

REVIEW



The physiological underpinnings of life-saving respiratory support

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Abstract

Treatment of respiratory failure has improved dramatically since the polio epidemic in the 1950s with the use of invasive techniques for respiratory support: mechanical ventilation and extracorporeal respiratory support. However, respiratory support is only a supportive therapy, designed to “buy time” while the disease causing respiratory failure abates. It ensures viable gas exchange and prevents cardiorespiratory collapse in the context of excessive loads. Because the use of invasive modalities of respiratory support is also associated with substantial harm, it remains the responsibility of the clinician to minimize such hazards. Direct iatrogenic consequences of mechanical ventilation include the risk to the lung (ventilator-induced lung injury) and the diaphragm (ventilator-induced diaphragm dysfunction and other forms of myotrauma). Adverse consequences on hemodynamics can also be significant. Indirect consequences (e.g., immobilization, sleep disruption) can have devastating long-term effects. Increasing awareness and understanding of these mechanisms of injury has led to a change in the philosophy of care with a shift from aiming to normalize gases toward minimizing harm. Lung (and more recently also diaphragm) protective ventilation strategies include the use of extracorporeal respiratory support when the risk of ventilation becomes excessive. This review provides an overview of the historical background of respiratory support, pathophysiology of respiratory failure and rationale for respiratory support, iatrogenic consequences from mechanical ventilation, specifics of the implementation of mechanical ventilation, and role of extracorporeal respiratory support. It highlights the need for appropriate monitoring to estimate risks and to individualize ventilation and sedation to provide safe respiratory support to each patient.

Keywords: Mechanical ventilation, Extracorporeal membrane oxygenation, Respiratory failure, Ventilator-induced lung injury, Myotrauma

Historical overview of respiratory support

The concept of respiratory support stretches back through history [1], but consistent assistance for human breathing using a machine only began in 1928 when Philip Drinker and Louis Agassiz Shaw Jr. invented a negative pressure ventilator for polio patients with respiratory muscle paralysis [2]. These devices were large, expensive, cumbersome for provision of nursing care, and provided no airway protection; they became widespread over the following decades but were infrequently

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used to care for patients without polio. During the same time-period, rudimentary positive pressure ventilators were invented for care of patients in the operating room. However, even throughout the 1940s, such machines were not in routine use, and were viewed as safe only for short-term care.

The Copenhagen polio epidemic provided the necessary demonstration that prolonged, positive pressure ventilation was a safe and effective means of respiratory support [3]. In a severe polio outbreak beginning in July 1952, hundreds of patients in Copenhagen and surrounding area needed respiratory support, but they were cared for at the infectious disease hospital which had only one tank respirator (iron lung) and 6 cuirass respirators. Out of necessity, they tracheostomized the patients and hand-ventilated them. The results were dramatic: mortality dropped from 87 to ~30%. Mechanical ventilators that could provide prolonged support for patients outside the operating room soon followed, and the first intensive care unit was created. It also did not take long for physicians to recognize the potential for this technology in patients with many different forms of respiratory failure. The stage was then set for 70 years of remarkable advancements in our understanding of respiratory physiology/pathophysiology, and improvements in ventilator technology and ventilatory strategies [4].

Pathophysiology of respiratory failure and rationale for respiratory support

General principles

Respiratory support in acute respiratory failure consists of techniques aimed at maintaining blood gases compatible with life by:

1. Modifying alveolar gas composition: fraction of inspired oxygen or FiO_2
2. Modifying end-expiratory lung volume: continuous or end-expiratory positive airway pressure (CPAP or PEEP respectively), and high-flow nasal cannula.
3. Substituting, partially or totally the ventilatory muscle function: non-invasive ventilation (NIV) and invasive mechanical ventilation (MV)
4. Substituting for lung function (extracorporeal devices)

In most cases, respiratory support is only a supportive therapy designed to “buy time” while the disease that causes respiratory failure abates. Therefore, the optimal respiratory support for a given patient at a given time is the one providing viable arterial blood gases (PaO_2 of 60–90 mmHg, $\text{PaCO}_2 < 60$ mmHg) and adequate oxygen delivery to the vital organs with minimal (ideally nil) adverse consequences (e.g., hemodynamic consequences,

Take-home message

Invasive mechanical ventilation and extracorporeal respiratory support are both life-saving and associated with substantial risks of harm. Understanding the pathophysiology, the acceptable trade-offs and carefully monitoring patient's physiological needs and responses can help individualizing sedation and ventilation to provide safe and effective respiratory support.

ventilation-induced lung injury (VILI) [5] and diaphragm dysfunction [6]). A rational approach for respiratory support must consider the fraction of physiological dead space and venous admixture, i.e., fraction of cardiac output flowing through gasless intra-pulmonary regions, or through a patent foramen ovale or bronchial-venous anastomoses, the mechanical status of the lung, i.e., lung volume and recruitability, the equation of motion of the respiratory system, and the potential iatrogenic harm (see Figs. 1, 2, 3).

The equation of motion describes the relationship between the total force applied to the respiratory system (P_{tot}) and its opposing forces (i.e., the elastic— P_{el} —and resistive pressures— P_{res}) (see Fig. 3). It helps the clinician understand the pressures measured and displayed by the ventilator and quantify the global work per breath or power of breathing per minute.

