with work of breathing [43]	Requires measurement of elastic chest wall recoil pressure under passive conditions; affected by muscle function
Use of accessory inspiratory and expiratory muscles	Breathing effort	Visual inspection	Assessment of the activity of extra-diaphragmatic muscles [37]	High inter-observer variability, qualitative assessment [37, 38]; affected by muscle function
Respiratory Rate	Ventilatory response	Ventilator or visual inspection	Easy to assess at the bedside	Inter-individual variability in values at rest and during stress [50]; affected by respiratory mechanics, muscle function [53–55], pain and emotional state
RSBI	Ventilatory response	Ventilator	Easy to assess at the bedside	Affected by respiratory mechanics and muscle function; developed as a predictor of weaning failure and not as a surrogate for drive
Mean inspiratory flow (Vt/Ti)	Ventilatory response	Ventilator/oesophageal catheter with electrodes or manometry	High Vt/Ti consistently reflects high drive [48–50]	Neural inspiratory time requires EAdi [32]; affected by muscle function

EAdi electrical activity of the crural diaphragm, $P_{0.1}$ airway occlusion pressure, P_{es} oesophageal pressure, P_{mus} pressure generated by the respiratory muscles, *RSBI* rapid shallow breathing index, V_t tidal volume, T_i inspiratory time

[a] Indices based on neural output more closely reflect the neural respiratory drive. However, they might be dissociated from breathing effort and ventilatory response due to neuromuscular dysfunction or compromised respiratory mechanics. "Downstream" indices (based on breathing effort and ventilatory response) might underestimate the neural respiratory drive, but more closely reflect the potentially detrimental effects of drive on lung injury

lung stress generated by spontaneous ventilation, which is the determinant of P-SILI [58]. Dyspnea results from the imbalance between load and muscle capacity or from the imbalance between motor output and lung expansion [59]. The complex neural network involved in dyspnea receives afferent information on the respiratory motor output from the brainstem and the motor cortex [60], as well as multiple sensory feedbacks from the chemoreceptors and the mechanoreceptors of the lung and chest wall [61]. The perception of dyspnea depends on the integration of this motor and sensory information, modulated by emotion [62]. Therefore, bedside assessment of dyspnea could allow estimation of the distance between brain and ventilation curves.

Clinical impact of abnormal respiratory drive in subjects with ARDS

Physiological and clinical consequences of high respiratory drive

Use of partially supported modes of ventilation in ARDS patients could entail the advantage of decreasing sedation, improving hemodynamics and preserving respiratory muscle function. However, indications for preserving or restoring spontaneous breathing in patients with ARDS are still controversial because, if respiratory drive is not controlled and causes vigorous spontaneous breathing efforts, this worsens lung and diaphragm injury [31, 63, 64].

The mechanisms underlying additional lung injury due to elevated efforts are multiple and complementary. *High transpulmonary pressure* during inspiration and *large tidal volumes* determine an increase in lung stress and strain. Patient–ventilator *asynchronies* due to high inspiratory effort such as double triggering can also lead to high tidal volume [65]. Even in the presence of protective V_t and pressure, regional injury can still occur because of *increased local stress* in dependent atelectatic lung regions due to the solid-like behaviour of the diseased lung. In addition, decrease of pleural pressure generated by diaphragmatic contraction is larger in the dependent lung regions drawing air from non-dependent regions before ventilator flow reaches the alveoli (i.e., *occult pendelluft* phenomenon) [66]. Distribution of tidal volume within the lungs is usually more homogenous during spontaneous breathing as compared to controlled ventilation, but too high effort can lead to *ventilation heterogeneity* with a larger portion of tidal volumes reaching dependent regions. The increased negative pleural pressure during forceful breathing effort also *increases transmural vascular pressure, which* promotes additional pulmonary oedema due to increased lung perfusion and lower alveolar pressure [67].

Few animal experimental studies show that high inspiratory effort due to excess inspiratory load might induce diaphragm inflammation [68, 69] and promote diaphragm injury [70].

