Introduction

The American Thoracic Society (ATS) has a long history, originating as the American Sanatorium Association in 1905, which was established to promote the treatment and prevention of tuberculosis. Since then, the scope of our mission has widened, and the Society has become the premier professional society in respiratory medicine, with more than 15,000 members worldwide who are dedicated to advancing our clinical and scientific understanding of pulmonary diseases, critical illnesses, and sleep-related breathing disorders. Our members provide care for millions of people who suffer daily from asthma, chronic obstructive pulmonary disease, cystic fibrosis, sleep apnea, and lung diseases related to prematurity, to name a few.

In celebration of our 110th anniversary, the ATS journals and 2015 ATS International Conference will highlight many of the advances in patient care and research in adult and pediatric pulmonary, critical care, and sleep medicine. The **ATS Discoveries Series** is a new collection of articles and talks that features major scientific and clinical breakthroughs, which have changed the lives of the patients we treat, as told by leading scientists and clinicians. With input from our membership, the topics range from the development of bronchoscopy to the discovery of surfactant, from insights into asthma pathogenesis to the potential of lung regeneration.

The following article, titled "History of Mechanical Ventilation: From Vesalius to Ventilator-induced Lung Injury," by Arthur S. Slutsky, M.D., M.A.Sc., Vice President of Research at St. Michael's Hospital and Professor of Medicine, Surgery, and Biomedical Engineering at the University of Toronto, is the first of the series published in the *American Journal of Respiratory and Critical Care Medicine*. I hope you enjoy learning about the seminal discoveries in respiratory medicine and their impact on patient care, now and in the future. Please be sure to read all of the articles in the Discoveries Series, which will appear not only in the "Blue" journal, but also the *American Journal of Respiratory Cell and Molecular Biology* and *Annals of the American Thoracic Society* during the coming months.

Thomas Ferkol, M.D.

President, American Thoracic Society

History of Mechanical Ventilation
From Vesalius to Ventilator-induced Lung Injury

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Abstract

Mechanical ventilation is a life-saving therapy that catalyzed the development of modern intensive care units. The origins of modern mechanical ventilation can be traced back about five centuries to the seminal work of Andreas Vesalius. This article is a short history of mechanical ventilation, tracing its origins over the centuries to the present day. One of the great advances in ventilatory support over the past few decades has been the development of lung-protective ventilatory strategies, based on our understanding of the iatrogenic consequences of mechanical ventilation such as ventilator-induced lung injury. These strategies have markedly improved clinical outcomes in patients with respiratory failure.

Keywords: artificial respiration; iatrogenic; history of medicine; ARDS; ventilators

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Mechanical ventilation is a life-sustaining therapy for the treatment of patients with acute respiratory failure. It is a very common modality in intensive care units, and indeed the advent of its use heralded the dawn of modern intensive care units. Interest in mechanical ventilation has increased markedly from both a research and a clinical perspective over the past 15 years since the publication of a milestone article in the *New England Journal of Medicine* by the ARDSNet investigators that highlighted the importance of a lung-protective ventilation strategy (1).

Although recognition of the importance of lung protection appears to be relatively new, there are fascinating accounts dating back hundreds of years that link ventilation to the development of lung injury. In this article, I provide a very brief, relatively personal perspective of the history of mechanical ventilation, with an emphasis on ventilator-induced lung injury (VILI). I focus on historical aspects of both ventilation and resuscitation, because their histories are intimately intertwined. Due to space limitations, this will not be an in-depth review; the interested reader is referred to other reviews for greater detail (2–7).

Galen, the noted Greek physician and scientist who lived in the second century A.D., played a major role in introducing the importance of structure (anatomy) to the understanding of disease (8). Although he made great advances, his dissections were limited to animals, and he assumed that the organs of humans and animals were identical. He also studied respiration and taught that breathing was required to maintain the circulation (i.e., the physical act of breathing caused the heart to beat). For almost the next 1,500 years, there were essentially no advances made in our understanding of ventilation, nor for that matter in any of the sciences; there is a good reason that a major part of this era was called the Dark Ages. However, Andreas Vesalius changed all of this in the mid-16th century.

Vesalius was born in Brussels and became Professor of Anatomy in Padua at the age of 23 (Figure 1). He incurred the wrath of the church because of his dissection of human cadavers, and many of his findings contradicted Galen's teachings. In 1543, he published a brilliant treatise on anatomy entitled *De Humani Corporis Fabrica*, which likely had the first definitive

Figure 1. (*Left*) Woodcut of the only known firsthand likeness of Andreas Vesalius (reprinted from Reference 48). (*Right*) Frontispiece of *De Humani Corporis Fabrica* (reprinted from Reference 49).

reference to positive pressure ventilation as we know it today (9). To quote: "But that life may be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air" (9). This essentially describes what we currently do in the intensive care unit (ICU) when we perform a tracheotomy, insert an endotracheal tube, and apply positive pressure ventilation. This was a dramatic demonstration of the power of mechanical ventilation, but it was essentially forgotten for a century and not incorporated into widespread medical practice for several centuries.