Oxygen administration

The simplest respiratory support is provided by increasing FiO_2 during spontaneous breathing. This support alone is often sufficient when the venous admixture fraction is lower than $\approx 20\%$, the lung mechanics are near normal and the necessary ventilation for CO_2 clearance is sustainable by unaided respiratory muscles, i.e., physiological dead space is modestly altered. Prolonged levels of very high FiO_2 can lead to pulmonary “oxygen toxicity” but the exact dose–response curve, or duration is unclear [7]: clinicians generally attempt to keep $\text{FiO}_2 < 60\text{--}70\%$. To accomplish this without escalating respiratory support usually requires a venous admixture $< \sim 30\%$. Administration of oxygen at high flow with active humidification through a nasal cannula provides a modest increase in positive end-expiratory pressure (4–8 cmH₂O), washout of CO_2 from the upper airways and is associated with decreased inspiratory effort in some patients [8].

CPAP/PEEP

Venous admixture may be decreased by CPAP sufficient to keep previously atelectatic units open and perfused. Such support may suffice if the lung volume returns to near-normal after recruitment, and if respiratory mechanics and dead space are only modestly altered so that the respiratory muscles can sustain adequate minute

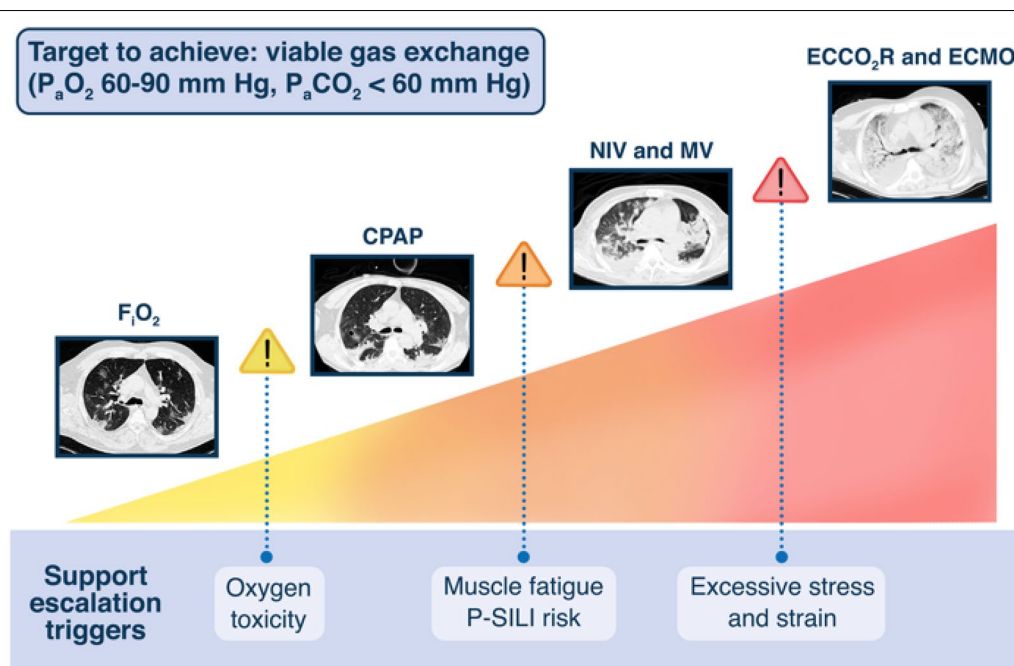


Fig. 1 Conceptual framework of the interaction between respiratory support techniques and physiological background. As shown, the same target requires different techniques depending on the physiological status of the lung. Representative computed tomography (CT) scans are shown. The consolidated/not aerated tissue is, from left to right, represents 5–12–34–63%. The triggers for escalating respiratory support are also indicated. The addition of positive pressure (CPAP) is intended to reduce atelectasis and therefore venous admixture and limit the risk of oxygen toxicity and further reabsorption atelectasis if the F_{iO_2} is close to 1. As the gas volume of the lung decreases (the lung becomes heavier and the compliance lower) the effort to move the lung increases and additional ventilatory support is necessary either non-invasively or invasively. Finally, with a very large venous admixture and refractory hypoxemia, extracorporeal support is the only viable option. PaO_2 arterial partial pressure of oxygen, $PaCO_2$ arterial partial pressure of carbon dioxide, F_{iO_2} inspiratory fraction of oxygen, CPAP continuous positive airway pressure, NIV non-invasive ventilation, MV mechanical ventilation, $ECCO_2R$ extracorporeal CO_2 removal, ECMO extracorporeal membrane lung oxygenation, P-SILI patient self-inflicted lung injury

ventilation, i.e., avoiding severe acidemia ($pH < 7.2$) without fatigue. However, spontaneous breathing may be harmful as discussed later. Most frequently PEEP is used in combination with some form of positive inspiratory pressure.

