The Injurious Effects of Elevated or Nonelevated Respiratory Rate during Mechanical Ventilation

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Abstract

Respiratory rate is one of the key variables that is set and monitored during mechanical ventilation. As part of increasing efforts to optimize mechanical ventilation, it is prudent to expand understanding of the potential harmful effects of not only volume and pressures but also respiratory rate. The mechanisms by which respiratory rate may become injurious during mechanical ventilation can be distinguished in two broad categories. In the first, well-recognized category, concerning both controlled and assisted ventilation, the respiratory rate *per se* may promote ventilator-induced lung injury, dynamic hyperinflation, ineffective efforts, and respiratory alkalosis. It may also be misinterpreted as distress delaying the weaning process. In the second category, which concerns only assisted ventilation, the respiratory rate may induce injury in a less apparent way by remaining relatively quiescent while being challenged by chemical feedback. By responding minimally to chemical feedback, respiratory rate leaves the control of V_E almost exclusively to inspiratory effort. In such cases, when assist is high, weak inspiratory efforts promote ineffective triggering, periodic breathing, and diaphragmatic atrophy. Conversely, when assist is low, diaphragmatic efforts are intense and increase the risk for respiratory distress, asynchronies, ventilator-induced lung injury, diaphragmatic injury, and cardiovascular complications. This review thoroughly presents the multiple mechanisms by which respiratory rate may induce injury during mechanical ventilation, drawing the attention of critical care physicians to the potential injurious effects of respiratory rate insensitivity to chemical feedback during assisted ventilation.

Keywords: control of breathing; diaphragmatic dysfunction; ventilator-induced lung injury; patient–ventilator interaction; respiratory rate

Mechanical ventilation is the cornerstone of supportive care for respiratory failure, tightly linked to the very existence of intensive care. As our understanding of the complex interactions between the patient and the ventilator has increased, it has become apparent that mechanical ventilation not only is lifesaving but, similarly to any other intervention, may also harm the patient. A series of studies paved the way to the first ARDSNet trial (ARMA), which catalyzed understanding of ventilator-induced lung injury (VILI) and has raised interest in the deleterious effects of mechanical ventilation (1). Extensive research has since been performed, aimed at thoroughly characterizing the mechanisms by which mechanical ventilation may harm the patient. It is now well established that lung overstretch and cyclic alveolar collapse promote lung injury. In the everyday clinical practice, physicians can rely on the results of several clinical and physiological studies for the titration of V_T, positive end-expiratory pressure, and end-inspiratory pressure during mechanical ventilation. Yet, the role and potential harmful effects of respiratory rate during mechanical ventilation have received less attention.

In this review, we describe the multiple mechanisms through which the respiratory rate during mechanical ventilation may adversely affect the patient. When the potential harmful effects of respiratory rate during mechanical ventilation are considered, one intuitively associates injury with a high respiratory rate. Indeed, such injurious effects of the respiratory rate *per se* can be observed during both controlled and assisted mechanical ventilation and are discussed in the first part of this review. Nevertheless, it is relatively underrecognized that the respiratory rate changes minimally or not at all in response to changes in assist level and Pa_{CO_2}. The mechanisms of this insensitivity of respiratory rate and the

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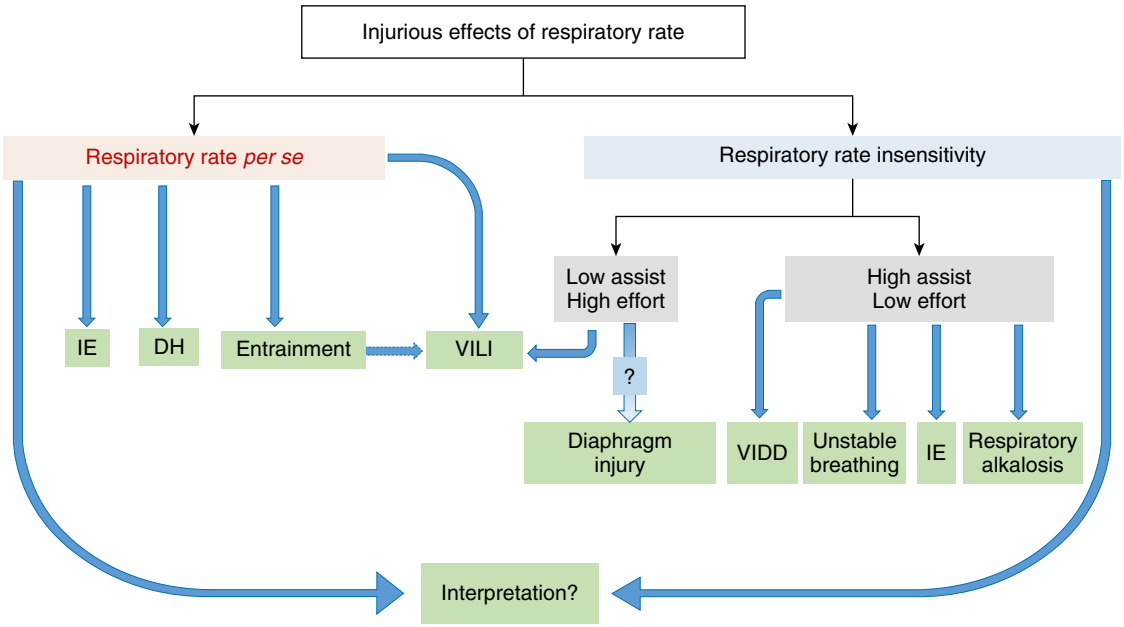

