Fifty Years of Mechanical Ventilation—1970s to 2020

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Positive-pressure ventilation (PPV) has been a mainstay of respiratory life support for over a century. The goals of PPV are to safely provide adequate alveolar ventilation and maintain lung recruitment. Current approaches to delivering PPV are generally patterned after the normal breathing pattern in which tidal volumes (VTs) are delivered at a certain respiratory rate (RR), often on the top of an elevated baseline airway pressure (positive end-expiratory pressure [PEEP]). Modern devices are also equipped with sophisticated monitoring/alarm systems, feedback controls enhancing patient-ventilator synchrony and safe ventilatory patterns, data storage capabilities with interfaces to electronic health records, and decision support systems.

Many of these PPV features have emerged over the last 50 years and are the result of technical advances and the translation of extensive basic and applied clinical research into clinical practice—much of which has been published in *Critical Care Medicine* over its 50 years of existence. This review looks back on these last 5 decades and has grouped the discussions into the decade in which a development first had real impact. It is an attempt to chronicle the important innovations, discoveries, and randomized trials that have transformed the simple concept of "in goes the good air, out goes the bad air" into the sophisticated life support system in common use today.

PPV–THE EVOLUTITON FROM ANCIENT TIMES TO THE 1970s

The concept of supporting respiratory function using positive-pressure gas sources delivered through an artificial airway dates back to ancient times (1, 2). Tracheostomies have been described for over 2 centuries and could be life-saving in warriors with airway injuries (2). Positive-pressure gas sources including mouth-to-mouth techniques or devices such as fireplace bellows to deliver fresh gas through natural or artificial airways have also been described for centuries (3). Similarly, a variety of negative pressure devices have also been described to inflate the thoracic cage externally (1, 2).

The first widespread use of mechanical ventilation was with the negative pressure "iron lung" during the polio epidemics beginning in 1928 (4). Mechanized positive-pressure devices were also introduced around this time and initially were used noninvasively (Draeger Pulmotor) for short-term rescue in coal miners (5).

By the middle of the 20th century, simple, pneumatically controlled positive-pressure devices developed by pioneers such as Forrest Bird and Ray Bennett

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were becoming widely available to support both postoperative patients as well as nonsurgical patients with respiratory failure (1, 2). These devices provided effective respiratory support and were much easier to use than the negative pressure iron lung. Also during this period, the benefits of maintaining airway pressure during expiration to treat pulmonary edema (continuous positive airway pressure [CPAP]) were first described by Barach et al (6) and evolved into the concept of using PEEP during PPV for similar purposes. Supporting these efforts was the development of oxygen and carbon dioxide electrodes, allowing direct assessment of ventilation and gas exchange (7, 8).

During this period, much of the literature on the management of PPV was coming from the operating room. The overall goals of respiratory support during general anesthesia were to mimic the normal human respiratory pattern and restore near normal gas exchange. Importantly, it was recognized that anesthetized, paralyzed patients were also prone to atelectasis and hypoxemia (9). Although PEEP could ameliorate this, hemodynamic concerns limited its use. As a consequence, anesthesia recommendations in the mid-20th century were to minimize PEEP and ventilate patients undergoing general anesthesia with VTs of 10–15 mL/kg predicted body weight (PBW), often with sigh breaths. These anesthesia PPV strategies were gradually transferred out of the operating room to manage a variety of patients with respiratory failure in acute care settings (10, 11). The use of these strategies was often justified by the observation that they had been employed in "several thousand ventilated patients with no evidence of development of pulmonary damage" (10).

Oxygen was often supplied with PPV throughout the early 20th century and, as noted above, was often used instead of PEEP to correct hypoxemia induced by atelectasis. However, it had been known for decades that hyperoxia had the potential to injure lungs (12). Nevertheless, it was not until the mid-20th century that concerns about lung oxygen toxicity were beginning to be expressed, initially in the neonatal population with hyaline membrane disease (13–15). Spread of this concern to the adult community would take longer.

In summary, PPV had come a long way during the first half of the 20th century. The focus during this time, however, was to use the technology to "normalize" physiology as much as possible with little regard for harm beyond overt barotrauma and cardiac compromise. Much would occur over the next 50 years (**Table 1** and **Figs. 1** and **2**).

PPV IN THE 1970s

By the 1970s (along with the formation of the Society of Critical Care Medicine and its journal *Critical Care Medicine*), dedicated respiratory (intensive) care units were being developed as PPV use became increasingly used throughout the developed world. However, PEEP use was uncommon and VT settings were still often two or more times normal in an effort to eliminate atelectasis. The safety concerns about PPV continued to be focused primarily on pneumothorax risk and hemodynamic compromise (1, 2, 16–18).

As the 1970s unfolded, electrically powered volume-cycled devices were becoming increasingly popular as clinicians could directly set the rate, VT, and inspiratory:expiratory (I:E) ratio. These early volume-cycled PPV devices initially provided only controlled ventilation (continuous or controlled mandatory ventilation). Any spontaneous efforts from the patient had to be suppressed. Ventilator liberation thus required sedation (or paralysis) reduction and a spontaneous unsupported breathing assessment (later to be known as a "spontaneous breathing trial" [SBT]).

To reduce sedation (or paralysis) needs, devices were developed to provide an "intermittent" mandatory ventilation (IMV) feature that allowed unsupported spontaneous VTs interspersed among the mandatory breaths (19). The subsequent development of assisted breath triggers for volume-targeted (volume controlled) devices in the late 1960s to early 1970s finally permitted patients to interact with the ventilator at least for delivery of a set VT. IMV thus could become "synchronized" IMV (SIMV) in that patient efforts could trigger either the set volume-cycled breath or simply be unsupported. Ventilator liberation could now be done by "weaning" the set mandatory rate and allowing increasing patient efforts to trigger unsupported tidal breaths (19, 20). Although controversial and having minimal supporting evidence, IMV (SIMV) weaning became an increasingly popular PPV technique.

