2004 Donald F Egan Memorial Lecture

Ventilator-Induced Lung Injury: From Barotrauma to Biotrauma

Arthur S Slutsky MD

Introduction

I am very honored to have been asked to give the Egan Lecture, especially as you are celebrating your golden anniversary Congress—50 years of international respiratory care. Donald Egan was a remarkable man. Through his vision, his hard work, and his textbook, he impacted respiratory care in a major way throughout his life, and posthumously. In preparation for this talk, I looked over the previous Egan lecturers and was very impressed with the individuals who have given this lecture in the past, and I was very humbled. In these talks, you've heard about everything from the alveolus to hyperoxia to the top of Mt Everest. What I'm going to talk to you about today is ventilator-induced lung injury: from barotrauma to biotrauma. I chose this topic for a number of reasons:

- First of all, it's a major interest of mine.
- Second, I think it's a terrific model of translational research; that is, taking important problems from the clinical arena, examining these problems in the laboratory, and applying the new knowledge generated to develop therapeutic approaches that are then tested in patients.
- And, third, I'm sure you all know of a recent publication, the ARDSNet publication, showing that ventilation strategies with low tidal volumes (V_T) saves lives in patients with acute respiratory distress syndrome (ARDS).[1] The rationale underlying that study is based on our understanding of ventilator-induced lung injury (VILI).

So what I'd like to do over the next 45 minutes or so is:

- Give you a brief historical review, dating back a few centuries, of where we've come from in mechanical ventilation and resuscitation
- Talk about current concepts of how mechanical ventilation can cause lung injury, and potentially can have systemic effects, which are potentially very important, and, finally
- Discuss how these concepts may lead to changes in therapy as we look forward over the next decade or so in the care of our patients

Historical Review

Let me start first with a brief historical review. This review starts with a famous 16th century physician named Andreas Vesalius. He was a professor of anatomy in Padua at the age of 23. In 1555 he published a remarkable ana-

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tomical treatise called *de Humani Corporis Fabrica*. The book described an experiment Vesalius had performed on a pig. What Vesalius wrote was, "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." This description, written almost 500 years ago, describes essentially what we do in the intensive care unit now. We do a tracheostomy, put a tube in, and use mechanical ventilation. Although this was one of the first examples of a modern-day approach to ventilation, much of what Vesalius taught us was essentially forgotten for a few hundred years.

Over the subsequent few centuries, a key issue addressed by physicians and other practitioners was how to resuscitate patients. It's important to put this into context—remember, this was back many years ago before the knowledge of such fundamental concepts as oxygen, carbon dioxide, and why we breathe. During this period it was thought that to resuscitate a patient, strong stimulation was important. So they would roll patients over barrels and ring loud bells near to patients' ears. They would burn patients with hot irons, shine bright lights in their eyes, and (one of my favorites) throw patients on their abdomens across a trotting horse. And, finally, if none of these worked, they would use the famous fumigator. I don't know how many of you have heard about this device, and I'm not sure in mixed company I can really describe it. Let me just say that they used cigarette smoke and blew it up some places that will remain unmentioned. I won't tell you the details, but let's just say that if this had been used widely, lung cancer wouldn't be the major problem with smoking—colon cancer would! Now, I don't know whether there were any randomized controlled trials to see whether any of these approaches were effective, but my guess is they were probably not tested in this way; pretty difficult to blind these studies in any event.

One of the first ventilators was patented in the late 1800s by Alfred Jones.[2] The ventilator was a box, and the patient sat in this box with only his neck and head protruding outside the ventilator (Fig. 1). There was a lever which increased the pressure in the box when it was pushed in; this increased pressure compressed the chest wall of the patient, producing exhalation. Inhalation occurred when the lever was withdrawn. The physiologic concepts on which this ventilator is based are very similar to current concepts. Now, this was more than just a ventilator—and I guess this was in the days before the patent offices required reproducible data—because, in this patent application Alfred Jones said that with this ventilator he had cured "paralysis, neuralgia, rheumatism, seminal weakness, asthma, bronchitis, and dyspepsia. I have cured also deafness. And. . .when judiciously applied, many other diseases may be cured."

