Prolonged Mechanical Ventilation: Outcomes and Management

Subjects: Critical Care Medicine

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Prolonged mechanical ventilation (PMV) is defined as successful extubation after more than three spontaneous breathing trials or taking more than 14 days. The pathophysiology of PMV includes the presence of an abnormal respiratory drive or ventilator-induced diaphragm dysfunction. Numerous studies have demonstrated that ventilator-induced diaphragm dysfunction is related to increases in in-hospital deaths, nosocomial pneumonia, oxidative stress, lung tissue hypoxia, ventilator dependence, and costs.

prolonged mechanical ventilation | reactive oxygen species | respiratory drive | ventilator-induced diaphragm dysfunction

1. Introduction

A percentage of critically ill patients experience chronic respiratory failure and require prolonged mechanical ventilation (PMV) [1]. PMV is defined as successful extubation after more than three spontaneous breathing trials or taking more than 14 days [1], although some studies have used different definitions, especially studies in the United Kingdom and Europe [2]. Approximately 5–13% of patients with acute respiratory failure require PMV, and a trend of increasing PMV exists worldwide [3].

Patients receiving PMV may experience complications, including limb muscle atrophy, impaired functional status, and diaphragm dysfunction [4]. Moreover, the basal respiratory drive levels may be altered in patients with PMV, depending on the pulmonary disease present and the cause of respiratory failure [5][6][7]. Brain stem lesions may impair the central and low respiratory drives, causing abnormal respiratory function, hypoventilation, or respiratory acidosis, any of which may lead to ventilator dependence [7].

2. Respiratory Drive

The brain stem responds to levels of O_2, CO_2, and pH in the blood and cerebrospinal fluid through chemoreceptive neurons and initiates automatic respiration [8]. Airway occlusion pressure (P0.1) or hypercapnic ventilatory response can be used to measure respiratory drive [5][7][9]. P0.1 is defined as the negative airway pressure generated during the first 100 ms of an occluded inspiration measured by a ventilator [9]. The hypercapnic challenge test is performed with the modified Read rebreathing method, and the hypercapnic challenge with CO_2 induces an increase in the ventilatory drive and the level of P0.1 recorded by bedside capnograph and

pneumotachograph [9]. The hypercapnic ventilatory response is used as a predictor of weaning outcomes in patients with short- or long-term use of MV; old age, comorbidities, and muscle weakness, which may lead to a low hypercapnic ventilatory response [7][10][11][12]. In patients receiving PMV with brainstem lesions (brain stem infarction, brain tumor, traumatic intracerebral hemorrhage), high P0.1 responses to a hypercapnic challenge are associated with higher rates of successful weaning from MV, and an increase in P0.1 of more than 6 cmH_2O after the hypercapnic challenge is a predictor of weaning success [7].

Mechanical power is the energy transferred to the respiratory system per unit of time, which is the product of respiratory rate, tidal volume, and the airway pressure during pressure-controlled ventilation [13][14]. Higher mechanical power is associated with ventilator-induced lung injury and worse clinical outcomes [15]. Mechanical power is a novel concept to guide mechanical ventilator adjustments for acute respiratory distress syndrome [16]. For patients with PMV, mechanical power may be a tool used as respiratory drive to assess ventilator weaning and needs further investigation.

3. Ventilator-Induced Diaphragm Dysfunction

The diaphragm is the primary skeletal muscle responsible for effective lung expansion [17]. The diaphragm is a thin, dome-shaped muscular and central membranous tendon structure that separates the thoracic and abdominal cavities. Under normal conditions, contraction of the diaphragm increases the internal height of the chest cavity and causes the inspiration of air. Relaxation of the diaphragm and the thoracic cage leads to expiration. The diaphragm strength is measured by the transdiaphragmatic pressure (Pdi) derived from the difference between the pressure in the stomach (gastric pressure, Pga) and the esophageal pressure (Pes, as an indicator of pleural pressure): Pdi = Pga − Pes. The gold standard in patients who cannot cooperate in the test is to calculate the Pdi via twitch magnetic stimulation of the phrenic nerves (Pdi,tw). Maximal inspiratory pressure (MIP) is recorded following a maximum inspiratory effort against an occluded airway [18][19][20]. PMV may induce the rapid debilitation of diaphragmatic strength and endurance and lead to a reliance on ICU ventilators or long-term facilities; Petrof and Vassilopoulos refer to this as ventilator-induced diaphragm dysfunction (VIDD) [21][22][23][24]. Demoule et al. revealed that approximately 80% of ICU patients receiving MV exhibit an altered pattern of ICU-acquired diaphragm weakness after the first use of MV [24]. Numerous studies have demonstrated that VIDD is associated with increases in in-hospital deaths, nosocomial pneumonia, oxidative stress, lung tissue hypoxia, ventilator dependence, and costs [18][19][24], suggesting that diaphragmatic weakness with a reduced capacity of the diaphragm to produce inspiratory pressure may be considered as an example of unacknowledged organ failure in patients with a critical illness. Respiratory muscle abnormalities in critically ill patients may arise from tissue hypoxia, abnormally high diaphragm activity, neuromyopathies, hypercapnic respiratory failure, sepsis, medications (sedatives, steroids, and neuromuscular blocking reagents), MV duration, and malnutrition [20][25]. Sepsis is linked to diaphragm dysfunction in more than half of the ICU patients with PMV [20][26]. Tissue hypoxia is frequently associated with inflammation in patients with sepsis, which is induced by several mechanisms, including microvascular hypoperfusion, microthrombi formation, and regional arteriolar vasoconstriction related to hypercoagulability and leucosequestration [20][26]. Previous animal and brain-dead human studies have revealed