Mechanical ventilation

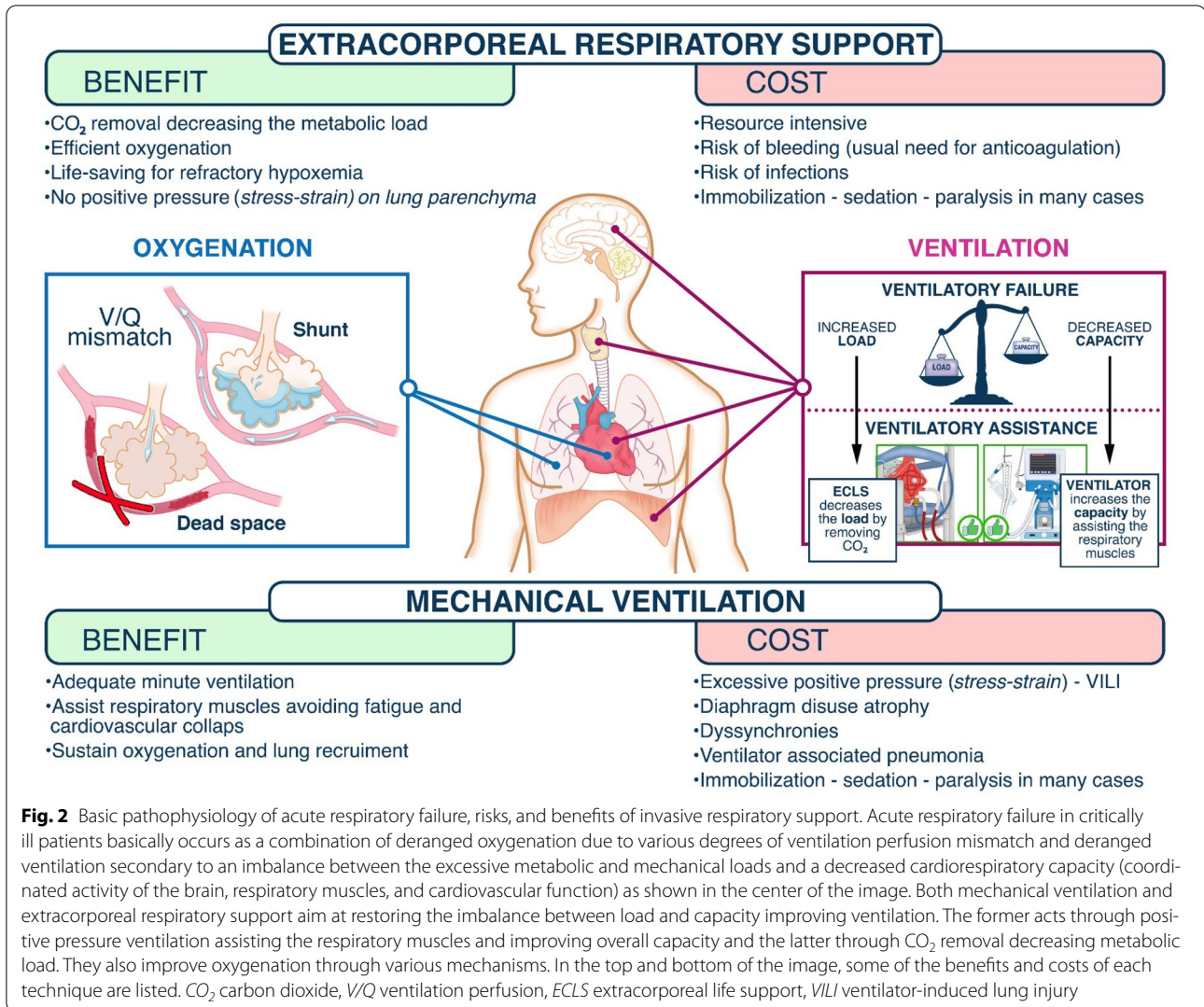
From a physiological standpoint, mechanical ventilation substitutes partially or totally for respiratory muscle function decreasing the oxygen cost of breathing to prevent a catastrophic event, while attempting to assure safe F_{iO_2} and airway pressures.

The ventilatory support is primarily applied when the lung volume is consistently reduced, atelectatic/consolidated units are extensive, and both venous admixture and physiological dead space fractions exceed $\approx 30\%$. In these conditions, to maintain adequate gas-exchange, minute ventilation must be higher than normal (Ventilatory Ratio ≥ 1.5 [9]) and oxygen cost of breathing might become excessive resulting in respiratory muscle fatigue and collapse as discussed later.

Timing for invasive mechanical ventilation

The decision to intubate a patient with respiratory failure is largely clinical, with no widely agreed upon objective criteria to guide decision-making. The most common trigger for intubation is “respiratory distress” which is determined by severe dyspnea and an estimated high work of breathing (i.e., excessive respiratory muscle phasic contraction including “accessory” muscles) due to increased ventilatory demands and altered respiratory mechanics. Respiratory distress can be associated with systemic consequences that all accelerate the indication for invasive ventilation, such as decreased level of consciousness, hemodynamic instability, and even cardiac arrest.

Importantly, in the case of shock, mechanical ventilation by decreasing the oxygen cost of breathing can effectively reduce lactate production and prevent death due to respiratory muscle fatigue [10]. Therefore, a major cardiovascular stress in patients with respiratory distress, accelerate the “indication” for invasive MV.

