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REVIEW

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An importance of respiratory drive and effort during mechanical ventilation

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ABSTRACT:

During mechanical ventilation, minimizing respiratory drive and effort becomes routine to prevent patient-ventilator asynchrony (PVA). As we know, PVA associates with poor outcomes in ICU patients. As a result, prescribing sedative drugs in combination with neuro-muscular blocking agents commonly appears in many ICUs. However, many patients develop adverse events from unloading respiratory muscles, resulting in prolonged mechanical ventilator and bad clinical outcomes. This review describes both sides of the adverse effect of respiratory drive and effort and tries to suggest the optimum point, believing that it may be associated with better outcomes.

Keywords: Respiratory drive, Respiratory effort, Asynchrony, P-SILI, ARDS

INTRODUCTION

The most common causes of respiratory failure in ventilated critically ill patients are pulmonary infections, sepsis, and neurological disease. [1] The main objectives are to keep and reduce the burden from the respiratory load, correct gas exchange abnormalities, and maintain acid-base homeostasis. Nevertheless, the incompatibility between the patient's demand, involved by the respiratory center, and respiration support by mechanical ventilation is observed in many cases, which causes patient-ventilator asynchrony (PVA). The importance of respiratory drive and effort is one of the factors contributing to treatment outcome, duration, and recovery time from acute respiratory failure. Furthermore, the existence of respiratory drive and effort is a double-edged sword. The patient breathing effort could improve the recruitment of atelectasis lung, advocate oxygenation, and prevent diaphragm disuse atrophy. On the other hand, the remaining high respiratory drive may generate more respiratory effort and more tidal breath that deviates from the principle of lung-diaphragm protective strategies and might cause the patient self-inflicted lung injury.

RESPIRATORY DRIVE AND EFFORT

To achieve the success of the treatment in the ventilated critically-ill patient, we must understand the physiology of respiratory drive and effort. The respiratory drive is a physiological consequence of neurological signals from the central brain generated across respiratory neuromuscular transmission nerves, muscles, and organs appear as respiratory work, better known that respiratory effort. Therefore, we define respiratory effort as mechanical output from driven respiratory mus-

cles. It is caused by respiratory interneurons signal from the pre-Bötzinger complex, also called PreBötC neuron cell positioned between the ventrolateral medulla and Bötzinger complex in the brain stem. During inspiration, it delivers a signal to the breathing-related medullary premotor region in Medullar and Pons, then sends motor output through the nerves in cervical vertebrae C3-C5, where it controls respiratory system muscles, diaphragm contraction, and suddenly terminates PreBötC signal, simultaneously activates lateral parafacial nucleus when expiration commences (as illustrated in Figure 1). [2, 3]

Generally, among critically ill patients, many causes could increase respiratory drive, and the relationship between respiratory drive and respiratory effort will be in the same direction. Four factors affect respiratory drive and effort contributed by the central cortical drive and the specific central nervous chemoreceptors positioned on the ventral surface of the medulla, also known as the retrotrapezoid nucleus.

Firstly, hypercapnia could stimulate central and peripheral chemoreceptors, usually found in any cause of hypoventilation, increase dead space, increase lung and chest wall elastance or increase carbon dioxide (CO_2) production. The CO_2 can commonly diffuse across the blood-brain barrier, and these receptors are sensitive to changes in pH levels that also depend on hydrogen proton concentration ($[H^+]$) in cerebrospinal fluid (CSF). Some increase in $PaCO_2$ above five mmHg of normal set point provides a strong provoked breath in double in healthy subjects. Moreover, the $PaCO_2$ decreases a few mm Hg below the set point will suppress the respiratory drive [4].

Secondly, hypoxemia could stimulate the peripheral chemoreceptors between carotid bifurcation called carotid bodies, making it easier to detect any imbalance of PaO_2, $PaCO_2$, and pH [5]. The main mechanism is explained by the intrapulmonary shunt, V/Q mismatch, or increased VO_2/DO_2 ratio. The respiratory drive would be stimulated when PaO_2 decreases below 80 mm Hg and considerably rises when PaO_2 falls below 60 mmHg. Similar dramatic drive increases are found in hypercapnia and acidosis, providing a robust contribution from a synergistic response effect.

Thirdly, the chest wall, lungs, respiratory muscles pump, and airways contain mechanoreceptors. In some situations, especially pulmonary edema, pulmonary fibrosis, and re-absorption atelectasis, they receive slowly adapting stretch receptor signals via vagal fiber, some involving the Hering-Breuer reflexes. This reflex terminates inspiration and encourages expiration at high tidal breath [6].

Finally, the emotional and behavioral feedback generated by higher cortical brain functions such as pain, agitation, delirium, and fear commonly provides high respiratory drive and effort in mechanically ventilated patients [5-7]. To crown it all, improper respiratory drive

KEY MESSAGES:

- The improper respiratory drive and effort cause problems in the lungs and the diaphragm
- Inadequate assisted ventilation causing high respiratory drive and effort are associated with patient-self inflicted lung injury (P-SILI).
- Over assisted ventilation, unloading respiratory muscle is related to respiratory muscle atrophy
- Both adverse events may result in poor outcomes. Therefore, monitoring and optimizing respiratory effort should be beneficial.