that the onset of diaphragm injury was rapid, occurring within 6 to 18 h after MV and the magnitude of impairment of diaphragmatic contraction increased with the time spent on the ventilator [19][20][21][22]. Because of the high medical care expenses and poor prognosis associated with delayed extubation and a prolonged hospital stay of PMV patients, it is, therefore, an important objective to assist ventilator-dependent patients in early weaning from ventilators. Although the specific etiology of PMV is unclear, long-term use of MV may result in the rapid development of VIDD because of concurrent critical ill neuromyopathy, severe infection, excessive or low-pressure support, and patient-ventilator asynchrony [19][20][21][22]. The underlying pathophysiological mechanisms posited for the decrease in diaphragm muscle contractility and endurance are thought to result from elevated oxidative stress, muscle proteolysis (arising from ubiquitin–proteasome system activation, calpain, caspase-3, and the autophagy–lysosomal pathway), and mitochondrial injuries within the diaphragm muscle fibers [20][22]. **Figure 1** illustrates the signaling pathway implicated in VIDD development.

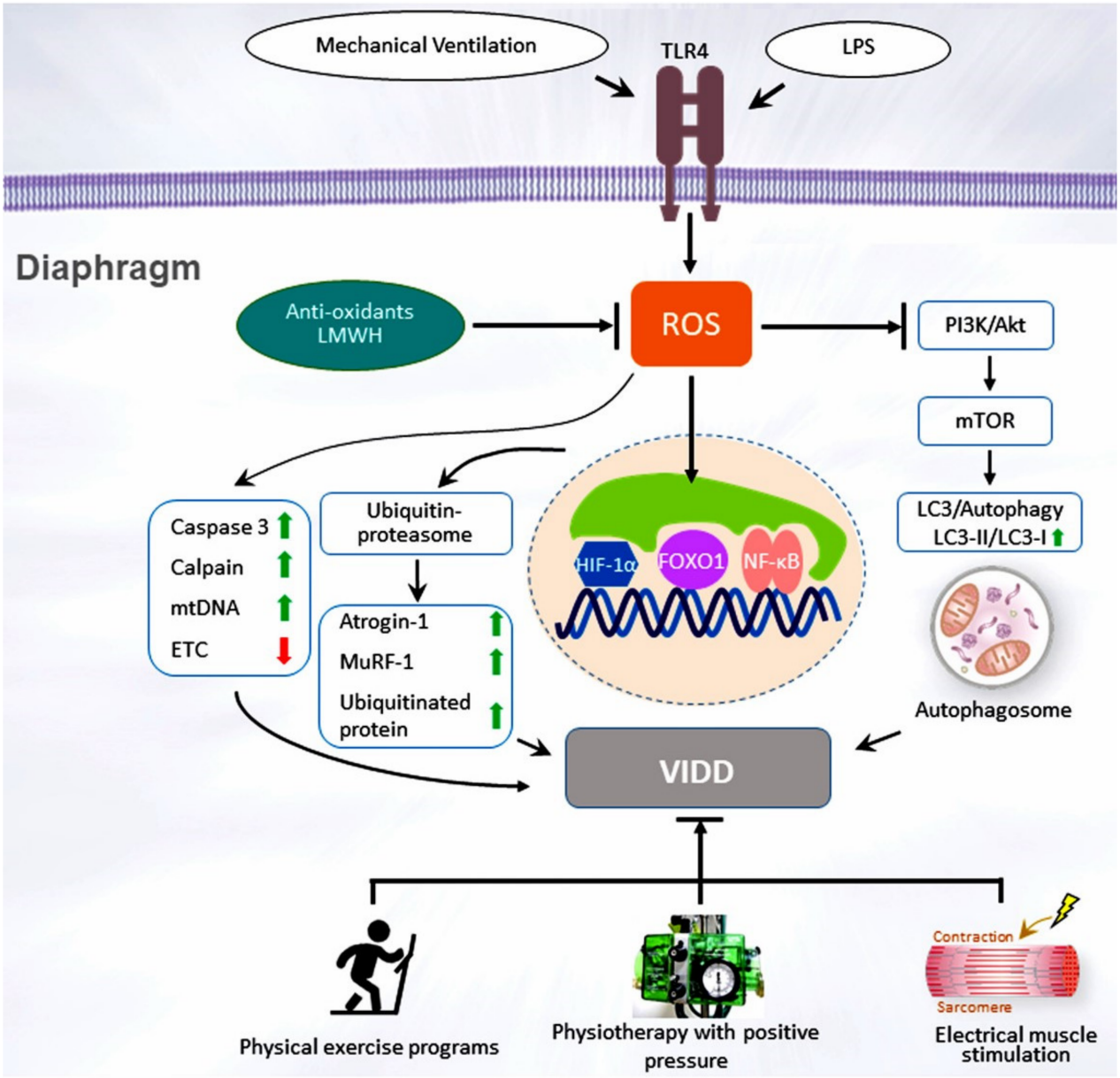

Figure 1. Schematic figure illustrating the signaling pathway implicated in VIDD development. Endotoxin-induced augmentation of mechanical stretch-mediated ROS generation and diaphragm injury are associated with diaphragm proteolysis, mitochondrial dysfunction, autophagy, as well as activation of the caspase-3, calpain, and ubiquitin–proteasome pathways. Diaphragm weakness can be attenuated by administering antioxidants, enoxaparin, or through partial support for mechanical ventilation or pulmonary rehabilitation. Akt = serine/threonine kinase/protein kinase B; ETC = electron transport chain; FoxO1 = Class O of forkhead box1; HIF = hypoxia-inducible factor; LC3 = light chain 3; LMWH = low-molecular-weight heparin; LPS = lipopolysaccharide; mtDNA = mitochondrial DNA; mTOR = mammalian target of rapamycin; MuRF-1 = muscle ring finger-1; NF-κB = nuclear factor κappa B; PI3-K = phosphoinositide 3-OH kinase; ROS = reactive oxygen species; TLR4 = toll-like receptor 4; VIDD = ventilator-induced diaphragm dysfunction.