The clinical impact of these mechanisms still needs to be fully defined. From the lung injury point of view, studies on the effects of early use of neuromuscular blocking agents in ARDS are controversial [52] and a few pilot articles reported beneficial effects of preserved spontaneous breathing versus controlled ventilation on lung aeration [39]. As far as diaphragm function is concerned, a small clinical study in critically ill patients reported that high inspiratory effort may lead to increased diaphragm thickness (which might reflect structural injury) and to prolonged mechanical ventilation [71].

Modulating the respiratory drive in the clinical setting

Ideally, control of respiratory drive in ARDS should reduce the dissociation between brain and ventilation curves [11]. High respiratory drive might be considered "appropriate" when the activating stimulus can be corrected by increased ventilatory response. This is the case for hypercapnia and hypoxemia. Increased ventilation is the physiologic response aimed at correcting these alterations. Conversely, several stimuli that increase the activity of respiratory centres in ARDS are not modified by the ventilation feedback. For example, inflammation, pain and anxiety induce an "inappropriate" high respiratory drive. In the case of an appropriate high neural respiratory drive, the treatment should facilitate the ventilatory response (for example by increasing ventilatory support); on the other hand, inappropriate high drive requires a specific treatment (for example medications for anxiolysis). In the context of ARDS, the effects on the lung should always be monitored and high respiratory drive, either appropriate or inappropriate, should be controlled if it results in the generation of excessive lung stress with consequent increased in the risk of P-SILI.

Multiple strategies are available to modulate the respiratory drive and/or effort in ARDS patients, according to the underlying causes and mechanisms of increased drive (Table 2). These include respiratory support modes and settings, medications and non-pharmacologic interventions.

Interventions for control of respiratory drive

Non-invasive respiratory support

Increased respiratory drive is a hallmark of acute respiratory failure from the outset, with the acute onset of dyspnea as the main presenting symptom [58]. The recommended initial management may now include various forms of non-invasive respiratory support: nasal high flow (NHF) [72], continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NIV) [73]. These options can directly modulate the respiratory drive, albeit by different mechanisms, generating relevant clinical consequences (Table 3).

NHF may reduce drive by wash-out of CO_2 from upper airways, decreased CO_2 production following decreased inspiratory effort, improved oxygenation and improved dynamic lung compliance [74].

CPAP potentially modulates drive by improving oxygenation by means of positive airway pressure, optimised oxygen delivery and improvement of lung mechanics [75].

NIV may decrease respiratory drive by several mechanisms: unloading respiratory muscles from inspiratory effort, which also reduces CO_2 production; as well

Table 2 Determinants of increased respiratory drive in ARDS, associated mechanisms and potential interventions to control drive

Determinant	Common etiologies	Mechanisms	Potential interventions (as appropriate)
Hypercapnia	↑ Dead space, ↑ lung and chest wall elastance, ↑ CO_2 production	Stimulation of central and peripheral chemoreceptors [3, 5, 14, 15]	Ventilatory support; fever and pain control; sedation; $ECCO_2R$ [95]
Hypoxemia	↑ Intrapulmonary shunt, V/Q mismatch, ↑ VO_2/DO_2	Stimulation of peripheral chemoreceptors [4, 16]	FiO_2 [78, 79], PEEP [26, 27]; mechanical ventilation cardiovascular support (fluids, inotropes, vasopressors, red cell transfusion); ECMO
Metabolic acidosis	Shock, acute kidney injury	Stimulation of central and peripheral chemoreceptors [16]	Cardiovascular support; bicarbonate; RRT
Inflammation	ARDS, P-SILI, sepsis	Increased sensitivity of peripheral chemoreceptors to hypoxemia; stimulation of lung chemoreceptors (C-fibers) [19–21]; direct stimulation of respiratory centres by cytokines [24]	Aetiologic treatment; lung- and diaphragm-protective mechanical ventilatory support
Lung atelectasis	Pulmonary edema, inflammatory cells, re-absorption atelectasis	↓ Inhibitory activity from lung slow adapting mechanoreceptors [20]	PEEP [26, 27] and respiratory support; prone positioning; physiotherapy
Agitation	Anxiety, pain, respiratory distress	↑ Descending input [28]	Respiratory support; sedation or anxiolysis; non-pharmacologic (and potentially pharmacologic) treatments of delirium [93, 94]
Poor patient–ventilator interaction	↑ Lung and chest wall elastance leading to flow starvation and increased inspiratory load; intrinsic PEEP causing delayed triggering	↑ Descending input due to discomfort; ↑ inspiratory load due to mismatch between mechanical inflation and neural inspiratory time [30]; stimulation of central and peripheral chemoreceptors in the case of hypercapnia	Adjust ventilation settings, change ventilation modes [80–82], titrate sedation, consider neuromuscular blockade [58]

