

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

Evangelia Akoumianaki, Katerina Vaporidi, and Dimitris Georgopoulos

Intensive Care Medicine Department, University Hospital of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece

ORCID IDs: 0000-0001-6108-8200 (E.A.); 0000-0002-7766-8688 (K.V.); 0000-0003-3689-9014 (D.G.).

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 P_{aCO_2}** . The mechanisms of this **insensitivity of respiratory rate** and the

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Correspondence and request for reprints should be addressed to Dimitris Georgopoulos, M.D., Ph.D., Intensive Care Medicine Department, University Hospital of Heraklion, Medical School, University of Crete, Stavrakia, 71110, Heraklion, Crete, Greece. E-mail: georgopd@uoc.gr.

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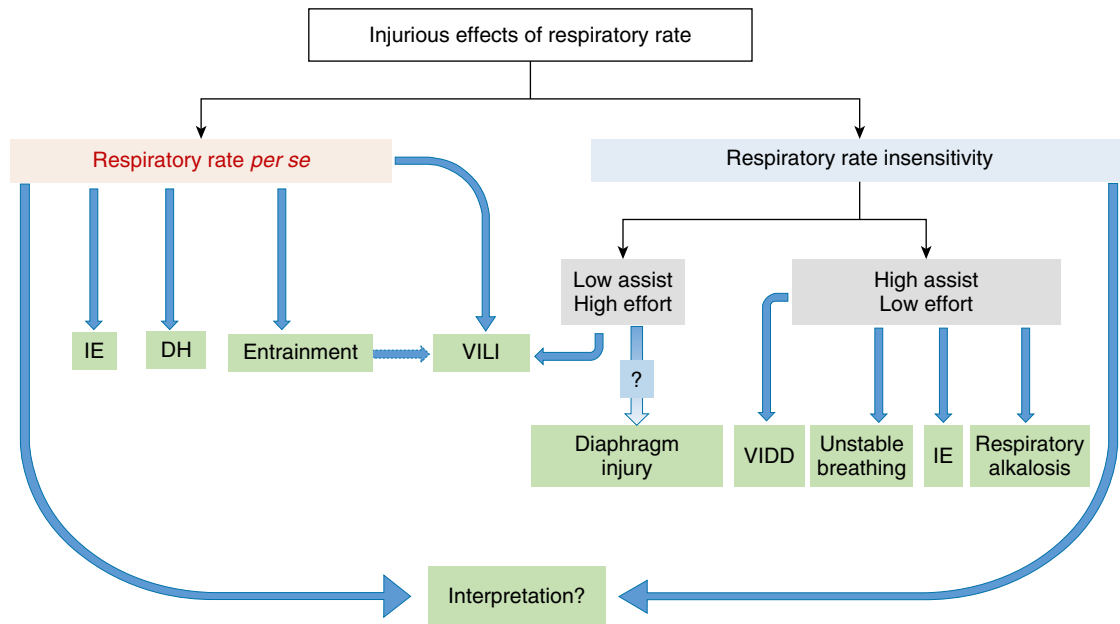


Figure 1. The main injurious effects of respiratory rate. Both the respiratory rate *per se* and the respiratory rate insensitivity may result, through multiple pathways, in ventilator-induced lung injury (VILI) and may be falsely interpreted with several adverse consequences for the patient. Respiratory rate insensitivity is related to inability of respiratory rate to control 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