Figure 1. The main injurious effects of respiratory rate. Both the respiratory rate *per se* and the respiratory rate insensitivity may result, through multiple pathways, in ventilator-induced lung injury (VILI) and may be falsely interpreted with several adverse consequences for the patient. Respiratory rate insensitivity is related to inability of respiratory rate to control $\dot{V}_E$ and, depending on the level of assist, results in high or low effort per breath. DH = dynamic hyperinflation; IE = ineffective efforts; VIDD = ventilator-induced diaphragmatic dysfunction.

clinical implications for assisted ventilation are presented in the second part of this review.

Real or Perceived Injurious Effects Associated with High Respiratory Rate

Respiratory rate is determined by the physician during controlled mechanical ventilation, by the patient during assisted ventilation, or by both during assist control ventilation. It is noteworthy that the respiratory rate displayed on the ventilator screen may be lower or higher than the respiratory rate of the patient in the presence of ineffective efforts or autotriggering, respectively. Regardless of its origin, the respiratory rate may become injurious for the patient in multiple ways (Figure 1).

VILI

It is well established that VILI is caused by the cyclic overstretch and/or collapse of alveoli. Thus, reducing V_T, limiting plateau airway pressure, and applying adequate positive end-expiratory pressure to improve lung compliance and increase the size of the "baby lung" constitute the three components of lung-protective ventilation. Lung-protective ventilation has been shown to decrease the risk of VILI and improve the survival of patients with acute respiratory distress syndrome (ARDS) (2). However, less attention has been paid to the respiratory rate. The protocol of the ARDS Network trial permitted respiratory rates of up to 35 breaths/min to maintain a pH greater than 7.30, underestimating respiratory rate as a cause of VILI (1, 2). Nevertheless, subsequent experimental studies have indicated that the higher the respiratory rate, the more susceptible the lung is to injury (3–6). Mechanical ventilation with lower respiratory rates in isolated and small-animal lungs lessened edema and perivascular hemorrhage formation, significantly ameliorating lung inflammation and injury (4, 7). High respiratory rates dramatically increased lung injury, especially in diseased lungs (8). In a recent study, pigs were ventilated with the same high V_T at different respiratory rates. All piglets developed whole-lung edema at 12 and 15 breaths/min, whereas no lung injury was observed at 3 and 6 breaths/min (8). Beyond animal studies, evidence that respiratory rate is injurious has emerged from the largest prospective epidemiological study of patients with ARDS so far conducted: the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) study (9). In the multivariate analysis, respiratory rate was among the potentially modifiable factors independently associated with hospital mortality. Although the association between respiratory rate and VILI has not been systematically studied during assisted ventilation, it is reasonable to assume that high respiratory rate can also be injurious during spontaneous breathing. In line with this assumption, the LUNG SAFE study identified high respiratory rate and a high nonpulmonary Sequential Organ Failure Assessment score as two factors independently associated with noninvasive ventilation failure, which in turn has been associated with higher mortality (10). Therefore, should tachypnea develop during assisted ventilation, regardless of the triggering factor, it may promote or aggravate lung injury, especially in injured lungs (11).

Entrainment

Respiratory entrainment, recently documented in deeply sedated critically ill

patients, refers to the establishment of a fixed temporal relationship between the patient's breath and the ventilator-delivered breath (12, 13). In simple terms, a ventilator-controlled breath triggers inspiratory muscle efforts through activation of stretch receptors, cortical influences, thoracic or diaphragmatic mechanoreceptors, spinal reflexes, or a more complex spinal pattern generator (12). Patients' inspiratory efforts, triggered by the ventilator during entrainment, have also been defined as "reverse triggered breaths" and may raise the risk of VILI as a result of breath stacking, which leads to considerable increases in V_T (12). Furthermore, reverse triggering may be associated with injurious stretch of dependent lungs even when V_T remains constant (14). Similarly to entrainment, autotriggered breaths may increase V_T or minute volume delivered by the ventilator (15).

