NARRATIVE REVIEW ARTICLE

Mechanical Ventilation, Past, Present, and Future

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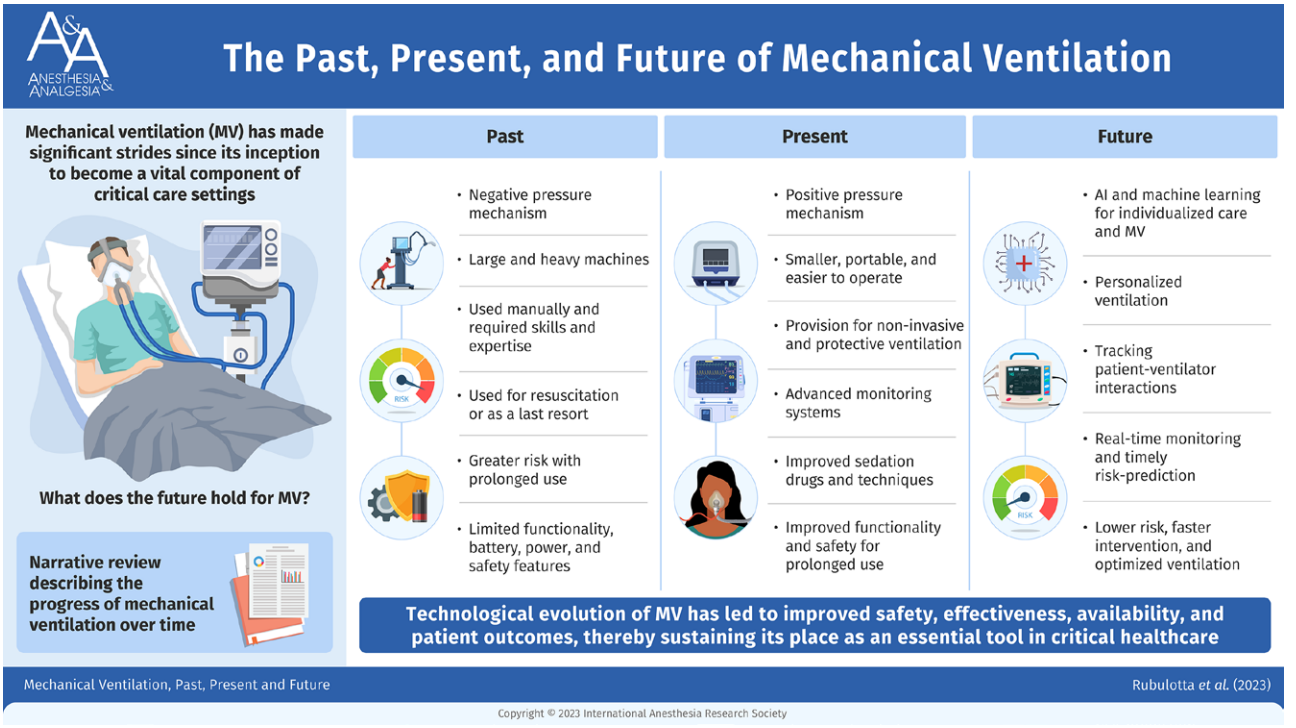

Mechanical ventilation (MV) has played a crucial role in the medical field, particularly in anesthesia and in critical care medicine (CCM) settings. MV has evolved significantly since its inception over 70 years ago and the future promises even more advanced technology. In the past, ventilation was provided manually, intermittently, and it was primarily used for resuscitation or as a last resort for patients with severe respiratory or cardiovascular failure. The earliest MV machines for prolonged ventilatory support and oxygenation were large and cumbersome. They required a significant amount of skills and expertise to operate. These early devices had limited capabilities, battery, power, safety features, alarms, and therefore these often caused harm to patients. Moreover, the physiology of MV was modified when mechanical ventilators moved from negative pressure to positive pressure mechanisms. Monitoring systems were also very limited and therefore the risks related to MV support were difficult to quantify, predict and timely detect for individual patients who were necessarily young with few comorbidities. Technology and devices designed to use tracheostomies versus endotracheal intubation evolved in the

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last century too and these are currently much more reliable. In the present, positive pressure MV is more sophisticated and widely used for extensive period of time. Modern ventilators use mostly positive pressure systems and are much smaller, more portable than their predecessors, and they are much easier to operate. They can also be programmed to provide different levels of support based on evolving physiological concepts allowing lung-protective ventilation. Monitoring systems are more sophisticated and knowledge related to the physiology of MV is improved. Patients are also more complex and elderly compared to the past. MV experts are informed about risks related to prolonged or aggressive ventilation modalities and settings. One of the most significant advances in MV has been protective lung ventilation, diaphragm protective ventilation including noninvasive ventilation (NIV). Health care professionals are familiar with the use of MV and in many countries, respiratory therapists have been trained for the exclusive purpose of providing safe and professional respiratory support to critically ill patients. Analgo-sedation drugs and techniques are improved, and more sedative drugs are available and this has an impact on recovery, weaning, and overall patients' outcome. Looking toward the future, MV is likely to continue to evolve and improve alongside monitoring techniques and sedatives. There is increasing precision in monitoring global "patient-ventilator" interactions: structure and analysis (asynchrony, desynchrony, etc). One area of development is the use of artificial intelligence (AI) in ventilator technology. AI can be used to monitor patients in real-time, and it can predict when a patient is likely to experience respiratory distress. This allows medical professionals to intervene before a crisis occurs, improving patient outcomes and reducing the need for emergency intervention. This specific area of development is intended as "personalized ventilation." It involves tailoring the ventilator settings to the individual patient, based on their physiology and the specific condition they are being treated for. This approach has the potential to improve patient outcomes by optimizing ventilation and reducing the risk of harm. In conclusion, MV has come a long way since its inception, and it continues to play a critical role in anesthesia and in CCM settings. Advances in technology have made MV safer, more effective, affordable, and more widely available. As technology continues to improve, more advanced and personalized MV will become available, leading to better patients' outcomes and quality of life for those in need. (Anesth Analg 2024;138:308–25)

GLOSSARY

AI = artificial intelligence; **ALI** = acute lung injury; **APACHE II** = Acute Physiology and Chronic Health Evaluation II; **ARDS** = acute respiratory distress syndrome; **ARDSNet** = ARDS Network; **ARF** = acute respiratory failure; **ARM** = alveolar recruitment maneuvers; **AUC** = area under the curve; **CCM** = critical care medicine; **COPD** = chronic obstructive pulmonary disease; **COVID-19** = coronavirus disease -19; **CPAP** = continuous positive airway pressure; **CPB** = cardiopulmonary bypass; **CT** = computed tomography; **DP** = driving pressure; **ECCO$_2$R** = extra corporeal carbon dioxide removal; **ECMO** = extracorporeal membrane oxygenation; **EELV** = end-expiratory lung volume; **EIT** = Electrical impedance tomography; **EPVent 2** = esophageal pressure-guided ventilation 2; **ESICM** = European Society of Intensive Care Medicine; **ETT** = endotracheal tube; **FiO$_2$**= fraction of inspired oxygen; **HFNC** = high-flow nasal cannula; **HFNO** = high-flow nasal cannula oxygenation; **HFOV** = high-frequency oscillatory ventilation; **ICM** = intensive care medicine; **ICU** = intensive care unit; **LOS** = length of stay; **Lv** = liquid ventilation; **LV** = left ventricle; **MP** = mechanical power; **MV** = mechanical ventilation; **NIV** = noninvasive ventilation; **NO** = nitric oxide; **OR** = operating room; **PACU** = postanesthesia care unit; **PaO$_2$** = arterial pressure of oxygen in the arterial blood gas; **Paw** = airway pressure; **PBW** = predicted body weight; **PEEP** = positive end-expiratory pressure; **PPCs** = postoperative pulmonary complications; **Pplat** = plateau pressure; **POCUS** = point-of-care ultrasound; **P-SILI** = patient-self-inflicted lung injury; **P/F ratio** = PaO2/FiO2 ratio; **REST** = xxxx; **RR** = respiratory rate; **RV** = right ventricle; **SE** = sample entropy; **SIMV** = synchronized intermittent mandatory ventilation; **SOB** = short of breath; **TLC** = TLC, total lung capacity; **VAP** = ventilator-associated pneumonia; **VILI** = ventilator-induced lung injury; **VT** = tidal volume; **WOB** = work of breathing

The history of modern mechanical ventilation (MV) dates back to the 1940s when the first mechanical ventilators were developed.[1,2] Nevertheless, ancient history has traces of machines used to support the manually and for short period of time the respiratory systems.[3] Most examples were related to resuscitation and emergency medicine when the ventilation and oxygenation was necessary to preserve life.[2,3] The early mechanical ventilators for planned or prolonged support during anesthesia or in the intensive care unit (ICU) were large and cumbersome.[3,4] These machines required significant expertise to operate and were dangerous for patients.[4] Over the years, MV has undergone significant improvements, including the development of smaller and more portable ventilators,[5] the implementation of lung-protective MV based on physiological concepts, the introduction of noninvasive ventilation (NIV), and the use of advanced algorithms and artificial intelligence (AI).[4,5] The art of ventilation is evolved together

with the monitoring systems which has allowed us to reduce injuries induced by these machines and therefore, improve survival.[6]

In 2050, MV is expected to undergo significant innovations. Personalized ventilation will allow for the optimization of ventilation based on the individual patient's physiology and condition. Advanced algorithms and AI will allow for the real-time monitoring of patients and adjustments, the prediction of respiratory distress before it occurs. Additionally, the use of innovative materials and designs may lead to the development of more comfortable interphases for NIV options as well as high-flow nasal cannula (HFNC) oxygen. The coronavirus disease-19 (COVID-19) pandemic has resulted in an increased need for ventilators. The potential to ventilate more than 1 patient with a single ventilator, a so-called split ventilator setup, was presented. A recent bench testing model shows that tidal volumes (VTs), positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FiO_2) can be individualized and monitored in a split ventilator.[6] This is interesting but in contrast with the idea of more personalized care. In the future, MV challenges will still remain and those include the potential for harm from prolonged ventilation, the need for ethical considerations, and increased patient and family inclusion in particular using MV and AI. Patients in the ICUs are elderly and frail but the rate of intubated individuals is decreased therefore ethical aspects are even more relevant[7] for those critically ill awake patients.

Opportunities exist for the continued improvement of MV, including the potential for increased patient safety and comfort. MV has come a long way since its inception, and it continues to be a critical tool in the management of respiratory, cardiac, multiorgan failure in ICU and beyond. For the benefit of the reader, the authors will divide this narrative review into 3 parts, namely: the past, the present, and the future.

