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Therapeutic range of spontaneous breathing during mechanical ventilation

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In the 4th century before the common era, the Greek philosopher and physician Hippocrates expressed his wisdom on the value of activity to the sick and the healthy by stating that: “The sick will of course profit to a great extent from gymnastics with regard to the restoration of their health and the healthy will profit with regard to its maintenance” (On Regimen in Acute Diseases, 3, 400 BCE). In contemporary critical care medicine, driven by the goal of protecting our patients from self-inflicted injury, pain, and anxiety – and in contrast to Hippocrates’ suggestions – we have built a culture of immobilizing our patients: we prescribe high doses of opioids, sedatives, anxiolytics, and anti-psychotics, and with the best intentions, place bed-rest and restraints orders. In patients with severe respiratory failure, we frequently use immobilizing ventilator settings such as volume control ventilation. Recent data have been increasingly challenging this tenet in relation to the fields of neuropsychiatry, rehabilitation, and respiratory medicine^{1–5}.

In this issue of *Anesthesiology*, two papers bring new information on why the concept of muscle activity is also relevant to lung biochemistry and regional function. Güldner et al.⁶ and Bruells et al.⁷ provide important experimental data on the relationship between the dose of diaphragmatic activity (spontaneous contribution to breathing during mechanical ventilation) and the resulting response in terms of lung mechanical stress, gas exchange, and markers of muscle deconditioning.

As the main respiratory muscle, the diaphragm contributes 72% for tidal breathing⁸ and its role in respiratory mechanics and gas exchange goes well beyond this global number. One of the reasons is its curvature during spontaneous breathing in the supine position, which facilitates expansion of dependent lung regions⁹, optimizes the regional distribution of lung ventilation, and prevents loss of dependent lung aeration and increase in shunt observed when muscle paralysis is produced¹⁰.

Accordingly, modes of ventilation proposed since the 1970s tried to explore those advantages in patients with acute respiratory failure. The beneficial effects of maintaining continuous spontaneous breathing during mechanical ventilation of patients with acute

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respiratory failure have been described by Putensen and coworkers in two well-designed studies^{11,12}. However, in patients with severe respiratory failure, barriers to spontaneous breathing during mechanical ventilation including patient-ventilator asynchrony, high oxygen consumption of the respiratory pump muscles, and the risk of barotrauma, have hindered a clear determination of the value of spontaneous breathing during mechanical ventilation.

Both, positive and negative (spontaneous) pressure ventilation can create harmful stress and strain

In order to characterize ventilator-induced lung injury, it is important to consider the consequences of the mechanical forces acting in the lung parenchyma. The fundamental physical concepts are those of mechanical stress and strain. Stress can be understood as the force per unit of area across a surface within the material under study (e.g., lung tissue), and strain as the relative deformation of that material. Methods to strictly assess lung stress and strain acting on lung cells are currently not available. Consequently, surrogate measurements are used to estimate those quantities. For stress, the transpulmonary pressure, i.e., the difference between the airway pressure and the esophageal pressure is used as an estimate of pleural pressure. For strain, measurements of relative volume change are used - the ratio of the change in lung volume to the resting lung volume during a breathing cycle can be quantified by imaging techniques^{13,14}.

Both positive pressure mechanical ventilation and spontaneous breathing expose the lung to variable degrees of stress and strain, which result in lung injury¹⁵. High levels of negative pressure created by respiratory muscles (typically observed in patients with hypercarbic respiratory failure) may critically increase transpulmonary pressure resulting in an increased risk of barotrauma. Indeed, contrasting with reports on the beneficial effects of spontaneous breathing^{11,12}, Papazian et al. recently suggested that large doses of a neuromuscular blocking agent could benefit patients in the course of acute respiratory distress syndrome by improving patient-ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels. These authors also reported a lower incidence of new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele with administration of cisatracurium, demonstrating the risk of high activity of respiratory pump muscles. It is highly likely that lower transpulmonary pressures due to the use of cisatracurium were responsible for a portion of the reported benefit.

When spontaneous breathing activity is allowed during mechanical ventilation, the increase in transpulmonary pressure in dependent lung zones may lead to recruitment of atelectatic lung tissue and reduction in lung elastance. Gueldner et al. demonstrate² that such improvement in dependent lung aeration is even associated with a reduction in transpulmonary pressure when spontaneous breathing represents a larger percentage of total ventilation with a biphasic positive airway pressure ventilation/airway pressure-release ventilation mode. The resulting increase in end-expiratory lung volumes resulted in a reduction in the ratio of regional inspired lung volume to end-expired lung volume, their surrogate measure of strain. Using imaging methods, the authors additionally established that the consequent oxygenation benefit was likely more associated with changes in aeration than in perfusion distribution. Overall, the findings imply that a larger contribution of spontaneous ventilation resulted in an improvement in the mechanical conditions in those injured lungs with reduction in lung stress and strain.