Dynamic Hyperinflation

Respiratory rate may contribute to the development of dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEPi) with multiple respiratory and hemodynamic consequences. There is no absolute value of respiratory rate causing dynamic hyperinflation. Respiratory rate and inspiratory-to-expiratory time ratio determine expiratory time. Dynamic hyperinflation development depends on the time constant of the respiratory system (the product of respiratory system compliance and resistance), the V_T, and the expiratory time (15, 16). When airway resistance is high (severe airflow obstruction), the effect of respiratory rate on dynamic hyperinflation depends on whether it is associated with short expiratory time (17). In the presence of high PEEPi, the respiratory system may operate near its TLC, resulting in respiratory system compliance decrease and transpulmonary pressure increase. High transpulmonary pressures increase the risk of VILI. Furthermore, PEEPi may cause diaphragm flattening and dysfunction, cardiovascular impairment due to venous return reduction, elevated pulmonary vascular resistance, and right ventricular afterload increase (18). Dynamic hyperinflation is a major challenge during both controlled and assisted mechanical ventilation, especially in patients with obstructive lung disease and long time constants. Notwithstanding this, dynamic hyperinflation is an issue also in patients with ARDS when a high respiratory rate is applied. Diffuse or localized airflow limitation is well described in ARDS, further increasing the risk of dynamic hyperinflation at high respiratory rates (15, 18–20).

Ineffective Efforts

Ineffective efforts refer to a patient's inspiratory efforts that fail to trigger the ventilator, and they represent the most common form of patient–ventilator asynchrony during assisted ventilation (21). In the presence of ineffective efforts, the patient's respiratory rate is higher than the ventilator's respiratory rate. The majority of ineffective efforts occur during expiration, leading to lengthening contraction of inspiratory muscles (inspiratory muscles are activated while lung volume decreases) (21). Lengthening contractions of skeletal muscles have been shown to cause muscle damage during exercise, although the same has not been proven for the diaphragm in mechanically ventilated patients (22, 23). In several studies, a high number of ineffective efforts has been related to prolonged mechanical ventilation, prolonged ICU stay, and higher mortality (21, 24, 25). Contrary to these studies, Rolland-Debord and colleagues did not find an association between patient outcomes and an asynchrony index higher than 10% during weaning (26). The asynchrony index was computed as the number of asynchronous breaths divided by the total number of breaths (both requested and delivered) multiplied by 100. Although the asynchrony index is traditionally used to quantify the severity of asynchrony, continuous prolonged recordings of patient–ventilator interaction revealed that this index may fail to capture ineffective efforts occurring in "clusters" (defined as >30 ineffective efforts in a 3-min period) (25). Clusters of ineffective efforts often follow periods with no asynchrony and have been shown to significantly correlate with prolonged mechanical ventilation and higher mortality (25).

Respiratory Rate during Weaning

Relying on the changes in respiratory rate to evaluate the weaning process can be particularly challenging. A respiratory rate higher than 35 breaths/min is traditionally used as a sign of weaning failure (27, 28). Furthermore, respiratory rate is incorporated into the more commonly used index to predict weaning failure, the rapid shallow breathing index, which is the ratio between respiratory rate and V_T. A rapid shallow breathing index higher than 105 during the spontaneous breathing trial is considered highly predictive of weaning failure (29). During the weaning process, respiratory rate increase may indeed signify respiratory distress as a result of ventilator underassistance. In this case, ventilator assist must increase to meet patient respiratory demands. Nevertheless, respiratory rate increase can be unrelated to ventilator support. For example, it is known that a high level of ventilator assist may induce dynamic hyperinflation and promote ineffective efforts, which may decrease or disappear upon reduction of assist level. In this scenario, the reduction of ventilator assist will increase the respiratory rate, sometimes considerably, not because of respiratory distress but because all inspiratory efforts now trigger the ventilator. A respiratory rate higher than 35 breaths/min does not necessarily indicate a high respiratory drive; it may simply represent the rate preferred by the patient's respiratory control system, defined as the undistressed respiratory rate (30–32). The undistressed respiratory rate varies greatly among healthy individuals and is, on average, 10 breaths/min higher in critically ill patients (30–32). In addition, high respiratory rates in awake or partly sedated patients may arise from pain, anxiety, or other behavioral responses unrelated to distress. Failure to identify and appropriately address the reasons for high respiratory rate may lead to improper actions and a delay in the weaning process.

Other Effects

In the mechanically ventilated patient, the right ventricle may suffer from significant increases in afterload during volume delivery as a result of transpulmonary pressure increase. This is more evident in patients with lung injury because their transpulmonary pressures are usually higher (33). The respiratory rate determines how many times per minute the afterload of the right ventricle will increase, as well as the duration of such an increase (duration of inspiration) (33). Moreover, a high respiratory rate may result in hypocapnia and respiratory alkalosis. Respiratory alkalosis and alkalemia induce significant neurological (cerebral