Reactive oxygen species (ROS), which are produced in mitochondria, sarcoplasmic reticula, sarcolemma, and transverse tubes, are the major oxidants and upstream regulators of proteolysis and mitochondrial dysfunction in the diaphragm [27][28]. Caspase-3 is a cysteine protease-evoking skeletal muscle proteolysis, which is initiated by class O of forkhead box 1 (FoxO1) and the oxidative load in VIDD [29][30][31]. When proteolysis is initiated, caspase-3 can disassemble actin and myosin complexes from the myofibrillar lattice and trigger the release of dissociated myofibrillar proteins which are susceptible to degeneration through the ubiquitin–proteasome system. Calpains are reported to be responsible for the occurrence of VIDD, and their primary function is to support myofibrillar protein turnover by releasing sarcomeric proteins for degradation by caspase-3 [25][32].

An MV-induced oxidative load may impair diaphragm contractility, which is vital for increased proteolytic pathway expression [33][34][35]. The principal proteases in skeletal muscles comprise the ubiquitin–proteasome system and lysosomal enzymes [20][36]. The upregulation of the diaphragm muscle-specific ubiquitin E3 ligases, atrogin-1 and RING-finger proteins-1, is crucial for the proteolysis of monomeric myofibrillar proteins in the diaphragms of patients and animals receiving MV [35][36][37]. Mitochondria are major resources of diaphragmatic ROS and serve as an essential upstream modulator that mediates molecular pathways, promoting diaphragm muscle atrophy during endotoxemia or MV [38][39]. Reduced mitochondrial biogenesis and cytochrome-c oxidase enzyme activity, but increased mitochondrial DNA activity and lipid accumulation were identified in the diaphragm of brain-dead patients receiving MV [40]. The respiratory chain complexes II, III, and IV, and the ratio of state 3 to 4 (respiratory control ratio) are reduced in mitochondria isolated from rodent diaphragms [39][41]. Elevated levels of autophagosomes also occur in MV-mediated diaphragmatic inactivity, as reflected in an increase in the autophagic marker microtubule-associated protein light chain 3 [25][42][43].

Nuclear factor-κB (NF-κB) activation has been implicated in diaphragm injury and atrophy through measurements of the maximal twitch airway pressure after magnetic stimulation of the phrenic nerve of patients receiving MV [25][32][44]. An oxidative load triggered by mediators produced from inflammatory cells may react with redox-sensitive NF-κB, leading to the progression of coagulation and inflammation, which are related to the pathogenesis of VIDD or sepsis [45][46].

The current approach to reducing VIDD is to avoid controlled MV and the use of unnecessary neuromuscular blocking agents. Notably, low-molecular-weight heparin (LMWH) can reduce lipopolysaccharide-induced acute lung injury and systemic inflammation in animal models of endotoxemia [47][48].

4. Clinical Impact and Multiple Comorbidities

50% of patients (95% confidence interval [CI]: 47–53) were successfully weaned from MV, in-hospital mortality was 29% (95% CI: 26–32), and only 19% (95% CI: 16–24) of patients were discharged home [1]. Recognized factors of weaning failure are underlying respiratory diseases, previous ICU admissions, a high acute physiology and chronic health evaluation (APACHE II) score, and pneumonia [49][50][51][52]. Other factors related to unsuccessful weaning are elevated blood urea nitrogen levels, low Glasgow coma scale (GCS) scores, low serum albumin, and low maximal inspiratory pressure levels [53].

The prognosis for patients requiring PMV is poor. Among 29 studies of PMV, the pooled mortality rate was 62% at year 1 [1]. In a cohort study in the United States, 53.7% of patients requiring PMV were successfully weaned from ventilation at discharge, and 66.9% of these patients were still alive at year 1 [54]. However, the survival rate of patients with ventilator dependence was only 16.4% at post-discharge year 1 [54].

Comorbidities exacerbate diseases and have a severe impact on the outcomes of patients requiring PMV. Chronic obstructive pulmonary disease (COPD), cardiac disease, cerebral vascular or neuromuscular disease, end-stage renal disease, and malignancy are common comorbidities in patients requiring PMV [53][55][56][57][58].

Patients requiring PMV often experience long-term immobilization complications, including limb muscle atrophy, diaphragm dysfunction, pressure ulcers, joint contracture, and deconditioning [59][60]. Muscle-strengthening activities aim to progressively improve mobility and functional activity [61]. Pulmonary rehabilitation has been used to improve physical capacity and the quality of life in patients with chronic pulmonary diseases [62][63][64][65]. For patients requiring PMV, pulmonary rehabilitation could provide clinical benefits [61][66][67][68][69].