ARDS acute respiratory distress syndrome, *CO_2* carbon dioxide, *DO_2* oxygen delivery, *$ECCO_2R$* extracorporeal CO_2 removal, *ECMO* extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *P-SILI* patient self-inflicted lung injury, *RRT* renal replacement therapy, *VO_2* oxygen consumption, *V/Q* ventilation/perfusion

as improving oxygenation and lung mechanics through increases in PEEP [76].

However, these effects may be mitigated by competing physiologic effects. CPAP can lead to CO_2 re-breathing and decreased efficiency of CO_2 clearance that could diminish the positive effects on respiratory drive. During NIV, patient intolerance or air leaks may result in intermittent mask removal and promote patient–ventilator dyssynchrony, which, in turn, could increase respiratory drive by discomfort and sleep disruption. Finally, NIV unloads the respiratory muscles by applying positive airway pressure during inspiration, which could lead to unchanged or even increased transpulmonary pressure and additional lung injury [77].

Invasive mechanical ventilation

When invasive mechanical ventilation is instituted, there is often an initial phase of deep sedation, which may decrease the respiratory drive and, occasionally, a period of neuromuscular blockade, which eliminates breathing effort. Once assisted breathing is restored, uncontrolled high respiratory drive may resume as well [63]. In this context, the choice of ventilation mode and settings should aim at decreasing the dissociation between the brain and ventilation curves, while limiting risks of additional lung injury. When the ventilatory response corresponds to the neural respiratory drive, controlling drive is crucial to ensure lung protection. On the other hand, in the presence of a large dissociation between the brain and ventilation curves, lung protection could be maintained even in the presence of increased neural respiratory drive; however, adjusting settings to decrease this dissociation could have additional benefits like improving dyspnea and preventing abnormal breathing patterns (e.g., rapid shallow breathing).

The most commonly used assisted ventilation modes are pressure/volume assist control and pressure support. During assist control, higher peak inspiratory flow delivered by pressure-based mode might better match the need of dyspneic ARDS subjects and mitigate drive, but, at the same time, presence of high inspiratory drive could lead to high tidal volumes, which are not lung-protective. On the other hand, volume assist control allows precise control of set tidal volume and driving transpulmonary pressure independent of the patient's drive, but, high drive can still generate occult pendelluft and regional overdistension [65].

During PSV, simple settings such as the support level, PEEP and FiO_2 [78, 79] could influence the respiratory drive. Potential mechanisms of benefit include unloading of the respiratory muscles, improved mechanics and better oxygenation. Oppositely, the drive increases when the ventilator support is reduced. However, unprotective levels of ventilation should not be tolerated in order to comply with the patient respiratory drive during PSV: switching back to controlled ventilation might be safer when inspiratory plateau pressure is higher than 30 cmH_2O, Vt greater than 6–8 ml/kg predicted body weight and high levels of FiO_2 (e.g., > 80%) are needed [58]. Alternative modes of assisted ventilation with non-fixed support proportional to diaphragm electrical activity [80] or to a desired range of work of breathing performed by the patient [81] are emerging as possibly safer alternatives to increase support without risking excessive additional lung injury. Indeed, during these modes, the drive decreases when support by the ventilator is increased, but, at the same time, the V_t and inspiratory pressure increases only up to a point below safe thresholds, likely because of preserved reflexes limiting lung volumes. Finally, artificially introducing some variability within the respiratory pattern by noisy pressure support [82] or by cyclic large breaths (i.e., using "sighs") [83] has been shown to safely modulate increased respiratory drive, by improving oxygenation or respiratory mechanics, or through the Hering–Breuer effect, or all the above.