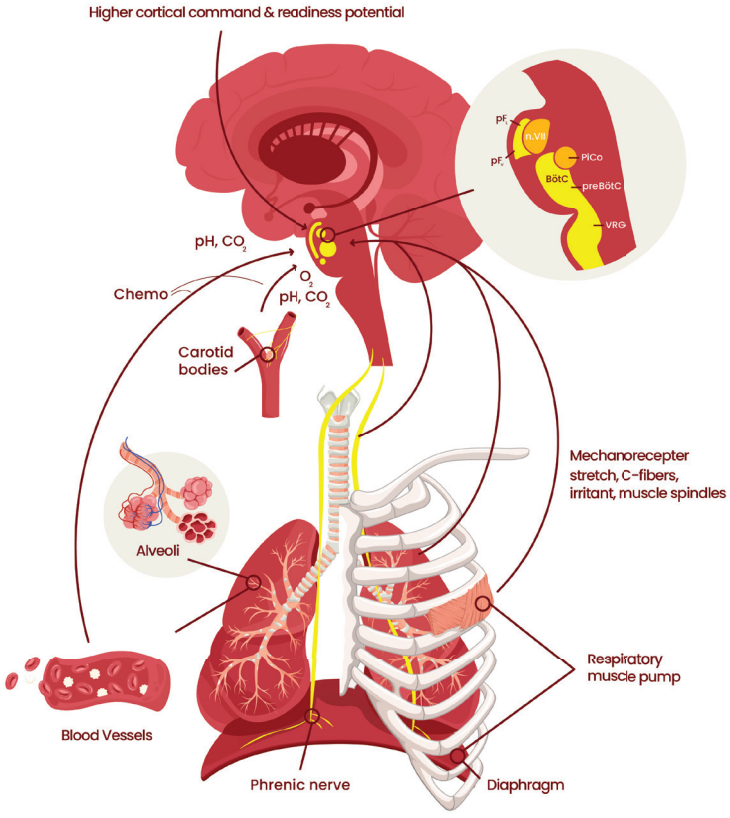

Figure 1. The illustration shows human respiration driven by voluntary respiratory force, cortical readiness potential. it started from stimulating PreBötC Neuron Cell in the ventrolateral medulla when inspiration, The PreBötC signal delivers to breathing-related medullary premotor region in Medullar and Pons then sends motor output through cervical vertebrae C3-C5, where it controls respiratory system muscles and diaphragm contraction. The factors that increase respiratory drive include high $PaCO_2$ (Hypercapnia) and low pH (Acidosis) in peripheral arterial blood which stimulate the peripheral chemoreceptor at carotid bifurcation called carotid bodies, also found in cerebrospinal fluid which stimulate retrotrapezoid nucleus of central nervous chemoreceptor. Meanwhile, low PaO_2 (Hypoxemia) increase the respiratory drive by provoke only peripheral chemoreceptor. In addition, thoracic stretching also has mechanoreceptor of themselves feedback through Hering-Breuer reflexes. This reflex terminates inspiration and encourages expiration at high tidal breath. Finally, the cortical stimuli by emotional and behavioral feedback such as pain, fear, agitation and delirium increase the respiratory drive.

and effort, either too high or too low, will cause adverse effects on patients, directly or indirectly.

THE CONSEQUENCES OF IMPROPER RESPIRATORY DRIVE AND EFFORT

Respiratory muscle injury

The improperly high respiratory drive and effort can lead to several problems, such as diaphragm injury (myotrauma) caused by excessive concentric or eccentric loading. (8-10) The eccentric respiratory muscle loading is more crucial. It occurs during its contraction in the lengthening period instead of shortening [11]. This type of injury is commonly found in PVA and causes more injuries. Moreover, vigorous respiratory effort can cause lung injury, namely patient self-inflicted lung injury (P-SILI), primarily related to high transpulmonary pressure [12]. The P-SILI can occur with or without patient-ventilator asynchrony (PVA). However, double-triggering plays a vital role in P-SILI [13], leading to increased lung stress-strain or intrinsic PEEP. We demonstrate the summary of excessive respiratory effort in figure 2

Orozco-Levi et al. reported the consequences of excessive respiratory effort [8]. Through the electron microscope, they have found diaphragm sarcomere injury in chronic obstructive pulmonary disease (COPD) patients. This condition is directly related to the obstructive pulmonary disease severity when negative pressure in the thoracic cavity increases during COPD exacerbation from high-intensity inspiratory loading. These findings are coherent with Scott et al.[14], who compared a deceased COPD patient's and healthy people's diaphragm through the light microscope. They have found dead muscle, thick membranes, and collagen accumulation. Also, the cytoplasm was found to be scattered and inconsistent arrangement. This research is considered the first post-mortem study demonstrating diaphragm injury from excessive respiratory load caused by excessive drive and effort.

Respiratory muscle disuse atrophy

The low respiratory effort, especially during mechanical ventilation under sedative drugs or muscle relaxants, affects the diaphragm's function and lungs. It restrains the diaphragm neural trophic factor, which causes ventilator-induced diaphragmatic dysfunction (VIDD) [15]. A study showed that over 30% of ventilated patients developed thin diaphragms, resulting in a problem during ventilator weaning and becoming ventilator-dependent patients [16].

Another, Goligher et al.[17] found that in about 41% of patients, the diaphragm thickness was decreased by more than 10% in the first week of using a ventilator, and it is correlated with a longer duration of using a ventilator and complications among critically ill patients. Furthermore, the study has concluded that the appropriate change in diaphragm thickness fraction in the first three days of 15-30% correlated with the shortest duration of mechanical ventilation. In summary, the excessive or low respiratory effort could affect the patients during mechanical ventilation. Therefore, keeping an optimum respiratory effort for mechanically ventilated patients is necessary.