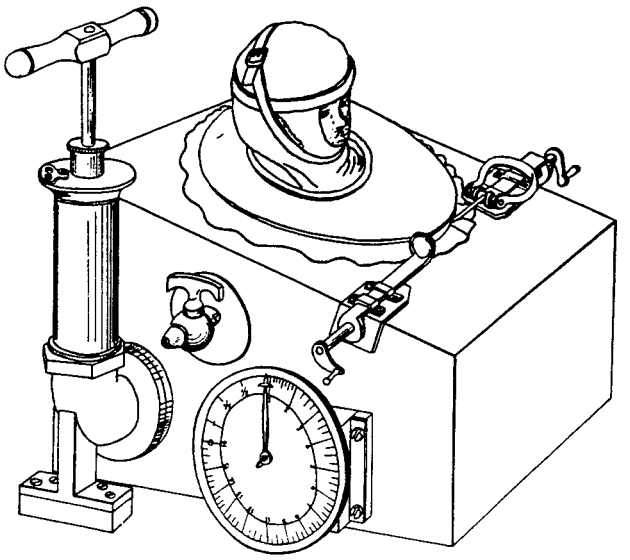

Fig. 1. Schematic drawing of one of the first body-enclosing ventilators, patented by Alfred Jones in 1864. (From Reference 2.)

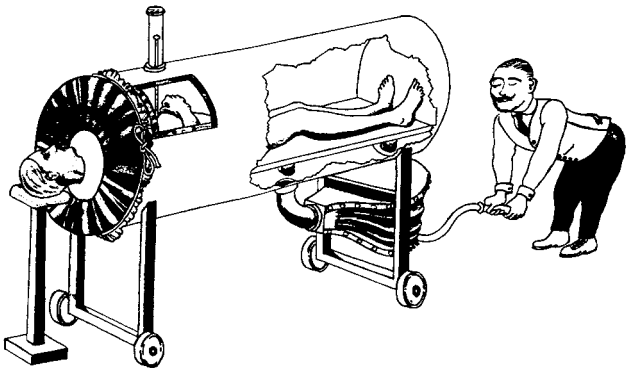

Fig. 2. An example of one the first iron lungs. This ventilator, built by Dr Woillez in 1876, had a metal rod that rested on the patient's chest, such that excursions of the rod provided an estimate of the patient's tidal volume (Courtesy of JH Emerson Company, Cambridge, Massachusetts. Source: *The Evolution of Iron Lungs: Respirators of the Body-Encasing Type*. Cambridge, Massachusetts: JH Emerson Company.)

Alfred Woillez was one of the first individuals to develop a ventilator that was similar to "modern day" iron lungs (Fig. 2).[3] This ventilator, developed in the late 1800s, was to be placed along the banks of the Seine river, to be used to save patients who had drowned. The basic concept underlying this ventilator is similar to what we talked about earlier—that is, a change in pressure in the ventilator caused gas to move in and out of the patient's lung. One interesting feature of the ventilator was a metal rod that rested on the patient's chest; excursions of this rod were a rough index of V_T. In 1931 John Emerson developed an iron lung that was similar to the ventilator developed by Woillez but had the addition of a motor.[3] Although these iron lungs

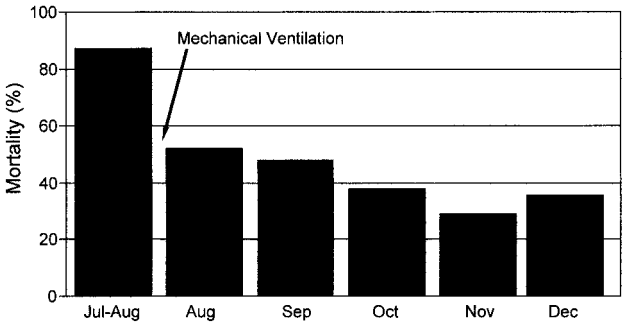

Fig. 3. Mortality rate versus month of the year for patients with paralytic polio. At the end of August 1952, Lassen introduced mechanical ventilation for these patients. There was an immediate drop in mortality, from over 80% to around 40%. (From Reference 4, with permission.)

were able to ventilate patients, the key problem was how to nurse patients, since it was very hard to get access to the patient.

There was an interesting solution to this problem: the development of a ventilation room. Essentially the iron lung was increased in size until it was the size of a room. The patient was placed with his body, from the neck down, in a room; the patient's head was outside the room. There were very large pistons in the room, and these pistons caused pressure changes in the room, which moved gas into and out of the lungs of the patient. The "ventilator room" had a door, and the medical staff could come in to take care of the patient; it was easy to nurse the patients from within the ventilator.