The notion that the ventilator (especially in the presence of high F_{IO_2}) could produce a lung injury at pressures below that associated with pneumothoraces was first introduced in the pediatric/neonatal literature in the late 1960s (1, 2, 15, 21–23). An example was a

TABLE 1.
Four Generations of ICU-Based Mechanical Ventilators 1970–2020[a]

First generation (pre-1970s). Basic pressure or volume-targeted devices, few (if any) monitors/alarms, and no built in PEEP. Examples:
Bird Mark 7
Bennett PR 2
Morch
Engstrom
Emerson postoperative ventilator
Second generation. Volume-targeted devices with assist triggering, built in PEEP, and basic monitors/alarms. Examples:
Puritan Bennett MA1 (1967), MA2 (1978)
JJ Monaghan, Ohio 560 (1968)
Siemens, Servo 900b (1971), 900c (1981)–900c offered pressure targeting features
Chemetron, Gill 1 (1975)
Bournes Bear 1 (1975), Bear 2 (1981), Bear 3 (1988)–Bear 3 offered pressure support
Drager UV1 (1977), EV-A (1982)–offered graphic displays
Third generation. Mircroprocessor controllers, complete pressure, and volume-targeted modes. Examples:
Puritan Bennett 7200 (1983)
Hamilton Veolar (1983)
Siemens, Servo 300 (1991)
Bear 1000 (1993)–offered standard graphic displays
Fourth generation. Novel feedback features (usually based on pressure-targeted modes), numerous proprietary breath delivery systems, and expanded monitoring capabilities with graphics. Examples:
Covidien PB 840 (1998), PB 980 (2014)–unique proportional assist feature
Drager Evita 4 (1995), Evita XL (2003), Evita V 500 (2009)–unique automated weaning algorithm
Maquet Servo I (2001), Servo U (2016)–unique neurologically-assisted ventilatory assist feature, advanced mechanics
Hamilton Galileo (1997), Raphael (2003), GS (2007)–unique adaptive support feature
CareFusion Avea (2002)–integrated esophageal pressure
General Electric Carestation (2011)–incorporates metabolic calculations and functional residual capacity measurements

[a]Generation concept adapted from Kacmarek (1).
PEEP = positive end-expiratory pressure.

report that premature infants with hyaline membrane disease ventilated at 20–40 cm H_2O and high F_{IO_2}s developed a subsequent lung injury (bronchopulmonary dysplasia). It was not clear whether it was the high distending pressure or high F_{IO_2} (or both) that caused the injury (15) but it changed thinking going into the 1970s about the potential harm associated with oxygen and even modestly elevated pressures from PPV.

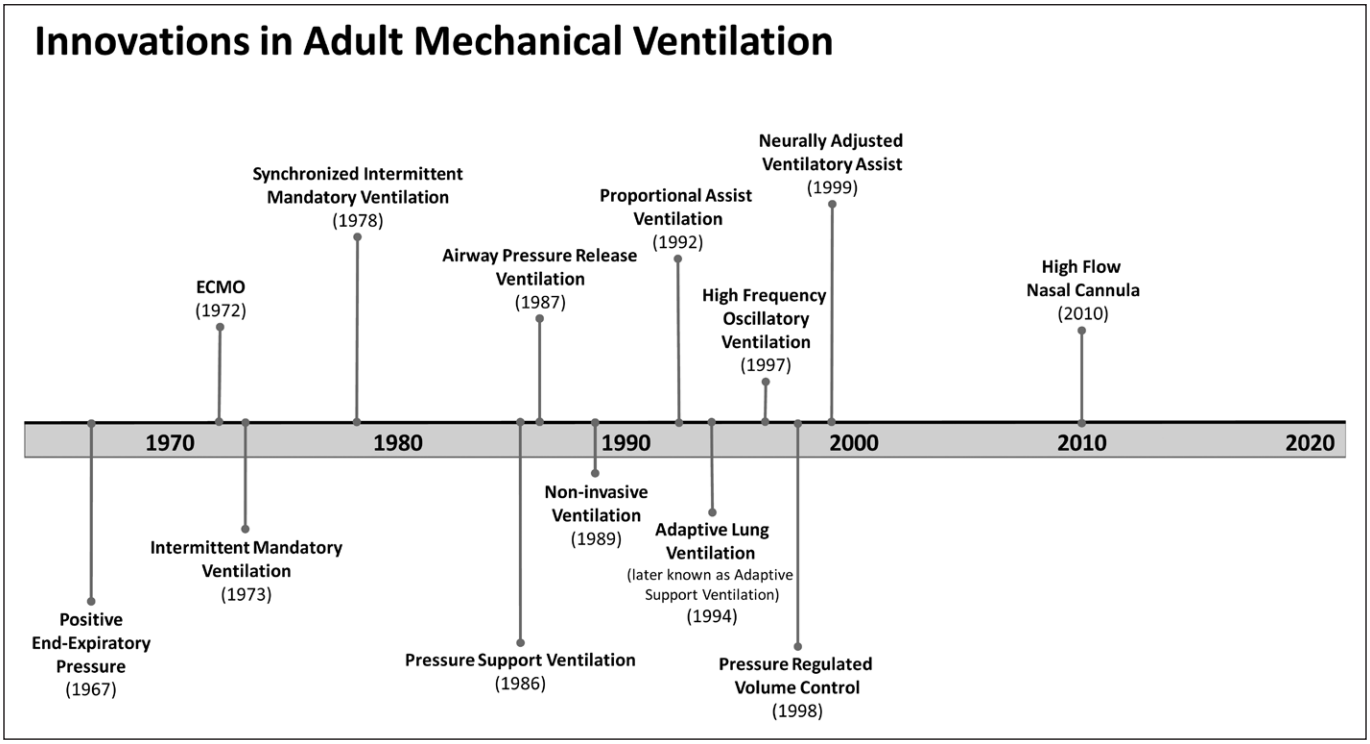

Figure 1. Innovations in adult mechanical ventilation. ECMO = extracorporeal membrane oxygenation.