P-SILI (Patient self-inflicted lung injury)

Lung injury from P-SILI was first mentioned by Leo Lobe, 1928 [18], describing high negative pressure in the thoracic cavity during inhalation precipitating the liquid in pulmonary capillaries entering alveoli, leading to pulmonary congestion and edema. Also, Moore and Binger [19] reported that intra-thoracic negative pressure during excessive inhalation among obstructive airway disease patients, such as tracheal stenosis, may cause pulmonary congestion and edema. In 1936, Barach et al.[20] conducted an observational animal experiment on dogs, creating negative intra-thoracic pressure by inhaling against the obstruction. The results showed pulmonary congestion and edema, especially in the lower lobe and peripheral lung zone. However, there was no significant congestion, and bleeding alveoli were found when exhaled, resisting positive pressure alone. In addition, Dreyfuss et al.[21] demonstrated that the deformation-induced injury of alveolar epithelial cells significantly increased high airway pressure and high tidal volumes in mice' lings ventilated with the negative pressure mechanical ventilator (NPV) simulating negative intra-thoracic pressure from the high spontaneous respiratory effort.

Another study by Mascheroni et al.[22] was conducted on sheep by provoking hyperventilation induced via sodium salicylate injection into their cisterna magna. As a result, pulmonary congestion occurred in experimented animals; meanwhile, such results were not observed in animals receiving sedation, muscle relaxants, and abdominal strapping to minimize respiratory effort. Interestingly, Yoshida et al.[23] studied an animal model with severe lung injury. They assigned doxapram to stimulate spontaneous breathing in the intervention group and assigned the other group to breathe without respiratory effort by injecting pancuronium bromide. Then, both groups were ventilated regarding lung protective mechanical ventilation with low tidal volume by 5-7 ml/kg and PEEP 9-11 cmH_2O. The results revealed that the group that received muscle relaxants without negative deflection of esophageal pressure (P_{es}) manifested fewer neutrophils, inflammatory cells, and protein in bronchoalveolar lavage. Also, the pathological result of the lung sample revealed less injury in the alveoli and interstitial tissues. Those results could explain that P-SILI is related to excessive respiratory effort, which increases transpulmonary pressure (P_L) and lung stress that intensifies and worsens lung injury. Moreover, the negative pleural pressure (P_{pl}) while increasing transpulmonary pressure (P_L) and tidal volume (Vt) leads to an increase in transmural vascular pressure, which causes pulmonary congestion and injury in ARDS [24, 25].

Another mechanism involving the presence of P-SILI is the pendelluft phenomenon in ARDS (In heterogeneity lung), as demonstrated in figure 2. Yoshida et al. reported the existence of pendelluft [23, 26] in severely injured lung patients. The pendelluft was demonstrated by electrical impedance tomography showing the air volume moving from the ventral zone to the dor-