Now, one of my favorite ventilators is one that was developed in the mid-20th century. It was also a body-enclosing device, which looked a little bit like an accordion. The patient stood in the ventilator (with his head outside the ventilator) and manually pulled a lever, causing pressure changes in the ventilator which caused gas to move into and out of the patient's lungs. For those of you who are interested in the work of breathing, with this ventilator the muscles of respiration would have been the biceps and triceps.

The modern era of mechanical ventilation and intensive care began during the polio epidemic. In 1953 Lassen published a classic paper on the use of mechanical ventilation in patients with paralytic polio.[4] Lassen knew that the mortality rate from paralytic polio was extremely high—over 80%—and he realized that patients were dying of respiratory failure. So, in August 1953 he instituted mechanical ventilation for these patients. As you can see from Figure 3, mortality dropped virtually instantly to less than half with the institution of mechanical ventilation. Just by applying mechanical ventilation he was able to save thousands of lives from polio. And this led to wards containing iron lungs that were used to ventilate patients with paralytic polio. This was the start of modern intensive care units, as it was much more efficient to take care of these patients in one location.

Thankfully, polio, which leads to weakness of the muscles of respiration, has been eradicated (albeit not completely) and is not a major disease for which we currently ventilate patients. Now, the disease that we are concerned about most in terms of mechanical ventilation, or the disease that is probably most difficult for us in terms of ventilation is ARDS. The syndrome is characterized by leaky, stiff lungs and severe hypoxemia.[5] Essentially, all patients require mechanical ventilation or they are going to die. It's also a disease in which the pathology is one of inflammation. And that becomes important because key inflammatory mediators are present in the lungs of patients with ARDS. As I will show you later, this has some relevance for VILI.

From an epidemiological point of view, the mortality of ARDS is very high—on the order of 35–60%, depending on a number of factors, including age and the predisposing factor that led to the development of ARDS. But what's very interesting is the fact that most patients who die with ARDS don't die of hypoxemia; they die of multiple-system organ failure. This has been a puzzle for clinicians for a long time. Why should patients who have a disease that looks like it largely affects the lungs die of renal failure and hepatic failure? The hypothesis I'll develop is that mechanical ventilation, which is clearly life-saving, may actually contribute to the development of multiple-system organ failure.

Key Physiologic Concepts

Now, before getting into the specifics of VILI, I think it's useful to develop some key physiologic concepts. The first concept is that ARDS is a heterogeneous disease. Until the mid-1980s, based on routine chest radiographs, we thought that the lung injury in patients with ARDS was relatively homogeneous. But studies using computed tomography scans (Fig. 4) showed us that ARDS was a heterogeneous disease.[6] The nondependent regions of the lung are relatively well aerated; the dependent regions are collapsed and filled with fluid. Positive end-expiratory pressure (PEEP) is able to recruit some of the lung, but not all. The concept that there is only a small part of the lung available for ventilation is relevant to our concept of VILI, since a V_T that may be fine for ventilation of a normal lung may cause regional overdistention of parts of the lung when only a small part of the lung is available for ventilation.

Now, what does a lung like this look like when you inflate it? Figure 5 is a composite of pictures published in *The Handbook of Physiology* over 40 years ago.[7] It's a picture of excised cat lungs as they are being inflated, along with the corresponding pressure-volume curve. The