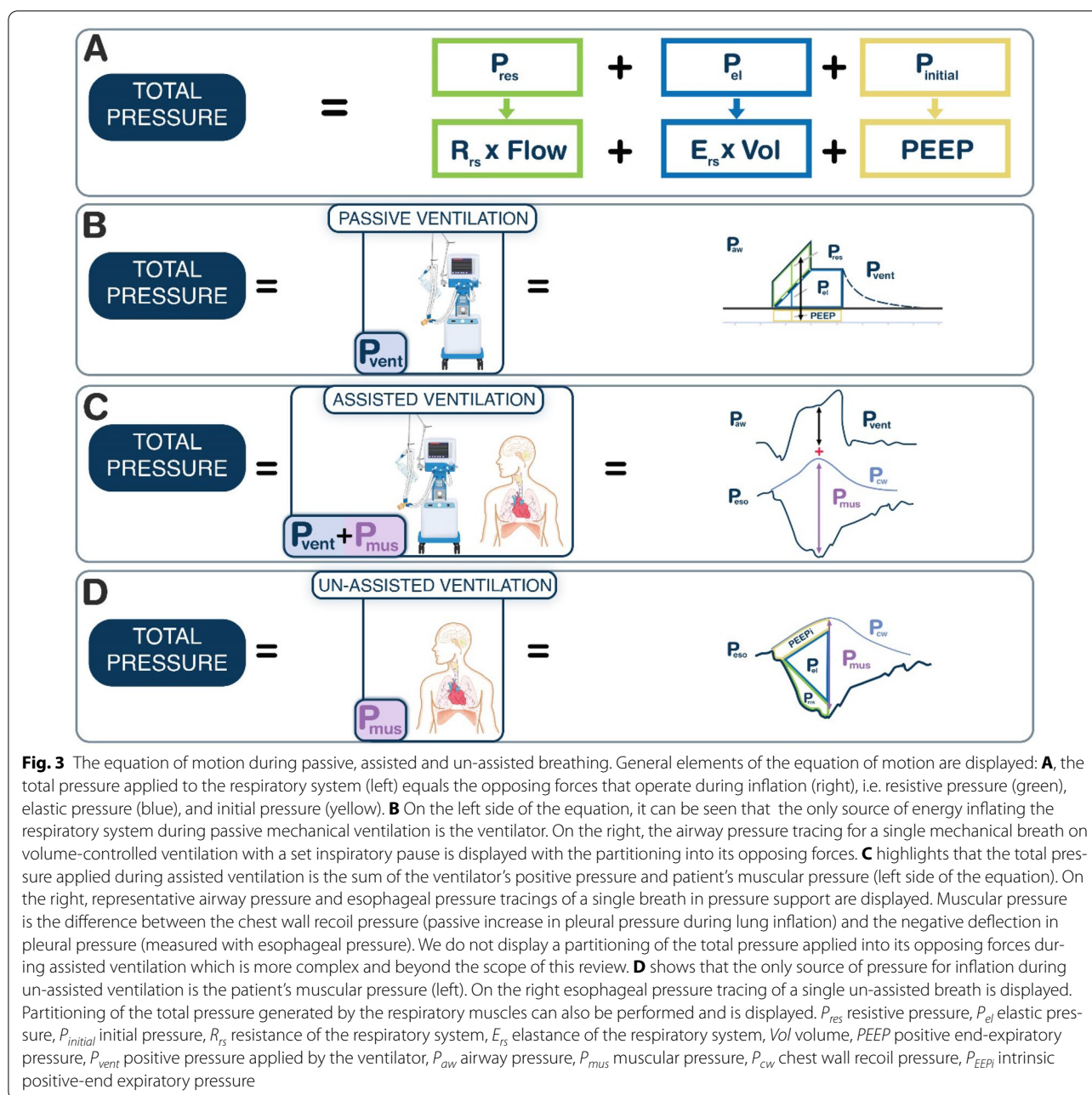


Another frequent trigger for intubation is deteriorating gas exchange. Although increasing hypercapnia and respiratory acidosis, often associated with a decreased level of consciousness, clearly indicate that the ventilatory system is failing, hypoxemia is more complex to interpret, making the decision to intubate (or not) more difficult. A good example of this difficulty is the perceived “excessive” use of mechanical ventilation during the early coronavirus disease 2019 (COVID-19) pandemic when the decision to intubate was based primarily on oxygenation levels [11].

One concept that has gained traction over the past few years is the use of invasive MV to prevent patient unintentional self-inflicted lung injury (P-SILI) in patients with very high respiratory effort [12]. However, there is a paucity of evidence to confirm this approach, and the lack of an explicit biomarker for P-SILI makes it difficult to standardize its clinical use.

Change in the philosophy of care

Over the past half century, there has been a change in philosophy with respect to MV. In the 1960s and ‘70 s, the major goal of MV was to maintain near-normal blood gases, with little regard to iatrogenic consequences of the ventilatory management. Therefore, tidal volumes were not uncommonly on the order of 10–20 ml/kg of actual body weight, with correspondingly high airway distending pressures [13]. The recognition that the forces on the lung generated during ventilation can cause harm (e.g., VILI [5], and severe hemodynamic consequences), and that respiratory acidosis may be reasonably well tolerated [14], led to a change in goals and philosophy. It became more important to minimize harm (see below) using lung protective strategies than to always have normal blood gases. This change in philosophy has been evident



not only in ventilatory strategy, but also in the increased use of extracorporeal lung support in many patients (see below), with the concept that the side effects of extracorporeal life support (ECLS) may be less injurious than with mechanical ventilation, especially in patients with extremely injured lungs.

Iatrogenic consequences of mechanical ventilation

General principles

The possible direct harm of mechanical ventilation on the lungs arises largely from the conflict between high minute ventilation/PEEP and the “baby-lung” size and the potential hemodynamic compromise due to excessive pleural and alveolar pressures [5]. VILI primarily depends on excessive dynamic lung strain, the volume deformation of the lung, (i.e., the ratio of end-inspiratory inflated volume including that due to PEEP relative to

the Functional Residual Capacity) and lung stress (i.e., transpulmonary pressure applied to the lung); and to a lesser extent on the respiratory rate. These factors determine the energy applied by the ventilator on the lung parenchyma as represented by the power equation [15].