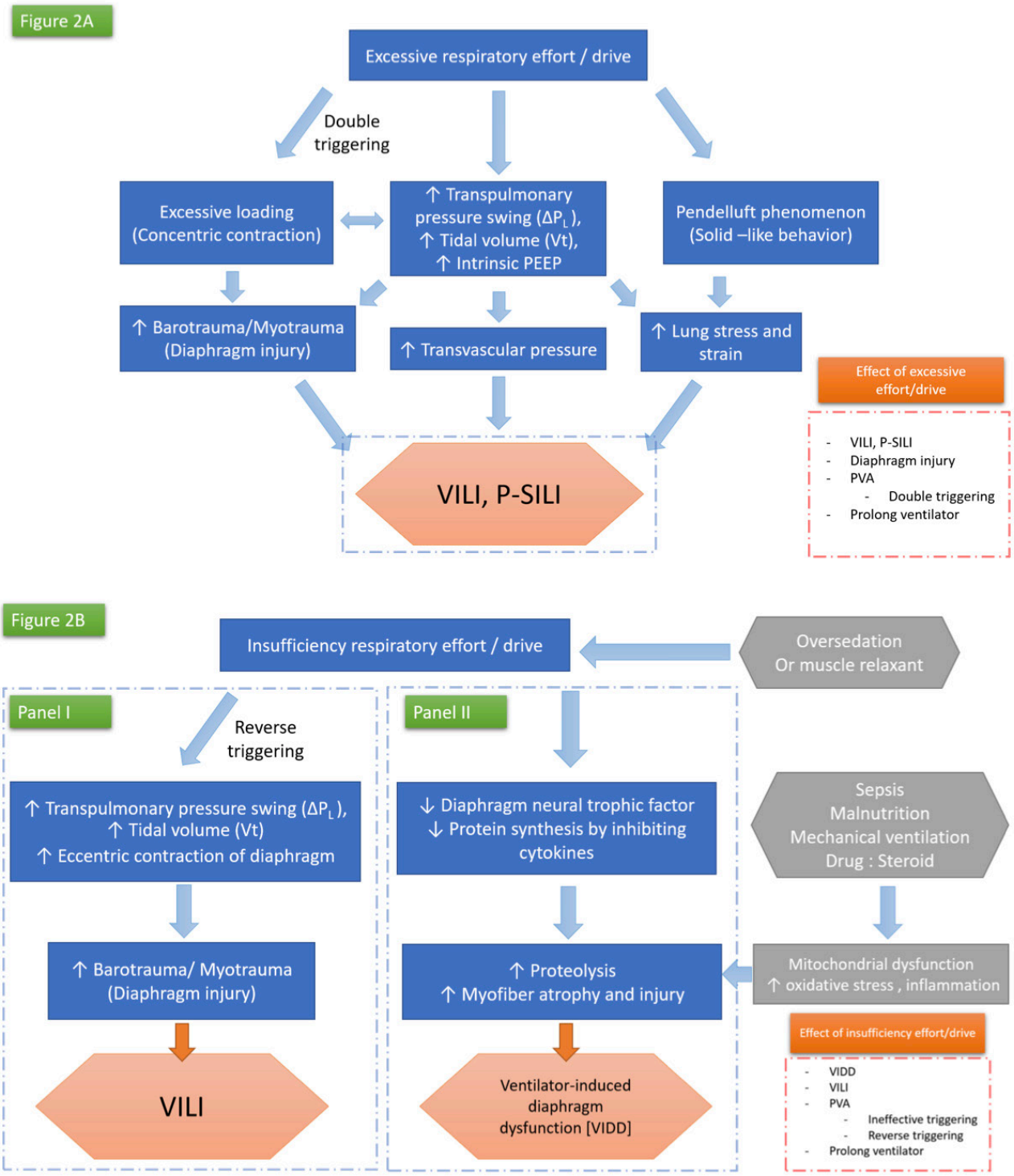

Figure 2A. Illustrates excessive respiratory drive and effort can cause of excessive concentric or eccentric loading by patient ventilator asynchrony (PVA), especially double triggering cause barotrauma and myotrauma (Diaphragm injury). The situation of excessive respiratory effort contributes increase transpulmonary pressure swing (ΔP_L), increase tidal volume (Vt), increase intrinsic PEEP which increase transvascular pressure and also myotrauma. Furthermore, the heterogeneity lung produces pendelluft's phenomenon increase lung stress and strain. Finally, excessive respiratory drive and effort generate double triggering, diaphragmatic injury and overall mechanisms contribute ventilator-induced lung injury (VILI), patient self-inflicted lung injury (P-SILI) leading to prolong ventilator.

Figure 2B. Insufficient respiratory effort especially from overuse sedation or neuromuscular blockage can cause VILI through breath stacking from reverse triggering, as occurs in double triggering of excessive effort in panel I. Insufficient respiratory drive and effort lead to decrease diaphragm neural trophic factor and decrease protein synthesis by inhibiting cytokines combine with contributing factors from sepsis, malnutrition, mechanical ventilation or steroid stimulate mitochondrial oxidative stress and inflammation produce proteolysis, myofiber atrophy and injury summarize to ventilator-induced diaphragm dysfunction (VIDD) as panel II. Finally, the consequences of insufficiency respiratory drive and effort are VILI, VIDD, reverse triggering (also ineffective triggering) and prolong ventilator.

sal zone during high spontaneous effort. The moving of gas causes too high tidal volume in the gravity-dependent lung zone, leading to overdistension lung injury. Such an effect is still found in patients ventilated with a tidal volume of fewer than 6 millimeters per kilogram.

P-SILI has also been demonstrated in PVA. The presence of PVA, especially in double triggering, was related to the rise in mortality [27] due to the excessive tidal volume from breath stacking [27, 28]. Notably, breath stacking can occur despite no respiratory effort, as seen in the reverse triggering characterized by the diaphragm contractions induced by passive thoracic insufflation in the passive ventilated patient. This PVA is associated with oversedation and raises P_L and Vt from breath stacking. Therefore, differentiating between the two distinct types of PVA is essential to provide appropriate management. The esophageal catheter insertion or measuring of the diaphragm's electrical activity is required to determine a particular type of PVA [29].

Usually, double triggering can be solved by increasing inspiratory time in volume-controlled ventilation (VCV) or pressure-controlled ventilation (PCV) mode or decreasing the cycling threshold percentage of peak flow (E-sense) in pressure support ventilation (PSV) mode [30]. However, if the adjusted mechanical ventilator settings cannot correct the PVA, another option is giving them sedation or muscle relaxant to eliminate high respiratory drive. On the other hand, for reverse triggering, this problem would be solved by reducing sedation or muscle relaxant [31, 32].

MONITORING RESPIRATORY EFFORT

The importance of monitoring patients' respiratory efforts aims to evaluate and protect them from the excessive inspiratory effort, which may lead to further complications previously mentioned. In this part, some examples of respiratory effort monitoring, such as esophageal pressure (P_{es}) monitoring, $P_{0.1}$, airway occlusion pressure (P_{occ}), diaphragmatic ultrasound, diaphragm electrical activity (EAdi), and sedation scale will be explained in the next paragraph which magnify objective to achieve patients' optimum respiratory support and sedation goal.

Monitoring respiratory effort by esophageal manometry

Esophageal manometry to evaluate pleural pressure (P_{pl}) is the gold standard in measuring respiratory effort, work of breathing, and lung stress [33, 34]. The main parameters to determine respiratory effort are the followings:

1) $P_{mus} = P_{cw} - P_{es}$, as illustrated in Figure 3, where P_{cw} is static chest wall elastic recoil pressure and P_{es}, is esophageal pressure [35].