The 1970s ushered in an increasing interest in using PEEP for several reasons. First, as noted above, it had been known for decades that maintaining a constant elevated airway pressure helped maintain alveolar recruitment in cardiogenic pulmonary edema (6). By the 1970s, this concept was being expanded (initially in neonates) into the notion that expiratory pressure (PEEP) following a positive-pressure breath could prevent lung derecruitment in parenchymal lung injury as well through both physical "splinting" of alveolar structures along with maintenance of the surfactant monolayer (24). These physiologic benefits to PEEP were finally shown to be associated with a mortality benefit in adults by Ashbaugh et al (25, 26) and Sugarman et al (27) in their original description of the adult (later acute) respiratory distress syndrome (ARDS). Second, the fear of hemodynamic compromise from PEEP was becoming less concerning as clinicians realized that airway pressures in the injured lung are transmitted less into the vascular space than in normal lungs. Furthermore, adequate intravascular volume could help ameliorate any effect on cardiac filling (28, 29). Third, the notion of oxygen toxicity as an important potential factor in lung injury was growing in importance and PEEP was being viewed as a viable option to help reduce F_{IO_2} exposure (24, 26, 28–30). Finally, the classic study by Webb and Tierney (31) demonstrated that PEEP, by preventing collapse-reopening of alveoli, could protect the lung from an injury produced by excessive end-inspiratory pressures and volumes. This lung-protective concept of preventing derecruitment with PEEP was supported by calculations made by Mead et al (32), suggesting that shear forces equivalent to 140 cm H_2O occurred at the interfaces of collapsed and opened alveoli during recruitment-derecruitment.

As the comfort level with PEEP use grew, some expanded the goal of maintaining recruitment to more aggressive "open lung" strategies using recruitment maneuvers and PEEP levels in excess of 40 cm H_2O (33, 34). Hemodynamic compromise was managed with fluids. There were also anecdotal reports of simultaneously using chest strapping to stiffen the thoracic cage in order to distribute the applied PEEP more evenly in the lungs. Importantly, small trials of this "super PEEP" failed to show a consistent outcome benefit. Nevertheless, interest in aggressive PEEP strategies (± recruitment maneuvers) persisted well into the 21st century (35).

In 1975, Suter et al (36) demonstrated the important concept that PEEP was in fact a "two-edged sword" and that competing goals for PEEP existed. On the one hand, raising PEEP could increasingly reduce shunt fraction in

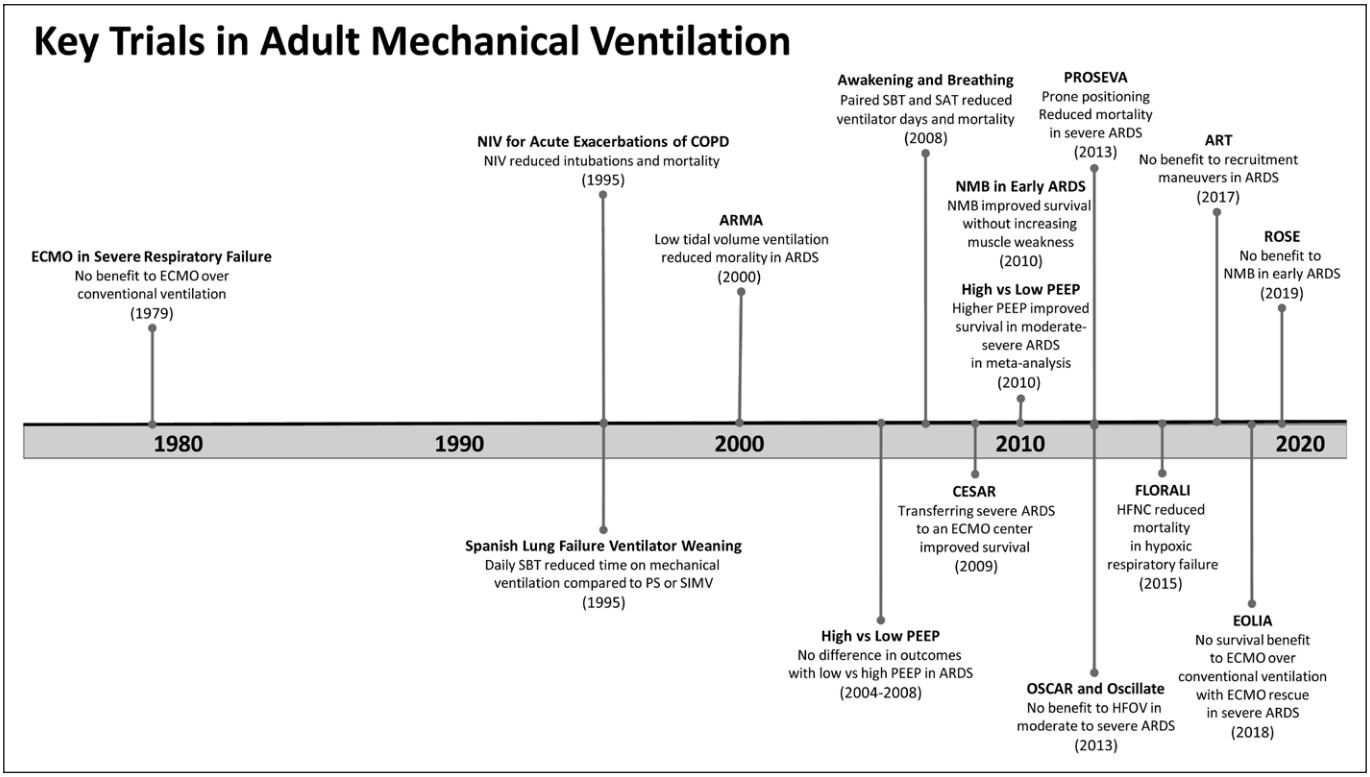

Figure 2. Key trials in adult mechanical ventilation. ARDS = acute respiratory distress syndrome, ARMA = and respiratory management in acute respiratory distress syndrome, ART = alveolar recruitment for acute respiratory distress syndrome trial, CESAR = efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure, COPD = chronic obstructive pulmonary disease, ECMO = extracorporeal membrane oxygenation, EOLIA = extracorporeal membrane oxygenation for severe acute respiratory distress syndrome, FLORALI = high flow oxygen through nasal cannula in acute respiratory failure, HFNC = high-flow nasal cannula, HFOV = high-frequency oscillatory ventilation, NIV = noninvasive ventilation, NMB = neuromuscular blockade, PEEP = positive-end expiratory pressure, OSCAR = oscillation in acute respiratory distress syndrome, OSCILLATE = oscillation for acute respiratory distress syndrome treated early, PROSEVA = prone positioning in severe acute respiratory distress syndrome, ROSE = reevaluation of systemic early neuromuscular blockade, SAT = spontaneous awakening trial, SBT = spontaneous breathing trial.