Normal strain is approximately 0.25 while, in acute lung injury, it may easily exceed 1.0 leading to baro- and volutrauma [16]. Additionally, repetitive small airways and alveoli opening and closure during tidal breathing can lead to atelectrauma and bronchiolotrauma [17], two additionally recognized mechanisms of VILI. PEEP represents a two-sided coin, on the one hand it keeps the lung and small airways open but, conversely, it increases stress and strain of open pulmonary units. Importantly, the harm of mechanical ventilation concerns only the aerated “baby-lung”, where stress and strain are applied [18]. Therefore, when lung volume is severely reduced, even low tidal volumes may cause intolerable stress and strain, particularly if associated with higher PEEP. In fact, higher driving pressure (plateau pressure minus PEEP) representing the ratio between tidal volume and the “size” of the “baby-lung” (estimated by the respiratory system’s compliance) has consistently been shown to be the strongest predictor of poor outcome in patients with acute respiratory failure [19].

Additionally, in patients with already hyperinflated lungs, e.g., chronic obstructive pulmonary disease, the main issue is avoidance or minimization of hyperinflation and auto or intrinsic PEEP [20].

Over the past decade, there has been a resurgence of interest in the impact of invasive MV on diaphragm function, both in terms of atrophy due to underuse, and diaphragm injury due to excessive use [21].

Deleterious effects of mechanical ventilation on hemodynamics can be significant. Excessive stress resulting in alveolar overdistention and increased pulmonary vascular resistance can lead to right ventricular failure and shock (i.e., acute cor pulmonale). Additionally, increased intrathoracic pressure in the context of relatively low intravascular volume can decrease cardiac output by primarily decreasing ventricular preload. These can lead to a lower cardiac output and oxygen delivery despite relatively adequate oxygenation and, therefore, need to be systematically considered.

Finally, there are other potential adverse short- and long-term consequences related to the need for sedation and opioids, relative immobility, sleep disruption [22], or distressing experiences during MV. For example, post-traumatic stress disorder was recently found to occur more frequently in patients that experienced dyspnea while receiving invasive MV [23].

Patient–ventilator interactions

There are different ways by which MV can be provided and often patients transition from one condition to another over the course of their stay in intensive care unit (ICU). Initially, passive (controlled) mechanical ventilation is frequently used, where the ventilator is the only energy source inflating the respiratory system at a fixed rate. Traditionally, when the patient’s condition improves, sedation is decreased allowing for respiratory muscle activity, and lung inflation results from the sum of positive pressure from ventilator and negative pressure generated by the patient’s respiratory muscles. The patient’s breathing activity combined with positive pressure from the ventilator can also become a potential source for excessive lung strain/stress [24] (see Fig. 3).

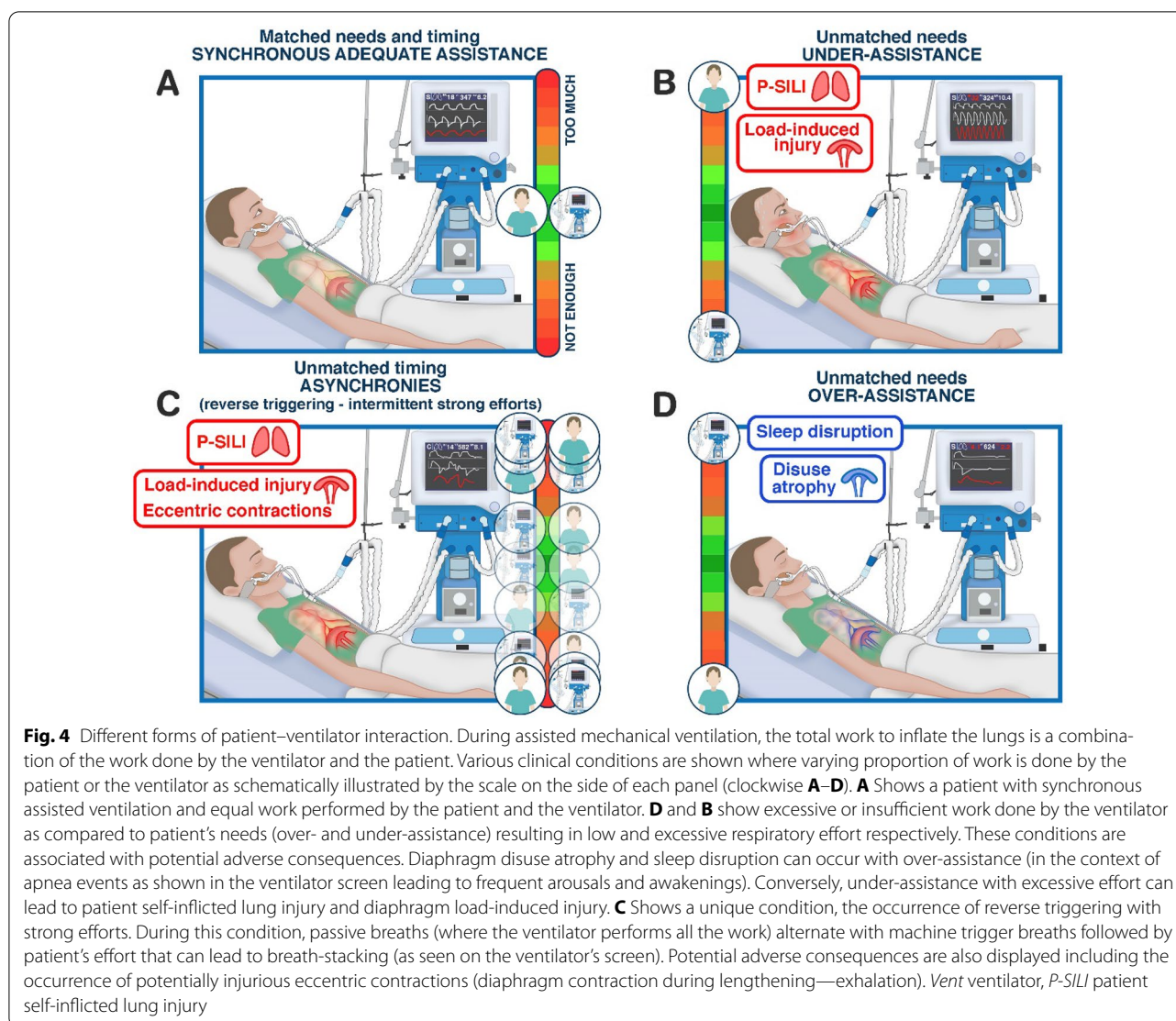
Additionally, timing of a patient’s respiratory effort can be synchronous or dyssynchronous with the ventilator’s insufflation and exhalation with important consequences, either directly, e.g., breath-stacking after double triggering, or indirectly, e.g., misleading monitoring of respiratory rate in case of ineffective efforts (see Fig. 4). Dyssynchrony has been associated with poor outcomes, although this does not necessarily mean causation [22].