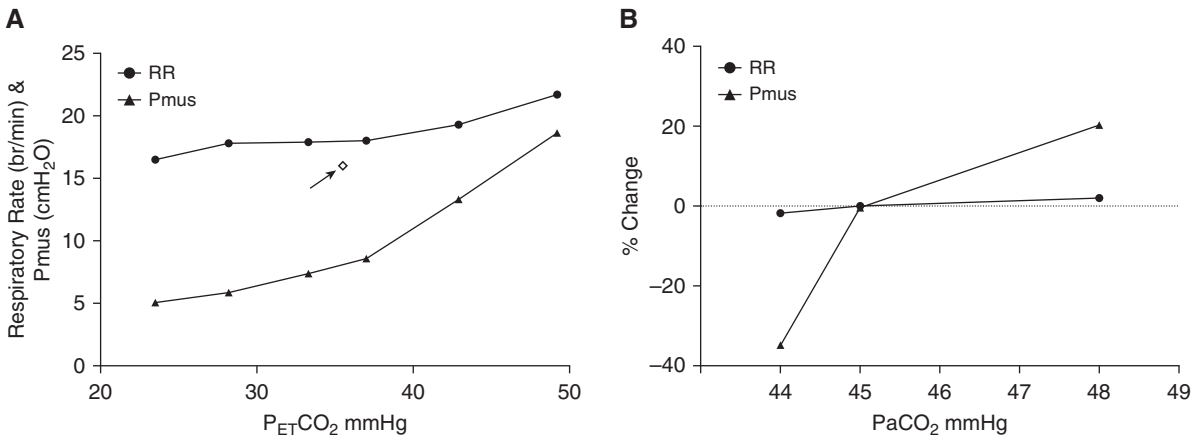

Figure 2. (*A*) Healthy, awake subjects. Mean respiratory rate (RR) and inspiratory muscle pressure (Pmus) measured at 50% of mechanical inflation time as a function of end-tidal (partial) carbon dioxide pressure ($P_{ET}CO_2$) in 16 volunteers during pressure support ventilation at various concentrations of inspired CO_2. Similar slopes of Pmus were obtained at 20% and 80% of mechanical inflation time (not shown). Notice that RR was relatively insensitive to CO_2 over a wide range of $P_{ET}CO_2$. Even at severe hypocapnia, the subjects continued to trigger the ventilator regularly with a rate that did not differ from that during spontaneous resting breathing. (Arrow and open diamond show RR and $P_{ET}CO_2$ during spontaneous resting breathing.) RR increased slightly at $P_{ET}CO_2$ well above 40 mm Hg. However, $Pmus_{50\%}$ increased progressively from low (23.5 mm Hg) to high (49.2 mm Hg) $P_{ET}CO_2$; at high $P_{ET}CO_2$, $Pmus_{50\%}$ was 318% of the value at low $P_{ET}CO_2$. At 37 mm Hg $P_{ET}CO_2$, $Pmus_{50\%}$ was 141% of that at low $P_{ET}CO_2$. (*B*) Critically ill, mildly sedated patients recovering from acute respiratory distress syndrome. Mean change of RR and peak muscle pressure ($Pmus_{peak}$) due to chemical feedback. The typical response of RR to changes in load includes an instant reflex response, as well as a more delayed response, driven by the change in Pa_{CO_2}, the chemical feedback. In this experiment, an abrupt change in pressure support by 6 cm H_2O was performed (random increase or decrease resulting in Pa_{CO_2} of 44 or 48 mm Hg, respectively), and RR and $Pmus_{peak}$ were measured at the second breath after the change and after 30 minutes, representing the reflex and chemical feedback responses, respectively. To examine the response solely to chemical feedback, the change of RR and $Pmus_{peak}$ at 30 minutes was expressed as a percentage change over the corresponding values at the second breath, calculated as (value at 30 min − value at second breath/value at second breath) × 100. The reported Pa_{CO_2} was measured at 30 minutes after the change in pressure support. Notice that chemical feedback affected the effort per breath but not RR. Data are reproduced by permission from References 35 (*A*) and 38 (*B*). SD bars are omitted for clarity of presentation.

vasoconstriction, syncope, seizures, encephalopathy, paresthesias, muscle cramps, tremor), cardiovascular (arrhythmia, myocardial ischemia), respiratory (bronchoconstriction, pulmonary vasodilatation and intrapulmonary shunt, decreased respiratory drive), and systemic (decreased oxygen delivery) adverse effects (34).