Airway pressure-release ventilation (APRV) is a mode that allows unsupported spontaneous breaths at two pressure levels (low and high) [84]. When APRV is set with a relatively low rate (10–12 bpm) and an inspiratory-to-expiratory (*I*:*E*) ratio of 1:1–1:0.8, the non-synchronized mandatory pressure changes generate mechanical breaths that could relieve the patient's respiratory drive and also be used to estimate the pressure generated by spontaneous breaths (e.g., similar delta pressure for similar V_t) [85].

Pharmacological interventions

Medications that may induce respiratory depression are commonly used for analgo-sedation in ICU patients. However, as most of these medications are associated with short- and long-term adverse effects, their use should be minimized and their effects closely monitored. Use of sedatives or analgesics for the sole purpose of

Table 3 Physiologic effects of different modes of non-invasive and invasive respiratory support and ventilation

	Neural drive	Mechanisms decreasing drive	Mechanisms increasing drive	Driving P_L	Mechanisms decreasing driving P_L	Mechanisms increasing driving P_L
Non-invasive support						
Venturi mask	High	Increased set FiO_2	Lung collapse, hypoxemia	High	–	High effort and poor respiratory mechanics
HFNC	Reduced	Increased alveolar FiO_2, small PEEP effect, CO_2 washout	Residual lung collapse	Decreased	Decreased effort	Poor respiratory mechanics
Helmet CPAP	Reduced	Higher PEEP	CO_2 rebreathing	Unchanged or increased	Improved respiratory mechanics	High effort
NIV	From high to almost suppressed	Higher PEEP, positive pressure support	Discomfort	Increased	Improved respiratory mechanics	Positive airway pressure during inspiration + residual effort
Invasive ventilation						
PSV	From high to almost suppressed	Higher PEEP, positive pressure support	Asynchronies, discomfort, poor patient–ventilator flows matching	Normal to high	Improved respiratory mechanics	Positive airway pressure during inspiration + residual effort
APRV	Reduced	Higher PEEP, mandatory breaths	Discomfort, low Vt	Decreased	Improved respiratory mechanics, decreased effort	High effort
Assist/control MV	Low	Higher PEEP, fixed Vt or DP	Asynchronies, discomfort, low Vt	Normal to high	Improved respiratory mechanics	Positive airway pressure during inspiration + residual effort

P_L transpulmonary pressure, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *HFNC* high flow nasal cannula, *CO_2* carbon dioxide, *CPAP* continuous positive airway pressure, *NIV* non invasive ventilation, *PSV* pressure support ventilation, *APRV* airway pressure release ventilation, *MV* mechanical ventilation, *Vt* tidal volume, *DP* driving pressure

control of respiratory drive may be disadvantageous. It might be more appropriate to look first for the main reason leading to increased respiratory drive (e.g., "fighting the ventilator" or pain) and choose the medication that specifically targets it.

Pain medications

Respiratory depression induced by opioids has long been recognized. A study from 1975 on subcutaneous morphine administered to healthy subjects [86], demonstrated altered ventilatory response to hypercapnia, with decreased slope of the minute ventilation/$PaCO_2$ curve. High doses of intravenous opioids decrease the electrical activity of the inspiratory muscles in opioid-tolerant subject [87]. Opioids are widely used in the ICU for analgosedation but only few studies have assessed their effects on respiratory drive. Remifentanyl decreases respiratory rate and increases expiratory timer without modifying EAdi in critically ill patients on assisted ventilation [88]. Reasons for this limited effect might be the use of lower doses compared with those used by opioid abusers and/or the increased respiratory drive of critically ill patients. Thus, opioids might be of limited value for controlling respiratory drive and the risk of P-SILI in ARDS patients.