Robert Hook was a natural philosopher and brilliant scientist. He was an active astronomer, architect, and biologist who coined the term "cell" to describe biological organisms. He was also the curator of the Royal Society of London and regularly performed experiments for the Fellows of the Society. In 1667 he performed an ingenious experiment to examine Galen's hypothesis that the movement of the lungs was required for the circulation. In his words "and because some eminent physician had affirm'd, that the Motion of the Lungs was necessary to Life upon the account of promoting the Circulation of the Blood, and it was conceiv'd the Animal would immediately be suffocated as soon as the Lungs should cease to be moved I did . . . make the following additional experiment" (10). His model was ingenious. He used a dog in which he made cuts in the chest wall and pleura. He then used bellows to generate a constant flow of gas at the airway opening into the lungs; this constant flow then exited through the holes in the chest. He gave the following graphic description of the results: "This being continued for a pretty while, the dog . . . lay still, as before, his eyes being all the time very quick, and the heart beating very regularly: But, upon ceasing this blast, then suffering the Lungs to fall and lye still, the Dog would immediately fall into Dying convulsive fits; but be as soon reviv'd again by renewing the fullness of his lungs with the constant blast of fresh air . . ." (10). He ends this brilliant paper with what sounds like the objectives of his next grant application "I shall shortly . . . make some other experiments, which, I hope, will thoroughly discover the Genuine use of Respiration; and afterwards consider of what benefit this may be to Mankind" (10).

In the 17th and 18th centuries, there were a number of approaches that were used to resuscitate patients—many not always as enlightened as those described above. It is important to understand that, as Hook

stated, it was still not clear to physicians why people breathed and why people became pulseless. It was believed that people were unconscious because of a lack of stimulation. This hypothesis led to a number of (mostly) unusual treatments whose goal was to stimulate the patients. These included: (*1*) rolling them over barrels, (*2*) throwing them onto a trotting horse, (*3*) flagellation, (*4*) hanging them upside down, (*5*) cooling them on ice, or (*6*) using the fumigator, in which smoke was blown up the patient's rectum.

In 1774, Joseph Priestly and Willhelm Scheele independently discovered oxygen, and subsequently Lavoisier discovered its importance in respiration, thus answering the question posed by Hook a century earlier as to the "genuine use of respiration." Ironically, this discovery temporarily hindered the application of effective resuscitation. Mouth-to-mouth resuscitation had been described earlier by Tossach (and others) (11), and was in use, but was largely discontinued after the discovery of oxygen because it was believed that exhaled air was lacking in oxygen since it had already been processed by another person's lungs.

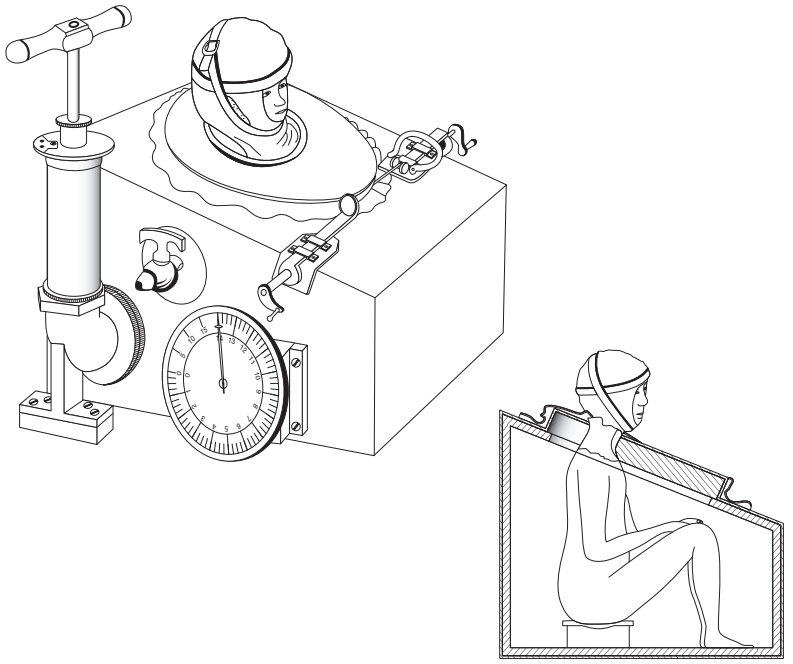

Figure 2. Body-enclosing box. One of the first known body-enclosing boxes; patented by Alfred Jones in 1864. Reprinted from Reference 12.

Negative Pressure Ventilation (Late 19th Century to 1950s)

In the late 19th century, ventilators based largely on (currently) accepted physiological principles were developed. Essentially, ventilation was delivered using subatmospheric pressure delivered around the body of the patient to replace or augment the work being done by the respiratory muscles. In 1864, Alfred Jones invented one of the first such body-enclosing devices (12). The patient sat in a box that fully enclosed his body from the neck down (Figure 2). There was plunger, which was used to decrease pressure in the box, which caused inhalation; the converse produced exhalation. This was a very special ventilator as described by Jones in his patent, because the ventilator ". . . cured paralysis, neuralgia, seminal weakness, asthma, bronchitis, and dyspepsia. Also deafness . . . and when judiciously applied, many other diseases may be cured" (12).

In 1876, Alfred Woillez built the first workable iron lung, which he called the "spirophore" (13). It was proposed to place these ventilators along the Seine River to help drowning victims. The spirophore had a metal rod that rested on the chest; movement of this rod was used as an index of the V_T. The first iron lung to be widely used was developed in Boston by Drinker and Shaw in 1929 and used to treat patients with polio (14).