Implementation of invasive mechanical ventilation

Technical aspects and modes of mechanical ventilation

Modern mechanical ventilators deliver a mixture of air and oxygen with positive pressure regulated by proportional, microprocessor-controlled valves to obtain a desired output of flow [23]. There are different ways by which mechanical insufflation can be delivered, these are called ventilatory modes. For any mode, each mechanical breath is characterized by different variables, also used for mode classification. First, the trigger variable determines the start of mechanical insufflation, it can be time (usually referred to as “controlled breaths” and determined by the set frequency in controlled modes) or patient’s effort, generating a change in flow or pressure sensed by the ventilator (usually referred to as “triggered breaths”). In spontaneous modes of ventilation (pressure support or proportional modes), all breaths are triggered. Second, the limit variable, which is the parameter that the ventilator controls during insufflation, being flow (and indirectly volume by also adjusting insufflation time) or pressure. Third, the cycling-off variable that determines the change from insufflation to exhalation. While in controlled modes the cycling-off variable is time, it can be flow or electrical activity of the diaphragm in spontaneous modes [20].

There is often a misconception that patient’s breathing effort is always lower or absent during controlled modes of ventilation compared to spontaneous modes of



ventilation, specifically pressure support (see Fig. 4) but there are several caveats.

First, controlled modes can be “overrun” by the patient’s own breathing when the patient’s respiratory rate becomes higher than the set respiratory rate. In these cases, patients usually trigger every breath and the ventilator’s set rate is used as a back-up. The same modes used for controlled “passive” ventilation can therefore become assisted modes, delivering the same output (pressure or volume) with every breath but at a rate determined by the patient, and therefore the term “assist-control” ventilation is frequently used.

Second, even when all mechanical breaths are initiated by time (i.e., controlled), a patient’s breathing effort might still occur in the form of reverse triggering efforts in which patient’s breathing efforts are “entrained” by the passive insufflations [25], a phenomenon which is very

frequent in the transition from fully controlled to assisted mechanical ventilation [26] (see Fig. 4).

Third, pressure support ventilation, the most frequently used spontaneous mode of ventilation [27], is user-friendly, rapidly decreases work of breathing with higher pressures, and decreases patient’s respiratory rate. However, the decrease in respiratory rate can be artificial and not reflect the “real” breathing pattern, especially in the context of patient–ventilator dyssynchronies [28]. One misconception here is that pressure support necessarily reflects a “good” spontaneous activity of the patient. However, as with any pressure targeted mode, once the ventilator is triggered by a minimal effort, it will deliver a breath that is similar to any breath delivered during “passive” controlled ventilation. In fact, during excessive levels of pressure support (over-assistance), it is common for the patient’s respiratory drive and breathing effort to

be extremely low, with insufflation occurring passively [29].

In several other modes “controlled” breaths can be delivered intermittently and intermixed with assisted breaths (synchronized intermittent mandatory ventilation), or combining breaths by removing synchronization and shortening expiratory time (airway pressure release ventilation), by adding volume or volume minute targets to pressure-controlled modes (dual modes, adaptive support ventilation) or even by adding complex algorithms to drive the whole ventilation (Intellivent). Despite some potentially useful features, they all have important drawbacks which should be taken into account by clinicians.

Proportional modes have a different approach for assisting ventilation, providing positive pressure instantaneously proportional to patient’s effort or drive to breathe. Proportional assist ventilation (PAV+) provides assistance in proportion to the pressure generated by the respiratory muscles (P_{mus}) [30] and Neurally adjusted ventilatory assist (NAVA) to the electrical activity of the diaphragm (EAdi) [31]. P_{mus} for PAV+ is calculated from airway pressure and flow using the equation of motion (see Fig. 3) [30] and EAdi for NAVA is measured via an array of electrodes placed via a nasogastric tube (NAVA catheter) [31]. From a physiological standpoint, given that support follows patient’s instantaneous effort, they reduce patient–ventilator dyssynchronies, and also help the patient adapt to any changes in demand. In clinical studies PAV+ and NAVA have been shown to improve patient–ventilator synchrony [32, 33], breathing variability [34, 35], diaphragm function relative to pressure support [36] and tolerance to assisted ventilation [37]. A recent clinical trial suggests that the use of NAVA may shorten duration of mechanical ventilation [38].