Drugs modulating agitation and anxiety

Both intravenous and inhaled general anaesthetics reduce the respiratory drive and have been tested in intubated ICU patients, with Propofol showing a more pronounced respiratory depressive effect than isoflurane or sevoflurane [89]. However, the level of sedation needed to obtain a significant impact of such mediations on the respiratory drive might be too deep to be clinically acceptable.

Dexmedetomidine has recently emerged as an alternative drug for awake sedation with the potential of reducing the incidence of delirium. However, dexmedetomidine does not affect the hypercapnic ventilatory response in healthy volunteers [90] and does not modify respiratory rate and gas exchanges in ICU patients compared to placebo [91].

Benzodiazepines are associated with many adverse effects in ICU patients and may be inferior to other sedatives, as suggested by multiple clinical trials [92]. Using benzodiazepines to suppress respiratory drive might not be an optimal approach in most patients.

New pharmacological perspectives

Finally, a recent study suggested that partial muscular paralysis by low-dose neuromuscular blocking agents could obtain protective tidal volumes and inspiratory pressures in patients with acute respiratory failure and uncontrolled high respiratory drive during assisted ventilation [52]. However, it is important to note that the use of neuromuscular blocking agents will induce a sudden uncoupling between respiratory drive and muscular efficiency and its impact on the respiratory drive and patient comfort needs to be better assessed and understood.

Non-pharmacological interventions

Future development of control of respiratory drive in hypoxemic patients might be related to non-pharmacological interventions such as targeted music therapy and extracorporeal CO_2 removal ($ECCO_2R$). Previous studies have described possible feed forward interaction between music rhythm and the breathing pattern of healthy and ICU subjects: this generates the fascinating hypothesis that music could act as a modulator of respiratory drive [93], potentially able to override metabolic inputs by decreasing stress and anxiety and increasing comfort (i.e., decreasing the behavioural drive) [94].

$ECCO_2R$ decreases the amount of CO_2 that must be eliminated through the lungs: this, rather than modifying the brain neural drive, will simply move the metabolic hyperbola downward, thus reducing the actual $PaCO_2$ and minute ventilation level. In the case of stable subjects recovering from ARDS, in whom the slope of brain drive is less steep and the metabolic hyperbola closer to healthy subjects, the decrease of VCO_2 through the natural lung by $ECCO_2R$ decreases ventilation to minimal levels [95]. In the most severe patients with extremely high respiratory drive and with the metabolic hyperbola significantly shifted upward, efficacy of ventilation reduction by $ECCO_2R$ should be more limited, as indicated by pilot data [96]. Moreover, to date, the burden of $ECCO_2R$-related complications is too high to consider the control of respiratory drive an indication for its use, in non-intubated patients with less severe ARDS. As $ECCO_2R$ systems become safer with advances in the technology, and the risk-to-benefit ratio improves, $ECCO_2R$ might become a more attractive method of controlling respiratory drive and avoiding further lung injury in patients with ARDS.

Conclusions

Respiratory drive may represent a unique synthesis of complex pathophysiologic mechanisms underlying and accompanying ARDS. Higher drive not only may correlate with ARDS severity but, if not carefully managed, could contribute to lung and diaphragm injury. Thus, monitoring of the respiratory drive and interventions able to confine its effects within physiologic limits should be top priorities for the ICU physician caring for subjects with ARDS.

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ES, TM and DB conceived the review. ES and TM conducted the articles search and drafted the manuscript. All authors revised the manuscript for critical intellectual content.

Compliance with ethical standards

Conflicts of interest
ES and JRB do not have any conflict of interests to disclose. TM reports personal fees from Drager, Fisher and Paykel and Mindray, outside the submitted work. AP reports personal fees from Maquet, Novalung/Xenios, Baxter and Boehringer Ingelheim, outside the submitted work. DB reports grants from ALung technologies, personal fees from Baxter, personal fees from BREETHE, personal fees from Xenios, other from Hemovent, outside the submitted work.

Search strategy and selection criteria
References for this review were identified through searches of PubMed for articles published from January 1950 to July 2019, by use of the terms "respiratory drive", "spontaneous breathing", and "acute respiratory distress syndrome". Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English were included.

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