THE PAST

Preautomatic/Manual Ventilators

Despite advanced respiratory support, specifically MV, being a relatively "young" branch within the grander tree of medical practice, the seeds of current practice can be traced back throughout the history of civilization.[1] Resuscitation and emergency medicine were therefore the true beneficiary in the pre-automatic or manual ventilator stage.[1] Egyptian mythology recounts the resurrection of Osiris by Isis, using the breath of life. The first biblical appearance of mouth-to-mouth resuscitation, traces back to the book of Kings in the Old Testament.[1,2] The first recorded use of device-assisted ventilation is attributed to Paracelsus, a 16th-century Swiss physician and alchemist, who was the first to use bellows in this manner.[1] Shortly thereafter, Andreas Vesalius, a professor of anatomy in Padua, attempted to ventilate animals with bellows via thoracostomies, going on to describe a process of positive pressure ventilation in 1543.[3] Despite the initial description of tracheostomy by Vesalius, it was Robert Hook in 1667 who successfully manually ventilated a dog using positive pressure via a tracheostomy.[1,3]

Negative Pressure Mechanical Ventilators

As the understanding of the physiological process of breathing evolved, interest in the development of negative pressure ventilators grew. Initial experiments were also conducted on animals. Gradually, these large machines were designed simply for resuscitation of adult and pediatric awake patients who experienced a transient or irreversible increased in their work of breathing (WOB). John Dalziel designed and built the first so-called tank ventilators in 1838. This machine consisted of an air-tight box in which the patient would sit, because this position was described comfortable by the sickest. No detailed explanation of causes leading to the increased WOB was published at the time but clinical evaluation of patients suggested the sitting position was best for ventilatory purposes. The air-tight box would allow for the required reduction in the ambient pressure around the thorax.[1,4,5] The added negative pressure provided by the MV was necessary for creating a delta pressure and a flow of air inside the lungs (assisted inspiration).[4] In 1864, Alfred Jones was responsible for the realization of Dalziel's theoretical concept. Jones patented his tank ventilator which allowed for manual assisted ventilation via the depression of a plunger placed outside the box which contained 1 individual. This manual movement worked simply by decreasing the pressure within the box (inhalation) and the release of the plunger, conversely produced exhalation. The extent of negative pressure generated within the device was monitored by a pressure gauge incorporated into the design, while patients' vital signs were not monitored.[2–4] Eligibly, these adult patients were awake so the state of consciousness as well as reported symptoms were used at the bedside. Nurses were trained for monitoring consciousness and they were a fundamental part of this process. Authors could assume these nurses were the predecessors of modern respiratory therapists. Ignez von Hauke developed the first cuirass ventilator but found it of limited use in agitated patients, which drove him to evolve his design into a tank respirator, the "Pneumastiche Panzer" in 1874.[5] In 1876 Alfred Woillez built the first functional mechanically powered negative pressure ventilator which was called the "iron lung" or "spirophore."[3–5] This was developed to help drowning victims in Paris and its' design included the first attempt at monitoring

VT. This was done by means of a metal rod placed on the patient's chest which measured the change in the size of the thorax and assumed the volume of the flow of air generated. Therefore, in the 19th century the movement of the rod served as a surrogate marker of the VT,[3] while the state of consciousness was a surrogate of ventilation, perfusion, and brain oxygenation.[3] Those machines were used mainly for resuscitation and emergency medicine purposes.[3] The start of the 20th century saw rapid progression in the evolution of mechanical ventilators to be used in anesthesia and CCM.[4,5,8] The end of the same century supported also the creation of positive pressure mechanical ventilators.[8]

Iron Lungs for Sick Patients

In 1904 Ferdinand Sauerbrach created the first negative-pressure operating chamber.[1,4] This machine housed the entirety of the patient from the neck down and was additionally large enough to accommodate the surgeon. The patient's head and the doctors acting as the anesthetist remained outside the chamber.[4] The design also incorporated a flexible sack around the patients' body which permitted the application of positive pressure in an attempt to reduce the accumulation of blood in the abdomen and legs. This sack could prevent a complication which had become known as "tank shock."[2] The "tank shock" was not well described physiologically but clinically it was reported as a frequent complication which could cause death secondary to cardiac arrest[2] In 1907 Heinrich Drager received the patent for his "Pulmotor" designed for "blowing fresh air or oxygen into the lungs."[8] After modifications of the original prototype, the "pressure controlled" Pulmotor was in production by 1908.[5,8] Drager was originally a watchmaker, this is possibly the reason why the Pulmotor was "time controlled." The Pulmotor was in production by 1908 and it was used extensively for resuscitation in both hospital and nonhospital environments.[4,5,8]

The devastating spread of poliomyelitis across North America and Europe accelerated further refinement of the "iron lung" negative pressure tank ventilators. The first attempt to treat critically ill poliomyelitis patients was likely by Thorsten Thunberg in Sweden, who developed a tank ventilator he called the "Barospirator."[9] Unfortunately, none of the patients survived which dampened interest in the device.[9] In 1928, Philip Drinker, with the assistance of Louis Agassiz Shaw, successfully adapted a device initially planned for implementation in industrial hygiene (work-related illness and injury), into the first "iron lung" which would enjoy widespread use.[10] Drinker published numerous landmark papers in contemporary medical literature.[9,10] By 1931, the "iron lung" was successfully modified by John Emerson.[9,10] Emerson's machine had "air-tight" ports which facilitated nursing access and included a bed that slid easily into the machine. It was believed to incorporate a superior mechanism, had a back-up pump, and allowed the practitioner to control respiratory rate.[10] Emerson's MV was also much lighter, less noisy, and cheaper than Drinkwater's machine.[10] The subsequent legal dispute between Drinkwater and Emerson was eventually settled in Emerson's favor in 1935 with the judge declaring that both men had merely modified preexisting technology rather than inventing the concept.[10] In 1908 Peter Lord patented the "respirator room" and in 1950 James Wilson created a multiperson negative pressure chamber which was installed at the Children's Hospital, in Boston.[2,3] A model of ventilation including a central station for many patients was recently advocated for the treatment of respiratory failure in the COVID-19 pandemic.[6] In 1901 Rudolf Eisenminger designed the "Biomotor," the first negative pressure chest cuirass ventilator to allow synchronization of mechanical ventilators with patient's effort.[11] Willian Steuart patented and built a cuirass in South Africa in 1918 to combat a poliomyelitis epidemic but his invention was never tested clinically.[4] In the 1950s the "iron lungs" remained the dominant ventilator mode despite limited successful application.

In 1917 Boyle's original anesthesia machine was built.[12] The breathing system consisted merely of a Cattlin bag, 3-way stopcock and a facemask. In 1945 John Blease invented a simple bellows ventilator, "the pulmoflator," which enabled automatic positive pressure ventilation for patients undergoing surgery.[12]

The 1952 surge of poliomyelitis cases in Copenhagen provided the impetus for the birth of modern MV.[3] Prof Bjorn Ibsen augmented the air flow generated by the iron lung in a 12-year-old critically ill child using manual positive pressure ventilation via a tracheostomy. The addition of manual positive pressure ventilation reduced the 87% mortality rate to 40% almost instantly.[3] By the end of the epidemic, mortality had dropped to just 23%.[5] Ibsen is additionally credited with the vision of accumulating these patients with enhanced needs into a singular dedicated area thereby ushering in the era of ICUs.[3] Monitoring was spare but expertise of people working in this area were higher compared to other wards. The transition from negative to predominantly positive pressure ventilation had important physiological consequences for the patients due to the increase in intrathoracic pressure. The interface between MV and cardiac function had been of great interest to Motley et al[11] who documented the impact on cardiac preload, ventricular filling, and cardiac output as early as 1948. The authors correctly alluded to the inverse relationship between thoracic pressure and the hemodynamic response of the patients.[11] These altered cardiopulmonary interactions

would have undoubtedly highlighted the concomitant need for better hemodynamic monitoring. The positive pressure inside the chest impacted cardiac preload, afterload as well as the ventricular function. Moreover, not all patients on positive pressure ventilation were awake and this further reduced the possibility of neurological monitoring.[4,11,12] Anesthesia drugs were also introduced in the same period so risks related to the use of positive pressure ventilation in combination with new drugs, in the context of no or minimal monitoring represented elevated risks even for young and healthy patients.

In summary, the decade that followed, major advances in engineering saw the refinement of mechanical positive pressure ventilators which had first become available in the 1940s.[3] These first-generation ventilators initially only provided volume-controlled ventilation and were perhaps defined by the uniform lack of patient-triggered breaths. These machines largely lacked any form of monitoring or alarms and none incorporated PEEP.[2,3] Nonetheless, this generation of ventilators peaked with the introduction of the double circuit Engstrom which was equally adept in the ICU or operating theater.[10] The Engstrom was a lighter and a more versatile ventilator. Most important was that this could perform airway pressure (Paw) monitoring, VT and exact respiratory rate setting.[2] The advances in MV management was augmented by the fact that blood gas monitoring became routine during the early 1960s.[11] In 1929 Kurt von Neergaard a German-born physiologist discovered surfactant an isotonic gum solution to eliminate surface tension.[13] The late 1960s saw the emergence of ventilators based on fluidic technologies.[14] These ventilators, despite favorable evaluations in the following years, would not go on to become widely popular.[14] In 1962 Kylstra described the liquid ventilation (Lv) as a technique of MV in which the lungs are insufflated with an oxygenated perfluorochemical liquid.[15]

Ashbaugh et al[16] described the "adult respiratory distress syndrome" (ARDS). These authors published the first evidence of the efficacy of PEEP to improve oxygenation.[16] They achieved the delivery of PEEP by immersing the expiratory limb of an Engstrom anesthesia ventilator under water.[2,16] The realization of the potential role of PEEP in improving end-expiratory lung volume (EELV) led to the widespread inclusion of PEEP into contemporary second-generation mechanical ventilators of the 1970s, heralded by the release of the Puritan Bennett MA1.[17] The second-generation, widely defined by the incorporation of patient-triggered inspiration, additionally saw the incorporation of basic monitoring and alarms such as high pressure, high rate and low VT. In 1970s the Puritan Bennett MA1 had patient-triggered inspiration, PEEP, basic monitoring and alarms for indicating high pressure in the system, high respiratory rate, and low VT.[17]

Synchronized intermittent mandatory ventilation (SIMV) is a type of volume control mode of ventilation. SIMV added as a mode option was possible by the introduction of intermittent mandatory ventilation. Another important innovation was the introduction of intermittent mandatory ventilation. Later, the use of demand valves allowed for improved synchronization with patient effort and saw SIMV added as a mode option. The early 1980s saw the Siemens Servo900C conclude the advancements of the era of second-generation machines by adding pressure-control and pressure support modes to the bouquet.[2] The Table contains a summary of innovations and innovators in the last centuries.