One problem with these devices was that it was extremely difficult to nurse patients because it was difficult to get access to the patient's body. To address this problem, Peter Lord patented a respirator room (Figure 3), in which the patient lay with her head outside the room (13); inside, huge pistons generated pressure changes, which caused air to move into and out of the lungs. The ventilator room had a door so that the medical staff could enter the ventilator to care for the patient. Of course these ventilators were extremely expensive, so James Wilson developed a ventilation room in which multiple patients could be treated (13). One such room was used at Children's Hospital, Boston, for several epidemics.

And finally, one of my favorite ventilators was the pneumatic chamber developed by Wilhelm Schwake in 1926 (Figure 4) (13). He was particularly concerned with matching the patient's breathing pattern and believed that this ventilator would help in this regard. He also stated that "negative pressure on the skin . . . draws out . . . the gaseous by-products" (quoted in Reference 13).

Positive Pressure Ventilation (1950s to the Present)

The resurgence of polio marked a watershed in the history of mechanical ventilation. Before this time, mechanical ventilation was believed to have some usefulness but was not used widely. Afterward, the benefits of ventilation were dramatic and obvious, leading to its widespread use worldwide. In 1951, there was an international polio conference in Copenhagen, attended by most of the world's polio experts. The following summer, Copenhagen experienced a terrible polio epidemic, likely triggered by the carriage of polio virus to Copenhagen during the previous year's conference. At the height of the epidemic, 50 patients a day were being admitted to the Blegdams Infectious Disease Hospital, many with respiratory muscle or bulbar paralysis (15). Mortality in these patients was exceedingly high (>80%). At the time, most physicians believed that the patients were dying from renal failure caused by an overwhelming systemic viremia; this conclusion was based on the patients' terminal symptoms of excessive sweating

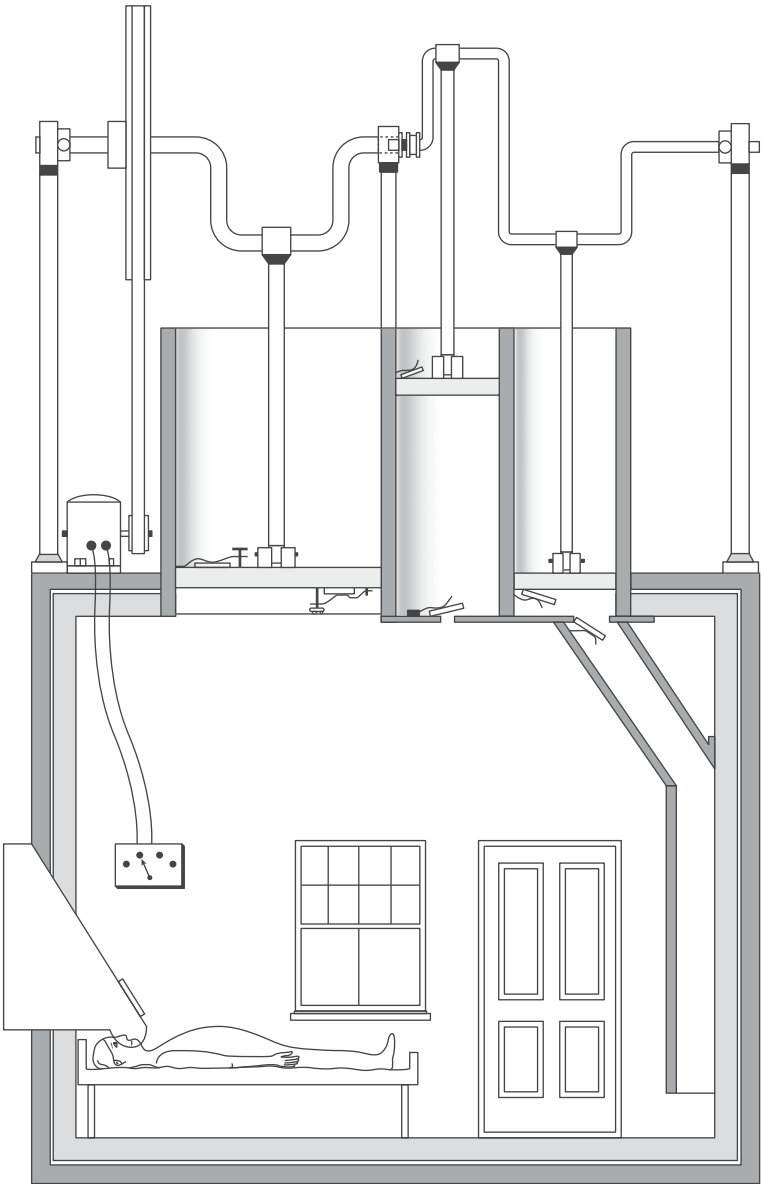

Figure 3. Respirator room. Pressure changes in the room were generated by huge pistons, which created pressure changes in the thoracic cavity, which in turn caused gas to move into and out of the patient who was connected via a manifold to a fresh gas supply outside the room. Adapted from Reference 50.

and hypertension, along with elevated total plasma CO_2.

Bjorn Ibsen, an anesthesiologist who had trained in Boston in Beecher's lab, realized that these symptoms were not caused by renal failure but by respiratory failure. As such, he recommended tracheostomy and positive pressure ventilation. Lassen, who was the hospital's chief physician, initially rejected this approach but soon relented when Ibsen demonstrated its efficacy. Mortality dropped dramatically—from 87% to approximately 40%, almost overnight (Figure 5) (16). Delivering care to all these patients was a major logistical problem, as there were no positive pressure ventilators, so that the patients had to be "hand bagged." At the height of the epidemic 70 patients were simultaneously being manually ventilated. In total, by the end of the epidemic, approximately 1,500 students provided manual ventilation for a total of 165,000 hours (15). One approach to the logistical challenge was to take care of all of these patients in one location. This led to the first ICUs as we know them today.