Injurious Effects Associated with Respiratory Rate Insensitivity

Respiratory rate may harm the patient not only directly, through its absolute value, but also indirectly, by remaining relatively quiescent to chemical feedback. Chemical feedback refers to the response of respiratory control to changes in P_{O_2}, Pa_{CO_2}, and pH. A widespread misconception is that mechanically ventilated patients respond to changes in assist level and thus Pa_{CO_2}, mainly through respiratory rate modifications. There are even automated algorithms that modify the level of ventilator assist on the basis of respiratory rate during assisted mechanical ventilation. Physicians intuitively assume that increasing and decreasing the level of ventilator assist decreases and increases, respectively, the patient's respiratory rate. Several data contradict this common misconception. Studies in normal conscious subjects consistently show that breathing frequency is fairly insensitive to assist level and corresponding CO_2 changes, even when the mode of assist yields large V_T values and excessive respiratory alkalosis (35–39). In fact, breathing frequency response is minimal over a Pa_{CO_2} range from 23 to 45 mm Hg (35–37, 39). Isolated changes in Pa_{CO_2} exert their influence mainly through modification of inspiratory effort per breath and much less through modification of respiratory rate. Relatively minimal increases in respiratory rate are observed at Pa_{CO_2} well above the eupneic levels (35–37) (Figure 2A). These findings are reproducible in critically ill patients (30, 31, 38–41). Nevertheless, when the assist increases (volume or pressure), the respiratory rate decreases as a result of a complex reflex feedback activation mediated by multiple pathways (38, 42). For instance, a rise in pressure support increases the insufflation time and volume delivery, which, via activation of the Hering-Breuer reflex, inhibit inspiration and prolong expiratory time, leading to a respiratory rate decrease. These reflex feedback changes in respiratory rate are only modest (10–20%), and they are observed immediately after an assist change and do not alter thereafter (38, 42). On the contrary, marked changes in patient effort in response to chemical feedback have been observed (38, 43) (Figure 2B).

Studies of breathing patterns in response to either external load or unloading with increasing levels of assist revealed that a patient's respiratory rate either does not change or changes modestly (usually up to 20%). This contrasts with the severalfold changes in a patient's effort per breath (30, 31, 40, 41, 44, 45). A recent study has shown that when

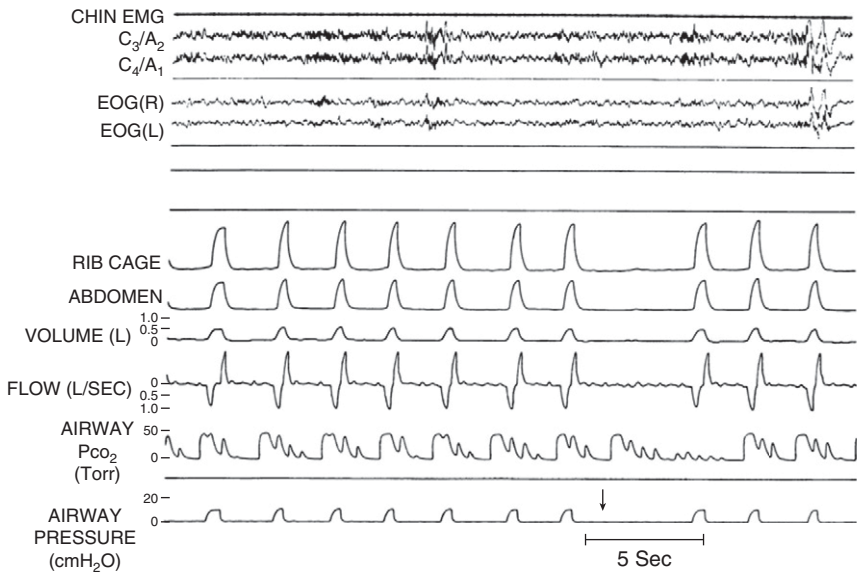

Figure 3. Polygraph tracings at 10 cm H_2O pressure support ventilation in a normal human during sleep. This level of pressure support decreased Pa_{CO_2} to values slightly higher than the apneic threshold. The response to discontinuation of pressure support for one breath is shown (arrow). Notice that although the subject triggers the ventilator regularly, the inspiratory effort per breath is so small (qualitative estimate) that without pressure support inspired volume, it is barely measurable. Respiratory rate did not react to Pa_{CO_2} decrease, leaving the inspiratory effort per breath to take account of the response to high assist, a highly inefficient strategy to control $\dot{V}_E$ during pressure support. In flow tracing, inspiratory flow is downward. C3/A2 and C4/A1 = EEG channels; EOG = electroocculogram, right (R) and left (L). Reproduced by permission from Reference 60.

partial neuromuscular blockade suppresses inspiratory effort, respiratory rate does not sufficiently increase to offset low $\dot{V}_E$ (46). These findings also apply to patients undergoing noninvasive mechanical ventilation (47). One may reasonably argue that in awake patients, an abrupt increase in respiratory load (induced by modification of ventilator settings or respiratory system mechanics alteration) quite often evokes high respiratory rates. This is largely attributed to cortical influence (behavioral feedback) due to a discrepancy between respiratory center output and ventilator output. The same reaction is observed with other unpleasant environmental stimuli, such as pain, fever, anxiety, or changes in sedation level. In these scenarios, disagreeable sensation or panic reaction elicits behavioral influences provoking tachypnea in an effort to enhance comfort (37, 48). We should not omit that behavior-derived tachypnea applies only to conscious or semiconscious patients. The potentially harmful effects of an insensitive respiratory rate during assisted ventilation relate to high and low levels of assist (Figure 1).