Table. Summary of Innovations and Innovators of Mechanical Ventilators in the Last Centuries

Date	Inventor/s	Country/place	Innovation	Mode of ventilation
1530	Parecelcus	Switzerland	Manual bellows resuscitation	Positive
1543	Vesalius	Italy—Padua	Bellows via chest	Positive
1667	Hooke	England—London	Bellows via tracheostomy	Positive
1838	Dalziel	Scotland	First tank ventilator	Negative
1864	Jones	United States—Kentucky	Patented tank ventilator	Negative
1874	Von Hauke	Austria	Pneumatische Panzer	Negative
1876	Woillez	France—Paris	First iron lung—Spirophore	Negative
1904	Sauerbrach	Germany	Operating chamber	Negative
1904	Eisenmenger	Hungary	Cuirass—Biomotor	Negative
1907	Drager	Germany	Pulmotor resuscitator	Positive
1908	Lord	United States—Worchester	Respirator room	Negative
1917	Boyle	England	Original anesthesia machine	Positive
1918	Stueart	South Africa	Cuirass	Negative
1920	Thunberg	Sweden—Lund	Tank ventilator—Barospirator	Negative
1927	Eisenmenger	Hungary	Motorised Biomotor	Negative
1928	Drinker and Shaw	United States—Boston	First commercial iron lung	Negative
1930	Wilson	United States—Boston	Multiperson chamber	Negative
1931	Emerson	United States—Boston	Modified iron lung	Negative
1945	Blease	England	Bellows ventilator for anesthesia—Pulmoflator	Positive
1952	Ibsen	Denmark	Bag ventilation and ICU	Positive

Abbreviation: ICU, intensive care unit.

By the mid-1980s, the inclusion of microprocessor control defined the arrival of third-generation ventilators.[2,3] The expansion in processing power enabled a marked improvement in machine response to patient demand including the use of flow triggering. Pressure support augmentation of inspiration was added to SIMV and Paw release ventilation became available. Extensive monitoring and alarms became standard of care. Mechanical ventilator scalars and loops were displayed graphically for the first time, forever changing the practice of MV as we headed into the modern era.[2,16]

THE PRESENT

MV is currently used in anesthesia and in CCM to support patients for a variety of reasons. There are differences in the way MV is applied and the use of MV may vary depending on the patient's underlying conditions and the type of procedure being performed.

MV is used in anesthesia during surgical procedures to maintain a patient's airway while ensuring adequate oxygenation and ventilation. The goals of MV in this setting are to secure normal blood gas values, avoid complications such as atelectasis and ventilator-induced lung injury (VILI), and prevent aspiration of gastric contents. In most of the cases, intraoperative MV settings are for patients with healthy lungs with a planned weaning and extubation at the end of the procedure.

MV in critical care medicine (CCM) is used to support critically ill patients with acute respiratory failure (ARF) or ARDS due to various medical conditions such as pneumonia, sepsis, or heart failure. MV including NIV techniques are used for chronic obstructive pulmonary disease (COPD) and Asthma. The goals of MV in the setting of CCM are to improve oxygenation and ventilation, decrease the WOB, and decrease the risk of complications such as ventilator-associated pneumonia (VAP) or VILI.[17]

Overall, MV plays a critical role in both the operating room (OR) and the ICU. MV is not a treatment per se, but it acts as an organ support and a bridge to recovery. Ideally, it should be provided in the acute phase and for the shortest period possible while aiming to avoid its associated complications such as VILI, VAP, hemodynamic decompensation (eg, right ventricle failure), diaphragmatic dysfunction and hyperoxymia with its related oxidative stress.[17,18] n this "Present" section author will do an overview of different physiological concepts and their clinical application in the OR and ICU.[19,20]

Figure 1 is a summary of concepts related to the physiology of MV and their application at the bedside in anesthesia and CCM. Hemodynamic consequences

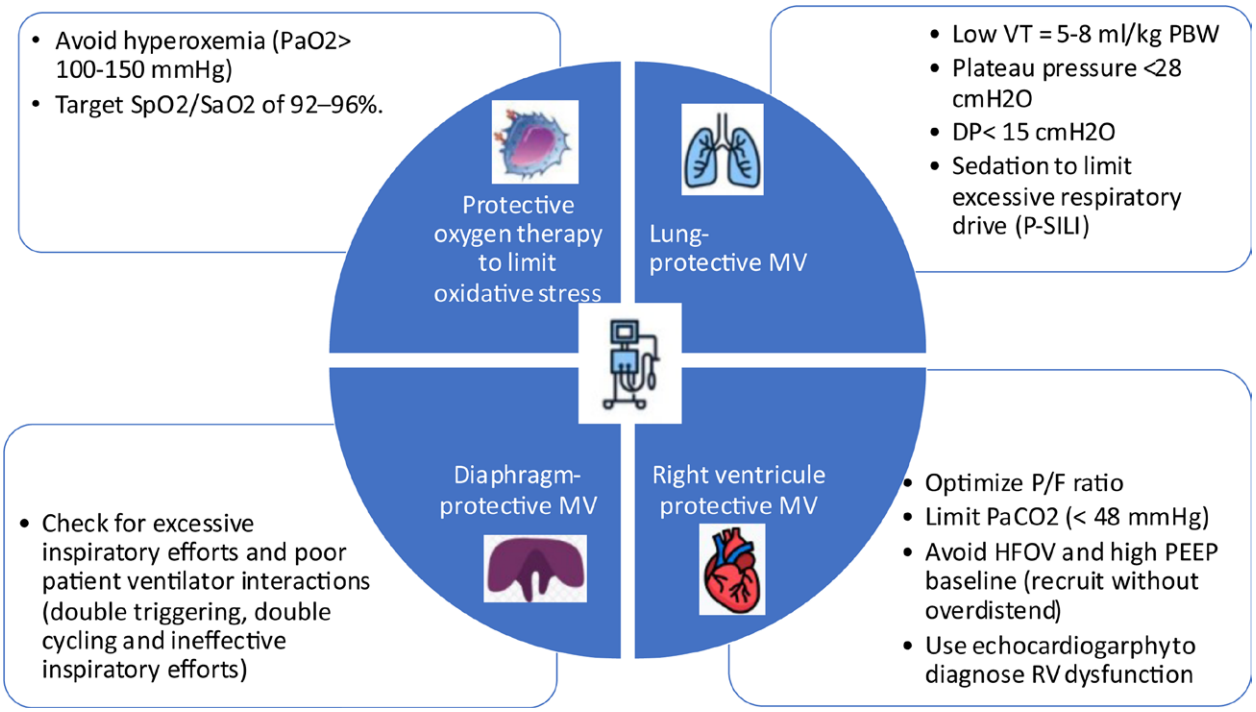

Figure 1. Physiological concepts of MV and their application at the bedside in anesthesia and critical care medicine. DP indicates driving pressure; FiO_2, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; MV, mechanical ventilation; PaO_2 = arterial pressure of oxygen in the arterial blood gas; PBW, predicted body weight; PEEP, positive end-expiratory pressure; P-SILI, patient-self-inflicted lung injury; RV, right ventricle; VT, tidal volume.

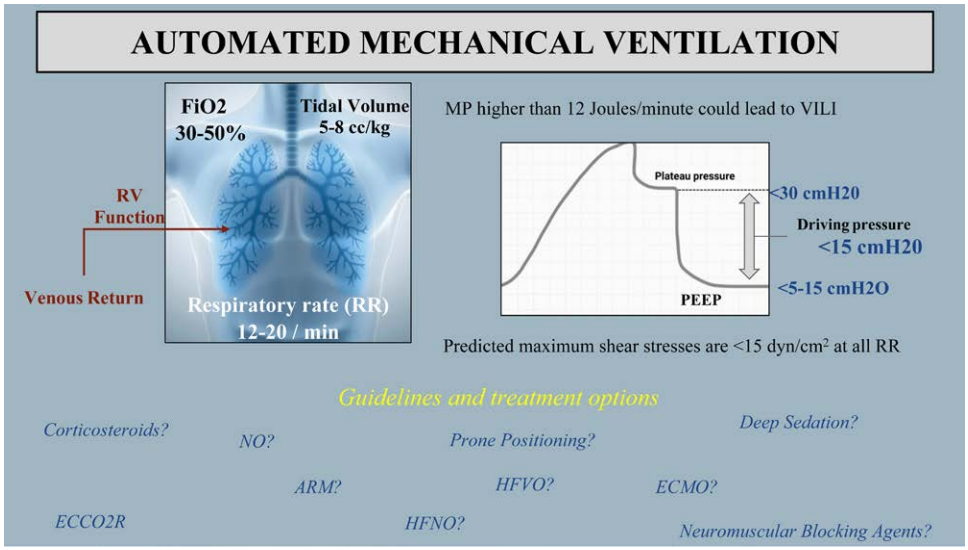

Figure 2. Challenges of mechanical ventilation and treatment options. Guidelines of treatment approved by the ESICM in 2023. ARM indicates alveolar recruitment maneuver; $ECCO_2R$, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; ESICM, European Society of Intensive Care Medicine; FiO_2, fraction of inspired oxygen; HFNO, high-flow nasal cannula oxygenation; HFOV, high-frequency oscillatory ventilation; MP, mechanical power; NO, nitric oxide; RR, respiratory rate; RV, right ventricle; PEEP, positive end-expiratory pressure.

of positive pressure MV are also summarized in Figure 2 and these are, namely:

- Positive intrathoracic pressure due to MV will be transmitted to the heart, pericardium, and great vessels.
- Positive pressure MV has long been known to have a significant effect on cardiovascular hemodynamics due to heart-lung interactions as it increased right ventricle (RV) afterload and reduced RV preload which could lead to a decrease in RV stroke volume and subsequently compromise left ventricle (LV) filling and cardiac output.
- Positive pressure MV could also reduce LV preload in patients with preserved LV systolic function (preload-dependent patients).

MV in the Operating Room

Patients undergoing general elective surgery have most of the time normal lungs. The patients are sedated and sometimes paralyzed for the purpose of surgery and intubated to allow positive pressure assisted-controlled ventilation for a short period of time (ie, several hours).[20] The patient has standard hemodynamic monitoring, respiratory monitoring, and temperature monitoring, and urinary catheter is discretional but used on many occasions. During elective surgery the 2 main complications related to MV are as follows: atelectasis and VILI.[20]

Physiological Concepts and Intraoperative/Perioperative Atelectasis and Ventilator-Induced Lung Injury

The onset of atelectasis in surgical patients undergoing general anesthesia is very frequent (more than 90 %) with distinct mechanisms.[20,21] Compression atelectasis is not only related to general anesthesia per se (ie, loss of muscle tone) but also to multiple other demographic and perioperative conditions (age, obesity, Trendelenburg position, abdominal/laparoscopic surgery, thoracic surgery / one-lung ventilation, nonventilated lungs during cardiopulmonary bypass [CPB]).[22,23] In the postoperative period, compression atelectasis is mostly related to persistent diaphragmatic dysfunction and pain-induced reduction of cough effectiveness with bronchial obstruction.[21] Another mechanism is resorption atelectasis that can be caused by high perioperative inspired FiO_2 levels.[22]

Perioperative atelectasis leads to a decrease in EELV, a ventilation/perfusion mismatch, and a decrease in lung compliance.[23,24] During MV, the initial lung volume corresponds to the EELV, and its change is induced by the insufflated VT. Volumetric lung strain is defined as the ratio of change in VT to initial volume (EELV). This relationship suggests that, while reducing VT is important in surgical patients, VT is not the only determinant of lung strain and injury.[25–27]