injured lung units (with accompanying improved compliance) and improve oxygenation. On the other hand, raising PEEP could also serve to increasingly overdistend less-injured lung regions that were not in need of PEEP (with accompanying reduced compliance). As noted above, raising PEEP could also progressively reduce cardiac filling and reduce cardiac output. From this work emerged the notion of a "best" PEEP that balanced these competing goals and resulted in a PEEP that optimized oxygen delivery and respiratory system compliance, even if the Po_2 was not maximal.

An alternative to PEEP that garnered some interest in the 1970s was the use of a long inspiratory time, even to the point of reversing the I:E time ratio above 1:1 (inverse ratio ventilation [IRV]) (37). The effects of this were two-fold. First, the longer inspiratory time allowed more time for gas mixing in the lung and a longer maintenance of inflation pressure. Mean airway pressure was thereby increased without raising applied PEEP or the end-inspiratory pressures. Second, if expiratory time was short enough, the lung could not return to functional residual capacity and intrinsic (auto) PEEP from gas trapping developed (37, 38). Although intrinsic PEEP had the potential to maintain recruitment, the distribution of intrinsic PEEP may be less optimal than the applied PEEP (39). In addition, when using the volume control modes of the 1970s, intrinsic PEEP would raise end-inspiratory pressures similar to applied PEEP. Although the physiology of IRV was interesting, outcome benefits were difficult to prove.

One final note about the 1970s—extracorporeal life support (ECLS) for respiratory failure was exported from the cardiothoracic operating room to the ICU in the mid 1970s (40). However, in a trial of 90 patients with severe respiratory failure, Zapol et al (41) reported 90+% mortality in both the ECLS and the control group. Unfortunately, optimizing gas exchange was the

therapeutic goal in both groups as the concept of using ECLS to protect the lung was not considered. As a consequence, injurious PPV settings were used in both groups and further interest in ECLS as a lung protective strategy would take several decades to resurface.

PPV IN THE 1980s

A major paradigm shift in PPV management away from "maximizing" gas exchange to "lung protection" began in the 1980s (42–44). Indeed, from the infancy of artificial respiration methods, it was clear that providing indiscriminate lung volumes could be harmful. However, the 1980s brought an explosion of primarily animal studies, clearly showing that ventilator-induced lung injury (VILI) was real and was associated with volume and pressures just above the upper limits of normal—levels far lower than what had previously been considered safe.

In a classic 1987 study, Kolobow et al (45) demonstrated that ventilating normal sheep at VTs of 50–70 mL/kg PBW (equivalent to the normal maximal inspiratory capacity) led to rapid deterioration and death from severe lung injury, whereas those ventilated at 10-mL/kg PBW remained stable. In later studies involving normal sheep, Mascheroni et al (46) group also demonstrated VTs only slightly larger than normal (9–15 mL/kg PBW) led to severe lung injury relative to VTs approximating the normal resting VT.

In an elegant group of studies, Dreyfuss et al (47) demonstrated that it was the volume change and not the applied pressure that caused the lung injury. Animals subjected to high airway pressures and normal chest wall mechanics developed high VTs and severe injury. In contrast, control animals had chest wall strapping that prevented excessive VTs despite similar high airway pressures and experienced no injury (47). These observations led to the later concepts of stress and strain with PPV (48). Stress is the pressure applied to alveolar structures (i.e., transpulmonary pressure) and strain is the resulting stretch or volume change. VILI was now thought to be in part a consequence of both excessive dynamic strain (VT) and excessive static strain (end-inspiratory lung volume) (49).

Much of the literature focusing on lung protective ventilation strategies in humans was coming from studies on ARDS. ARDS was originally viewed through the lens of the chest x-ray and thought to be a relatively homogeneous disease characterized by uniform damage to the alveolar capillary membrane causing the lungs to become heavy and stiff. However, by the mid-1980s, CT scans were able to better characterize the distribution of injury and showed patchy infiltrates, worse in dependent lung zones, and interspersed with areas of normal-appearing lung (49, 50) This brought about the concept of the "baby lung" where, radiographically, the aerated portion of lung in a patient with severe ARDS is similar in volume to that of a 5–6 year old child (50, 51). This in turn led to the notion that VILI was a regional phenomenon, wherein the delivered positive-pressure breath preferentially went to healthier regions. A "normal" global VT could thus produce excessive regional VTs with excessive regional dynamic and static strain (50–52).

An interesting alternative to PPV to enhance lung protection was the introduction of high-frequency ventilation in the early 1980s (53–56). The idea behind HFV (usually produced by either jets or oscillators) was to maximize lung recruitment with a high mean airway pressure and then provide high-frequency pulses or oscillations around that mean to effect alveolar ventilation. These pulses or oscillations were usually much smaller than anatomic dead space and thus nonconvective (nonbulk flow) mechanisms of gas transport through the airways needed to be invoked. Because tidal distentions were minimal with HFV (CPAP with a "wiggle"), it was theorized that lung injury might be minimized. HFV was first used in neonatal and pediatric populations with mixed results (57–59). Adult use of HFV developed more slowly. Nevertheless, HFV use, especially in neonates/pediatric patients, has persisted into the 21st century. An interesting variation on the HFV concept was developed near the end of this decade that used high-frequency pulsations to stepwise inflate and deflate the lungs. Known as high-frequency percussive ventilation, observational studies suggested benefit, especially in patients with copious airway secretions (60).