2) Transpulmonary pressure or $P_L = P_{aw} - P_{pl}$; by substituting P_{pl} with P_{es}

In addition, the WOB can be calculated according to the parameters below:

1) Esophageal pressure-time product (PTP_{es}) [31, 36] is considered the reliable gold standard in measuring inspiratory effort because it is close to inspiratory muscle energy expenditure calculation, in which a PTP value between 50-100 $cmH_2O/s/min$ might correlate with oxygen consumption and acceptable respiratory effort [37].

2) Work of breathing [33, 36] by calculating $WOB = \int P_{mus} \cdot dV$

The appropriate P_{mus} value has not been defined clearly, but in a healthy person, during resting conditions, the P_{mus} ranging from 5-10 cm H_2O is safe and can prevent diaphragm atrophy [17].

Usually, P_{cw} will be low. Therefore, we may estimate that the ΔP_{mus} approximates to ΔPes; thus, ΔPes can be interpreted in the same way as Pmus, in which the value ranging from 3-8 cmH_2O can be used. The ΔPes less than 2-3 cmH_2O suggest over-assistance. On the other hand, a value greater than 8-12 cmH_2O favors under-assistance[38].

Esophageal manometry can measure P_L, which is directly related to lung stress. However, it has some drawbacks. Firstly, it requires expertise for insertion and interpretation. Secondly, in patients with lung heterogeneity, the measured value of P_L will underestimate the actual lung stress in the dependent lung areas. In addition, the esophageal catheter is not available in ev-

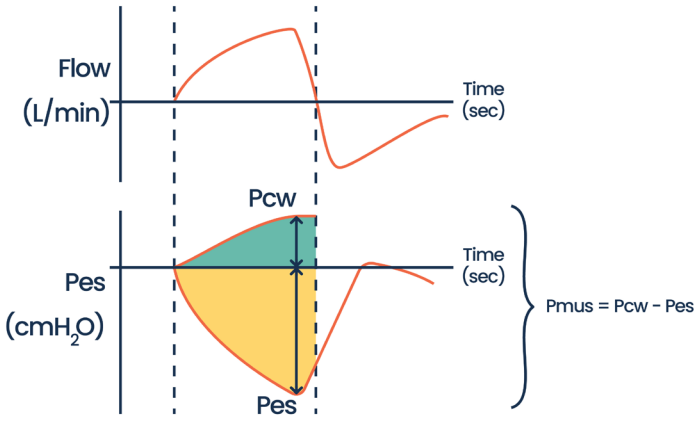

Figure 3. Shows the relationship of esophageal pressure (Pes), chest wall pressure (Pcw) and respiratory muscle pressure (Pmus) through the graph of flow-time waveform and Pressure (Pes)-time waveform. We can find the computed Pcw when we measure Pes on passive ventilation patient in condition of Pmus by zero, we can demonstrate computed pleural pressure that equal to esophageal pressure when we measure Pes on active ventilation (Spontaneous effort). Finally, Pmus can calculated by the difference between Pes and Pcw (Pmus = Pcw – (-Pes)). In individuals, the Pcw value is usually constant, so the Pmus value is directly related to the Pes value (Pmus α Pes). In addition, when we calculate the sum of the area under the graph of P¬mus (the green plus yellow area), we will get the value of the pressure-time product (PTP).

Table 1. Summarizes the characteristics of methods to monitor respiratory effort.

Maneuvers	Parameters	Preference values	Comments
Esophageal pressure (P_{es}) monitoring	$P_{es,}$ P_{di}	5–10 cmH_2O	**Advantage:** it can be monitored as dynamic transpulmonary pressure and transpulmonary driving pressure. It provides high accuracy in interpretation. **Limitations:** it is a procedure that requires expertise for esophageal catheter insertion and interpretation, and due to the high cost of equipment per unit, mostly, it is found only in the research and treatment of high chest wall compliance patients such as obese patients or thick chest wall patient, or the patients who have limited chest wall expansion like the circumferential burn, etc. Another limitation is present when pendelufft occurs and causes heterogeneous regional ventilation, in which measured transpulmonary pressure will be less than the actual lung stress, especially in the dependent lung area. In other words, global transpulmonary pressure as global lung stress cannot represent regional lung stress
	PTP_{es}	50-100 cmH_2O/s/min	
	$WOB = \int P_{mus} \cdot dV$	2.4–4 J/min [38,39] and 0.35–0.7 J/L [12,38] in healthy subjects at rest	
	$P_L = P_{aw} - P_{pl}$; by substituting $P_{pl} = P_{es}$	$P_L \leq 20$ cmH_2O $\Delta P_L \leq 15 cmH_2O$	
	ΔP_{di}	5–10 cmH_2O	
	$P_{mus} = P_{CW} - P_{es}$	5-10 cmH_2O	
	ΔP_{es}	3–8 cmH_2O	
The diaphragm electrical activity (EA_{di})	EA_{di}	The amplitude of 5–20 μV per breath in ICU patients	**Advantage:** this method directly measures the electrical activity of the diaphragm. The EA_{di} in NAVA mode has been proven to decrease patient-ventilator asynchronies [41] **Limitation:** It cannot be used when respiratory drive and effort do not stay in connection. Moreover, it may cause further injury in patients with problems in pharyngeal or maxillo-facial structure
End-expiratory occlusion maneuver	$P_{0.1}$	During ventilation is 1.5-3.5 cmH_2O, >3.5 cmH_2O indicates excessive inspiratory effort. [44-46]	**Advantage:** It can be assessed with NIF or NIP function at the bedside ventilator. The P_{occ} represents the respiratory effort and relates to the transpulmonary pressure. Therefore, the lung and the diaphragm can be protected with an assessment of P_{occ} alone. **Limitation:** require particular function in a mechanical ventilator. The estimated P_L is not as precise as the transpulmonary pressure measurement by an esophageal balloon catheter.
	P_{occ} Predicted calculated $P_{mus} = 0.75 \times \Delta P_{occ}$(47, 48) ΔP_L=(Peak airway pressure - PEEP) – (2/3× ΔP_{occ})[47]	Less than -10 to -15 cmH_2O. [35] But if it is greater than -20 cmH_2O, it indicates excessive inspiratory effort.	
Diaphragm ultrasound	TF_{di}	An appropriate effort ranges from 15%-30% > 40% suggest under-assisted ventilation < 15% suggests overassisted ventilation	**Advantage:** It is non-invasive and can be performed at the bedside. Its reliability is high in well-trained operators. **Limitation:** This procedure requires expertise and experience.