3. Conrad SA, Zhang S, Arnold TC, Scott LK, Carden DL. Protective effects of low respiratory frequency in experimental ventilator-associated lung injury. *Crit Care Med* 2005;33:835–840.
4. Hotchkiss JR Jr, Blanch L, Murias G, Adams AB, Olson DA, Wangenstein OD, et al. Effects of decreased respiratory frequency on ventilator-induced lung injury. *Am J Respir Crit Care Med* 2000;161:463–468.
5. Hammerschmidt S, Kuhn H, Grasenack T, Gessner C, Wirtz H. Apoptosis and necrosis induced by cyclic mechanical stretching in alveolar type II cells. *Am J Respir Cell Mol Biol* 2004;30:396–402.
6. Tschumperlin DJ, Oswari J, Margulies AS. Deformation-induced injury of alveolar epithelial cells: effect of frequency, duration, and amplitude. *Am J Respir Crit Care Med* 2000;162:357–362.
7. Vaporidi K, Voloudakis G, Priniannakis G, Kondili E, Koutsopoulos A, Tsatsanis C, et al. Effects of respiratory rate on ventilator-induced lung injury at a constant PaCO₂ in a mouse model of normal lung. *Crit Care Med* 2008;36:1277–1283.
8. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, et al. Mechanical power and development of ventilator-induced lung injury. *Anesthesiology* 2016;124:1100–1108.
9. Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, et al.; LUNG SAFE Investigators and the ESICM Trials Group. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med* 2016;42:1865–1876.
10. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al.; LUNG SAFE Investigators; ESICM Trials Group. Noninvasive ventilation of patients with acute respiratory distress syndrome: insights from the LUNG SAFE Study. *Am J Respir Crit Care Med* 2017;195:67–77.
11. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa ELV, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420–1427.
12. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, et al. Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest* 2013;143:927–938.
13. Simon PM, Zurub AS, Wies WM, Leiter JC, Hubmayr RD. Entrainment of respiration in humans by periodic lung inflations: effect of state and CO₂. *Am J Respir Crit Care Med* 1999;160:950–960.
14. Yoshida T, Nakamura MAM, Morais CCA, Amato MBP, Kavanagh BP. Reverse triggering causes an injurious inflation pattern during mechanical ventilation. *Am J Respir Crit Care Med* 2018;198:1096–1099.
15. Kondili E, Priniannakis G, Georgopoulos D. Patient-ventilator interaction. *Br J Anaesth* 2003;91:106–119.
16. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis* 1987;136:872–879.
17. Laghi F, Segal J, Choe WK, Tobin MJ. Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1365–1370.
18. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis* 1992;146:607–615.
19. de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, et al. ARDSNet lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2002;165:1271–1274.
20. Vieillard-Baron A, Prin S, Augarde R, Desfonds P, Page B, Beauchet A, et al. Increasing respiratory rate to improve CO₂ clearance during mechanical ventilation is not a panacea in acute respiratory failure. *Crit Care Med* 2002;30:1407–1412.
21. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006;32:1515–1522.
22. Gosselin LE, Burton H. Impact of initial muscle length on force deficit following lengthening contractions in mammalian skeletal muscle. *Muscle Nerve* 2002;25:822–827.
23. Watchko JF, Johnson BD, Gosselin LE, Prakash YS, Sieck GC. Age-related differences in diaphragm muscle injury after lengthening activations. *J Appl Physiol (1985)* 1994;77:2125–2133.
24. Blanch L, Villagra A, Sales B, Montanya J, Lucangelo U, Luján M, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;41:633–641.