Driving pressure (DP) provides an easily measured (difference between plateau pressure [Pplat] and PEEP) indicator of volumetric lung strain.[24] Above the pure volumetric information provided by VT, DP offers additional information on volumetric lung strain (ie, VT adjusted to aerated lung volume, ie, EELV) (Figures 2 and 3).[25] Recent studies in surgical patients are in agreement with these physiological concepts and reported that high DP may be a more important trigger than VT to cause VILI as it is more associated with postoperative pulmonary complications (PPCs; eg, hypoxemia, pulmonary infections)[25,26]

Along this line, intraoperative lung-protective and personalized ventilation that avoids both alveoli overdistension and derecruitment (eg, alveolar recruitment maneuvers [ARMs], individualized PEEP levels

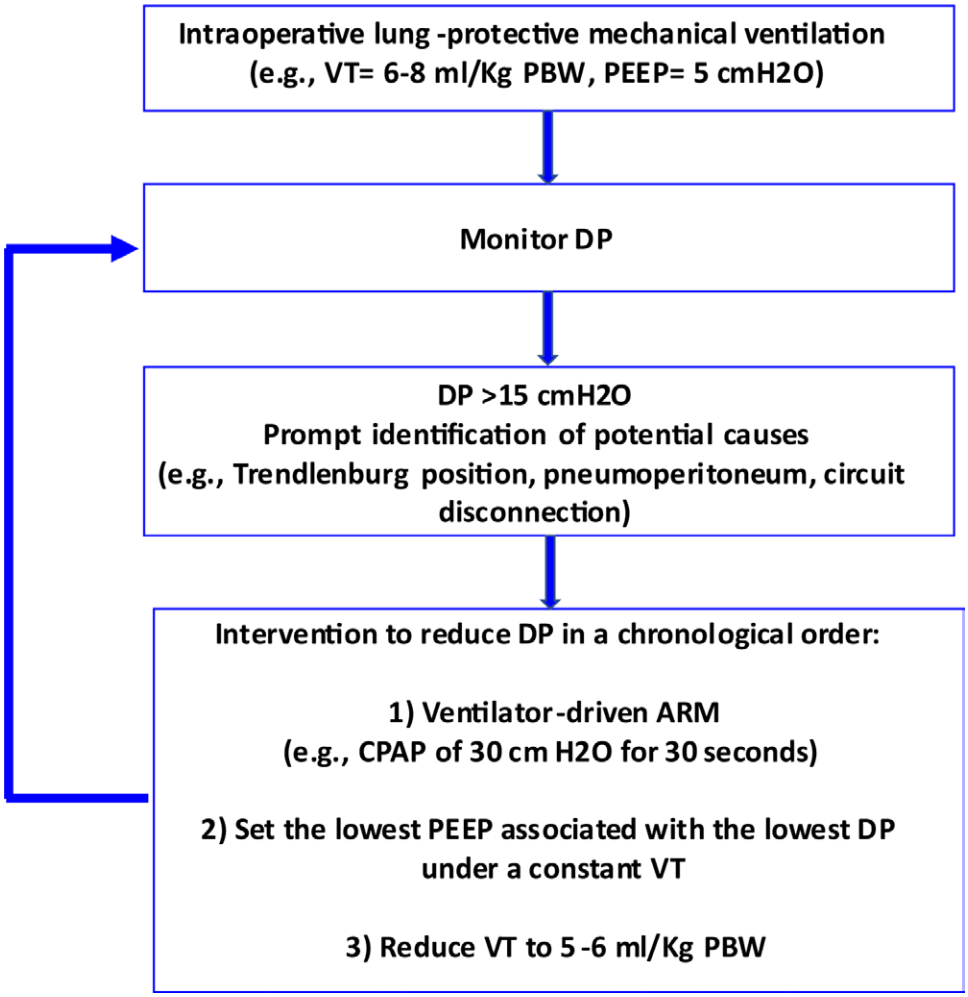

Figure 3. Suggested approach for an intraoperative lung-protective ventilation based on driving pressure optimization. ARM indicates alveolar recruitment maneuver; CPAP, continuous positive airway pressure; DP, driving pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; VT, tidal volume.

and low VT) may decrease lung injury and its related inflammatory response and subsequently PPCs.[26] Although ARM and high PEEP levels may be beneficial for the lungs, they may impact hemodynamics with a decrease in venous return and cardiac output especially after induction and during major surgical bleeding. Such an approach has to be avoided during hemodynamic instability or in patients that are more complex.[27]

Protective MV in the Operating Room

Lung-protective ventilation may improve surgical patients' outcomes especially those with increased risk of PPCs (eg, elderly, obese patients, pulmonary disease, preoperative hypoxemia, prolonged anesthesia, urgent surgery, and abdominal/thoracic surgery).[28]

During induction of anesthesia, continuous positive airway pressure (CPAP)/NIV or high-flow nasal cannula oxygenation (HFNO) could be considered especially in obese patients.[30] Their combination with head-up position limits EELV decrease, improves oxygenation, and increases the duration of nonhypoxic apnea[29–32] Nonetheless, in a very recent meta-analysis including adult studies that compared HFNO and traditional facemask preoxygenation in surgical obese patients, no difference between the 2 interventions was found in preventing oxygen desaturation <92% or the lowest oxygen saturation before intubation[33] Lung-protective ventilator setting during surgery includes low VT and individualized PEEP levels. Low VT alone (ie, 5–8 mL/kg predicted body weight [PBW]), has been reported as associated with a reduction in PPCs when compared to high VT (>8 mL/kg PBW).[34] Nonetheless, low VT alone was described as insufficient to protect healthy lungs in surgical patients. It has been suggested to apply an adequate PEEP and ARM in addition to low VT to minimize the risk of atelectrauma and decrease PPCs.[35] Multiple clinical trials highlighted that intraoperative MV with low VT, high levels of PEEP (6–10 cm H_2O) and ventilator-driven ARM (eg, CPAP of 30 cm H_2O for 30 seconds) are associated with improved oxygenation and respiratory system compliance and less PPCs.[23,36,37] Neto et al[26] reported in a meta-analysis including 17 randomized controlled trials (n = 2250 surgical

patients) that intraoperative high DP and changes in the level of PEEP that result in an increase of DP are associated with more PPCs. This study suggests that PEEP level could be personalized based on intraoperative DP (ie, lowest PEEP associated with the lowest DP).[27] A Suggested approach for an intraoperative lung-protective ventilation based on DP is presented in Figure 3.

The concept of mechanical power (MP) calculation in the OR was described to integrate the complexity of the interaction between multiple respiratory variables which may cause VILI. MP is calculated with the following equation:

MP (joules/min) = 0.098 × respiratory rate × VT × (PEEP + 0.5) × (Pplat – PEEP) × (peak pressure – Pplat).[37,38]

The static, dynamic elastic, and dynamic resistive components are approximated by the PEEP, (DP = Pplat – PEEP), and (peak pressure – Pplat) part of the formula, respectively.[38] In recent studies including surgical patients, higher intraoperative MP was associated with a greater risk of PPCs and postoperative respiratory failure requiring reintubation.[39,40] A personalized MP-based lung-protective ventilation strategy based on the potential modification of its actionable ventilatory parameters (ie, VT, PEEP, DP, and respiratory rate) could be assessed in future surgical patients' studies.[41]

In the postoperative period, the administration of prophylactic CPAP or HFNO immediately after extubation in high-risk and/or obese patients has been reported to improve oxygenation and decrease PPCs.[42,43]

Monitoring MV in the Operating Room

Current standards for intraoperative ventilation basic monitoring during general anesthesia (American Society of Anesthesiologists) include pulse oximetry, oxygen concentration in the inspired gas, expired carbon dioxide, and expired gas volume.[44] As the respiratory system may be modified by multiple dynamic conditions related to general anesthesia or surgery, a continuous monitoring of the different biophysical characteristics (ie, pressure-volume curves reflecting its dynamic compliance) should be applied.[27]

Electric impedance tomography and transpulmonary pressure monitoring using an esophageal manometry were also suggested to personalize PEEP level in surgical patients with a low respiratory system compliance (obese patients, laparoscopic surgery/steep Trendelenburg position).[45,46] Nonetheless, even if implementing this specific monitoring has a solid physiological background, it requires additional equipment and training in use and interpretation, which may make its daily use at the bedside challenging for the clinicians, especially for a short-term period of MV.

Weaning From MV in the Operating Room

During emergence and before extubation, anesthesiologists should avoid conditions that negate the intraoperative efforts to recruit and avoid atelectasis. A similar approach to the 1 applied during induction should be used including the optimization of patient positioning (head-up position, 30°) and avoiding zero end-expiratory pressure. Routine suctioning of the tracheal tube just before extubation should be avoided as well as it causes derecruitment and a decrease in lung volume. During emergence, increasing FiO_2 may improve oxygenation, but it may alter the respiratory system compliance by promoting atelectasis formation.[22] A pragmatic approach for extubation is to deliver 80% to 100% oxygen for the shortest time possible, reducing it to a lower level depending on the patient's requirement.

MV in the Intensive Care Unit

MV in CCM has to take in account that DP and MP are concepts that can also relate to VILI and RV failure, as well as poor outcome and death in the ICU.[47,48] Similarly, the association between over-assistance with the use of mechanical ventilators, excessive respiratory effort, and diaphragm dysfunction can lead to poor prognosis.[47] Authors will describe the impact of these concepts on the current practice in the ICU. Recent guidelines have indicated the increased role of advanced treatments, for example, proning, nitric oxide (NO), extracorporeal carbon dioxide removal ($ECCO_2R$), and extracorporeal membrane oxygenation (ECMO), corticosteroids, deep sedation, neuromuscular blocking agents, and others (Figure 2).[48]

The Concepts of Driving Pressure and Mechanical Power in Critically Ill Patients

Several factors have been considered as possible triggers for VILI and these include:

- Pressure (barotrauma).
- Volume (volutrauma).
- The repetitive cyclic opening and closing of lung units using insufficient VT (shear stress) Note: For a normal lung, the predicted maximum shear stresses are <15 dyn/cm^2 at all respiratory rates, whereas for a lung with elevated surface tension or viscosity, the maximum shear stress will notably increase, even at a slow respiratory rate.
- End-expiratory pressures (atelectrauma).
- The consequent damage due to release of inflammatory mediators (biotrauma).