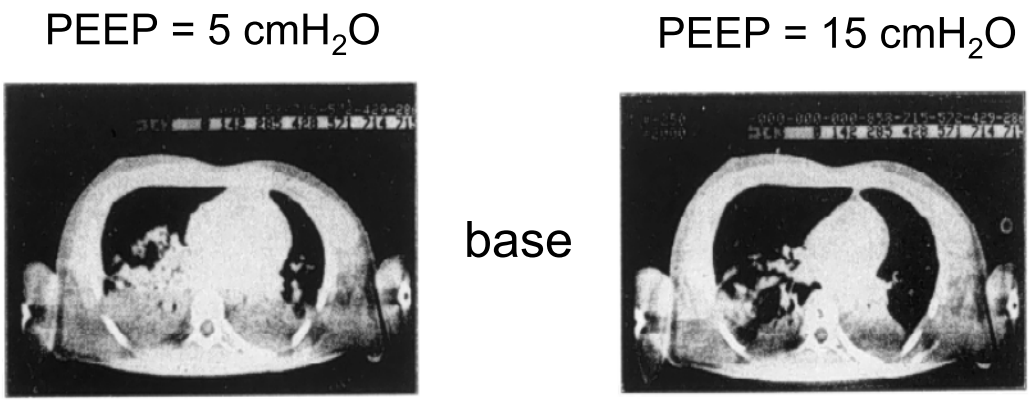

Fig. 4. Single slice from a computed tomography scan of a patient with acute respiratory distress syndrome (ARDS) obtained at a positive end-expiratory pressure (PEEP) of 5 cm H_2O (left) and a PEEP of 15 cm H_2O (right). Note the inhomogeneous distribution of abnormalities, with consolidation, atelectasis, and fluid in the dependent lung zones, and relatively well-aerated lung in the nondependent zones. Note that increasing levels of PEEP recruited parts of the lung. (From Reference 6, with permission.)