25. Vaporidi K, Babalis D, Chytas A, Lilitsis E, Kondili E, Amargianitakis V, et al. Clusters of ineffective efforts during mechanical ventilation: impact on outcome. *Intensive Care Med* 2017;43:184–191.
26. Rolland-Debord C, Bureau C, Poitou T, Belin L, Clavel M, Perbet S, et al. Prevalence and prognosis impact of patient-ventilator asynchrony in early phase of weaning according to two detection methods. *Anesthesiology* 2017;127:989–997.
27. Esteban A, Alía I, Gordo F, Fernández R, Solsona JF, Vallverdú I, et al.; Spanish Lung Failure Collaborative Group. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. *Am J Respir Crit Care Med* 1997;156:459–465.
28. Esteban A, Alía I, Tobin MJ, Gil A, Gordo F, Vallverdú I, et al.; Spanish Lung Failure Collaborative Group. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999;159:512–518.
29. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med* 1991;324:1445–1450.
30. Marantz S, Patrick W, Webster K, Roberts D, Oppenheimer L, Younes M. Response of ventilator-dependent patients to different levels of proportional assist. *J Appl Physiol (1985)* 1996;80:397–403.
31. Giannouli E, Webster K, Roberts D, Younes M. Response of ventilator-dependent patients to different levels of pressure support and proportional assist. *Am J Respir Crit Care Med* 1999;159:1716–1725.
32. Jammes Y, Auran Y, Gouvermet J, Delpierre S, Grimaud C. The ventilatory pattern of conscious man according to age and morphology. *Bull Eur Physiopathol Respir* 1979;15:527–540.
33. Jardin F, Vieillard-Baron A. Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings. *Intensive Care Med* 2003;29:1426–1434.
34. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med* 2002;347:43–53.
35. Georgopoulos D, Mitrouska I, Bshouty Z, Webster K, Patakas D, Younes M. Respiratory response to CO₂ during pressure-support ventilation in conscious normal humans. *Am J Respir Crit Care Med* 1997;156:146–154.
36. Georgopoulos D, Mitrouska I, Webster K, Bshouty Z, Younes M. Effects of inspiratory muscle unloading on the response of respiratory motor output to CO₂. *Am J Respir Crit Care Med* 1997;155:2000–2009.
37. Mitrouska J, Xirouchaki N, Patakas D, Siafakas N, Georgopoulos D. Effects of chemical feedback on respiratory motor and ventilatory output during different modes of assisted mechanical ventilation. *Eur Respir J* 1999;13:873–882.
38. Xirouchaki N, Kondili E, Mitrouska I, Siafakas N, Georgopoulos D. Response of respiratory motor output to varying pressure in mechanically ventilated patients. *Eur Respir J* 1999;14:508–516.
39. Meric H, Calabrese P, Pradon D, Lejaille M, Lofaso F, Terzi N. Physiological comparison of breathing patterns with neurally adjusted ventilatory assist (NAVA) and pressure-support ventilation to improve NAVA settings. *Respir Physiol Neurobiol* 2014;195:11–18.
40. Carreaux G, Córdoba-Izquierdo A, Lyazidi A, Heunks L, Thille AW, Brochard L. Comparison between neurally adjusted ventilatory assist and pressure support ventilation levels in terms of respiratory effort. *Crit Care Med* 2016;44:503–511.
41. Akoumianaki E, Priniannakis G, Kondili E, Malliotakis P, Georgopoulos D. Physiologic comparison of neurally adjusted ventilator assist, proportional assist and pressure support ventilation in critically ill patients. *Respir Physiol Neurobiol* 2014;203:82–89.
42. Kondili E, Priniannakis G, Anastasaki M, Georgopoulos D. Acute effects of ventilator settings on respiratory motor output in patients with acute lung injury. *Intensive Care Med* 2001;27:1147–1157.
43. Viale JP, Duperret S, Mahul P, Delafosse B, Delpuech C, Weismann D, et al. Time course evolution of ventilatory responses to inspiratory unloading in patients. *Am J Respir Crit Care Med* 1998;157:428–434.

44. Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, *et al*. Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001;164:419–424.
45. Brochard L, Harf A, Lorino H, Lemaire F. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am Rev Respir Dis* 1989;139:513–521.
46. Doorduyn J, Nollet JL, Roesthuis LH, van Hees HWH, Brochard LJ, Sinderby CA, *et al*. Partial neuromuscular blockade during partial ventilatory support in sedated patients with high tidal volumes. *Am J Respir Crit Care Med* 2017;195:1033–1042.
47. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, *et al*. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med* 2012;38:796–803.
48. Georgopoulos D. Effects of mechanical ventilation on control of breathing. In: Tobin MJ. Principles and practice of mechanical ventilation. 3rd ed. New York: McGraw-Hill; 2013. pp. 805–820.
49. Younes M. Patient-ventilator interaction with pressure-assisted modalities of ventilatory support. *Semin Respir Med* 1993;14:299–322.
50. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P. Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. *Intensive Care Med* 2008;34:2010–2018.
51. Schmidt M, Demoule A, Cracco C, Gharbi A, Fiamma MN, Straus C, *et al*. Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. *Anesthesiology* 2010;112:670–681.
52. Spahija J, de Marchie M, Albert M, Bellemare P, Delisle S, Beck J, *et al*. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med* 2010;38:518–526.
53. Terzi N, Pelieu I, Guittet L, Ramakers M, Seguin A, Daubin C, *et al*. Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. *Crit Care Med* 2010;38:1830–1837.
54. Hudson MB, Smuder AJ, Nelson WB, Bruells CS, Levine S, Powers SK. Both high level pressure support ventilation and controlled mechanical ventilation induce diaphragm dysfunction and atrophy. *Crit Care Med* 2012;40:1254–1260.
55. Goligher EC, Fan E, Herridge MS, Murray A, Vorona S, Brace D, *et al*. Evolution of diaphragm thickness during mechanical ventilation: impact of inspiratory effort. *Am J Respir Crit Care Med* 2015;192:1080–1088.
56. Zambon M, Beccaria P, Matsuno J, Gemma M, Frati E, Colombo S, *et al*. Mechanical ventilation and diaphragmatic atrophy in critically ill patients: an ultrasound study. *Crit Care Med* 2016;44:1347–1352.
57. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, *et al*. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med* 2013;188:213–219.
58. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, *et al*. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med* 2018;197:204–213.
59. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med* 2011;39:2627–2630.
60. Meza S, Mendez M, Ostrowski M, Younes M. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol* (1985) 1998;85:1929–1940.
61. Parthasarathy S, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med* 2002;166:1423–1429.
62. Fanfulla F, Delmastro M, Berardinelli A, Lupo ND, Nava S. Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease. *Am J Respir Crit Care Med* 2005;172:619–624.
63. Delaere S, Roeseler J, D’hoore W, Matte P, Reynaert M, Jolliet P, *et al*. Respiratory muscle workload in intubated, spontaneously breathing patients without COPD: pressure support vs proportional assist ventilation. *Intensive Care Med* 2003;29:949–954.
64. Bosma K, Ferreyra G, Ambrogio C, Pasero D, Mirabella L, Braghiroli A, *et al*. Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. *Crit Care Med* 2007;35:1048–1054.
65. Delisle S, Ouellet P, Bellemare P, Tétrault JP, Arsenault P. Sleep quality in mechanically ventilated patients: comparison between NAVA and PSV modes. *Ann Intensive Care* 2011;1:42.
66. Klimathianaki M, Kondili E, Alexopoulou C, Priniakis G, Georgopoulos D. Effect of propofol on breathing stability in adult ICU patients with brain damage. *Respir Physiol Neurobiol* 2010;171:232–238.
67. Trompeo AC, Vidi Y, Locane MD, Braghiroli A, Mascia L, Bosma K, *et al*. Sleep disturbances in the critically ill patients: role of delirium and sedative agents. *Minerva Anesthesiol* 2011;77:604–612.
68. Weinhouse GL, Schwab RJ, Watson PL, Patil N, Vaccaro B, Pandharipande P, *et al*. Bench-to-bedside review: delirium in ICU patients - importance of sleep deprivation. *Crit Care* 2009;13:234.
69. Parra O, Arboix A, Montserrat JM, Quintó L, Bechich S, García-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J* 2004;24:267–272.
70. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, *et al*. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999;99:1435–1440.
71. Hey EN, Lloyd BB, Cunningham DJ, Jukes MG, Bolton DP. Effects of various respiratory stimuli on the depth and frequency of breathing in man. *Respir Physiol* 1966;1:193–205.
72. Jiang TX, Reid WD, Belcastro A, Road JD. Load dependence of secondary diaphragm inflammation and injury after acute inspiratory loading. *Am J Respir Crit Care Med* 1998;157:230–236.
73. Orozco-Levi M, Lloreta J, Minguella J, Serrano S, Broquetas JM, Gea J. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1734–1739.
74. Vassilakopoulos T, Divangahi M, Rallis G, Kishta O, Petrof B, Comtois A, *et al*. Differential cytokine gene expression in the diaphragm in response to strenuous resistive breathing. *Am J Respir Crit Care Med* 2004;170:154–161.
75. Hillas G, Perlikos F, Toumpanakis D, Litsiou E, Nikolakopoulou S, Sagris K, *et al*. Controlled mechanical ventilation attenuates the systemic inflammation of severe chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2016;193:696–698.
76. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. *Crit Care Med* 2012;40:1578–1585.
77. Magder SA, Lichtenstein S, Adelman AG. Effect of negative pleural pressure on left ventricular hemodynamics. *Am J Cardiol* 1983;52:588–593.