Liberation from mechanical ventilation

Liberating patients from mechanical ventilation requires at least partial resolution of the underlying reason for mechanical support and relative general clinical stability (readiness to wean) together with an acceptable balance between mechanical and metabolic loads and cardiorespiratory capacity [39]. Both delayed and premature liberation is associated with poor clinical outcomes [40, 41]. Patients should start the liberation process as soon as possible and be adequately assessed for the likelihood of being able to breathe independently.

A systematic approach to weaning includes screening patients first to determine their readiness to wean, followed by a diagnostic test simulating post-extubation conditions (“spontaneous breathing trial” (SBT)) where patients receive little or no ventilator support [42]. Patients who tolerate an SBT, and who can maintain airway protection, and generate an adequate cough can

usually be safely extubated. Daily screening and appropriate conduct of SBTs were shown to reduce duration of mechanical ventilation compared to an approach using gradual reduction of ventilatory support [43, 44]. According to a large observational study, most patients (>60%) are extubated within 1 week of starting the liberation process. However, there is a subgroup of patients in whom the liberation process takes longer, and mortality is substantially higher [41]. Weaning-induced pulmonary edema (often associated with fluid overload) is probably the most frequent reason for initial weaning difficulties and can be adequately treated [45]. Respiratory muscle weakness is also often a major determinant of weaning failure [46], and thus preserving respiratory muscle function during mechanical ventilation is key for a faster liberation process.

Lung and diaphragm protective ventilation

Understanding the pathophysiology of VILI allowed the design of strategies to minimize harm during passive mechanical ventilation. The use of low tidal volumes (4–8 ml/kg of predicted body weight (PBW)) and limiting inspiratory pressures (plateau pressure < 30 cmH₂O) to prevent volu- and barotrauma has been shown to improve clinical outcomes compared to higher tidal volumes (12 ml/kg PBW), and a higher limit on plateau pressure [47]. Limiting driving pressure and titrating PEEP on recruitability are examples of physiologically sound approaches that will need to be tested in future trials (NCT03963622).

Applying adequate PEEP can limit atelectrauma by keeping alveolar units open at end-expiration and potentially increase the size of the aerated lung (recruitment), decreasing the strain during tidal inflation. However, selecting the best PEEP for a specific patient is always a compromise between potential for recruitment and overdistention, which needs to be carefully assessed even during low tidal volume ventilation [48]. Another approach to limiting VILI in patients with ARDS is to place the patient in the prone position which makes the distribution of ventilation more uniform, minimizing regional stress and strain. This approach has been shown to improve survival in patients with moderate-severe ARDS [49].

Additionally, recognizing the relevance of maintaining adequate respiratory muscle function during invasive MV has led to the development of ventilatory strategies that simultaneously optimize protection of both the lung and diaphragm. These strategies include minimizing sedation and neuromuscular blocking agents, avoiding excessive and very low inspiratory efforts, and optimizing patient–ventilator synchrony [50].

Monitoring to minimize iatrogenesis

Numerous physiological parameters can be measured at the bedside to estimate the risk of harm and, can be used to individualize ventilator settings and sedation to best match a patient's respiratory mechanics and metabolic needs.

During passive ventilation, measuring basic respiratory mechanics (e.g., plateau and driving pressure) is key to adjusting tidal volume or set pressure to avoid excessive stress to minimize VILI [19]. Based on recent data, the benefit of using lower tidal volumes may be greater in patients with smaller "baby-lungs" (i.e., higher elastance) suggesting that using respiratory mechanics, specifically measurement of driving pressure, to titrate tidal volume might be beneficial [51]. Other specific maneuvers can be used to help maximize lung recruitment while minimizing overdistension; these include the single breath maneuver for measurement of the recruitment to inflation ratio [52], or more complex maneuvers using sophisticated monitoring devices (electrical impedance tomography) [53]. An esophageal balloon can be used to measure end-expiratory transpulmonary pressure (lung distending pressure at end-expiration) to help estimate the risk of atelectrauma and may be particularly relevant in obese patients [54].

Monitoring respiratory drive and inspiratory effort may be helpful in estimating patient's ventilatory needs, respiratory muscle energy consumption, and risk of harm related to excessive and low inspiratory effort. The gold standard to measure inspiratory effort is change in pleural pressure generated by respiratory muscle contraction, which allows quantification of strength and timing of respiratory efforts (synchronous or dyssynchronous), as well as the lung distending pressure during assisted ventilation [55]. Several non-invasive techniques (e.g., airway occlusion pressure (P_{0.1}), single breath expiratory occlusion pressure (P_{oc})) can be used to estimate respiratory drive and hence of potentially injurious inspiratory efforts [56, 57]. Additional techniques such as respiratory muscle ultrasound and electrical activity of the diaphragm are available. Current and future randomized clinical trials (e.g., NCT03963622, NCT03612583) will inform about the efficacy of the widespread use of these techniques aiming for a "safe" drive and effort to improve clinical outcomes and define relevant targets.

Future of mechanical ventilation

As physiological understanding of the complex interaction between the risks of harm and benefits of mechanical ventilation and technical development of monitoring tools progress, the amount of data for decision-making becomes overwhelming. In this context, automated tools for analysis [58], decision support systems aided by

artificial intelligence integrating physiological data [59, 60], and automated modes of ventilation might help clinicians efficiently care for patients while minimizing harm. These will need to be rigorously developed, validated, and prospectively tested.