The focus until this time was largely on providing ventilatory support (i.e., providing a replacement of the respiratory muscles). This changed over the ensuing few decades with a greater focus on oxygenation failure, catalyzed by easier approaches for measuring blood gases; the identification of the acute respiratory distress syndrome (ARDS) (17); and the increased physiologic understanding of the impact of pressures in the lung on gas exchange. Although Barach had investigated the use of positive pressure for the treatment of a number of diseases, including heart failure (18), it was the observation by Ashbaugh of the possible usefulness of positive end-expiratory pressure (PEEP) (three of five patients treated with PEEP survived, compared with two of seven not treated with PEEP), the understanding of atelectasis in supine patients, along with advances in ventilator design that heralded the widespread use of PEEP. Interestingly, despite this very long history of the use of PEEP in ARDS, the precise approach to use in choosing PEEP in individual patients remains controversial.

Over the past 60 years, many technical aspects of ventilators have dramatically improved with respect to flow delivery, exhalation valves, use of microprocessors, improved triggering, better flow delivery, and the development of new modes of ventilation (e.g., intermittent mandatory ventilation, high-frequency ventilation, pressure-controlled inverse ratio ventilation, airway pressure release ventilation, proportional assist ventilation [PAV], neurally adjusted ventilatory assist [NAVA], etc.). In the 1980s and 1990s, there was a paradigm shift from controlled ventilation to partial ventilation support, then to pressure support ventilation. The focus has been on improving the interaction between the patient's drive to breathe and the ventilator's delivery of each breath. Essentially, many current modes focus on increased patient control of ventilation to the point of allowing the patient to fully drive the ventilator (e.g., proportional modes such as PAV and NAVA). These latter modes are still under physiological evaluation and only starting to be tested widely in clinical trials. The focus on increased patient contribution to ventilation is in line with our increasing

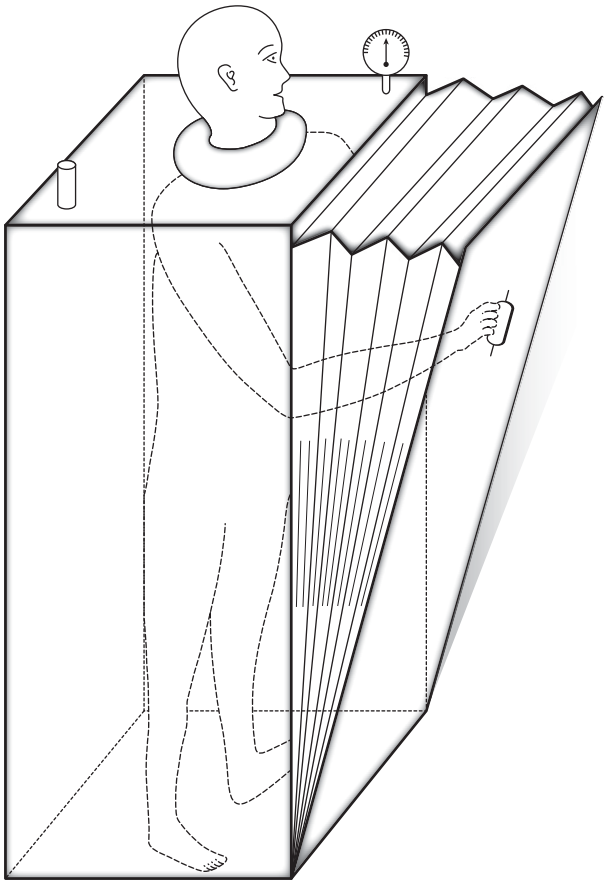

Figure 4. Pneumatic chamber: Patented by Wilhelm Schwake in Germany in 1926 (51). Schwake was concerned with precise matching of the ventilator and the patient's breathing pattern. Reprinted from Reference 13.

understanding of ventilator-induced diaphragmatic dysfunction (19).

Many of these improvements have clearly led to much better ventilators and much better care of ventilated patients, but the major recent advances in mechanical ventilation are not related to these improvements but to our better understanding of the pathophysiology of ventilation, both the good and the bad.

Evolution of Mechanical Ventilation and Recognition of Potential for Harm

Arguably the greatest advance over the past few decades in delivering mechanical ventilation has been in minimizing its side effects. The concept that ventilation may be harmful is certainly not new. In 1744, John Fothergill published an essay in the *Philosophical Transactions of the Royal Society of Medicine* (11) in which he discussed a previous publication by William Tossach. Tossach had helped resuscitate a coalminer who was apneic and pulseless. "Tossach had applied his mouth close to the patient's and by blowing strongly, holding the nostrils at the same time, raised his chest fully by his breath. The surgeon felt 6–7 quick beats of the heart . . . . In one hour the patient began to come to himself, within four hours, he walked home, and in as many days returned to his work" (11).