Injurious Effects of Respiratory Rate Insensitive to High Assist

Wakefulness. HYPERVENTILATION AND RESPIRATORY ALKALOSIS. In patients with spontaneous respiratory activity, breathing frequency could play a key role in counteracting high levels of assist. In assist volume control, once triggered, the ventilator delivers a preset volume regardless of respiratory effort. Because the respiratory rate is insensitive to hypocapnia and thus will not change to decrease $\dot{V}_E$, awake patients in assist volume control may develop respiratory alkalosis when the level of assist exceeds their needs. In pressure support ventilation (PSV), neuroventilatory coupling is better preserved because V_T may vary with the intensity of inspiratory effort. However, PSV delivers a minimum V_T even if the patient relaxes all inspiratory muscles immediately after triggering, and this V_T depends on the level of assist, the mechanical properties of the respiratory system, and cycling off criteria (49). Therefore, provided that the ventilator is triggered, minimum $\dot{V}_E$ is delivered with PSV. Whenever assist in PSV results in a minimum ventilation that is higher than demand (i.e., high assist and/or improvement in mechanics), the inability of respiratory rate to defend a high minimum V_T leads to hyperventilation and respiratory alkalosis with the aforementioned adverse effects. Furthermore, hypocapnia could decrease the respiratory drive and promote ineffective efforts and is considered a significant cause of weaning failure (49). The adverse consequences of respiratory rate insensitivity to chemical stimuli are less evident in proportional ventilation modes (proportional assist ventilation [PAV+] and neutrally adjusted ventilator assist [NAVA]). With proportional modes, delivered pressure and V_T do not increase even at high levels of assist, because they are proportional to the inspiratory muscle effort that is downregulated (50–53). There are studies in which Pa_{CO_2} did not significantly decrease between PSV and proportional ventilation as the level of assist increased (40, 52, 53). Nevertheless, arterial blood gases were examined only 5–10 minutes after the change in assist, a very short period to detect changes in Pa_{CO_2}. Moreover, high assist was associated with ineffective efforts during PSV but not with proportional ventilation. Approximately 31% of all patient efforts were ineffective in the study by Spahija and colleagues (52), and nine efforts per minute was ineffective in the study of Carteaux and colleagues (40) at high levels of PSV. Hence, despite higher V_T at high pressure support, the lower respiratory rate due to ineffective efforts resulted in similar $\dot{V}_E$ between the two modes. This may have minimized the effects of ventilation mode on Pa_{CO_2}.

DIAPHRAGM DYSFUNCTION. Respiratory rate insensitivity during high assist may contribute to diaphragmatic atrophy and development of ventilator-induced diaphragmatic dysfunction (VIDD). Owing to the fact that respiratory rate changes minimally when assist is high, inspiratory effort decreases to control V_T and $\dot{V}_E$. Assist may be great enough to provoke a significant or even complete diaphragmatic inactivity immediately after triggering (40).The lower the diaphragmatic contraction and the longer the duration of diaphragm inactivity, the greater the risk is for VIDD. Besides controlled ventilation, high levels of assisted mechanical ventilation

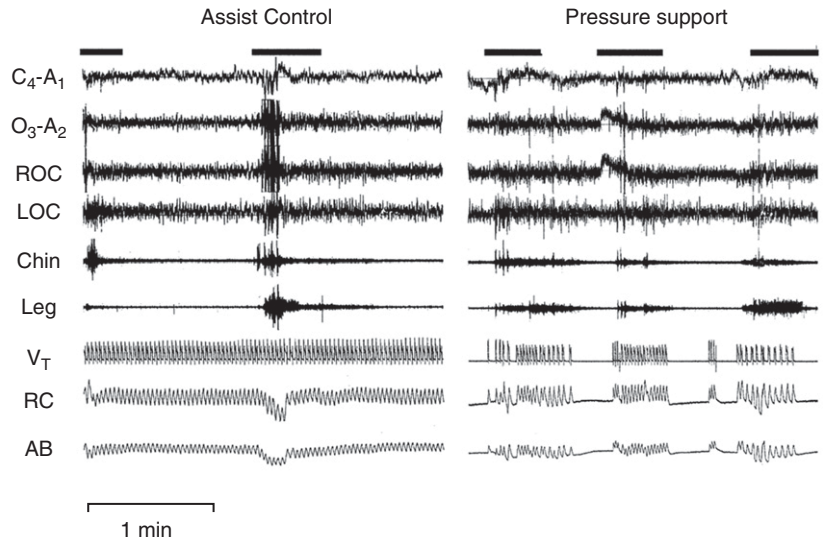

Figure 4. Polysomnographic tracings during assist volume control with backup rate and pressure support in a critically ill patient during sleep. EEG channels (C_4-A_1 and O_3-A_2), right (ROC) and left (LOC) electrooculograms, EMGs (chin and leg), integrated V_T, and rib cage (RC) and abdominal (AB) excursions on respiratory inductive plethysmography are shown. Horizontal bars indicate arousals and awakenings. In this patient, the level of pressure support decreased Pa_{CO_2} below the apneic threshold, and apneas ensued. Because respiratory rate above the apneic threshold did not react to Pa_{CO_2} changes, $\dot{V}_E$ is determined mainly by the level of assist. With assist volume, the backup rate prevented the occurrence of apneas. Notice that sleep fragmentation, measured as the number of arousals and awakenings, was greater during pressure support than during assist control ventilation with backup rate. Reproduced by permission from Reference 61.