A comprehensive physical exercise program includes cardiopulmonary endurance exercises and peripheral muscle training. Upper and lower limb exercises include passive leg raising, weighted resistance, and stationary cycle ergometry training [61][70][71]. Respiratory muscle training consists of placing a sandbag on the abdomen during breathing, using a threshold device, or performing diaphragmatic breathing control [61][69][70][71][72][73][74]. The goal is for the patient to increase their mobility and functional activity and gradually recover from being bedridden to sitting, standing, and walking [67][70][73][74]. The benefits of physical exercise programs for patients requiring PMV include functional improvement, increased weaning rates, shorter duration of hospitalization, and reduced mortality [67][70][73][74]. Notably, Dong et al. showed that early rehabilitation training lessened the diaphragm dysfunction during ventilator use, increased weaning rates from the ventilator, and shortened the intubation duration in patients with MV in the ICU [70].

In patients requiring PMV, immobility and long-term ventilator use result in complications, such as the atrophy of respiratory muscles, decreased lung volume, and atelectasis [4]. When performing rehabilitation exercises, patients requiring PMV may experience respiratory muscle fatigue and intolerance to exercise because of the increased ventilatory demand [66]. Intermittent positive pressure breathing (IPPB) can increase the delivery of inspiratory positive pressure to the airway to achieve homogeneous gas distribution, recruit collapsed alveoli, and facilitate lung expansion [75]. During the weaning process, IPPB and positive end-expiratory pressure (PEEP) may increase lung volume and reduce the work of breathing during the expiratory phase, thus helping patients requiring PMV to tolerate the rehabilitation program [76].

Electrical muscle stimulation triggers muscle contraction and could be used to recover muscle atrophy and improve muscle strength after prolonged bed rest [77][78][79][80]. The majority of patients requiring PMV have increased muscle catabolism and decreased muscle mass synthesis after prolonged bed rest, particularly in the lower limbs [81][82].

Malnutrition is common in PMV patients and associated with poor outcomes, including difficult wound healing, nosocomial infections, and increased mortality [83]. Nutritional support is important, however, there is no standardized protocol regarding the administration route, type of nutrients and timing of nutrition support.

References

1. Damuth, E.; Mitchell, J.A.; Bartock, J.L.; Roberts, B.W.; Trzeciak, S. Long-term survival of critically ill patients treated with prolonged mechanical ventilation: A systematic review and meta-analysis. Lancet Respir. Med. 2015, 3, 544–553.
2. Rose, L.; McGinlay, M.; Amin, R.; Burns, K.E.; Connolly, B.; Hart, N.; Jouvet, P.; Katz, S.; Leasa, D.; Mawdsley, C.; et al. Variation in Definition of Prolonged Mechanical Ventilation. Respir. Care 2017, 62, 1324–1332.
3. Zilberberg, M.D.; de Wit, M.; Pirone, J.R.; Shorr, A.F. Growth in adult prolonged acute mechanical ventilation: Implications for healthcare delivery. Crit. Care Med. 2008, 36, 1451–1455.
4. Goligher, E.C.; Dres, M.; Fan, E.; Rubenfeld, G.D.; Scales, D.C.; Herridge, M.S.; Vorona, S.; Sklar, M.C.; Rittayamai, N.; Lanys, A.; et al. Mechanical Ventilation–induced Diaphragm Atrophy Strongly Impacts Clinical Outcomes. Am. J. Respir. Crit. Care Med. 2018, 197, 204–213.
5. Hilbert, G.; Gruson, D.; Portel, L.; Vargas, F.; Gbikpi-Benissan, G.; Cardinaud, J.P. Airway occlusion pressure at 0.1 s (P0.1) after extubation: An early indicator of postextubation hypercapnic respiratory insufficiency. Intensive Care Med. 1998, 24, 1277–1282.
6. Sato, R.; Hasegawa, D.; Hamahata, N.T.; Narala, S.; Nishida, K.; Takahashi, K.; Sempokuya, T.; Daoud, E.G. The predictive value of airway occlusion pressure at 100 msec (P0.1) on successful

weaning from mechanical ventilation: A systematic review and meta-analysis. J. Crit. Care 2021, 63, 124–132.