Esophageal Pressure (P_{es}),Transdiaphragmatic pressures (P_{di}), Esophageal pressure-time product (PTP_{es}), Work of breathing (WOB), Transpulmonary pressure (P_L), Airway pressure (P_{aw}), Pleural pressure (P_{pl}), Transdiaphragmatic pressure swing (ΔP_{di}), Respiratory muscle pressure (P_{mus}), Static chest wall elastic recoil pressure (P_{cw}), Esophageal pressure swing (ΔP_{es}), Diaphragm Electrical Activity (EA_{di}), The airway occlusion pressure at first 100 milliseconds ($P_{0.1}$), Airway Occlusion Pressure (P_{occ}), Diaphragm thickening fraction (TF_{di})

ery hospital and is costly. However, in case of availability, the optimum value of ΔP_{es}, P_{mus}, PTP_{es}, and WOB are shown in Table 1.

Monitoring respiratory effort by airway occlusion pressure at first 100 milliseconds ($P_{0.1}$)

$P_{0.1}$ is the airway occlusion pressure at the first 100 milliseconds (ms) of the beginning of inspiration. It can monitor involuntary respiratory effort [5, 39, 40]. If the ventilator is installed with this function, it can be done at the bedside without additional equipment. Otherwise, the $P_{0.1}$ can be measured during the end-expiratory occlusion maneuver when the patients start their inspiration (Figure 4). During this procedure, the $P_{0.1}$ must be recorded manually at 100 ms, which may need specific equipment or software to analyze the waveform. Nevertheless, $P_{0.1}$ is a reliable parameter for evaluating central respiratory drive and involuntary respiratory effort [41]. The $P_{0.1}$ value ranging from 1.5-3.5 cmH_2O is considered an optimum respiratory effort. A value greater than 3.5 cmH_2O indicates excessive inspiratory effort with a sensitivity of 80-92% and specificity of 77-89% [37, 40, 41].

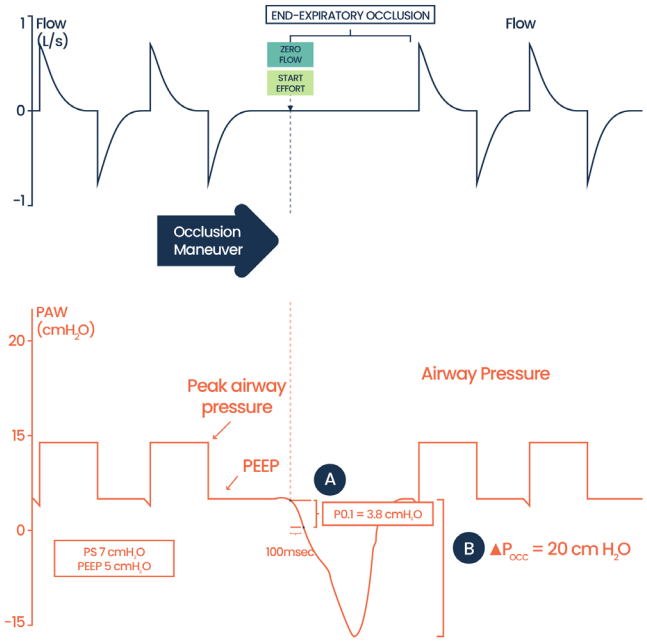

Figure 4. Illustrates flow-time waveform and pressure (P_{aw})-time waveform during end-expiration occlusion maneuver (EEO) in ventilated patient receiveing PEEP of 5 cm H_2O and pressure support by 7 cm H_2O. The negative airway pressure existing during EEO provides the $P_{0.1}$ (presure A), and P_{occ} (pressure B) at the same time. The $P_{0.1}$ in this sample is 3.8 cm H_2O; meanwhile, the P_{occ} is 20 cm H_2O. Those values can be applied to detemine the degree of respiratory effort (see detail in the text).

Monitoring respiratory effort by airway occlusion pressure (P_{occ})

Other than $P_{0.1}$, the measurement of P_{occ} can be done during the end-expiratory occlusion maneuver. The maximum negative pressure is present when the patients create the inspiratory effort during this maneuver [37], as shown in Figure 4. This result relates to the pleural pressure swing; therefore, it can be used to estimate the Pmus and P_L. The predicted calculated Pmus is equal to 0.75× ΔP_{occ} [42, 43], whereas the ΔP_L= (Peak airway pressure - PEEP) – (2/3× ΔP_{occ})[42].