Extracorporeal respiratory support

Physiological rationale and potential iatrogenesis

There is a subgroup of patients with very severe hypoxemia and severely deranged respiratory mechanics in whom application of sufficient positive pressure ventilation to achieve minimally viable gas exchange markedly increases the risk of harm. In these patients, an alternative approach for providing adequate gas-exchange while allowing the lung to heal is extracorporeal respiratory assistance provided through a membrane lung. Two main techniques are available: low-flow extracorporeal carbon dioxide removal (ECCO₂R) and high-flow Extracorporeal Membrane Oxygenation (ECMO). ECCO₂R allows reduction of minute ventilation (tidal volume and frequency) by carbon-dioxide removal while ECMO also provides substantial oxygenation.

One of the major physiological benefits of ECMO is the potential complete replacement of ventilation, minimizing or possibly eliminating the risk of harm due to excessive lung stress and strain in patients with higher risk of VILI due to small "baby-lungs". However, there are substantial costs associated with extracorporeal respiratory support. Using ECMO is resource intensive requiring specific expertise. Most patients under ECMO require anticoagulation and the risk of bleeding is considerable (18% (CI 6–30%) absolute risk difference vs best conventional ventilation in a recent randomized controlled trial (RCT) [61]). Additionally, there are specific deleterious consequences on the lungs when patients are connected to ECMO and ventilation is reduced (or eliminated): reduction in end-expiratory lung volume, reabsorption atelectasis and elimination of the mechanism of hypoxic vasoconstriction. For this reason, some positive pressure and, possibly, ventilation still needs to be applied carefully. Evidence on how to set the ventilator during ECMO is scarce, however aiming for a lower driving pressure (<14 cmH₂O) while maintaining some PEEP (provided inspiratory pressures are in the safe range) seems reasonable based on limited current evidence [61, 62].

Clinical evidence on the use of extracorporeal respiratory support

The development of the artificial membrane lung allowed the application of extracorporeal respiratory assistance outside the operating room, with the first successful use of this technique published in 1972 [63]. Early results

(150 patients, up to 1974), however, were disappointing (approximately 90% mortality) [64].

The first randomized trial ever performed in the intensive care setting tested the efficacy of ECMO [65]. Unfortunately, it showed a similar mortality rate (90%) in both the ECMO and control groups, and the technique was nearly abandoned. In this trial, the configuration of ECMO was veno-arterial and mechanical ventilation was applied with high pressures and volumes in all groups, with the only difference being a lower FiO_2 with ECMO. The technique itself also had considerable technical problems, with an average daily blood loss of nearly 5 liters!

Kolobow introduced a new device and a new concept: the carbon-dioxide membrane lung. Its application at relatively low extracorporeal blood flow rates (1–1.5 l/min) achieved the clearing of nearly all the total metabolic CO_2 production, allowing a proportional decrease of mechanical ventilation, thus providing almost total lung rest [66]. Although this ECCO₂R, did not demonstrate a survival advantage in a small randomized study [67], several centers continued using extracorporeal respiratory support. Bartlett et al. in the United States [68] used ECMO in neonates and adults (establishing the Extracorporeal Life Support Organization registry in 1989), along with others (using ECCO₂R or ECMO) [69, 70] in Europe. A promising positive randomized trial in 2009 (the CESAR trial [71]) renewed interest in extracorporeal support.

However, the worldwide dissemination of this technique was largely attributable to the influenza A(H1N1) pandemic in 2009 with the publication of a cohort from Australia and New Zealand with high survival with ECMO [72]. Since the H1N1 pandemic, the use of ECMO and ECCO₂R has progressively increased in clinical practice. The benefits of ECMO were once again tested in the EOLIA trial [61]. The results did not show a statistically significant mortality benefit in the ECMO group. However, a subsequent post hoc analysis, along with several meta-analyses, demonstrated a mortality benefit with ECMO [73]. During COVID-19 pandemic, ECMO has played a prominent role in many parts of the world. However, outcomes with ECMO appear to be evolving (in the wrong direction) over the course of the pandemic, highlighting the importance of careful patient selection and management together with adequate expertise and organization in centers providing ECMO [74].

A European study demonstrated feasibility of ECCO₂R [75], but a more recent randomized trial did not show an advantage of using ECCO₂R with lower tidal volumes as compared to standard low tidal volume ventilation (6 ml/kg) [76]. It must be noted, however, that the CO_2 extraction in this trial was too limited to allow sufficient reduction in the intensity of mechanical ventilation.

Future of extracorporeal respiratory support

Beyond technical improvements of extracorporeal systems, it is likely that extracorporeal support will proceed along two main paths: low-flow ECCO₂R, which allows reduction of the intensity of mechanical ventilation; and high-flow ECMO, a technique providing adequate oxygenation and CO_2 removal allowing for virtual “lung rest”. Both ECCO₂R and ECMO buy time for the patient to heal. Which patients will benefit the most and which of these “buying-time” techniques provides the greatest balance of effective support while minimizing damage in a given patient will need to be determined.

Conclusions

The treatment of respiratory failure has improved dramatically since the 1950's polio epidemic. Although there have many been technological advances (better ventilators, improved monitors, more effective and smaller ECMO devices), the major advance has likely been a better physiological and biological understanding that life-saving respiratory support (mechanical ventilation) can also markedly harm patients. This can occur by inflicting injury to the lungs, the diaphragm, impairing hemodynamics and having a potential negative impact on patient's physical status and mental health. The way specific pathophysiological conditions are interpreted at the bedside and how ventilatory strategies are applied should also be considered. Future research to improve outcomes in patients with respiratory failure will have to address these existential trade-offs of current ventilators and extracorporeal respiratory support systems.

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Declarations

Conflicts of interest

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