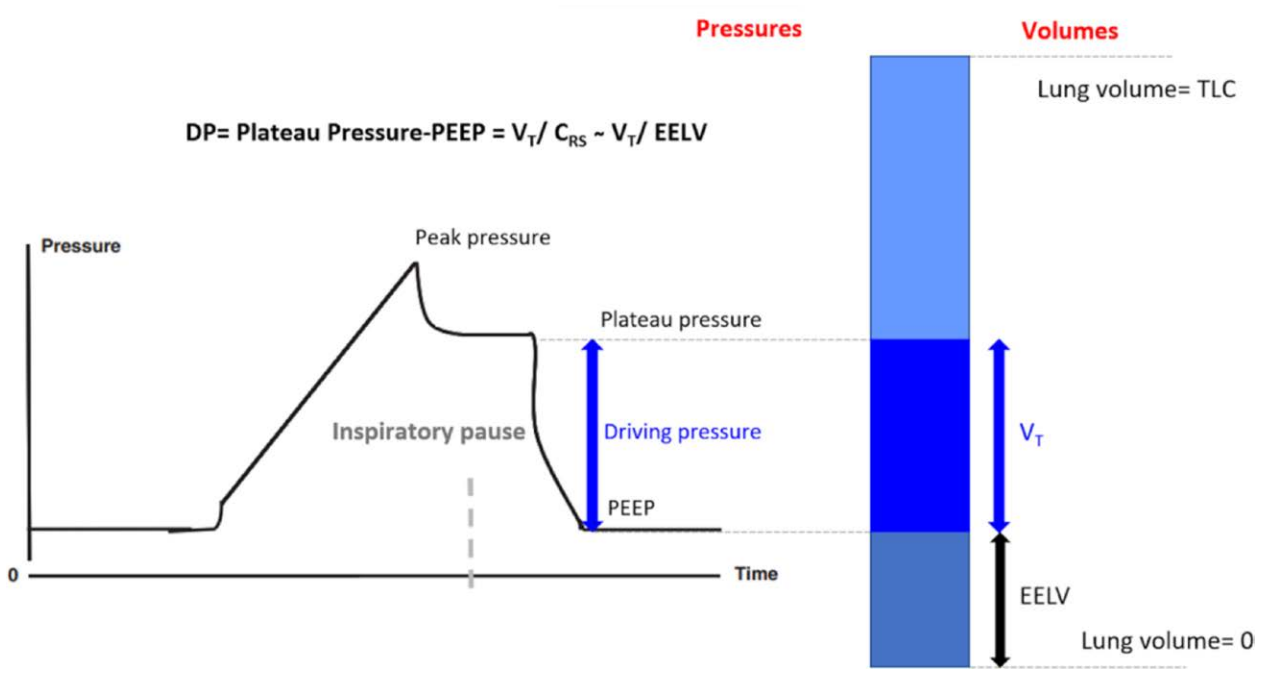

Figure 4. Driving pressure added information on volumetric lung strain (ie, VT adjusted to EELV). CRS indicates respiratory system compliance; DP, driving pressure; EELV, end-expiratory lung volume; PEEP, positive end-expiratory pressure; TLC, total lung capacity; VT, tidal volume.

The DP (ie, Pplat – PEEP) was reported as strongly associated with VILI in patients with ARDS.[47] Randomized trials and retrospective analysis reported that high VT, PEEP, and DP were related to poor outcomes.[47,49] Conversely, lower peak inspiratory pressure and lower respiratory rates were associated with reduced in-hospital mortality.[50,51] However, less attention was given to the effect of respiratory rate and flow although the latest experimental evidence demonstrated that they play a significant role in the development of VILI[52] (Figure 2). MP has been proposed as unifying parameters for the main mechanical drivers of VILI and is considered the main determinant of its pathogenesis.[53] MP is the amount of energy per unit of time generated by MV and released to the respiratory system. The classical equation of motion of the respiratory system states that the energy applied to the respiratory system per unit of time depends on the mechanical properties of the lungs (resistance and elastance), VT, PEEP level, and inspiratory flow.[54] MP has been reported as more associated with the development of VILI than each of the individual components of ventilation settings when taken separately. Experimental studies in piglets using characterization with pulmonary computed tomography (CT) scans suggested that an MP higher than 12 joules/min could lead to VILI irrespective of the individual combinations of each component.[51] A retrospective analysis of 8207 mechanically ventilated patients in the ICU found that an MP > 17 J/min calculated on day 2 after ICU admission was independently associated with increased hospital mortality.[55] However, heterogeneity of ventilated lung surface area and the relationship between chest wall and lung compliance (ie, transpulmonary pressure) indicates that a fixed threshold of MP is not attainable in different patients as a predictor for VILI. Indexing MP to PBW (a surrogate for lung size) was found to be a predictor of mortality in patients with ARDS.[56] A retrospective analysis of 7 published studies which included 224 patients with ARDS concluded that there was no causal relationship between MP itself and mortality.[57] MP normalized to compliance of the amount of well-aerated lung tissue was independently associated with ICU mortality. MP normalized to well-aerated lung tissue seemed to better predict outcome compared to MP normalized to the respiratory system compliance.[57] The measurement of DP and MP supported the definition of criteria for a lung-protective MV ventilation in ICU.

Lung-Protective MV in Intensive Care Unit

Goligher et al[58] performed a reanalysis of ARDSNet trial data (randomized controlled trials) and they found that the limitation of VT has a varied impact on mortality which was determined by baseline lung compliance, and it had no effect when the compliance was high. These results show that DP (is determined by both VT and respiratory system compliance, rather than VT alone), may represent a better target for adopting lung-protective ventilation strategies. PEEP selection during MV in the ICU is very difficult and it

can influence regional transpulmonary pressures and mitigate VILI.[61,62] Nonetheless, it is still not clear how to choose the "best PEEP" as to influence patient outcomes. No difference in mortality or ventilator-free days was found between technology-guided PEEP titration versus empirical PEEP and FiO_2 settings[59,60] (Figures 2 and 4).

A post hoc analysis of EPVent 2 study showed differences in the treatment effects in patients according to severity of multiorgan dysfunction and a lower mortality rate was observed in patients with less severe illness (lower APACHE II scores).[61] After adjusting to multiorgan dysfunction, optimum PEEP titration to achieve Pes-guided transpulmonary pressure closer to 0 was associated with improved survival.[60] REST trial aimed at testing the effect of ultraprotective lung ventilation by lowering VTs to less than 6 mL/kg of PBW in patients with moderate-to-severe ARDS by using $ECCO_2R$.[62] The study was stopped early due to feasibility and futility as the intervention group had more serious adverse events (intracranial bleeding) and fewer ventilator-free days.[62] Several questions arise such as the variable experience across the study centers in dealing with $ECCO_2R$, the quality of the $ECCO_2R$ device used and the heterogeneity of groups of patients investigated. Current guidelines describe these concerns and make clinical suggestions easy to follow.[48] Overall, lung-protective MV in ICU especially in ARDS patients, includes low VT volume 4 to 6 mL/kg of PBW, the potential use of high PEEP, early consideration of prone positioning, and the use of extracorporeal mechanical support (ECMO).[48] More details can be found on the European Society of Intensive Care Medicine (ESICM) guidelines for the management of ARDS (Figure 2).[48] Hemodynamic consequences of positive pressure in critically ill patients are the same presented at the beginning of this section, namely:

1. Positive intrathoracic pressure transmitted to the heart, pericardium, and great vessels.
2. Heart-lung interactions including increased RV afterload and reduced RV preload.
3. Reduced LV preload in patient's preload-dependent.

Right Ventricle Protective Ventilation in Critically Ill Patients. More than 20% of ARDS patients were found to have echocardiographic signs of RV dysfunction which is associated with higher mortality.[63] Changing VT can also have a profound impact on pulmonary vascular resistance, RV afterload, and high lung volumes can also compress the heart. Current understanding of the concept of intrinsic PEEP and the use of lung-protective ventilation has enabled to safely reduce the hemodynamic consequences associated with positive pressure ventilation by using lower VT and setting a PEEP for the lower DP.[64,65] Modern ventilators no longer deliver the standard square-shaped pressure or volume control breathing but rather used auto-modes in adjusting delivered breaths according to the need of the patient and the triggered patient's effort which aims to eventually reduce the negative hemodynamic consequences of MV.[66] Another important point to reduce the hemodynamic consequences of MV, especially on the RV and venous return. Figure 2 shows the challenges related to MV, RV, venous return, and the treatment options mentioned in the recent ESICM guidelines.[48]

The inspiratory-to-expiratory (I:E) ratio is an important variable in patients with expiratory flow limitation (eg, bronchospasm) as insufficient time for expiration could lead to accumulation of intrinsic PEEP which could lead to hemodynamic deterioration. Pressure ramp time or percentage is the time or percentage of inspiratory time to reach maximum flow or pressure. This is useful in patient-initiated ventilation modes as it can help in achieving patient-ventilator synchrony.[67]

MV-Induced Diaphragm Dysfunction (Myotrauma) and Implication for Diaphragm Protective Ventilation in Intensive Care Unit

The utilization of MV has been associated with diaphragm atrophy, particularly in the case of prolonged MV in chronic ICU patients. There are multiple possible mechanisms of MV-related myotrauma, namely:

1. Insufficient inspiratory effort related to overassistance, which may lead to myofibrillar atrophy and contractile dysfunction.
2. Excessive respiratory effort related to insufficient ventilatory assistance, which may cause acute diaphragm weakness, delayed muscle inflammation, and proteolysis.
3. Excess contractile loading developed while a muscle is lengthening (ie, eccentric contraction), which may occur in patient-ventilator dyssynchrony.[68]

The risk of myotrauma could be minimized by optimizing patient inspiratory effort, avoiding under/overassistance, and reducing patient-ventilator synchrony and drive.[57] Nonetheless, the precise degree of inspiratory effort necessary to prevent atrophy must be assessed and may differ between different patients and at different timings during ICU stay.[68]

Weaning of MV in Intensive Care Unit

Weaning is the process of reducing the degree of ventilatory support which will ultimately lead to the liberation of patients from MV as the patient starts breathing spontaneously and then being extubated. This can be achieved in around 80% of mechanically ventilated patients in the ICU when the cause of respiratory failure resolves. The remaining 20% of patients often require a longer and more gradual process for weaning. Failure to wean from MV is associated with longer ICU stay[69] increased cost[70] and worse morbidity and mortality.[70,71] Failed extubation puts the patient at risk of life-threatening complications.[72] Weaning failure could be due to cardiac dysfunction, or respiratory dysfunction with increasing evidence of the role diaphragmatic dysfunction plays in weaning failure.[72] Weaning-induced pulmonary edema has been reported to represent around 60% of weaning failure by the largest study published to date.[73] The same study found concomitant myocardial ischemia to be an uncommon finding during weaning failure.[73] The increase in venous return on shifting from positive to negative pressure ventilation is often the cause of increased LV filling pressures when LV compliance (diastolic function) is impaired. Furthermore, increase venous return could lead RV dilation, especially with RV function being impaired, and a further steep elevation in LV afterload when significant inspiratory efforts generate a large drop in pleural pressure[74](Figure 2). Caution should be warranted as cardiac ejection fraction is neither a sensitive nor specific parameter in evaluating LV systolic function and further studies on novel echocardiographic parameters (strain imaging) are needed to assess the effect of LV systolic function on the weaning outcome. Integrating multiple echocardiographic and lung ultrasound parameters into the weaning process is probably the best approach to improve the sensitivity and specificity of each individual parameter and therefore enhance the clinical assessment at the bedside.

Monitoring MV in the Intensive Care Unit

MV is a life-saving intervention, but it can also lead to complications and iatrogenesis if not properly monitored. To minimize the risks associated with MV, several monitoring strategies are used, including:

Oxygenation Monitoring. This involves monitoring the patient's oxygen saturation, pulse oximetry, expired carbon dioxide, and arterial blood gases to ensure that the patient is receiving adequate oxygenation and minute ventilation.