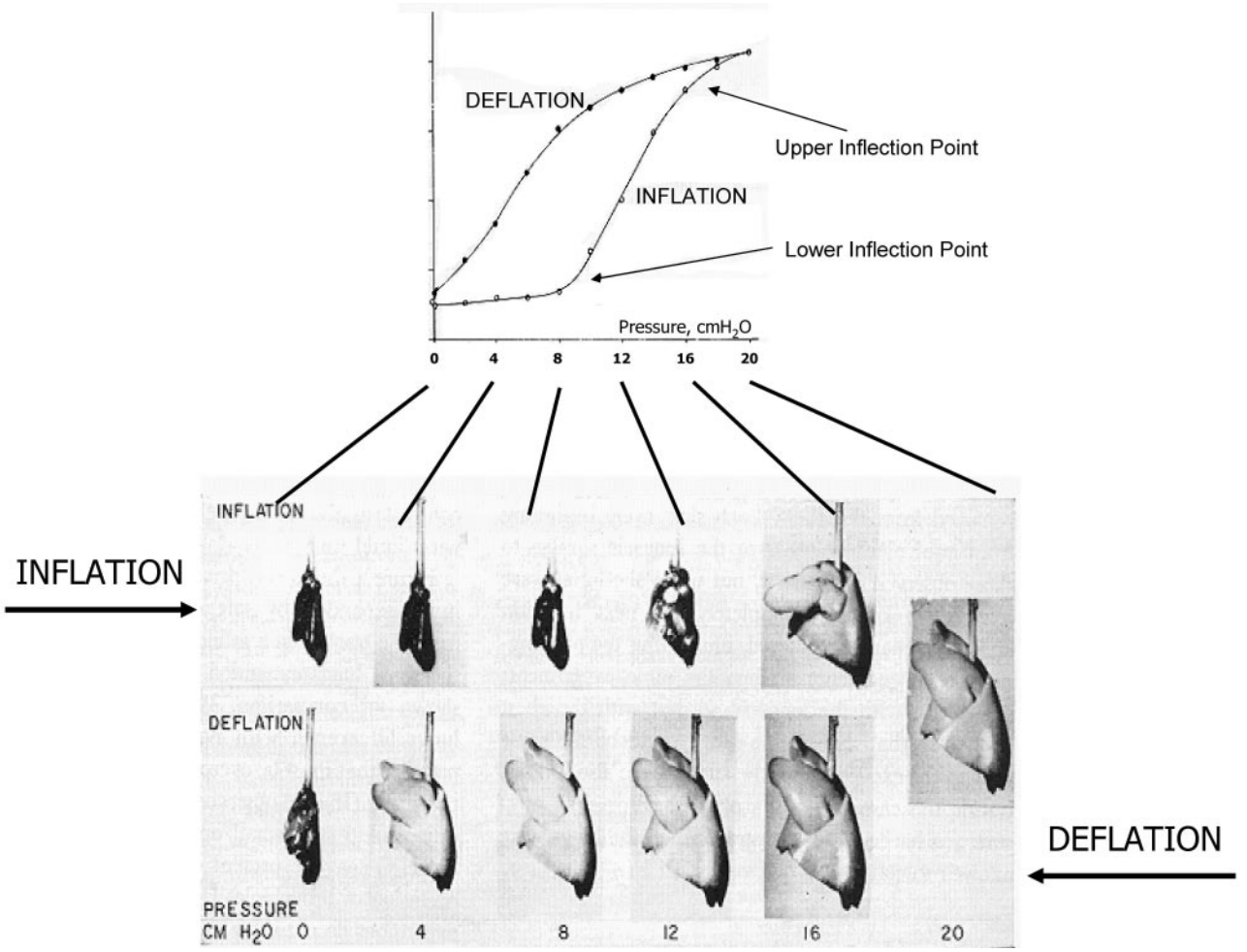

Fig. 5. Upper panel: Pressure-volume curve of an excised cat lung. The bottom panels represent photographs taken at each pressure level during inflation and deflation. Note the marked hysteresis, with much greater inflation and more homogeneous inflation on the deflation limb. Also note that recruitment continues along the inflation limb of the pressure-volume curve as pressure increases above the lower inflection point. (Adapted from Reference 7, with permission.)