Later on in the Discussion Fothergill writes "It has been suggested to me by some that a pair of bellows might possibly be applied with more advantage in these cases, than the blast of a man's mouth; but if any person can be got to try the charitable experiment by blowing, it would seem preferable to the other [because] the lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined" (11). Fothergill clearly understood the possibility of injury caused by ventilation and in many ways can be viewed as the father of VILI, with his incredibly insightful conclusions 270 years ago.

In 1829, d'Etioles demonstrated that using bellows for ventilation could cause pneumothoraces, leading to death. This study was widely interpreted as suggesting that the lungs of a patient who was pulseless could not tolerate positive pressure ventilation. This likely set the field back many years. Indeed, in 1837 the Royal Humane Society removed the use of bellows as well as mouth-to-mouth resuscitation from its list of recommended treatments (20).

Mechanical ventilation was originally introduced in patients with normal lung function, essentially to replace the neuromuscular pump (e.g., comatose

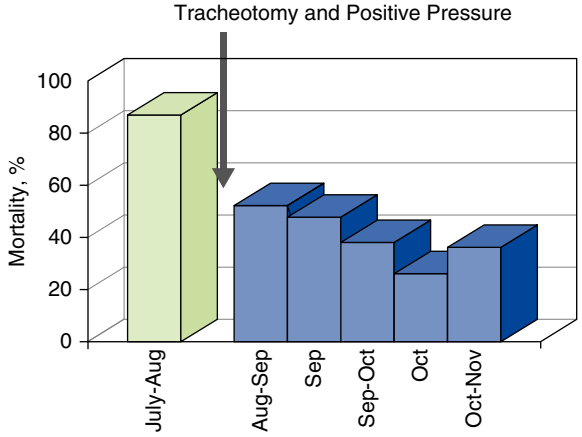

Figure 5. Mortality rate from bulbar polio. The mortality rate in July and August 1952 (up to August 27) for bulbar polio in the Blegdams Hospital was 87%. On August 27, 1952, tracheotomy and positive pressure ventilation were introduced (*arrow*). Mortality immediately dropped dramatically and was about 40% in the ensuing months. Adapted by permission from Reference 16.

patients during surgery, polio). In these patients ventilation was delivered with low pressures that were relatively safe. This is fundamentally different from its use to assist gas exchange in patients with severely diseased lungs, which are much more sensitive to mechanical injury. As this use of mechanical ventilation spread, it became apparent that negative pressure ventilators were less effective in maintaining gas exchange, and this, combined with technological advances and the experience of Ibsen and coworkers, led to the predominant use of positive pressure ventilation. These ventilators could apply greater pressures, which made them more effective in facilitating gas exchange but, combined with the fact that the lung was already injured, led to recognition of adverse consequences (e.g., pneumothoraces). This was termed "barotrauma."

In the 1940s Macklin and Macklin discovered the mechanisms leading to the development of pneumothoraces and barotrauma (21). They observed that the alveoli were in direct apposition to the bronchovesicular sheath, and as the pressure across the membrane increased at high lung volumes, the membrane could tear, causing air to spread proximally leading to the manifestations of barotrauma.

In the 1960s there was a major focus on oxygen toxicity based on animal studies demonstrating a dramatic increase in mortality in animals ventilated with an $F_{I_{O_2}}$ of 1, and serious complications in infants ventilated with high $F_{I_{O_2}}$. In the late 1960s, investigators observed that low V_T (along with low PEEP levels) was associated with atelectasis and hypoxemia. Given the reluctance to use high $F_{I_{O_2}}$, physicians used very high V_Ts. This often temporarily improved hypoxemia but, as we now know, likely led to lung injury in many patients. For example, in the late 1970s Bone and colleagues published an abstract in which they described patients with ARDS who were ventilated with PEEPs of 16 ± 4 cm H_2O and V_Ts of 22 ± 4 ml/kg; 40% of these patients developed severe barotrauma (22).

Webb and Tierney demonstrated that use of high distending pressures in rats could lead to pulmonary edema, which could be fatal (Figure 6) (23). Over the past 40 years we have developed a greater understanding of the mechanisms and consequences of VILI (Figure 7). We understand that the key variable is not airway pressure *per se*, as elegantly demonstrated by Bouhuys in studies of musicians playing musical instruments (Figure 8) (24), but was due to overdistension of the lung as demonstrated by Dreyfuss and Saumon, who suggested the term volutrauma to highlight that it was not the absolute airway pressures *per se* that were important, but the overdistension (25).

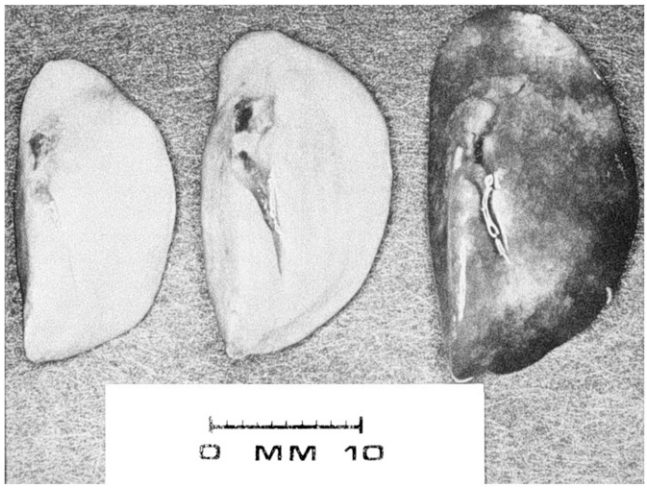

Figure 6. Excised rat lungs ventilated for 1 hour using different ventilatory pressures. (*Left*) Lung ventilated at peak inspiratory pressure (PIP) = 14 cm H_2O. (*Middle*) Lung ventilated at PIP of 45 cm H_2O and positive end-expiratory pressure (PEEP) = 10 cm H_2O. (*Right*) Lung ventilated at PIP = 45 cm H_2O and PEEP = 0. Reprinted by permission from Reference 23.