This measurement is non-invasive and can be done at the bedside with built-in functions in the mechanical ventilator, such as negative inspiratory pressure (NIP) measurement. However, if the NIP measurement is unavailable, the ΔP_{occ} must be recorded during the end-expiratory occlusion maneuver by special equipment, then the waveform analysis software is required. The ΔP_{occ} value should be between -10 to -15 cmH_2O [36]. However, if it is below -20 cmH_2O, it suggests excessive inspiratory effort.

Monitoring respiratory effort by diaphragmatic ultrasound

Diaphragmatic ultrasound can be used to evaluate patient-ventilator interactions under quantitative measurement of diaphragm thickening fraction (TF_{di}). It can be calculated in B-mode or M-mode as the percentage inspiratory increase in diaphragm thickness relative to end-expiratory thickness during tidal breathing [TF_{di} = (end-inspiratory thickness – end-expiratory thickness)/end-expiratory thickness × 100%], as shown in Figure 5. This parameter correlates to the inspiratory effort [44].

The optimum TF_{di} is ranging from 15%-30%. Therefore, the over-assistance should be a concern if the value is less than 15%; a value greater than 40% suggests under-assistance [45].

The diaphragmatic ultrasound is a totally non-invasive procedure. In places with available ultrasound machines, it can be done at the bedside. The reliability is high if it is performed by well-trained physicians. Therefore, training is required.

Monitoring respiratory effort by diaphragm electrical activity (EA_{di})

The Diaphragm Electrical Activity (EA_{di}) measures the respiratory effort through neuro-electrical respiratory muscle monitoring [45-48] by inserting an esophagogastric tube and measuring the signal from the diaphragm directly. This method can detect patient-ventilator asynchronies, which can help medical personnel adjust the mechanical ventilator and enhance synchronization.

As shown in Figure 6, some ventilator has a special mode, such as neurally adjusted ventilatory assist (NAVA), which can measure the EA_{di} through the catheter. The NAVA mode has been proven to decrease patient-ventilator asynchronies [49]. However, this mode requires that drive and effort function in the same direction. Therefore it is not suitable for neurological diseases. Moreover, if there is a problem with the pharyngeal or maxillo-facial structure, it may lead to a problem in esophagogastric tube insertion and causes injury.

Because the optimum EA_{di} varies across individuals, there is no particular threshold determining over or under-assistance. Therefore, the trending is used to adjust the assisted ventilation. In addition, at a given EA_{di}, the different P_{mus} would be appeared depending on

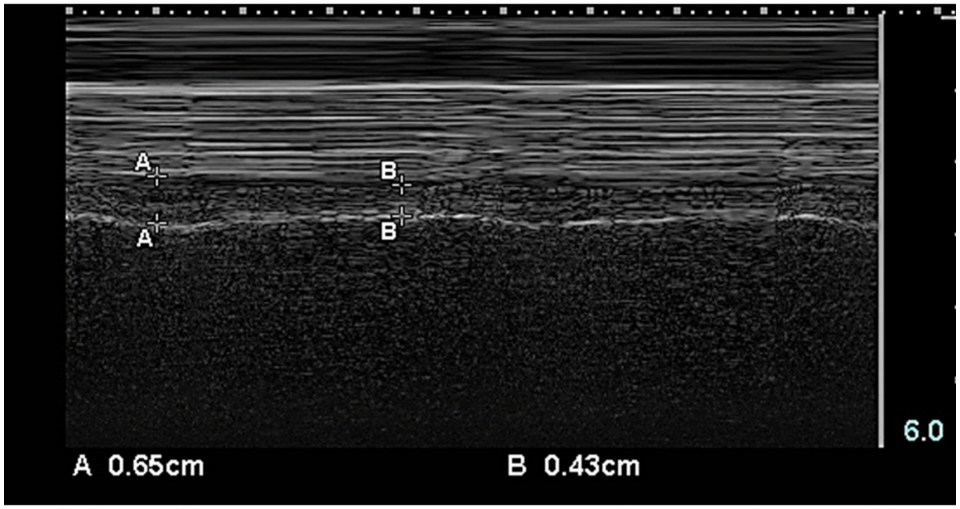

Figure 5. Diaphragmatic thickness fraction is measured in M-mode ultrasonography at the area of lung opposition. Point A is the end-inspiratory thickness, and point B is the end-expiratory thickness. The thickness fraction is the end-inspiratory thickness minus end-expiratory thickness divided by the end-expiratory thickness and presented in percentage.