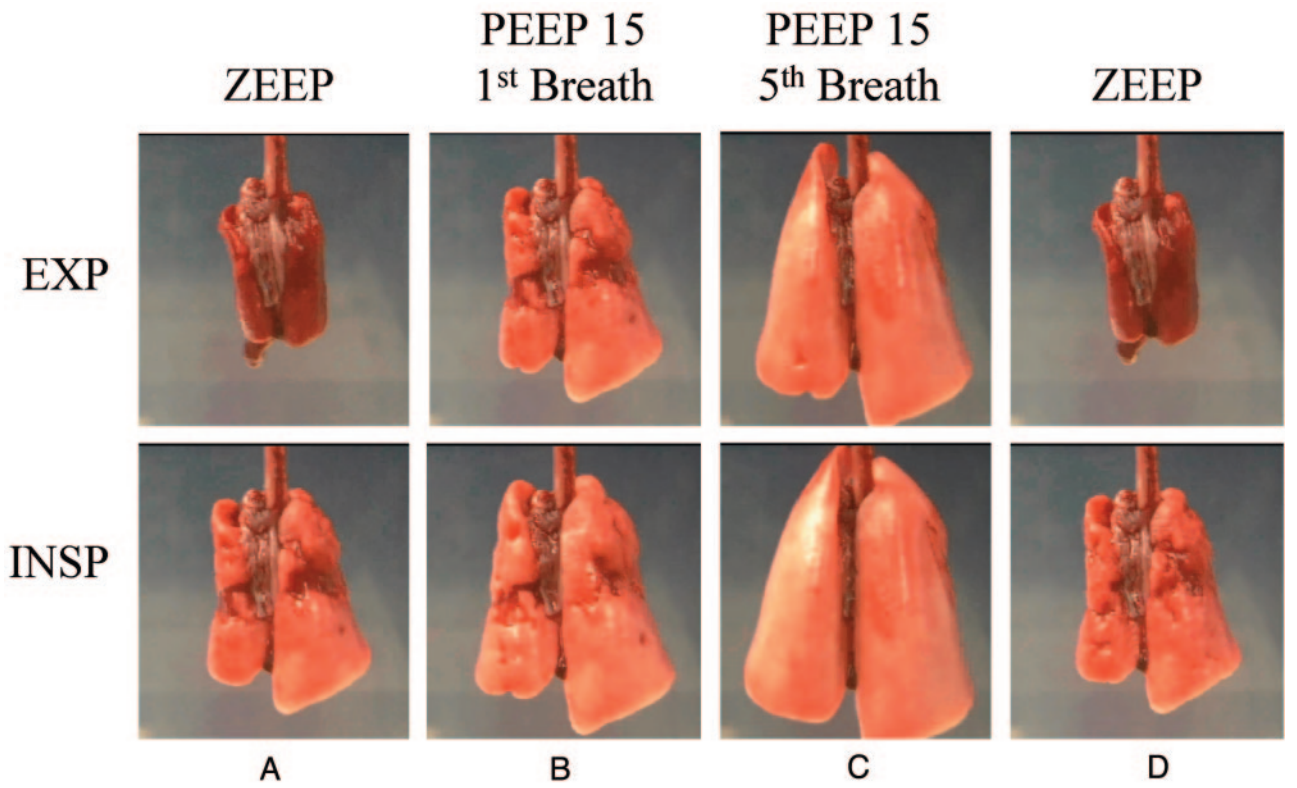

Fig. 6. Still images obtained from a rat lung being ventilated at 0 and then at 15 cm H_2O positive end-expiratory pressure (PEEP). The top 4 images were obtained at end-expiration (exp), and the bottom 4 images were obtained at end-inspiration (insp). Note the areas of atelectasis, even at end-inspiration, other than after the 5th breath at a PEEP of 15 cm H_2O. Full recruitment of the lungs took a number of breaths, even after PEEP was increased to 15 cm H_2O. At end-inspiration following the first breath at PEEP 15 cm H_2O there are still many areas of atelectasis. It was not until the 5th breath that these atelectatic areas were fully recruited. After PEEP was returned to zero, the inhomogeneity and areas of atelectasis returned within a couple of breaths. ZEEP = zero end-expiratory pressure. EXP = expiration. INSP = inspiration.

heterogeneity of lung inflation is clear. At the lower inflection point of the pressure-volume curve, the lung starts to open and the pressure-volume relationship becomes very steep. The lung is certainly not fully recruited at this point, or even at a few cm H_2O above the inflection point. As pressure increases, the lung starts to look relatively homogeneous, and as pressure is further increased, there is an upper inflection point, and the lung is fully recruited.

On the descending limb (deflation), the lung is quite well inflated at all these pressures. The difference between the inflation on inspiration and expiration is termed hysteresis. So when one looks at a pressure-volume curve in a textbook or at the bedside, I think that it is useful to think about what the lung actually looks like. And this tells us a couple of things. First of all, on the inflation limb when the lung is above the inflection point does not necessarily mean that the lung is fully recruited. The second point is that as the lung is inflated and deflated from a relatively low pressure to a higher pressure, recruitment/derecruitment can occur.

Now, this figure represents the static, or at least quasi-static properties of the lung; but what does the lung look like dynamically during ventilation? Figure 6 presents some still pictures from a video of a rat lung that is being ventilated ex vivo. As the lung is being ventilated at zero PEEP, there are areas of collapse, and fully inflated areas at end-inspiration. Figure 6B represents what happens as we increase PEEP to 15 cm H_2O, with recruitment starting to occur. But recruitment takes some time, and the lung is fully recruited only after a few breaths (see Fig. 6C). In fact, at end-inspiration, the lung looks like it may be somewhat over-inflated. When the PEEP level is subsequently decreased to zero, areas of collapse start to appear again, but only after a couple of breaths. So what this tells us is that, in terms of recruitment, one has to maintain a relatively high PEEP level if one wants to maintain the benefits of a recruitment maneuver. The major idea I want to get across here is what the lungs look like as they are being ventilated, because, in terms of VILI, what we want to do is prevent this opening and closing of lung units, and to prevent the over-distention that occurs.

Now, the final physiologic concept I want to explore is that lung distention, not airway pressures, is the critical

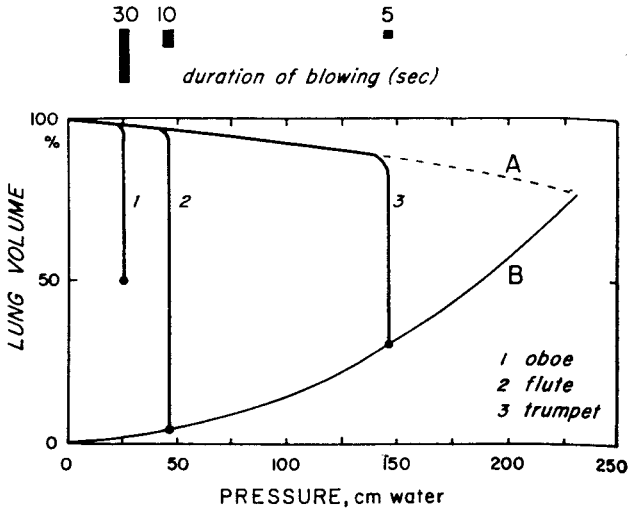

Fig. 7. Plot of lung volume versus pressure as musicians play the oboe, flute, or trumpet. Note that the pressure reached by the trumpet player is 150 cm H_2O. (From Reference 8, with permission.)