In 1997, we identified a mechanism of injury that we called biotrauma (i.e., the biological consequences associated with mechanical ventilation) (26, 27). We showed that injurious forms of ventilation (i.e., those that promote atelectrauma or overdistension) could lead to release of mediators in the lung. Coupled with the increased permeability due to the underlying disease being treated (e.g., ARDS) or the increased permeability caused by overdistension, mechanical ventilation could lead to translocation of mediators, bacteria, or endotoxin into the systemic circulation (27, 28). This in turn could cause end-organ dysfunction distal to the lung (e.g., kidneys) and lead to multiorgan failure (Figure 9) (29). This mechanism could explain the fact that most patients with ARDS who die do so not because of hypoxemia but because of multiorgan failure.

Lung-Protective Ventilatory Strategies

The identification of the detrimental consequences of mechanical ventilation has had a profound impact on the philosophy/strategy of how ventilation is applied and how ventilated patients are currently managed. Before this understanding, the primary goal of ventilation was to correct the underlying blood gas abnormalities and do so as quickly as possible. This often led to early intubation, more ventilation, and more pressure. However, with the realization that this "more" led to more injury, strategies were introduced to minimize the side effects of ventilation. The use of noninvasive ventilation was shown to be beneficial for patients with COPD (30). The rationale underlying this approach is: (*1*) avoidance of intubation with its well-known complications (e.g., tracheal complications of the tube, increased sedation, increased propensity for respiratory infections due to tube colonization and decreased secretion clearance), and (*2*) maintenance of the benefits of positive pressure ventilation and partial support on gas exchange and work of breathing. It is largely effective for ventilatory failure and minimally or not effective for oxygenation problems.

If intubation is required, other approaches to decrease complications included controlled hypoventilation in patients with status asthmaticus (31) to minimize auto-PEEP, a concept described by Pepe and Marini in 1982 (32), and the use of permissive hypercapnia, first described by Hickling and colleagues in

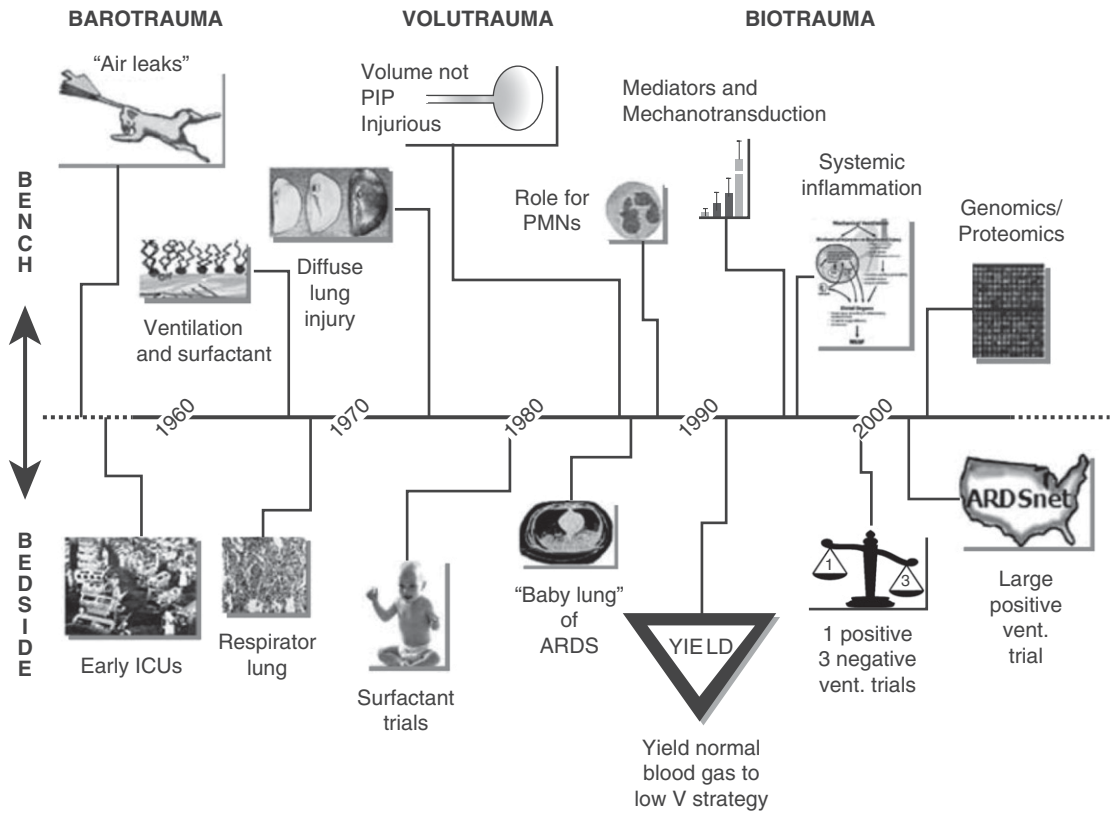

Figure 7. Timeline highlighting a number of basic science (*top*) and clinical (*bottom*) observations that have had an impact on our current understanding of ventilator-induced lung injury and on ventilatory support of the critically ill over the past 5 decades. ARDS = acute respiratory distress syndrome; ICU = intensive care unit; PIP = peak inspiratory pressure; PMNs = polymorphonuclear leukocytes. Reprinted by permission from Reference 52.