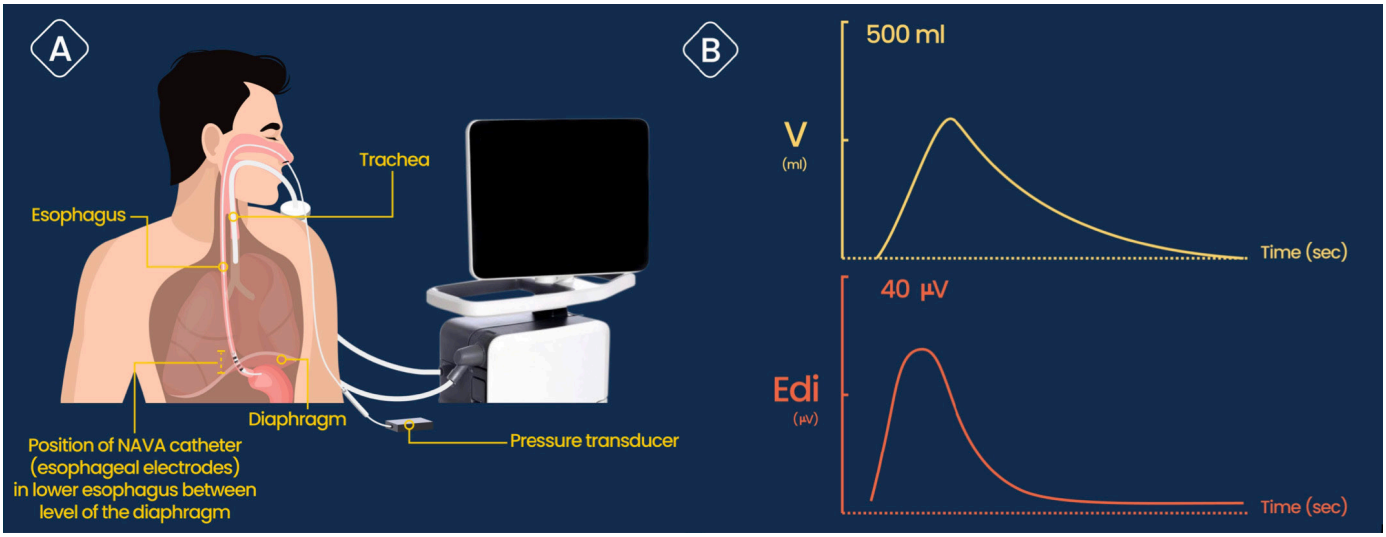

Figure 6A. Illustrates the method to acquire the EA_{di} for respiratory effort monitoring. The EA_{di} is obtained from the specific mechanical ventilator via the neurally-adjusted ventilatory assist (NAVA) catheter insertion through the esophagus. The NAVA catheter has multiple electrodes implanted at the end of the catheter. The electrodes must be positioned between the level of diaphragm, which can be ensured from the signal shown in the ventilator screen.
Figure 6B. shows the waveform of the EA_{di} obtained from NAVA catheter during assisted mechanical ventilation. The EA_{di} would be detected when the diaphragm is moved from patient's effort. We can use the value of EA_{di} to determine the degree of respiratory effort during assisted mechanical ventilation.

Table 2. Depicts Richmond Agitation-Sedation Scale or RASS.

+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on / removes tube(s) or catheter(s) or has aggressive behavior to staff
+2	Agitated	Frequent non-purposeful movement or patient–ventilator asynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

individuals. It means that the EA_{di} cannot be used to predict P_{mus}. However, each patient would belong to his/her own constant P_{mus}/EA_{di} ratio. In this scenario, the Pmus can be personalized [5, 50]

MONITORING OF SEDATION LEVEL

Besides measuring the parameters mentioned above, the respiratory effort can be assessed through the sedation level using Richmond Agitation-Sedation Scale (RASS)[51]. The level of sedation by RASS is shown in Table 2.

The RASS ranges from -5 to +4. However, the goal for light sedation is approximately -1 to 0 in most mechanically ventilated patients. A study on RASS among mechanically ventilated patients who required sedative drugs revealed that this method could shorten ventilator duration by 5 days ($P<0.001$), as well as hospitalization duration by 9 days respectively ($P<0.001$), and reduced the cost of hospitalization significantly [52]. In addition, it is convenient and easy to process as it can be done at the besides without any additional equipment required.

Furthermore, the RASS was also found to correlate with BIS in the study of Karamchandani et al. [53]. However, a recent study by Dzierba et al. [54] reported no relationship between the RASS and $P_{0.1}$. Furthermore, this study showed that the $P_{0.1}$ between 0.2-1.0 was associated with lower ventilator-free days compared to the $P_{0.1} < 0.2$ or > 1.0.

CONCLUSION

In conclusion, improper respiratory effort during mechanical ventilation brings patients to be hazardous. Even if this issue is a new medical perspective; however, appropriate monitoring to find the optimum target to help patients have proper respiratory effort will benefit the patient's outcomes from a lower risk of respiratory muscle atrophy and injury, P-SILI, and over sedation. Nonetheless, further researches still require confirming those benefits.

ABBREVIATIONS

PVA, Patient-ventilator asynchrony; P-SILI, Patient self-inflicted lung injury; COPD, Chronic obstructive pulmonary disease; VIDD, Ventilator-induced diaphragmatic dysfunction; NPV, Negative pressure mechanical ventilator; Pes, Esophageal pressure; P_L, Transpulmonary pressure; Ppl, Pleural pressure; Vt, Tidal volume; ARDS, Acute respiratory distress syndrome; VCV, Volume-controlled ventilation; PCV, Pressure-controlled ventilation; PSV, Pressure support ventilation; Pmus, Respiratory muscle pressure; Pcw, Static chest wall elastic recoil pressure; Paw, Airway pressure; WOB, Work of breathing; PTPes, Esophageal pressure-time product; ms, Milliseconds; $P_{0.1}$, Airway occlusion pressure at first 100 milliseconds; Pocc, Airway Occlusion Pressure; NIP, Negative inspiratory pressure; TFdi, Diaphragm thickening fraction; EAdi, Diaphragm Electrical Activity; NAVA, Neurally-adjusted ventilatory assist; RASS, Richmond Agitation-Sedation Scale; BIS, Bispectral index.

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