7. Wu, Y.-K.; Lee, C.-H.; Shia, B.-C.; Tsai, Y.-H.; Tsao, T.C.Y. Response to hypercapnic challenge is associated with successful weaning from prolonged mechanical ventilation due to brain stem lesions. Intensive Care Med. 2008, 35, 108–114.
8. Benarroch, E.E. Brainstem respiratory chemosensitivity: New insights and clinical implications. Neurology 2007, 68, 2140–2143.
9. Montgomery, A.B.; Holle, R.H.; Neagley, S.R.; Pierson, D.J.; Schoene, R.B. Prediction of successful ventilator weaning using airway occlusion pressure and hypercapnic challenge. Chest 1987, 91, 496–499.
10. De Jonghe, B.; Bastuji-Garin, S.; Durand, M.C.; Malissin, I.; Rodrigues, P.; Cerf, C.; Outin, H.; Sharshar, T.; Groupe de Reflexion et d'Etude des Neuromyopathies en Reanimation. Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit. Care Med. 2007, 35, 2007–2015.
11. Raurich, J.M.; Rialp, G.; Ibáñez, J.; Campillo, C.; Ayestarán, I.; Blanco, C. Hypercapnia test as a predictor of success in spontaneous breathing trials and extubation. Respir. Care 2008, 53, 1012–1018.
12. Lee, C.-S.; Chen, N.-H.; Chuang, L.-P.; Chang, C.-H.; Li, L.-F.; Lin, S.-W.; Huang, H.-Y. Hypercapnic Ventilatory Response in the Weaning of Patients with Prolonged Mechanical Ventilation. Can. Respir. J. 2017, 2017, 7381424.
13. Gattinoni, L.; Tonetti, T.; Cressoni, M.; Cadringher, P.; Herrmann, P.; Moerer, O.; Protti, A.; Gotti, M.; Chiurazzi, C.; Carlesso, E.; et al. Ventilator-related causes of lung injury: The mechanical power. Intensive Care Med. 2016, 42, 1567–1575.
14. Chiumello, D.; Gotti, M.; Guanziroli, M.; Formenti, P.; Umbrello, M.; Pasticci, I.; Mistraletti, G.; Busana, M. Bedside calculation of mechanical power during volume- and pressure-controlled mechanical ventilation. Crit. Care 2020, 24, 417.
15. Parhar, K.K.S.; Zjadewicz, K.; Soo, A.; Sutton, A.; Zjadewicz, M.; Doig, L.; Lam, C.; Ferland, A.; Niven, D.J.; Fiest, K.M.; et al. Epidemiology, Mechanical Power, and 3-Year Outcomes in Acute Respiratory Distress Syndrome Patients Using Standardized Screening. An Observational Cohort Study. Ann. Am. Thorac. Soc. 2019, 16, 1263–1272.
16. Paudel, R.; Trinkle, C.A.; Waters, C.M.; Robinson, L.E.; Cassity, E.; Sturgill, J.L.; Broaddus, R.; Morris, P.E. Mechanical Power: A New Concept in Mechanical Ventilation. Am. J. Med. Sci. 2021, 362, 537–545.
17. O'Leary, A.J.; Drummond, S.E.; Edge, D.; O'Halloran, K.D. Diaphragm Muscle Weakness Following Acute Sustained Hypoxic Stress in the Mouse Is Prevented by Pretreatment with N-

Acetyl Cysteine. Oxidative Med. Cell. Longev. 2018, 2018, 4805493.

18. Jung, B.; Moury, P.H.; Mahul, M.; De Jong, A.; Galia, F.; Prades, A.; Albaladejo, P.; Chanques, G.; Molinari, N.; Jaber, S. Diaphragmatic dysfunction in patients with ICU-acquired weakness and its impact on extubation failure. Intensive Care Med. 2016, 42, 853–861.
19. Dot, I.; Pérez-Teran, P.; Samper, M.-A.; Masclans, J.-R. Diaphragm Dysfunction in Mechanically Ventilated Patients. Arch. Bronconeumol. 2017, 53, 150–156.
20. Dres, M.; Goligher, E.; Heunks, L.M.A.; Brochard, L.J. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017, 43, 1441–1452.
21. Vassilakopoulos, T. Ventilator-induced diaphragm dysfunction: The clinical relevance of animal models. Intensive Care Med. 2007, 34, 7–16.
22. Li, L.-F.; Yu, C.-C.; Huang, H.-Y.; Wu, H.-P.; Chu, C.-M.; Huang, C.-Y.; Liu, P.-C.; Liu, Y.-Y. Suppression of Hypoxia-Inducible Factor 1α by Low-Molecular-Weight Heparin Mitigates Ventilation-Induced Diaphragm Dysfunction in a Murine Endotoxemia Model. Int. J. Mol. Sci. 2021, 22, 1702.
23. Peñuelas, O.; Keough, E.; López-Rodríguez, L.; Carriedo, D.; Gonçalves, G.; Barreiro, E.; Lorente, J. Ángel Ventilator-induced diaphragm dysfunction: Translational mechanisms lead to therapeutical alternatives in the critically ill. Intensive Care Med. Exp. 2019, 7, 48.
24. Demoule, A.; Molinari, N.; Jung, B.; Prodanovic, H.; Chanques, G.; Matecki, S.; Mayaux, J.; Similowski, T.; Jaber, S. Patterns of diaphragm function in critically ill patients receiving prolonged mechanical ventilation: A prospective longitudinal study. Ann. Intensive Care 2016, 6, 75.
25. Smuder, A.J.; Sollanek, K.J.; Nelson, W.B.; Min, K.; Talbert, E.E.; Kavazis, A.N.; Hudson, M.B.; Sandri, M.; Szeto, H.H.; Powers, S.K. Crosstalk between autophagy and oxidative stress regulates proteolysis in the diaphragm during mechanical ventilation. Free Radic. Biol. Med. 2018, 115, 179–190.
26. Saccheri, C.; Morawiec, E.; Delemazure, J.; Mayaux, J.; Dubé, B.-P.; Similowski, T.; Demoule, A.; Dres, M. ICU-acquired weakness, diaphragm dysfunction and long-term outcomes of critically ill patients. Ann. Intensive Care 2020, 10, 1.
27. Moroz, N.; Maes, K.; Leduc-Gaudet, J.-P.; Goldberg, P.; Petrof, B.J.; Mayaki, D.; Vassilakopoulos, T.; Rassier, D.; Gayan-Ramirez, G.; Hussain, S.N. Oxidants Regulated Diaphragm Proteolysis during Mechanical Ventilation in Rats. Anesthesiology 2019, 131, 605–618.
28. Duan, H.; Bai, H. Is Mitochondrial Oxidative Stress the Key Contributor to Diaphragm Atrophy and Dysfunction in Critically Ill Patients? Crit. Care Res. Pract. 2020, 2020, 8672939.
29. Hussain, S.N.A.; Mofarrahi, M.; Sigala, I.; Kim, H.C.; Vassilakopoulos, T.; Maltais, F.; Bellenis, I.; Chaturvedi, R.; Gottfried, S.B.; Metrakos, P.; et al. Mechanical Ventilation–induced Diaphragm

Disuse in Humans Triggers Autophagy. Am. J. Respir. Crit. Care Med. 2010, 182, 1377–1386.