patients with ARDS (33). A defining moment with respect to lung-protective strategies in ARDS was the 2000 publication of the ARDSNet randomized clinical trial, which demonstrated a decreased mortality from 40 to 31% (1). This study was followed by other randomized clinical trials addressing various approaches for minimizing VILI, including use of higher PEEP levels, prone position (34), and early, short-term neuromuscular blockade (35). There is also increasing evidence that lung-protective strategies are useful in ICU patients without ARDS to help prevent the development of ARDS (36), in anesthetized patients undergoing operative procedures to prevent respiratory complications (37), and in patients with brain death to help preserve lungs for transplantation (38).

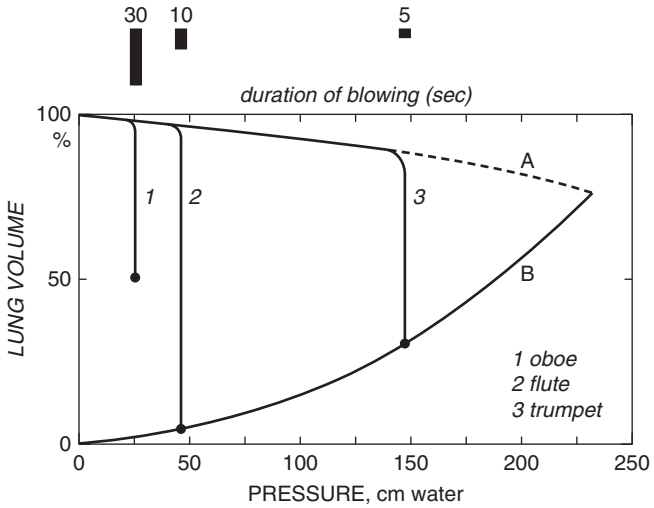

Figure 8. Plot of maximum expiratory pressure–volume for musicians playing musical instruments. *Curve B* (starting at zero lung volume) represents the highest expiratory pressures at any given lung volume. *Lines 1*, *2*, and *3* are the pressure–volume trajectories when musicians play single tones on the oboe, flute, and trumpet, respectively. The purpose of these experiments was not to study ventilator-induced lung injury, but they clearly demonstrated that high pressures at the airway opening do not necessarily lead to barotrauma. Reprinted by permission from Reference 24.

The Future

As Yogi Berra famously stated, "It's hard to make predictions . . . especially about the future," but I will give it a try, nonetheless. I will not address a number of ancillary approaches that are very important but can equally apply to ICU patients not requiring ventilatory support; these include early and increased ambulation, decreased sedation, and end-of-life care.