The 1980s also saw a growing interest in pressure-targeted (pressure controlled) modes of ventilation. This was originally driven by the introduction of the pressure support breath in 1986 (53). By allowing patients to trigger and adjust the delivered flow, this breath was shown in several studies to improve patient-ventilator synchrony with the hope of reducing sedation (54). In addition, because the inspiratory pressure could be reduced as patients recovered, it was viewed

as an alternative weaning method to IMV—either as a stand-alone mode or in combination with IMV.

The earlier concept of IRV reemerged with description of airway pressure release ventilation (APRV) (55). APRV uses a pressure-targeted long inflation period with a short deflation period designed to produce significant intrinsic PEEP. Pressure targeting allowed spontaneous breaths during the long inflation period—a strategy that would improve patient comfort over older IRV strategies but would also increase the ultimate end-inspiratory volume. APRV is still in use today at some centers but definitive beneficial outcome studies are still lacking.

In the 1980s, there was also growing interest in the unique challenges posed by airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Foremost among these challenges was the potential for significant intrinsic PEEP (38) as a consequence of high airway resistance and high lung compliance. The mechanical effects of intrinsic PEEP raises all airway pressures in volume-targeted modes or reduces VTs in pressure-targeted modes. These undesired effects gave rise to the concept of "permissive" hypercapnia, a strategy of trading CO_2 clearance (and accepting hypercapnia) for reduced lung distention—a concept that has also been applied to other disease states with high ventilatory pressures (56, 61).

The importance of intrinsic PEEP imposing a breath triggering threshold load was also first appreciated in the 1980s (38, 62, 63). Over the ensuing decade, the strategy of applying PEEP to "counterbalance" this triggering load grew in popularity (64, 65).

Finally, the 1980s also introduced microprocessors as PPV controllers (Table 1). This greatly expanded the sensitivity and responsiveness of devices to patient effort, increased monitoring/alarm capabilities, and allowed for future interactions with electronic health records, data storage capabilities, novel feedback mechanisms, and decision support tools.

PPV IN THE 1990s

By the 1990s, the long-standing clinical practices of VTs of 10–15 mL/kg PBW and allowing plateau pressures (Pplat) of up to 40–50 cm H_2O were being increasingly called into question (66). Small clinical trials, however, failed to demonstrate benefits to modest VT and Pplat reductions until Amato et al (67) published a randomized trial in 98 patients, demonstrating a significant survival benefit to ventilating with VTs of 6- versus 12-mL/kg IBW in patients with ARDS.

Providing convincing evidence to support a dramatic change in clinical practice, however, would need a large multicenter trial with sufficient power to detect a realistic reduction in mortality. To address the need for trials such as this, the U.S. National Institutes of Health formed the ARDS network (ARDSnet), a unique consortium of 10 major academic centers charged with conducting large clinical trials, addressing ARDS issues that would not normally be funded by industry sources.

Importantly, the first trial chosen by the ARDSnet was the landmark ARMA trial comparing VTs of 6- versus 12-mL/kg PBW and Pplat limits of 30 versus 50 cm H_2O (68). The trial was initiated in the late 1990s and was designed to randomize 1,000 patients. It was stopped early at 861 patients in 1999 because of a significant decrease in mortality associated with the use of the low VT strategy. The results were published in 2000 and details are reviewed in the "*PPV in the 2000s* section."

In the late 1990s, the concept of "biotrauma" with VILI was being increasingly appreciated (42, 43, 69, 70). This described the phenomenon of systemic cytokine release from VILI, often accompanied by bacterial translocation across the injured alveolar-capillary interface. Biotrauma helped explain the observation that patients with severe respiratory failure requiring PPV often died of multiorgan failure rather than refractory hypoxemia.

The approach to ventilator liberation also changed significantly in the 1990s as the result of two large randomized trials, demonstrating that SBTs appeared to be the most effective way to assess liberation potential (71–73). Indeed, the whole notion of having to wean patients with decreasing levels of pressure support (PS) or IMV before performing an SBT was being called into question (74). However, if gradual support reduction was deemed appropriate for a given patient, these trials suggested that PS was superior to IMV. Importantly, it was increasingly recognized that ventilator liberation could be significantly delayed by excessive sedation and the concept of linking SBTs to sedation reduction strategies grew in popularity (75). A corollary to this was the growing appreciation that prolonged diaphragm inactivity produced progressive diaphragm weakness (ventilator-induced

diaphragmatic dysfunction [VIDD]), often worsened by the presence of a systemic inflammatory response (76, 77). This provided further impetus to limit sedation (and paralysis) and would lead to efforts promoting early mobility in the ensuing decades (78).

The 1990s also witnessed a number of technical advances. Feedback control systems were developed to maintain VT with pressure-targeted breaths. These initially included pressure-regulated volume control and volume support (79–82). The goal of these approaches was to combine the synchrony benefits of pressure targeting while assuring a minimum VT. The most sophisticated feedback system for pressure-targeted breaths was adaptive lung ventilation, later adaptive support ventilation (ASV) (82–84). ASV can deliver both assisted breaths (PS-like) or controlled breaths (pressure-controlled-like). ASV automatically adjusts the applied pressure, I:E ratio, and RR (in the absence of patient-triggered breaths) to reach a minute ventilation target set by the clinician and a rate/VT combination that minimizes the work of breathing. Although theoretically attractive, whether any of these feedback features improved outcomes was unclear.

Although the notion of using esophageal pressures (Pes) to measure patient effort, work of breathing, and transpulmonary pressure had been longstanding, it was not until the 1990s that commercially available devices were developed to do this clinically. Initial uses focused on Pes to assist in the ventilator liberation process using patient muscle work to guide settings (85, 86). Although physiologically appealing, however, it was difficult to show outcome benefits. Subsequent use of Pes to assess transpulmonary pressures as a guide to lung protection would come later in the mid 2000s (see below).