30. Horn, A.G.; Davis, R.T., 3rd; Baumfalk, D.R.; Kunkel, O.N.; Bruells, C.S.; McCullough, D.J.; Opoku-Acheampong, A.B.; Poole, D.C.; Behnke, B.J. Impaired diaphragm resistance vessel vasodilation with prolonged mechanical ventilation. J. Appl. Physiol. 2019, 127, 423–431.
31. Smuder, A.J.; Sollanek, K.J.; Min, K.; Nelson, W.B.; Powers, S.K. Inhibition of forkhead boxO-specific transcription prevents mechanical ventilation-induced diaphragm dysfunction. Crit. Care Med. 2015, 43, e133–e142.
32. Hyatt, H.W.; Ozdemir, M.; Yoshihara, T.; Nguyen, B.L.; Deminice, R.; Powers, S.K. Calpains play an essential role in mechanical ventilation-induced diaphragmatic weakness and mitochondrial dysfunction. Redox Biol. 2021, 38, 101802.
33. Smuder, A.J.; Hudson, M.B.; Nelson, W.B.; Kavazis, A.N.; Powers, S.K. Nuclear factor-kappaB signaling contributes to mechanical ventilation-induced diaphragm weakness. Crit Care Med. 2012, 40, 927–934.
34. Qiu, Y.-W.; Chen, D.; Xu, M.-Y.; Li, S.-T. Beneficial effects of dantrolene on sepsis-induced diaphragmatic dysfunction are associated with downregulation of high-mobility group box 1 and calpain-caspase-3 proteolytic pathway. J. Surg. Res. 2016, 200, 637–647.
35. Files, D.C.; D'Alessio, F.R.; Johnston, L.F.; Kesari, P.; Aggarwal, N.R.; Garibaldi, B.T.; Mock, J.R.; Simmers, J.L.; DeGorordo, A.; Murdoch, J.; et al. A critical role for muscle ring finger-1 in acute lung injury-associated skeletal muscle wasting. Am. J. Respir. Crit. Care Med. 2012, 185, 825–834.
36. Moarbes, V.; Mayaki, D.; Huck, L.; Leblanc, P.; Vassilakopoulos, T.; Petrof, B.J.; Hussain, S.N.A. Differential regulation of myofibrillar proteins in skeletal muscles of septic mice. Physiol. Rep. 2019, 7, e14248.
37. Tang, H.; Shrager, J.B. The Signaling Network Resulting in Ventilator-induced Diaphragm Dysfunction. Am. J. Respir. Cell Mol. Biol. 2018, 59, 417–427.
38. Picard, M.; Azuelos, I.; Jung, B.; Giordano, C.; Matecki, S.; Hussain, S.N.A.; White, K.; Li, T.; Liang, F.; Benedetti, A.; et al. Mechanical ventilation triggers abnormal mitochondrial dynamics and morphology in the diaphragm. J. Appl. Physiol. 2015, 118, 1161–1171.
39. Dridi, H.; Yehya, M.; Barsotti, R.; Reiken, S.; Angebault, C.; Jung, B.; Jaber, S.; Marks, A.R.; Lacampagne, A.; Matecki, S. Mitochondrial oxidative stress induces leaky ryanodine receptor during mechanical ventilation. Free Radic. Biol. Med. 2020, 146, 383–391.
40. Tang, H.; Lee, M.; Budak, M.T.; Pietras, N.; Hittinger, S.; Vu, M.; Khuong, A.; Hoang, C.D.; Hussain, S.N.; Levine, S.; et al. Intrinsic apoptosis in mechanically ventilated human diaphragm: Linkage to a novel Fos/FoxO1/Stat3-Bim axis. FASEB J. 2011, 25, 2921–2936.