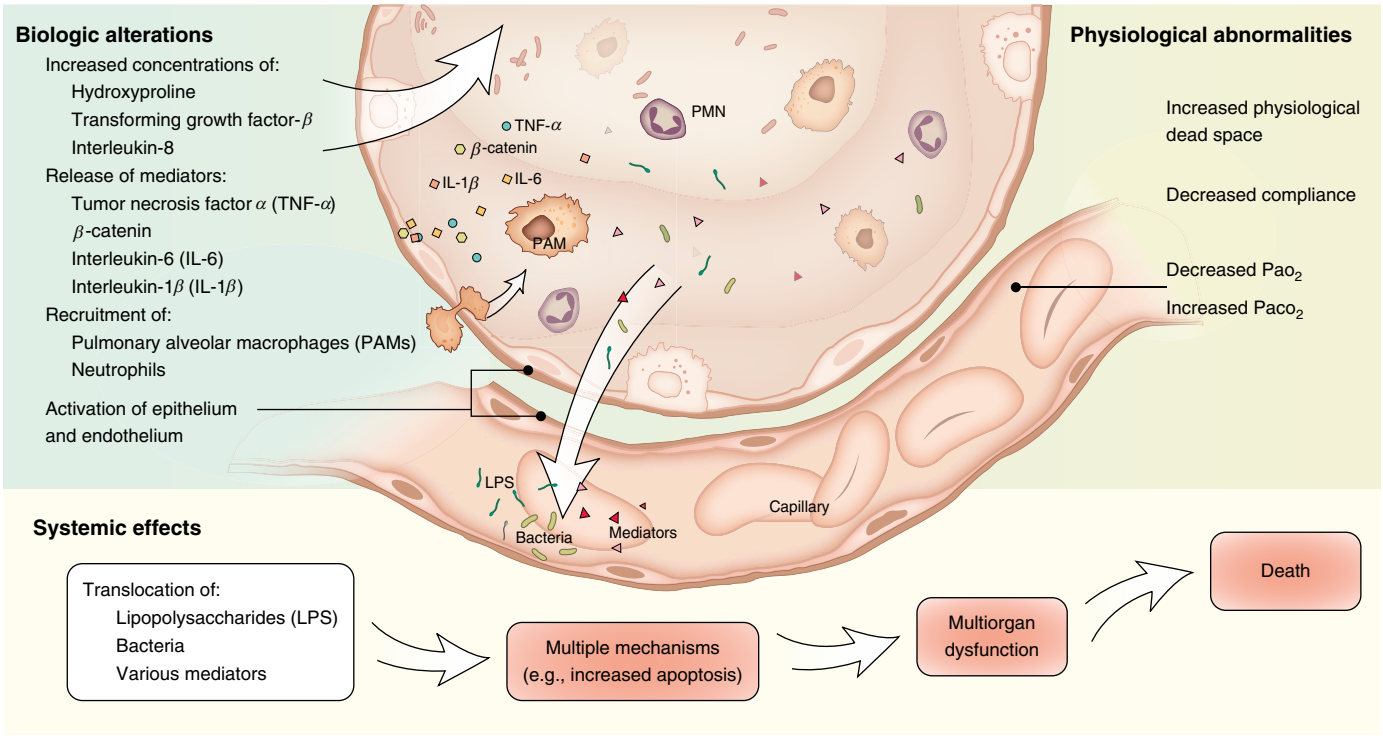

Figure 9. Alterations caused by ventilator-induced lung injury (VILI). Biologic, physiologic, and systemic effects caused by injurious ventilatory strategies. Further injury can be caused by mediators released into the lung. These mediators can recruit neutrophils into the lung or cause changes that can promote pulmonary fibrosis. VILI can also lead to increased alveolar–capillary permeability that in turn can facilitate translocation of mediators, bacteria, or lipopolysaccharides into the systemic circulation. These can then potentially lead to multiorgan dysfunction syndrome and death. PMN = polymorphonuclear leukocytes. Reprinted by permission from Reference 29.

There is evidence that current lung-protective strategies are not protective enough in some patients (39). There are a few approaches that hold promise to address this issue: (*1*) One way to decrease VILI is to get rid of cyclic swings in pressure/volume, which lead to overdistension and atelectrauma. Hook proposed one way of doing this in the 17th century, but generating lung leaks to provide ventilation with a constant flow of gas from the airway opening through the chest wall is not going to be a viable technique in patients (10). However, there is a technique of constant flow ventilation that is effective in dogs (40) that may minimize VILI. (*2*) Another approach to limit the injury due to ventilation is to eliminate ventilation. This is possible through the use of extracorporeal lung support (ECLS). This technique has been studied for a number of years with early negative trials (41, 42), but technological approaches have minimized its side effects, and there are some encouraging data (43). The key issue is whether the side effects of ECLS are less than the side effects of mechanical ventilation. This is a moving target, as both ECLS and mechanical ventilation continue to improve. (*3*) Developing a strategy that minimizes driving pressure (ΔP = plateau pressure − PEEP) may prove to be a better strategy than one focusing largely on V_T (44); this clearly has to be tested in the context of a clinical trial.

Patients who die with ARDS usually die of multiple organ failure, which may be related at least in part to biotrauma. Pharmacogenomics focuses on the role of genetics in a patient's response to drugs and is being used for precision therapy of some drugs, identifying who might benefit and who might be at increased risk of drug side effects. In the future we may be able to identify a genetic basis for risk of biotrauma, a field that might be called ventilogenomics. Patients who are genetically predisposed to VILI might be targeted in clinical trials of mechanical ventilation and perhaps more aggressive approaches to lung protection (e.g., ECLS) or pharmacological therapies aimed at mediators causing end-organ damage.

Intubation is very important in helping to protect a patient's airway but is associated with a host of complications. We will see an increased focus on trying to minimize intubation time with increased use of noninvasive ventilation and possibly ECLS to prevent intubation or to accelerate extubation in intubated patients.

Another area in which progress is required is patient–ventilator synchrony; patients with poor synchrony have poorer outcomes, but it is unclear whether this is cause or effect. New approaches to increase synchrony include PAV (45) and NAVA (46), and if dyssynchrony is shown to be a cause of poor outcomes, then techniques such as these or newly developed approaches will become more important in the future.

Finally, there will be an increasing focus on collecting and analyzing large volumes of data, which will include capture of detailed patient data (e.g.,

including genomic, biomarker, ethnocultural, socioeconomic) and real-time data (e.g., ventilator waveforms, physiological data, laboratory data, etc.). Specially designed analytic algorithms will be used to provide more clever monitoring tools (e.g., for assessing synchrony, for determining propensity for VILI, for predicting acute changes in outcomes, etc.). Data derived from such large databases will be applied in real time to assess prognosis, to provide feedback for—and control of—the ventilator, and to suggest other targeted therapeutic approaches. Such a database will also prove to be a wonderful platform to imbed large-scale clinical trials to make them faster, more impactful, and less expensive.

Conclusions

Novel physiological approaches, combined with new biological insights and engineering approaches, will undoubtedly continue to improve the delivery of mechanical ventilation as we move further into the 21st century. Such advances will certainly be welcome as the number of patients requiring mechanical ventilation is expected to increase substantially (47). Reviewing the history of the progress of mechanical ventilation is enlightening in a number of respects. First, it's humbling to consider how many discoveries, such as the usefulness of positive pressure ventilation or the iatrogenic consequences of ventilatory support, took literally centuries to change practice, despite convincing evidence. Second, it is intriguing to sit back and think what ventilatory approaches we are currently using that in the future will be viewed at best as somewhat naive and at worst as harmful. Perhaps viewing our current practices critically using a "future historical lens" will allow us to identify these harmful practices earlier rather than later and hence to accelerate the future history of mechanical ventilation. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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