Ventilator-induced diaphragmatic dysfunction

Another mechanism of spontaneous breathing on the ventilator relates to protective effects on ventilator-induced diaphragmatic dysfunction (VIDD), which is defined as the loss of diaphragmatic force-generating capacity specifically related to the use of passive mechanical ventilation. It is characterized by structural damage to muscle fibers from oxidative stress, mitochondrial dysfunction and lipid accumulation as well as muscle atrophy¹⁶. Atrophy from prolonged inactivity heavily affects the most active skeletal muscles and respiratory muscles are susceptible to disuse atrophy given their constant high activity levels.

Respiratory depressants decrease the drive to the phrenic nerve and may lead to diaphragm atrophy. Recent data suggest that the time course as well as the mechanisms of immobilization-induced diaphragmatic weakness observed in preclinical models, including early disruption of the myofilament protein structure, translate to intensive care unit (ICU) patients^{16–18}. In a clinical scenario, high-dose opioids and propofol infusions do not allow for the appropriate diaphragmatic contractions required to avoid ventilator-induced diaphragmatic weakness that delays weaning from the ventilator. Bruells et al.⁷ suggest that high doses of anesthetic agents such as propofol are sufficient to abolish the beneficial effects of spontaneous breathing.

Neuromuscular blocking agents (NMBA) add significantly to the effects of immobilizing ventilator modes to worsen VIDD¹⁹, which is the reason why the long-term use of NMBA to facilitate mechanical ventilation should be avoided in critical care medicine. Of note, the harmful effects of NMBA resulting in VIDD occur while the drive of the phrenic nerve remains high (in contrast to the effects of centrally acting respiratory depressants such as propofol). This clinical scenario increases vulnerability to posttraumatic stress disorder²⁰, particularly if NMBAs are given in the absence of monitoring of cognitive function.

Limitations

Both studies were quite circumspect in acknowledging their limitations. Ultimately, the results will need further clarification of mechanisms in experimental models and confirmation in clinical investigations. Importantly, respiratory mechanics, distribution of lung ventilation and perfusion, and consequent gas exchange will vary in different presentations of clinical respiratory failure, which are not those described in the presented animal models. Those could lead to different results in terms of lung mechanical forces, gas exchange, and optimal range of spontaneous breathing contribution. Indeed, the relatively small differences in transpulmonary pressures, oxygenation, aeration and perfusion observed by Gueldner et al. at the different levels of spontaneous breathing during biphasic positive airway pressure ventilation/airway pressure-release ventilation suggest that different functional conditions could shift the optimal setpoint for that spontaneous breathing contribution in individual cases.

Clinical implications

Rapid recovery of spontaneous breathing should be the goal in patients requiring intubation and mechanical ventilation, and it is important to optimize the level of diaphragmatic contractions during mechanical ventilation (figure 1). Gueldner et al. and Bruells et al. works are consistent with the concept that NMBA or high doses of respiratory depressants that minimize or even abolish diaphragmatic activity during mechanical ventilation should be avoided due to the risk for VIDD, increased lung stress, and suboptimal gas exchange. On the other hand, excessive diaphragmatic contractions leading to increased work of breathing and increased lung stress should also be prevented.

In summary, the works of Güldner et al.⁶ and Bruells et al.⁷ support the view that management strategies allowing for diaphragmatic exercise through an increase in spontaneous breathing could allow for improved respiratory mechanics, gas exchange, and diaphragmatic function and help decrease the incidence of respiratory muscle dysfunction in the ICU. They point toward an approach of judicious use of respiratory depressant anesthetics and neuromuscular blocking agents, and ventilation modes that allow for spontaneous breathing or noninvasive ventilation whenever possible.

One of Hippocrates' heuristics was that "things which can be done well or properly should all be done properly" (On Regimen in Acute Diseases, 400 BCE). As far as mechanical ventilation in the ICU is concerned, we agree with his statement that "If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health." (Regimen Book 1, 2).

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Figure 1.

Effects of the different contribution of spontaneous breathing on the ventilator on different factors influencing the recovery from respiratory failure. Increasing levels of ventilatory support achieved with neuromuscular blockade, anesthetics, and ventilator settings, suppress diaphragmatic contractions, leading to ventilator-induced diaphragmatic dysfunction, and increased mechanical stress in the lungs. Among the several mechanisms leading to ventilator-induced lung injury present in this condition, those associated with low-volume lung injury and increased lung stress are presented by Gueldner et al⁶.

In contrast, minimal or no ventilator support in severe respiratory failure leads to excessive diaphragmatic contractions that require a high oxygen delivery resulting from the increased work of breathing. In addition, excessive spontaneous-breathing efforts with increased negative pleural pressures may lead to undesirably high levels of transpulmonary pressures and expose the patient to increased risk of barotrauma and volutrauma.

The green region represents the mid-path, that is, optimized diaphragmatic contractions that provide the ideal environment for recovery from respiratory failure.