The 1990s also saw the introduction of two truly novel modes of ventilation (87): proportional assist ventilation (PAV) (88) and neurally adjusted ventilatory assist (NAVA) (89). PAV delivers a breath similar to PS ventilation. However, instead of having a constant pressure target with each breath, the pressure applied by the ventilator is proportional to the pressure generated by the respiratory muscles and is adjusted based on the instantaneous flow and volume the patient generates. With PAV, the airway pressure is thus amplified according to patient respiratory mechanics and a clinician chosen level of assistance (from 0% to 100%).

Subsequent improvements upgraded PAV to PAV+, which automatically adjusts the flow and volume gain factors to represent constant fractions of the measured values of resistance and elastance of the respiratory system (90). Unfortunately, the benefit of this mode is that it provides the level of support the patient "requests" and this can lead to injuriously high VTs with vigorous efforts or to inadequate support in the setting of respiratory muscle insufficiency or sedating medications. Meaningful outcome studies are still lacking.

NAVA is a mode in which the ventilator delivers a level of assistance throughout a breath that is dependent on and proportional to the electrical activity of the diaphragm (EAdi) (89, 91). An improvement over PAV is that the breath is independent of the muscle function of the diaphragm, assuming that the respiratory drive, phrenic nerves, and neuromuscular junctions are intact. Therefore, NAVA has the potential to enhance patient-ventilator synchrony and avoid issues related to intrinsic PEEP or air leaks. Although there are many potential advantages to NAVA, the stability of the EAdi signal over long periods of ventilation or during patient movement may be problematic, and it remains to be established whether patient-ventilator synchrony improvement results in a substantial clinical outcome advantage.

Finally, although the early pressure-cycled devices of the mid 20th century were often used with noninvasive mask interfaces (e.g., intermittent positive pressure breathing), the more versatile invasive PPV devices of the 1980s and 1990s were difficult to use noninvasively because of patient tolerance and significant mask leaks. In the early 1990s, however, single limb bilevel pressure devices were being developed and dedicated pressure-targeted NIV systems were introduced that provided both effective mask PS and pressure assist-control ventilation. NIV was subsequently demonstrated to reduce significantly the need for intubations and invasive PPV in acute exacerbations of COPD (92, 93). Less convincing benefits for NIV were reported in smaller studies of non-COPD patients.

PPV IN THE 2000s

The 21st century began with a continuation of prioritizing lung protective goals for PPV. As noted above, in 2000, the landmark ARMA trial was published. In this trial, ventilating with lower VTs led to a 9% absolute

reduction in mortality compared with higher VTs despite the lower VT group experiencing worsened gas exchange (68). On further analysis, it appeared that it was both high VTs and high end-inspiratory plateau pressures that drove the increased mortality in the control group (94). Following this study, VT and plateau pressure targets progressively decreased over time for critically ill patients with ARDS (95, 96). In addition, because lung protection is aimed at limiting regional injury in the healthier lung units that exist in virtually all forms of lung disease, these protective strategies increasingly were being used in many non ARDS patients as well (96).

As part of the ARMA trial, the concept of the PEEP/FIO_2 table was introduced, providing a standard method of adjusting PEEP and FIO_2 proportional to the supplemental oxygen needs of the patient (68). Investigators understood that more severe ARDS was associated with worsened consolidation and atelectasis, leading to worsened hypoxia. Increasing PEEP in the setting of high oxygen requirements would ideally allow for improved lung recruitment, reduced shunt fraction, improved oxygenation, and lowered FiO2. Importantly, the table also limited PEEP values to assure Pplat did not exceed 30–35 cm H_2O.

Subsequent clinical trials evaluated variations on the ARDSnet PEEP-FIO_2 table that employed both conservative (lower) and more aggressive (higher) PEEP values. These trials on their own failed to show a benefit to higher versus lower PEEP-targeted tables across broad populations of patients with mild, moderate, and severe ARDS (97–99). However, as these data were aggregated and reanalyzed, it became clear that patients with more severe ARDS, and thus more potentially recruitable lung, had better outcomes with higher levels of PEEP. Conversely, those who had less severe ARDS with less recruitable lung had better outcomes with proportionally lower PEEP levels (100). This underscores the aforementioned "two-edged sword" properties of PEEP—in severe disease, the recruitment benefits of a higher PEEP outweighed the overdistention risk, whereas it is the opposite in less-injured lungs.

The 2000s also saw an extension of the use of Pes to measure transpulmonary pressure in order to guide ventilator settings. The concept was that in the setting of a stiff chest wall (e.g., abdominal compartment syndrome and obesity), high pleural pressures for a given airway pressure reduced transpulmonary pressures, thereby compromising applied PEEP effects. Knowing Pes would thus allow clinicians to add additional PEEP beyond the conventional range (and tolerate higher Pplats) to create a positive expiratory transpulmonary pressure. This strategy actually was associated with a mortality benefit in one randomized controlled trial (RCT) (101). A subsequent trial (102) illustrated that routine Pes monitoring in the absence of an abnormal chest wall offered no real benefit.

Along with safer ventilation strategies came more of a desire to minimize the negative effects of sedation on mechanically ventilated patients. In 2008, the Awakening and Breathing Controlled trial was published. This clinical trial demonstrated that pairing a daily sedation hold with an SBT led to shorter duration of mechanical ventilation and earlier discharge from both intensive care and the hospital, and reduced 1-year mortality (103). Following this study, the U.S. Centers for Disease Control performed the Wake Up and Breathe Collaborative study, which confirmed a significant decrease in the duration of mechanical ventilation and hospital length of stay with paired sedation holds and SBTs (104).

Finally, an interesting consensus group was convened in 2005, addressing a little appreciated group—the prolonged mechanically ventilated (PMV) patient (105). This was a patient group in whom traditional liberation strategies had failed and for whom management guidelines were nonexistent. Although there was little evidence to guide the consensus group, a definition of PMV was developed (need for PPV > 21 d) and strategies for more protracted liberation strategies (including judicious SBTs) were offered.