have also been implicated in the development of diaphragmatic atrophy (54–56). VIDD is two times more common than critical illness peripheral polyneuropathy and myopathy, and recent studies have shown that it is independently associated with delayed weaning or weaning failure, increased risk of serious complications including reintubation and tracheostomy, prolonged mechanical ventilation and ICU stay, and possibly higher mortality (57–59). In the study by Goligher and colleagues, the level of inspiratory effort was correlated with diaphragmatic thickness (55). It has been suggested that diaphragm thickness and thickening fraction, indexes of diaphragmatic atrophy and function assessed by ultrasound, declined rapidly with high levels of assist and low inspiratory effort during PSV (55, 56). Although more data are required to draw definitive conclusions, the insensitivity of respiratory rate response to a low Pa_{CO_2} resulting from an inappropriately high level of assist, and the associated decrease in inspiratory effort, may increase the risk of VIDD during assisted mechanical ventilation.

Sleep and sedation. During sleep or sedation, control of breathing is dominated principally by chemical feedback (60). Indeed, by removing the wakefulness stimulus to breathe, respiratory rate critically depends on Pa_{CO_2}. In normal humans, a drop in Pa_{CO_2} by 3–4 mm Hg from Pa_{CO_2} during eupnea causes apnea. The Pa_{CO_2} at which apnea occurs is referred to as the apneic threshold. However, during sleep, similarly to wakefulness, as Pa_{CO_2} decreases, respiratory rate remains rather stable, and when Pa_{CO_2} decreases to the apneic threshold, respiratory rate drops immediately to zero and central apnea occurs. During the time of Pa_{CO_2} decrease, effort per breath is progressively downregulated (Figure 3). Between eupneic Pa_{CO_2} and the apneic threshold, humans control ventilation exclusively by changing effort per breath, whereas respiratory rate remains insensitive to Pa_{CO_2} changes (60). This feature of control of breathing has a tremendous influence on the effect of the mode of mechanical ventilation on breathing stability during sleep. With assist volume control and PSV, a minimum V_T and $\dot{V}_E$ is delivered, even if there is no inspiratory effort immediately after triggering (37, 60). In assist volume control, the delivered $\dot{V}_E$ depends on the volume chosen by the physician and on the respiratory rate. In PSV, minimum $\dot{V}_E$ depends on the assist level, the mechanics of the respiratory system, and the respiratory rate. When delivered $\dot{V}_E$ lowers Pa_{CO_2} below the eupneic value, only inspiratory effort decreases, whereas respiratory rate does not change (60). At Pa_{CO_2} values above the apneic threshold, inspiratory effort is so weak that it only triggers the ventilator (Figure 3). The presence of triggering ensures a minimum $\dot{V}_E$, which can induce periodic breathing during sleep if the level of assist is sufficient to decrease Pa_{CO_2} below the apneic threshold (60, 61) (Figure 4). This applies not only in critically ill patients but also in individuals undergoing long-term ventilation (62).

Meza and colleagues found that the Pa_{CO_2} apneic threshold during non-REM sleep varies among individuals, but is only a few millimeters of mercury (1.5–5.8 mm Hg) below the eupneic Pa_{CO_2} (60). This difference determines individuals' susceptibility to periodic breathing. In their study, periodic breathing could be induced in all subjects with pressure support at levels between 5.5 and 10 cm H_2O. The pressure support level at which periodic breathing developed was primarily related to respiratory system elastance. Several studies showed that in critically ill patients with normocapnia, there was no change, or even small decreases, in $\dot{V}_E$ with assist increases during PAV+ (30, 31, 63). This happens because pressure delivered with PAV+ follows inspiratory effort, which is significantly downregulated as Pa_{CO_2} decreases. Near the apneic threshold, when inspiratory effort is very low, V_T and $\dot{V}_E$ are independent of assist level with PAV+. Moreover, there is no minimum $\dot{V}_E$ with PAV+, because, in the absence of inspiratory muscle activity after triggering, there is no pressure and/or V_T delivered. The same operational principles apply to NAVA and explain why proportional modes have been shown to reduce the risk of periodic breathing (64, 65). Notwithstanding this, proportional modes do not entirely avert apneas when high assist is applied in susceptible patients, such as those with heart failure or central nervous system damage (66). The insensitivity of respiratory rate is therefore