Ventilator Settings and Lung Mechanics Monitoring. This involves monitoring the patient's expired VT, respiratory rate, and PEEP. Peak/Pplat is also monitored to ensure that the patient is receiving appropriate protective ventilation and assess the respiratory system compliance as a target of ventilator settings (eg, pressure-volume curves modifications to different PEEP levels).

Esophageal Pressure and Calculated Transpulmonary Pressure (ie, Pplat - Esophageal Pressure) Monitoring. This monitoring provides a more accurate measurement of lung stress and risk of VILI especially in obese patients (ie, low chest wall compliance). They also allow quantification of strength and timing of respiratory efforts (ie, identification of dyssynchrony).[24]

Electrical Impedance Tomography. Electrical impedance tomography (EIT) is a noninvasive imaging technique that uses changes in electrical conductivity to create images of lung function. By monitoring changes in lung impedance, EIT can provide real-time information on lung volume, ventilation distribution, and regional lung compliance. This information can be used to optimize MV settings and minimize the risk of lung injury.[75]

Hemodynamic Monitoring. This involves monitoring the patient's blood pressure, heart rate, central venous pressure as an indicator of RV congestion, and cardiac output to ensure that the patient is adequately perfused, and that the ventilation is not causing hemodynamic instability (Figures 2 and 4).

Point-of-Care Ultrasound. Point-of-care ultrasound (POCUS) of the heart, lung, and diaphragmatic can provide useful information for the evaluation of mechanically ventilated patients. It can help assess lung aeration, adjusting MV, assessing complications, and guiding weaning from MV. Integrated cardiopulmonary ultrasound can provide essential information in managing acutely unwell patients in the ICU.[76] POCUS can be utilized to evaluate heart-lung interactions and the negative consequences of MV especially overdistension and right ventricular dysfunction due to increased right ventricular afterload. Acute core pulmonale can be assessed by transthoracic echocardiography by the presence of RV dilation and paradoxical motion of the interventricular septum.[77] Significant elevation of right-sided pressure can lead to arterial hypoxemia due to right to left shunt via a patent foramen ovale,[78] which is best assessed with transthoracic echocardiography with bubble study or transesophageal echocardiography. Alveolar overdistension can lead to impaired alveolar ventilation and perfusion predominantly in the anterior lung zones and it can be detected by lung ultrasound by the reduction of the physiological pleural sliding in the anterior zones while augmenting positive

pressure ventilation.[79] Moreover, lung ultrasound can assess lung aeration, presence or absence of congestion, degree of congestion, pneumonia, atelectasis, and pleural effusion with a much high sensitivity and specificity than chest radiography and was very useful during COVID-19 pandemic.[80] Lung ultrasound can directly assess recruitment/derecruitment in mechanically ventilated patients and the response to various recruitment maneuvers as the appearance of a dynamic change of the consolidation (tissue-like pattern) to an artefactual vertical (B-lines) or horizontal (A-lines) indicating the increased aeration within the recruited lung zone.[81]

Moschietto et al[82] found that diastolic dysfunction had moderate sensitivity and specificity in predicting weaning failure from MV while systolic function showed no correlation. Assessment of lung ultrasound aeration score at the end of a spontaneous breathing trial predicted extubation failure with an area under the curve (AUC) of 0.86.[83] Several authors demonstrated that diaphragmatic dysfunction during a spontaneous breathing trial was associated with failed weaning.[84,85] A combined integrated approach which includes cardiac, lung, and diaphragmatic ultrasound was useful not only to predict weaning failure but also to understand the underlying etiology of weaning failure and to optimize chances of success.[86]

THE FUTURE

Importance of Physiologic Waveforms

Sources of noninterventional and continuous data and waveforms outside any clinical trial will constitute a valuable form of data. Physiologic waveforms relating to patient health status (hemodynamic monitors) and/or the delivery of health care (mechanical ventilators) routinely collected from various sources (different manufactures) will feed noninterventional studies that analyze primary data/waveforms collected from registries.[87] A key aspect of this monitoring/collection process is to minimize measurement errors. Physiological measurements from waveforms continuously acquired during routine clinical care may not be collected with the same fidelity as those obtained during prospective studies. Automatic measurement recordings from monitors or ventilators are subject to random error arising from events occurring at time of data collection.[88,89] Measuring true Pplat during MV to calculate DP must be done in breaths where reverse triggering, double cycling, or double triggering is not present.[90] Moreover, granular data reveal differences between physiologic trajectories that were not evident from the sparse data or the median values. Recording mean arterial pressure hourly will miss hypotensive episodes lasting minutes therefore these episodes' potential influence on treatment effects or outcomes is ignored.[89]

The potential of high-precision alerts based on AI to detect complex alterations in physiologic waveforms like poor patient ventilation interactions detection is promising, but their impact on patient's comfort, less days on MV, faster weaning or decrease length of ICU stay or mortality is still under research. Poor patient-ventilator interactions or asynchronies are common throughout MV and reflect a mismatch between ventilator cycles and patients' respiratory demands. Asynchronies are associated with prolonged MV and ICU stay, discomfort, dyspnea, sleep disruption, respiratory muscle dysfunction, and lung injury, and increased mortality.[91] Using software and AI has been recently shown that clustered asynchronies could affect outcome when accounting for determinate power and duration of the clusters. All ICU patients receiving MV developed clusters of asynchronies, suggesting clusters are common. Remarkably, the total number of clusters was associated with increased probability of being alive at ICU discharge. Importantly, however, the power and duration of clusters were associated with longer duration of MV and ICU stay and increased probability of death, mainly during the first 48 hours of MV. Thus, clusters of asynchronies are potentially more harmful than isolated asynchronies and their detection should alert clinicians to the need for caution.[92]

Once again, the impact of physiologic events is not on the event per se which could be even physiologically good but on how this event, in this case clustering of asynchronies, occurs during MV or in the ICU stay.[91–93] Similarly, estimating of respiratory dynamics by applying an entropy approach on entire datasets of airflow or Paw tracings during MV yielded promising results on hidden patterns of poor patient ventilator interactions potentially leading to unplanned extubations (Figure 5).

Representative tracings of airflow (Flow), Paw, and sample entropy (SE) derived from Flow and Paw in 2 patients 2 hours before the unplanned extubation event (self extubation).[94] These advances will allow us to have alert systems beyond the traditional alarms and bedside observation and to build AI–assisted ventilator-management systems. From now on, synergy of human knowledge and wisdom (human neurons), and AI (artificial neural networks) to achieve diagnostic excellence must coexist.[95]

Tools for Precision Medicine in the Critically Ill Patient

The design of a modern ICU must include health care technology, informatics systems, and appropriate software to facilitate the improvement of health care delivery

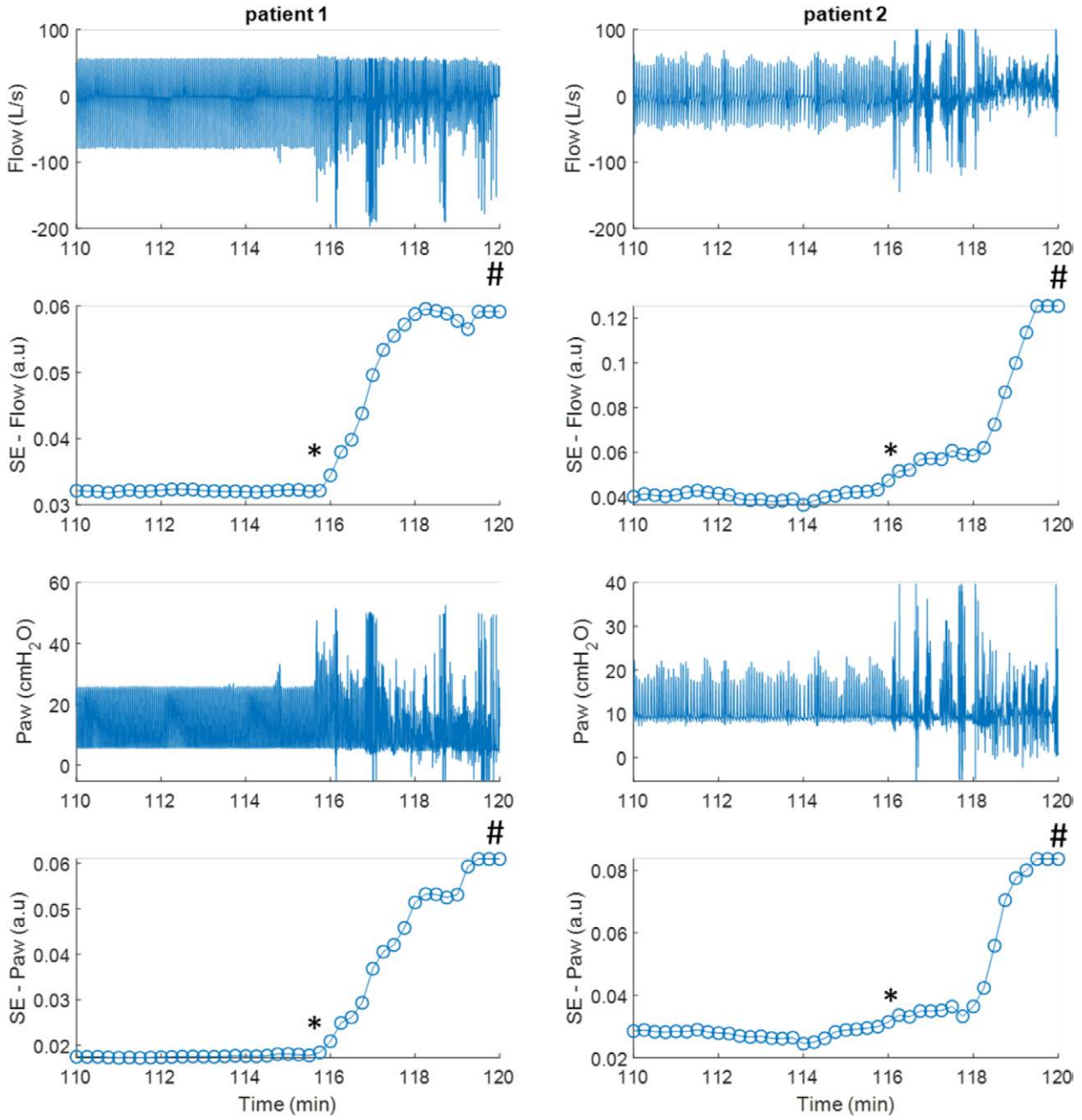

Figure 5. Representative examples of ventilator tracings for airway flow (Flow) and airway pressure (Paw) and SE derived from Flow and Paw in 2 patients 10 min before to the self extubation event. The onset of poor patient-ventilator interaction (*) and self extubation event (#) were represented. SE is a nonlinear technique that measures the randomness of a series of data. SE-Flow (m = 2; r = 0.2) and SE-Paw (m = 4; r = 0.2) were calculated using a 30-s sliding window with 50% overlap (8). SE shows a high sensitive to changes in irregularity during MV. MV indicates mechanical ventilation; Paw, airway pressure; SE, sample entropy.

and the environment of care for critically ill patients. These implementations require collaborative work between health care professionals and varied disciplines. Each medical device has the capability to export data and critically ill patients generate data from stationary or mobile bedside devices (monitors, ventilators, infusion pumps, and vital organ support systems), image diagnostics, biological samples, and responses to environmental changes that linked the patient to hospital servers.[96,97] Therefore, data from any medical device must have agnostic connectivity with any information system. A platform to support AI systems should enable centralized and interoperable connectivity of biomedical data generated by the patient at any point along the care pathway, not only in critical care facilities, but from home before hospital admission to home after hospital discharge. Again, an ideal platform should provide access to a set of indicators resulting from the application of digital

signal processing techniques and AI to help in decision-making not only in the ICU facilities but throughout the whole process of disease until curation.[98,99]

AI can now be trained to automatically extract and comprehend relevant information from electronic health records, physiologic data from medical devices, and diagnostic tools with the advancement of computer memory and processing speed.[100] This capability has the potential to greatly enhance diagnostic and decision-making processes in health care. It is important to note that while AI systems hold promise in augmenting health care, they should always be used in conjunction with human expertise.[101] The collaboration between AI systems and health care professionals can lead to more efficient and informed decision-making processes, benefiting both caregivers and patients.