PPV IN THE 2010s

The previous sections have described a number of advances in mechanical ventilation that helped prevent VILI and more safely manage acute respiratory failure (106). To assess how well clinicians recognize ARDS and adhere to evidence-based management, the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure was undertaken (107). This study represented an international, multicenter, prospective cohort of patients undergoing invasive or noninvasive ventilation, conducted during 4 consecutive weeks in the winter of 2014 across hundreds of ICUs in 50 countries. Clinical recognition of ARDS was poor, ranging from 51.3% for mild ARDS

to 78.5% for severe ARDS. Greater than one-third of patients received VTs greater than 8 mL/kg of PBW, and less than half had measured plateau pressures. This study highlighted the difficulties in changing long imbedded habits, even in the face of strong evidence.

Throughout this decade, our understanding of the mechanisms underlying VILI was rapidly increasing. Although the basic notions of excessive stress and strain along with collapse-reopening phenomenon as major drivers of VILI remained true, it was becoming increasingly apparent that acceleration forces, vascular factors, force multipliers, breathing rate/pattern, and integrated factors such as mechanical power were also likely important (108–112).

The role of neuromuscular blockade (NMB) in mechanically ventilated patients had been argued for decades. On the pro side, NMBs could reduce oxygen consumption and eliminate any patient-ventilator dyssynchrony. The pro NMB argument was bolstered in the early 21st century by the appreciation that strong patient efforts could magnify the VILI risk by generating spontaneous or assisted VTs and transpulmonary pressures greater than what is thought to be safe (so called "self-induced lung injury [SILI]") (113–115). On the con side, NMBs had the potential to magnify critical illness myopathy and VIDD. NMB also needed simultaneous heavy sedation that conceivably could worsen delirium and delay ventilator liberation (116, 117).

Two large trials in the 2010s addressed this controversy. The first, in 2010, was a large clinical trial comparing early use of NMB with placebo in patients with early severe ARDS (118). Results demonstrated a reduced occurrence of barotrauma and reduced mortality with the use of NMBs. Importantly, there was no difference in the rate of ICU-acquired paresis. A second large trial published in 2019 was performed in a cohort of patients with moderate-to-severe ARDS comparing a 48-hour continuous infusion of NMB with concomitant deep sedation to a usual-care approach without routine NMBs and with lighter sedation targets (119). The trial demonstrated no significant difference in the 90-day mortality between the groups. Importantly, there was again no difference in ICU-acquired weakness. Given the results of these two trials, there does not appear to be a clear benefit to routinely giving NMBs and deep sedation to all patients with severe ARDS for 48 hours. However, the safety profile would support consideration for short-term use in selected patients with unmanageable dyssynchronies and/or high oxygen demands. Whether potential SILI protection conferred by NMBs superseded the negative effect of the deep sedation required for administration of NMB remained unclear.

Another major change in practice that occurred during this decade is related to patient positioning during mechanical ventilation. The use of prone positioning to help improve oxygenation and lung recruitment had been described in the 1970s. However, several clinical trials produced mixed results, and prone positioning remained largely a rescue maneuver in the setting of severe ARDS. In 2010, a meta-analysis of several clinical trials suggested a survival benefit to prone positioning in patients with ARDS who had the most severe hypoxia (120). Following this, in 2013, the landmark PROSEVA trial was published (121). This clinical trial compared prone positioning for at least 16 hr/d to supine positioning in patients with ARDS and a Pao_2/Fio_2 ratio less than 150 mm Hg. The investigators demonstrated that early application of prolonged prone-positioning sessions significantly decreased mortality in patients with severe ARDS. Based largely on the results of this clinical trial, current management guidelines strongly recommend prone positioning in patients with severe ARDS (122, 123).

A concept that rose to prominence in the latter half of the 2010s was assessing driving pressure (DP) as a management tool to reduce VILI (124). DP can be thought of as the pressure required to "drive" a given VT into a patient's lungs. DP is Pplat-total PEEP and actually reflects the compliance characteristics of the respiratory system during a given VT and PEEP setting. DP may be an attractive approach to optimizing the VT and PEEP. With regard to the VT, recall that in ARDS, there is often marked mechanical heterogeneity such that a "safe" global VT may predominantly distribute to the smaller, more compliant units causing regional tidal overdistention and VILI. Conventional scaling of VT to PBW assumes a normal functional lung size and ignores these regional effects. In contrast, using compliance as the scaling factor (DP = VT/C) conceptually would more appropriately set the global VT. With regard to PEEP, aiming for the lowest DP for a given VT could be used to optimize PEEP. Interestingly, a retrospective reanalysis of several thousand patients is enrolled in clinical trials evaluating mechanical ventilation strategies, DP was more strongly associated with

survival than VT, plateau pressure, or PEEP, and a DP exceeding 15 cm H_2O was associated with a significant increase in both barotrauma and death (124).

An extension of the drive pressure concept to assess lung mechanics during tidal breath delivery at a set PEEP is the "stress index" (SI). First introduced in 2004 (125) and gaining interest over the following decade, the SI is the slope of the airway pressure curve during a constant flow breath in a passive patient. A straight upward diagonal pressure tracing implies no excessive overdistension (an upward bending curve) or recruitment-derecruitment (a downward bending curve) is occurring. Whether using this assessment improves outcomes has not been tested as yet.

Although there was not a proliferation of new modes of mechanical ventilation during this decade, one mode largely saw its demise in adults. As noted above, high-frequency oscillatory ventilation (HFOV) is a form of HFV used in pediatric and neonatal populations dating back to the 1970s. Its use in adults grew more slowly, largely as a rescue mode of mechanical ventilation for patients with severe ARDS refractory to conventional ventilation (126). However, two large clinical trials published in 2013 failed to show a benefit to HFOV over conventional management in patients with moderate-to-severe ARDS (127, 128). Based on the results of these two trials, most current guidelines for the management of ARDS recommend against the use of HFOV in moderate-to-severe ARDS.

Another strategy that approached its demise was the routine use of aggressive recruitment maneuvers coupled with high PEEP. As noted above, many authorities for years had espoused the "open lung" approach with recruitment maneuvers and aggressive PEEP strategies focused on mechanics and/or oxygenation. However, an important RCT clearly illustrated the potential harm from this strategy (hypotension and barotrauma) without any appreciable improvement in outcomes (129, 130). An accompanying editorial noted "the door on the open lung approach is closing" (131).