41. Supinski, G.S.; Schroder, E.A.; Callahan, L.A. Mitochondria and Critical Illness. Chest 2020, 157, 310–322.
42. Azuelos, I.; Jung, B.; Picard, M.; Liang, F.; Li, T.; Lemaire, C.; Giordano, C.; Hussain, S.; Petrof, B.J. Relationship between Autophagy and Ventilator-induced Diaphragmatic Dysfunction. Anesthesiology 2015, 122, 1349–1361.
43. Oliveira, T.S.; Santos, A.T.; Andrade, C.B.V.; Silva, J.D.; Blanco, N.; Rocha, N.N.; Woyames, J.; Silva, P.L.; Rocco, P.R.M.; da-Silva, W.S.; et al. Sepsis Disrupts Mitochondrial Function and Diaphragm Morphology. Front. Physiol. 2021, 12, 704044.
44. Demoule, A.; Divangahi, M.; Yahiaoui, L.; Danialou, G.; Gvozdic, D.; Labbe, K.; Bao, W.; Petrof, B.J. Endotoxin triggers nuclear factor-kappaB-dependent up-regulation of multiple proinflammatory genes in the diaphragm. Am. J. Respir. Crit. Care Med. 2006, 174, 646–653.
45. Huang, M.; Cai, S.; Su, J. The Pathogenesis of Sepsis and Potential Therapeutic Targets. Int. J. Mol. Sci. 2019, 20, 5376.
46. Li, L.F.; Liu, Y.Y.; Chen, N.H.; Chen, Y.H.; Huang, C.C.; Kao, K.C.; Chang, C.H.; Chuang, L.P.; Chiu, L.C. Attenuation of ventilation-induced diaphragm dysfunction through toll-like receptor 4 and nuclear factor-kappaB in a murine endotoxemia model. Lab Investig. 2018, 98, 1170–1183.
47. Ning, F.; Wang, X.; Shang, L.; Wang, T.; Lv, C.; Qi, Z.; Wu, D. Low molecular weight heparin may prevent acute lung injury induced by sepsis in rats. Gene 2015, 557, 88–91.
48. Luan, Z.-G.; Naranpurev, M.; Ma, X.-C. Treatment of Low Molecular Weight Heparin Inhibits Systemic Inflammation and Prevents Endotoxin-Induced Acute Lung Injury in Rats. Inflammation 2014, 37, 924–932.
49. Scheinhorn, D.J.; Chao, D.C.; Hassenpflug, M.S.; Gracey, D.R. Post-ICU weaning from mechanical ventilation: The role of long-term facilities. Chest 2001, 120, 482S–484S.
50. Schönhofer, B.; Euteneuer, S.; Nava, S.; Suchi, S.; Kohler, D. Survival of mechanically ventilated patients admitted to a specialised weaning centre. Intensive Care Med. 2002, 28, 908–916.
51. Bigatello, L.M.; Stelfox, H.T.; Berra, L.; Schmidt, U.; Gettings, E.M. Outcome of patients undergoing prolonged mechanical ventilation after critical illness. Crit. Care Med. 2007, 35, 2491–2497.
52. Mauri, T.; Pivi, S.; Bigatello, L.M. Prolonged mechanical ventilation after critical illness. Minerva Anestesiol. 2008, 74, 297–301.
53. Wu, Y.-K.; Kao, K.-C.; Hsu, K.-H.; Hsieh, M.-J.; Tsai, Y.-H. Predictors of successful weaning from prolonged mechanical ventilation in Taiwan. Respir. Med. 2009, 103, 1189–1195.
54. Jubran, A.; Grant, B.J.B.; Duffner, L.A.; Collins, E.G.; Lanuza, D.M.; Hoffman, L.A.; Tobin, M.J. Long-Term Outcome after Prolonged Mechanical Ventilation. A Long-Term Acute-Care Hospital

Study. Am. J. Respir. Crit. Care Med. 2019, 199, 1508–1516.

55. Kao, K.-C.; Hu, H.-C.; Fu, J.-Y.; Hsieh, M.-J.; Wu, Y.-K.; Chen, Y.-C.; Chen, Y.-H.; Huang, C.-C.; Yang, C.-T.; Tsai, Y.-H. Renal replacement therapy in prolonged mechanical ventilation patients with renal failure in Taiwan. J. Crit. Care 2011, 26, 600–607.
56. Lone, N.I.; Walsh, T.S. Prolonged mechanical ventilation in critically ill patients: Epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. Crit. Care 2011, 15, R102.
57. Shih, C.-Y.; Hung, M.-C.; Lu, H.-M.; Chen, L.; Huang, S.-J.; Wang, J.-D. Incidence, life expectancy and prognostic factors in cancer patients under prolonged mechanical ventilation: A nationwide analysis of 5,138 cases during 1998–2007. Crit. Care 2013, 17, R144.
58. Huang, H.-Y.; Lee, C.-S.; Chiu, T.-H.; Chen, H.H.; Chan, L.-Y.; Chang, C.-J.; Chang, S.-C.; Hu, H.-C.; Kao, K.-C.; Chen, N.-H.; et al. Clinical outcomes and prognostic factors for prolonged mechanical ventilation in patients with acute stroke and brain trauma. J. Formos. Med. Assoc. 2021, 121, 162–169.
59. Angus, D.C. Caring for the critically ill patient: Challenges and opportunities. JAMA 2007, 298, 456–458.
60. Brower, R.G. Consequences of bed rest. Crit. Care Med. 2009, 37, S422–S428.
61. Chen, Y.-H.; Lin, H.-L.; Hsiao, H.-F.; Chou, L.-T.; Kao, K.-C.; Huang, C.-C.; Tsai, Y.-H. Effects of Exercise Training on Pulmonary Mechanics and Functional Status in Patients with Prolonged Mechanical Ventilation. Respir. Care 2012, 57, 727–734.
62. Van Wetering, C.R.; Hoogendoorn, M.; Mol, S.J.; Rutten-van Molken, M.P.; Schols, A.M. Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: A randomised controlled trial. Thorax 2010, 65, 7–13.
63. Ho, S.-C.; Lin, H.-C.; Kuo, H.-P.; Chen, L.-F.; Sheng, T.-F.; Jao, W.-C.; Wang, C.-H.; Lee, K.-Y. Exercise training with negative pressure ventilation improves exercise capacity in patients with severe restrictive lung disease: A prospective controlled study. Respir. Res. 2013, 14, 22.
64. Huang, H.-Y.; Chou, P.-C.; Joa, W.-C.; Chen, L.-F.; Sheng, T.-F.; Lin, H.-C.; Yang, L.-Y.; Pan, Y.-B.; Chung, F.-T.; Wang, C.-H.; et al. Pulmonary rehabilitation coupled with negative pressure ventilation decreases decline in lung function, hospitalizations, and medical cost in COPD: A 5-year study. Medicine 2016, 95, e5119.
65. Huang, H.-Y.; Lo, C.-Y.; Yang, L.-Y.; Chung, F.-T.; Sheng, T.-F.; Lin, H.-C.; Lin, C.-W.; Huang, Y.-C.; Chang, C.-J.; Chung, K.F.; et al. Maintenance Negative Pressure Ventilation Improves Survival in COPD Patients with Exercise Desaturation. J. Clin. Med. 2019, 8, 562.