a key element of apneas and periodic breathing during assisted ventilation, especially during sleep or sedation, when behavioral stimuli affecting respiratory rate are removed (61). Periodic breathing results in severe sleep fragmentation and reduced deep sleep. Poor sleep quality is associated with catecholamine and blood pressure elevation, cardiopulmonary and autonomic nervous system abnormalities, neurocognitive dysfunction, and delirium (67, 68). Finally, periodic breathing may affect the decision-making process; it is a common reaction to place patients with apneas back on controlled modes, unnecessarily prolonging mechanical ventilation. Thus, it is not surprising that periodic breathing is an independent factor for increased morbidity and mortality (69, 70).

Absence of Respiratory Rate Response during Low Assist

If the level of assist does not satisfy patients' ventilatory demands, the inspiratory muscles mainly undertake the task of maintaining V_E at desired levels. This is again the consequence of limited respiratory rate response to chemical feedback changes. Small increases in ventilatory demands evoke considerable increases in inspiratory effort per breath, leaving respiratory rate relatively unaffected (71). Nevertheless, beyond a level of respiratory drive increase, which is approximately three to four times higher than that of resting ventilation, respiratory rate increases substantially (71). However, at such high levels of respiratory drive, high respiratory rate is not an efficient strategy to meet the ventilatory demands, because it may cause dynamic hyperinflation and increase dead space/V_T ratio. Intense inspiratory efforts induce stress in various ways, and the amount of stress relates to the intensity of efforts. Several studies have demonstrated that not only low but also excessive inspiratory muscle effort can be injurious to the diaphragm (55, 72–74). In a recent study, Goligher and colleagues found that diaphragm thickness above a certain threshold, suggestive of intense patient effort, predicted prolonged mechanical ventilation and ICU stay and higher risk of complications (58). Insufficient respiratory muscle unloading has also been associated with lung injury and systemic effects through inflammatory upregulation (73–75). Apart from diaphragmatic injury, intense respiratory efforts can be detrimental to the lung, especially at the early phases of ARDS (76). Strong muscle contractions cause lung injury because of *1*) high V_T and transpulmonary pressures and *2*) "occult pendelluft" phenomenon, the movement of gas from nondependent to dependent lung regions during inspiration. This movement increases regional distention of already injured lung regions (11, 76). Strenuous respiratory efforts during assisted ventilation may lead to patient–ventilator asynchronies such as multiple ventilator triggering (15). Finally, increased negative pleural pressure swings, caused by inspiratory muscle contractions, may considerably increase pulmonary transcapillary pressure and induce hydrostatic pulmonary edema (77).

Clinical Implications

When using controlled modes of mechanical ventilation, physicians should consider that respiratory rate *per se* may promote lung injury and/or dynamic hyperinflation. Although no safe threshold of respiratory rate has been identified, it appears reasonable to reduce patients' ventilatory demands to maintain Pa_{CO_2} and/or pH within acceptable limits. When using assisted modes of ventilation, physicians should acknowledge that respiratory rate is not a sensitive indicator of patient comfort or appropriateness of the level of assist. In patients presenting with respiratory alkalosis, ineffective efforts, or apneas, ventilator overassist should be suspected. A correction of ventilator overassist could result in an increase of the respiratory rate, sometimes abruptly, often because a patient's true neural (undistressed) rate is revealed. However, it is important to remember that tachypnea is not an imminent sign of inadequate assist. Patients with high respiratory drive and demands not satisfied by the level of assist may exhibit injurious strenuous breathing without high respiratory rate. In all cases, a careful physical examination of the patient during titration of assist could help the physician select the appropriate level of assist much more than reliance on the "insensitive" respiratory rate.

Conclusions

Respiratory rate is one of the key variables by which mechanical ventilation may injure the patient, and therefore it is important for physicians to appreciate its harmful effects. These harmful effects can be separated into two broad categories. In the first, and more easily recognized, the respiratory rate *per se*, whether set by the physician, determined by the patient, or both, may promote VILI, dynamic hyperinflation, ineffective efforts, or respiratory alkalosis. Furthermore, it may be falsely interpreted as distress, delaying the weaning process. The second category includes cases in which respiratory rate remains relatively idle while being challenged by ventilator settings. In such cases, occurring only during assisted ventilation, respiratory rate responds poorly to chemical feedback, leaving the control of V_E almost exclusively to inspiratory effort. Hence, high assist results in weak inspiratory efforts, promoting ineffective efforts, periodic breathing, and diaphragmatic atrophy. However, low assist results in intense efforts, increasing the risk for respiratory distress, asynchronies, VILI, and possibly diaphragmatic injury. As the injurious effects of mechanical ventilation on both the lungs and the diaphragm gain attention, it is important for physicians to be aware of the multiple adverse effects of the respiratory rate during mechanical ventilation. ■

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