The 2010s saw a rebirth and subsequent exponential growth in the use of ECLS for the management of very severe respiratory failure (132). This growth was prompted by several factors including the H1N1 influenza outbreak in 2009, clinical trials demonstrating good safety and efficacy profiles, movement away from HFOV as a rescue mode, and the development of smaller, lighter, and portable ECLS devices that are more user-friendly and can more easily be used for patient transport (133). Perhaps more importantly was the realization that ECLS had the potential to allow substantial reductions in PPV settings, thereby offering significant lung protection ("ultraprotective PPV").

The first large clinical trial of ECLS in this era was the CESAR trial, which was performed in the United Kingdom. The investigators demonstrated a benefit to managing patients with severe ARDS at experienced centers capable of performing extracorporeal membrane oxygenation (ECMO) (134). However, the trial failed to answer the question effectively of whether ECMO was superior to conventional management in this population. Despite the lack of a clearly defined benefit, the use of this technology continued to grow over this decade, and in 2018, another large clinical trial (EOLIA) sought to determine an ECMO-specific benefit (135). Although it was underpowered to show a clear mortality benefit, there was a trend toward improved survival with the use of ECMO and 27% of patients in the conventional management group were ultimately placed on ECMO due to severe refractory respiratory failure. A subsequent reanalysis of this trial using a Bayesian approach suggested a lower mortality with ECMO in severe ARDS (136). ECMO has now become a common intervention at many centers, seeing high volumes of severe respiratory failure unable to be managed with conventional ventilation.

In this decade, the introduction of the heated humidified high-flow nasal cannula (HFNC) changed the landscape in managing adult patients with early acute respiratory failure (137, 138). Unlike traditional nasal cannula, HFNC provides flows up to 50–60 L/min, thereby markedly reducing upper airway dead space and providing a low level CPAP effect. Providing supplemental oxygen via HFNC led to reduced dyspnea, reduced risk of intubation, and reduced risk of death in patients with ARDS not yet requiring intubation (138). Additionally, placing patients directly onto HFNC following extubation was also shown to reduce the risk of reintubation, potentially reducing the overall burden of mechanical ventilation (139).

Finally, at the end of the decade, the emergence of the coronavirus disease 2019 (COVID-19) global pandemic raised several mechanical ventilation issues. First was the logistics challenge of providing adequate mechanical ventilatory support (both devices and operators) to large "surges" in demand from patients with devastating lung injuries. Going forward, extensive planning

is in order to address these needs in the future. Second, the manifestations of COVID-19 lung injury reminded clinicians of the heterogeneity in ARDS physiology, pathology, and trajectory. For example, one often recognized COVID-19 phenotype was "hypoinflammatory" with features of vascular involvement and less PEEP recruitability (140). Despite this heterogeneity, however, the principles of lung-protective ventilator management remained a cornerstone of management (141). Third, the benefits of prone positioning and HFNC/high-humidity nasal cannula in avoiding intubation and PPV were highlighted in management strategies for COVID-19 pneumonia (122, 123).

PPV–THE FUTURE

What the future holds for mechanical ventilation is unclear. Certainly, for the foreseeable future, PPV will continue to play a major role in the management of patients with severe respiratory failure. At the same time, our understanding of the mechanisms of lung injury will grow and changes in management will be made to reduce patient harm in the forms of VILI and SILI (112). Importantly, if the previous 2 decades are an indication of things to come, then we will continue to see a shift toward noninvasive support in patients with milder respiratory failure and extracorporeal support for more severe respiratory failure.

Better imaging to guide PPV settings in heterogeneously injured lungs is also an area of likely growth. On the immediate horizon, electrical impedance tomography (EIT) may soon provide on a wide scale a useful bedside image "slice" through the mid thorax (142–144). The principle of operation is based on changes in electrical conductivity that occurs as a function of changes in lung volume during ventilation. The use of EIT as a modality for assessing regional lung ventilation and consolidation has been described since the 1980s. However, it was not until the early 2000s that EIT was validated as a means to measure ventilation distribution reliably throughout the lung in a heterogeneous population of critically ill patients receiving mechanical ventilation. Although EIT is currently used predominantly for research purposes, it holds potential for future use to help optimize regional ventilation and PEEP on a continuous basis.

As the use of extracorporeal support has grown over the previous decade with improvements in technology, it is likely that this growth will continue with the future of ECLS representing awake, ambulatory, and extubated patients managed without anticoagulation for more prolonged periods of time, even outside of the ICU in longer term facilities or at home (145). Smaller, lower flow devices used for extracorporeal CO_2 removal will likely play a larger role in the management of diseases of CO_2 retention, such as acute exacerbations of COPD or status asthmaticus, that cannot be managed with NIV alone. Finally, ECLS management may begin to follow a similar trajectory to mechanical ventilators with closed-loop systems that will automatically adjust blood flow and sweep gas flow based on patient needs and changes in pressures within the system.

Technological advances likely will allow for the utilization of machine learning to improve patient ventilator synchrony and make closed-loop modes of ventilation more effective (146). The ventilators of the future may be able to incorporate real-time data from dynamic changes in pulmonary physiology, EIT imaging data, EAdi, and noninvasive blood gas monitoring to adapt and adjust to the individualized needs of the patients throughout the course of respiratory failure. They will also be able to detect readiness for liberation from mechanical ventilation, potentially further shortening course of mechanical ventilation.

Finally, the need for PPV to support patients with respiratory failure may diminish as we learn ways to pharmacologically reduce lung injury and discover ways to better tolerate/adapt to hypoxemia. Concepts such as induced hibernation and the ability to exploit the mechanisms in the fetus and high altitude dwellers that allow them to thrive in severely hypoxemic environments will become realities (147). Indeed, the 2019, Nobel prize for physiology or medicine was awarded for discoveries in the cellular adaptations to hypoxia. Perhaps over the next 50 years, PPV devices will be slowly relegated to only museums!

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