66. Chen, Y.-H.; Lin, H.-L.; Hsiao, H.-F.; Huang, C.-T.; Kao, K.-C.; Li, L.-F.; Huang, C.-C.; Tsai, Y.-H. Effects of an additional pressure support level on exercise duration in patients on prolonged mechanical ventilation. J. Formos. Med. Assoc. 2015, 114, 1204–1210.
67. Dunn, H.; Quinn, L.; Corbridge, S.J.; Eldeirawi, K.; Kapella, M.; Collins, E.G. Mobilization of prolonged mechanical ventilation patients: An integrative review. Heart Lung 2017, 46, 221–233.
68. Schreiber, A.F.; Ceriana, P.; Ambrosino, N.; Malovini, A.; Nava, S. Physiotherapy and Weaning From Prolonged Mechanical Ventilation. Respir. Care 2018, 64, 17–25.
69. Bissett, B.; Gosselink, R.; Van Haren, F.M.P. Respiratory Muscle Rehabilitation in Patients with Prolonged Mechanical Ventilation: A Targeted Approach. Crit. Care 2020, 24, 103.
70. Chen, S.; Su, C.-L.; Wu, Y.-T.; Wang, L.-Y.; Wu, C.-P.; Wu, H.-D.; Chiang, L.-L. Physical training is beneficial to functional status and survival in patients with prolonged mechanical ventilation. J. Formos. Med. Assoc. 2011, 110, 572–579.
71. Clini, E.M.; Crisafulli, E.; Degli Antoni, F.; Beneventi, C.; Trianni, L.; Costi, S.; Fabbri, L.M.; Nava, S. Functional Recovery Following Physical Training in Tracheotomized and Chronically Ventilated Patients. Respir. Care 2011, 56, 306–313.
72. Martin, U.J.; Hincapie, L.; Nimchuk, M.; Gaughan, J.; Criner, G.J. Impact of whole-body rehabilitation in patients receiving chronic mechanical ventilation. Crit. Care Med. 2005, 33, 2259–2265.
73. Chiang, L.-L.; Wang, L.-Y.; Wu, C.-P.; Wu, H.-D.; Wu, Y.-T. Effects of Physical Training on Functional Status in Patients with Prolonged Mechanical Ventilation. Phys. Ther. 2006, 86, 1271–1281.
74. Yang, P.-H.; Wang, C.-S.; Wang, Y.-C.; Yang, C.-J.; Hung, J.-Y.; Hwang, J.-J.; Wang, T.-H.; Chuang, I.-C.; Huang, M.-S. Outcome of Physical Therapy Intervention on Ventilator Weaning and Functional Status. Kaohsiung J. Med. Sci. 2010, 26, 366–372.
75. Handelsman, H. Intermittent positive pressure breathing (IPPB) therapy. Health Technol. Assess. Rep. 1991, 1, 1–9.
76. Chen, Y.-H.; Yeh, M.-C.; Hu, H.-C.; Lee, C.-S.; Li, L.-F.; Chen, N.-H.; Huang, C.-C.; Kao, K.-C. Effects of Lung Expansion Therapy on Lung Function in Patients with Prolonged Mechanical Ventilation. Can. Respir. J. 2016, 2016, 5624315.
77. Snyder-Mackler, L.; Delitto, A.; Bailey, S.L.; Stralka, S.W. Strength of the quadriceps femoris muscle and functional recovery after reconstruction of the anterior cruciate ligament. A prospective, randomized clinical trial of electrical stimulation. J. Bone Jt. Surg. 1995, 77, 1166–1173.

78. Sillen, M.J.H.; Speksnijder, C.M.; Eterman, R.A.; Janssen, P.P.; Wagers, S.S.; Wouters, E.F.M.; Uszko-Lencer, N.; Spruit, M.A. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: A systematic review of the English-language literature. Chest 2009, 136, 44–61.
79. Maffiuletti, N.A. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. Eur. J. Appl. Physiol. 2010, 110, 223–234.
80. Rodriguez, P.O.; Setten, M.; Maskin, L.P.; Bonelli, I.; Vidomlansky, S.R.; Attie, S.; Frosiani, S.L.; Kozima, S.; Valentini, R. Muscle weakness in septic patients requiring mechanical ventilation: Protective effect of transcutaneous neuromuscular electrical stimulation. J. Crit. Care. 2012, 27, 319.e1–319.e8.
81. Ferrando, A.A.; Lane, H.W.; Stuart, C.A.; Davis-Street, J.; Wolfe, R.R. Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. Am. J. Physiol. Content 1996, 270, 627–633.
82. Kortebein, P.; Ferrando, A.; Lombeida, J.; Wolfe, R.; Evans, W.J. Effect of 10 Days of Bed Rest on Skeletal Muscle in Healthy Older Adults. JAMA J. Am. Med. Assoc. 2007, 297, 1769–1774.
83. Ambrosino, N.; Vitacca, M. The patient needing prolonged mechanical ventilation: A narrative review. Multidiscip. Respir. Med. 2018, 13, 6.