MV in 2050

The potential to ventilate more than 1 patient with a single ventilator, a so-called split ventilator setup, has been proposed during COVID-19.[6,102] This recalls the "respirator room" patented in 1908 by Peter Lord and the multi-person negative pressure chamber which was created in 1950 by James Wilson and installed at the Children's Hospital, in Boston.[2] The idea of a centralized machine seems in contrast with the concept that the future most likely will focus on automation based on AI. A bench testing model has proven that a shared ventilator setting is feasible with readily available equipment in a regional hospital.[6] VTs, PEEP, and FiO_2 can be individualized and monitored in a split ventilator.[6] However, the split ventilator, as well as the multiperson chamber, were used in the contest of limited resources during the Polio epidemic[2] or the COVID-19 pandemic.[6] In general, personalized MV approach has been advocated for OR as well as for critically ill patients.[103,104] The balance between the need for enhancing limited resources supporting the use of split ventilators or multiperson devices and the prevention of side effects leading to the use of individualized care is key for the future.[105,106] Easy rules can be used at the bed side to limit risks associated with MV[105,106] and these include a personalized monitoring and MV settings. AI will contribute further to patients' safety. In 2050, less patients will remain intubated for an extensive period of time unless this is part of their documented wishes.[7] Safety for prolonged MV will be possible using AI but hopefully a multidisciplinary ethical team will also support the ICU and respiratory therapists daily at the bedside.

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REFERENCES

1. Baker AB. Artificial respiration, the history of an idea. *Med Hist*. 1971;15:336–351.
2. Kacmarek RM. The mechanical ventilator: past, present, and future. *Respir Care*. 2011;56:1170–1180.
3. Slutsky AS. History of mechanical ventilation: from Vesalius to ventilator-induced lung injury. *Am J Respir Crit Care Med*. 2015;191:1106–1115.
4. Woollam CHM. The development of apparatus for intermittent negative pressure respiration. *Anaesthesia*. 1976;31:537–547.
5. Young JD, Sykes MK. Artificial ventilation: history, equipment and techniques. *Thorax*. 1990;45:753–758.
6. Hong Y, Chen L, Pan Q, Ge H, Xing L, Zhang Z. Individualized mechanical power-based ventilation strategy for acute respiratory failure formalized by finite mixture modeling and dynamic treatment regimen. *EClinicalMedicine*. 2021;36:100898.
7. Pelosi P. A personal trip into spirituality and religion in critical care. *Int Care Med*. 2023. doi:https://doi.org/10.1007/s00134-023-07120-w.
8. Bahns E. It began with the pulmotor: one hundred years of artificial ventilation. https://www.draeger.com/Products/Content/history-artificial-ventilation-bk-9051407-en-us-1507-3.pdf.
9. McNamee JJ, Gillies MA, Barrett NA, et al. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA*. 2021;326:1013–023.
10. Dhawan N. Philip Drinker versus John Haven Emerson: battle of the iron lung machines, 1928–1940. *J Med Biogr*. 2020;28:162–168.
11. Petty TL. The modern evolution of mechanical ventilation. *Clin Chest Med*. 1988;9:1–10.
12. Jain RK, Swaminathan S. Anaesthesia ventilators. *Indian J Anaesth*. 2013;57:525–532.

13. Halliday HL. The fascinating story of surfactant. *J Paediatr Child Health*. 2017;53:327–332.
14. Patterson JR, Russell GK, Pierson DJ, Levin DC, Nett LM, Petty TL. Evaluation of a fluidic ventilator: a new approach to mechanical ventilation. *Chest*. 1974;66:706–711.
15. Tawfic QA, Kuasalya R. Liquid ventilation. *Oman Med J*. 2011;26:4–9.
16. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet*. 1967;2:319–323.
17. Dellaca RL, Veneroni C, Farre R. Trends in mechanical ventilation: are we ventilating our patients in the best possible way? *Breathe (Sheff)*. 2017;13:84–98.
18. Telias I, Brochard LJ, Gattarello S, et al. The physiological underpinnings of life-saving respiratory support. *Intensive Care Med*. 2022;48:1274–1286.
19. Gattinoni L, Quintel M, Marini JJ. Volutrauma and atelectrauma: which is worse? *Crit Care*. 2018;22:264.
20. Miskovic A, Lumb AB. Postoperative pulmonary complications. *Br J Anaesth*. 2017;118:317–334.
21. Edenstierna G, Rothen HU. Atelectasis formation during anesthesia: causes and measures to prevent it. *J Clin Monit Comput*. 2000;16:329–335.
22. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. *Anesthesiology*. 2005; 102:838–854.
23. Bluth T, Serpa Neto A, Schultz MJ, et al; Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of AnaesthesiologyPROBESE Collaborative Group. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. *JAMA*. 2019;321:2292–2305.
24. Williams EC, Motta-Ribeiro GC, Vidal Melo MF. Driving pressure and transpulmonary pressure: how do we guide safe mechanical ventilation? *Anesthesiology*. 2019;131:155–163.
25. Douville NJ, McMurry TL, Ma JZ, et al; Multicenter Perioperative Outcomes Group (MPOG) Perioperative Clinical Research Committee. Airway driving pressure is associated with postoperative pulmonary complications after major abdominal surgery: a multicentre retrospective observational cohort study. *BJA Open*. 2022;4:100099.
26. Neto AS, Hemmes SN, Barbas CS, et al; PROVE Network Investigators. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med*. 2016;4:272–280.
27. Young CC, Harris EM, Vacchiano C, et al. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. *Br J Anaesth*. 2019;123:898–913.
28. Musch G, Vidal Melo MF. Intraoperative protective mechanical ventilation: fact or fiction? *Anesthesiology*. 2022;137:381–383.
29. Couture EJ, Provencher S, Somma J, Lellouche F, Marceau S, Bussieres JS. Effect of position and positive pressure ventilation on functional residual capacity in morbidly obese patients: a randomized trial. . *Can J Anaesth*. 2018;65:522–528.
30. Nimmagadda U, Salem MR, Crystal GJ. Preoxygenation: physiologic basis, benefits, and potential risks. *Anesth Analg*. 2017;124:507–517.
31. Heinrich S, Horbach T, Stubner B, Prottengeier J, Irouschek A, Schmidt J. Benefits of heated and humidified high flow nasal oxygen for preoxygenation in morbidly obese patients undergoing bariatric surgery: a randomized controlled study. *J Obes Bariatrics*. 2014;1:7.
32. Binks MJ, Holyoak RS, Melhuish TM, Vlok R, Bond E, White LD. Apneic oxygenation during intubation in the emergency department and during retrieval: a systematic review and meta-analysis. *Am J Emerg Med*. 2017;35:1542–1546.
33. Bright MR, Harley WA, Velli G, Zahir SF, Eley V. High-flow nasal cannula for apneic oxygenation in obese patients for elective surgery: a systematic review and meta-analysis. *Anesth Analg*. 2023;136:483–493.
34. Serpa Neto A, Hemmes SN, Barbas CS, et al; PROVE Network Investigators. Protective versus conventional ventilation for surgery: a systematic review and individual patient data meta-analysis. *Anesthesiology*. 2015;123:66–78.
35. Yang D, Grant MC, Stone A, Wu CL, Wick EC. A meta-analysis of intraoperative ventilation strategies to prevent pulmonary complications: is low tidal volume alone sufficient to protect healthy lungs? *Ann Surg*. 2016;263:881–887.
36. Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. *Anesthesiology*. 2013;118:1307–1321.
37. Futier E, Constantin JM, Paugam-Burtz C, et al; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369:428–437.
38. Costa ELV, Slutsky AS, Brochard LJ, et al. Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2021;204:303–311.
39. Santer P, Wachtendorf LJ, Suleiman A, et al. Mechanical power during general anesthesia and postoperative respiratory failure: a multicenter retrospective cohort study. *Anesthesiology*. 2022;137:41–54.
40. Karalapillai D, Weinberg L, Neto AS, et al. Intra-operative ventilator mechanical power as a predictor of postoperative pulmonary complications in surgical patients: A secondary analysis of a randomised clinical trial. *Eur J Anaesthesiol*. 2022;39:67–74.
41. Marini JJ, Thornton LT, Rocco PRM, Gattinoni L, Crooke PS. Practical assessment of risk of VILI from ventilating power: a conceptual model. *Crit Care*. 2023;27:157.
42. Neligan PJ, Malhotra G, Fraser M, et al. Continuous positive airway pressure via the Boussignac system immediately after extubation improves lung function in morbidly obese patients with obstructive sleep apnea undergoing laparoscopic bariatric surgery. *Anesthesiology*. 2009;110:878–884.
43. Chaudhuri D, Granton D, Wang DX, et al. High-flow nasal cannula in the immediate postoperative period: a systematic review and meta-analysis. *Chest*. 2020;158:1934–1946.
44. https://www.asahq.org/standards-and-guidelines/standards-for-basic-anesthetic-monitoring.
45. Eichler L, Truskowska K, Dupree A, Busch P, Goetz AE, Zöllner C. Intraoperative ventilation of morbidly obese patients guided by transpulmonary pressure. *Obes Surg*. 2018;28:122–129.
46. Buonanno P, Marra A, Iacovazzo C, et al. Electric impedance tomography and protective mechanical ventilation in elective robotic-assisted laparoscopy surgery with steep Trendelenburg position: a randomized controlled study. *Sci Rep*. 2023;13:2753.
47. Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med*. 2015;372:747–755.
48. Grasselli G, Calfee CS, Camporotta L, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. *Intensive Care Med*. 2023. doi:https://doi.org/10.1007/s00134-023-07050-7.

49. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi PM. ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med*. 2009;151:566–576.
50. Laffey JG, Bellani G, Pham T, 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 [published correction appears in Intensive Care Med. 2017 Nov 14;]. *Intensive Care Med*. 2016;42:1865–1876.
51. Cressoni M, Gotti M, Chiurazzi C, et al. Mechanical power and development of ventilator-induced lung injury. *Anesthesiology*. 2016;124:1100–1108.
52. Tonetti T, Vasques F, Rapetti F, et al. Driving pressure and mechanical power: new targets for VILI prevention. *Ann Transl Med*. 2017;5:286.
53. Marini John J, Rocco Patricia RM. Gattinoni L. Static and dynamic contributors to ventilator-induced lung injury in clinical practice. pressure, energy, and power. *Am J Respir Crit Care Med*. 2020;201:767–774.
54. Marini JJ, Rodriguez RM, Lamb V. Bedside estimation of the inspiratory work of breathing during mechanical ventilation. *Chest*. 1986;89:56–63.
55. Serpa Neto A, Deliberato RO, Johnson AEW, et al; PROVE Network Investigators. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med*. 2018;44:1914–1922.
56. Zhang Z, Zheng B, Liu N, Ge H, Hong Y. Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome. *Intensive Care Med*. 2019;45:856–864.
57. Coppola S, Caccioppola A, Froio S, et al. Effect of mechanical power on intensive care mortality in ARDS patients. *Crit Care*. 2020;24:246.
58. Goligher EC, Telias I, Sahetya SK, et al. Physiology is vital to precision medicine in acute respiratory distress syndrome and sepsis. *Am J Respir Crit Care Med*. 2022;206:14–16.
59. Wong IMJ, Ferguson ND, Urner M. Invasive mechanical ventilation. *Intensive Care Med*. 2023;49:669–672.
60. Beitler JR, Sarge T, Banner-Goodspeed VM, et al; EPVent-2 Study Group. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure-guided strategy vs an empirical high PEEP-FiO2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2019;321:846–857.
61. Sarge T, Baedorf-Kassis E, Banner-Goodspeed V, et al; EPVent-2 Study Group. Effect of esophageal pressure–guided positive end-expiratory pressure on survival from acute respiratory distress syndrome: a risk-based and mechanistic reanalysis of the EPVent-2 trial. *Am J Respir Crit Care Med*. 2021;204:1153–1163.
62. McNamee JJ, Gillies MA, Barrett NA, et al; REST Investigators. Effect of lower tidal volume ventilation facilitated by extracorporeal carbon dioxide removal vs standard care ventilation on 90-day mortality in patients with acute hypoxemic respiratory failure: the REST randomized clinical trial. *JAMA*. 2021;326:1013–1023.
63. Sato R, Dugar S, Cheungpasitporn W, et al. The impact of right ventricular injury on the mortality in patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care*. 2021;25:172.
64. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol*. 1957;189:609–615.
65. Pham T, Brochard LJ, Slutsky AS. Mechanical ventilation: state of the art. *Mayo Clin Proc*. 2017;92:1382–1400.
66. Corp A, Thomas C, Adlam M. The cardiovascular effects of positive pressure ventilation. *BJA Educ*. 2021;21:202–209.
67. Oto B, Annesi J, Foley RJ. Patient–ventilator dyssynchrony in the intensive care unit: A practical approach to diagnosis and management. *Anaesth Intensive Care*. 2021;49:86–97.
68. Goligher EC. Myotrauma in mechanically ventilated patients. *Intensive Care Med*. 2019;45:881–884.
69. Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. . *Am J Respir Crit Care Med*. 2013;187:1294–1302.
70. Béduneau G, Pham T, Schortgen F, et al; WIND (Weaning according to a New Definition) Study Group and the REVA (Réseau Européen de Recherche en Ventilation Artificielle) Network. Epidemiology of weaning outcome according to a new definition. The WIND study. *Am J Respir Crit Care Med*. 2017;195:772–783.
71. Frutos-Vivar F, Esteban A, Apezteguia C, et al. Outcome of reintubated patients after scheduled extubation. . *J Crit Care*. 2011;26:502–509.
72. Dres M, Demoule A. Diaphragm dysfunction during weaning from mechanical ventilation: an underestimated phenomenon with clinical implications. *Crit Care*. 2018;22:73.
73. Liu J, Shen F, Teboul JL, et al. Cardiac dysfunction induced by weaning from mechanical ventilation: incidence, risk factors, and effects of fluid removal. *Crit Care*. 2016;20:369.
74. Peters J, Fraser C, Stuart RS, Baumgartner X, Robotham JL. Negative intrathoracic pressure decreases independently left ventricular filling and emptying. *Am J Physiol*. 1989;257:H120–H131.
75. Bachmann MC, Morais C, Bugedo G, et al. Electrical impedance tomography in acute respiratory distress syndrome. *Crit Care*. 2018;22:263.
76. Soliman-Aboumarie H, Breithardt OA, Gargani L, Trambaiolo P, Neskovic AN. How-to: focus cardiac ultrasound in acute settings. *Eur Heart J Cardiovasc Imaging*. 2022;23:150–153.
77. Repessé X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. *Chest*. 2015;147:259–265.
78. Mekontso Dessap A, Boissier F, Leon R, et al. Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome. *Crit Care Med*. 2010;38:1786–1792.
79. Markota A, Golub J, Stožer A, et al. Absence of lung sliding is not a reliable sin of pneumothorax in patients with high positive end-expiratory pressure. *Am J Emerg Med*. 2016;34:2034–2036.
80. Gargani L, Soliman-Aboumarie H, Volpicelli G, Corradi F, Pastore MC, Cameli M. Why, when, and how to use lung ultrasound during the COVID-19 pandemic: enthusiasm and caution. *Eur Heart J Cardiovasc Imaging*. 2020;21:941–948.
81. Nguyen M, Benkhadra S, Douguet C, Bouhemad B. Real-time visualization of left lung consolidation relief using lung ultrasound. *Am J Respir Crit Care Med*. 2016;193:e59–e60.
82. Moschietto S, Doyen D, Grech L, Dellamonica J, Hyvernat H, Bernardin G. Transthoracic echocardiography with Doppler tissue imaging predicts weaning failure from mechanical ventilation: evolution of the left ventricle relaxation rate during a spontaneous breathing trial is the key factor in weaning outcome. *Crit Care*. 2012;16:R81.
83. Soummer A, Perbet S, Brisson H, et al; Lung Ultrasound Study Group. Ultrasound assessment of lung aeration loss

during a successful weaning trial predicts postextubation distress. *Crit Care Med*. 2012;40:2064–2072.
84. Spadaro S, Grasso S, Mauri T, et al. Can diaphragmatic ultrasonography performed during the T-tube trial predict weaning failure? The role of diaphragmatic rapid shallow breathing index. *Crit Care*. 2016;20:305.
85. Kim WY, Suh HJ, Hong SB, Koh Y, Lim C-M. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med*. 2011;39:2627–2630.
86. Mayo P, Volpicelli G, Lerolle N, Schreiber A, Doelken P, Vieillard-Baron A. Ultrasonography evaluation during the weaning process: the heart, the diaphragm, the pleura and the lung. *Intensive Care Med*. 2016;42:1107–1117.
87. Concato J, Corrigan-Curay J. Real-world evidence: where are we now?. *N Engl J Med*. 2022;386:1680–1682.
88. Lucangelo U, Bernabè F, Blanch L. Lung mechanics at the bedside: make it simple. *Curr Opin Crit Care*. 2007;13:64–72.
89. Maslove DM, Lamontagne F, Marshall JC, Heyland DK. A path to precision in the ICU. *Crit Care*. 2017;21:79.
90. Dianti J, Morris IS, Urner M, et al. Linking acute physiology to outcomes in the ICU: challenges and solutions for research. *Am J Respir Crit Care Med*. 2023;207:1441–1450.
91. de Haro C, Ochagavia A, López-Aguilar J, et al; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Patient-ventilator asynchronies during mechanical ventilation: current knowledge and research priorities. *Intensive Care Med Exp*. 2019;7(suppl 1):43.
92. Magrans R, Ferreira F, Sarlabous L, et al; ASYNICU group. The effect of clusters of double triggering and ineffective efforts in critically ill patients. *Crit Care Med*. 2022;50:e619–e629.
93. de Haro C, López-Aguilar J, Magrans R, et al; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Double cycling during mechanical ventilation: frequency, mechanisms, and physiologic implications. *Crit Care Med*. 2018;46:1385–1392.
94. Sarlabous L, Aquino-Esperanza J, Magrans R, et al. Development and validation of a sample entropy-based method to identify complex patient-ventilator interactions during mechanical ventilation. *Sci Rep*. 2020;10:13911.
95. Adler-Milstein J, Chen JH, Dhaliwal G. Next-generation artificial intelligence for diagnosis: from predicting diagnostic labels to "wayfinding.". *JAMA*. 2021;326:2467–2468.
96. Anderson DC, Jackson AA, Halpern NA. Informatics for the modern intensive care unit. *Crit Care Nurs Q*. 2018;41:60–67.
97. Acosta JN, Falcone GJ, Rajpurkar P, Topol EJ. Multimodal biomedical AI. *Nat Med*. 2022;28:1773–1784.
98. Esperanza JA, Sarlabous L, de Haro C, Magrans R, Lopez-Aguilar J, Blanch L. Monitoring asynchrony during invasive mechanical ventilation. *Respir Care*. 2020;65:847–869.
99. Maslove DM, Tang B, Shankar-Hari M, et al. Redefining critical illness. *Nat Med*. 2022;28:1141–1148.
100. Haug CJ, Drazen JM. Artificial intelligence and machine learning in clinical medicine, 2023. *N Engl J Med*. 2023;388:1201–1208.
101. Navarra-Ventura G, Gomà G, de Haro C, et al. Virtual reality-based early neurocognitive stimulation in critically ill patients: a pilot randomized clinical trial. *J Pers Med*. 2021;11:1260.
102. Neyman G, Irvin CB. A single ventilator for multiple simulated patients to meet disaster surge. *Acad Emerg Med*. 2006;13:1246–1249.
103. Branson RD, Blakeman TC, Robinson BR, Johannigman JA. Use of a single ventilator to support 4 patients: laboratory evaluation of a limited concept. *Respir Care*. 2012;57:399–403.
104. Stiers M, Mergeay M, Pinson H, et al. Individualized mechanical ventilation in a shared ventilator setting: limits, safety and technical details. *J Clin Monit Comput*. 2021;35:1299–1309.
105. Pelosi P, Ball L, Barbas CSV, et al. Personalized mechanical ventilation in acute respiratory distress syndrome. *Crit Care*. 2021;25. doi:https://doi.org/10.1186/s13054-021-03686-3.
106. Denise B, Marco S, Lorenzo B, Chiara R, Patricia R.M. R, Paolo P. Ten golden rules for individualized mechanical ventilation in acute respiratory distress syndrome. *J Intensive Med*. 2021;Volume 1:42–51.