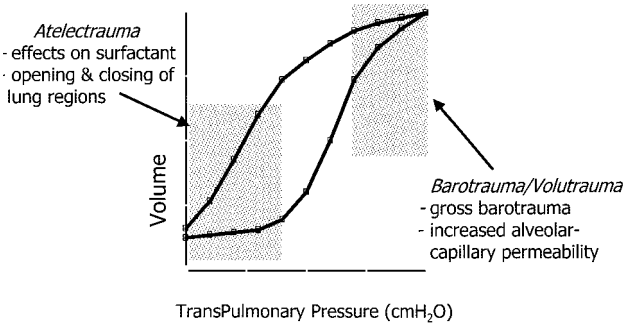

Fig. 8. Pressure-volume curve of the lung, demonstrating 2 regions that are thought to be associated with increased ventilator-induced lung injury. At relatively high pressures, barotrauma and volutrauma can occur, leading to gross air leaks and increased alveolar capillary permeability. When lungs are ventilated at relatively low volumes, atelectrauma can occur. With opening and closing of lung regions, lung injury can occur due to hypoxia, effects on surfactant, and the repetitive opening and closing of the lung units.

variable driving VILI. What we often measure at the bedside is pressure—either peak pressure or plateau pressure—but really what's important in terms of VILI is regional inflation, not airway pressures per se. High airway pressures do not necessarily mean that the lung is being subjected to an injurious ventilatory pattern. This was well documented in an interesting study by Bouhuys in 1969.[8] His interest was not mechanical ventilation; he was interested in the physiology associated with playing musical instruments. Figure 7 is a graph of lung volume versus pressure from Bouhuys's study. When a musician plays the oboe, pressures are about 25 cm H_2O, and lung volume decreases relatively slowly over 30 seconds. When a musician plays the trumpet, pressures at the airway opening are about 150 cm H_2O!; the trumpet player blows for only about 5 seconds, and there is a rapid drop in lung volume. Trumpet players generate these high pressures hundreds or even thousands of times a day, but they don't get barotrauma; they don't get VILI.

The reason is that it's not the airway pressure per se that's important; what's important is lung stretch or the transpulmonary pressure—the pressure across the lung (airway pressure minus pleural pressure). And, for a trumpet player to generate such high airway pressures, he has to contract his respiratory muscles to generate a high pleural pressure, so the transpulmonary pressure (alveolar minus pleural) is not increased. So the final important concept is that lung distention, not airway pressure, is the critical determinant in generating VILI. That has very important clinical implications in patients who have stiff chest walls (eg, patients with massive ascites). In these situations, peak airway pressure and plateau pressures may be high, but most of the pressure is dissipated in distending the chest wall. The lung is not necessarily being over-distended.

So, given that background, what are the physical factors causing VILI? Well, there's a process that we've called atelectrauma,[9] collapse and reopening of lung units leading to lung injury (Fig. 8). There is barotrauma, and there is volutrauma,[10] a term coined by Dreyfuss to indicate that it's not the pressure at the airway opening that's important, it's the distention of the lung that's important in causing lung injury.

Now, this concept of barotrauma is, in fact, not a new one. And I'll go back again to the history of mechanical ventilation and tell you about an interesting case report that appeared in the *Philosophical Transactions of the Royal Society of Medicine* in 1745.[11] This article described the case of a patient who was revived by a physician by the name of Tossack. Tossack discovered a man who ". . . had suffocated because of fumes from a coal pit." The patient was unconscious, not breathing, and pulseless. Tossack resuscitated this patient by "applying his mouth close to the patient's and, by blowing strongly, raised his chest fully. He immediately felt 6 or 7 quick beats of the heart. In one hour, the patient began to come to himself. In 4 hours, he returned home and, in as many days, returned to work." What was interesting was the discussion of this paper. Remember, this was a paper that was published over 250 years ago. What the author stated was that, in terms of resuscitation (bracketed interjections mine), "a number of individuals had suggested using a bellows to ventilate the patient" [similar to a mechanical ventilator]. . . . But blowing would be preferable, [ie, mouth-to-mouth resuscitation would be preferable] as the lungs of one man may bear, without injury, as great a force as those of another man which by the bellows cannot always be determined." I

think this is exactly the general concept we think about when we contemplate VILI or barotrauma. High pressures generated by a ventilator with subsequent over-expansion of the lungs can lead to injury. And they realized over 250 years ago that mouth-to-mouth resuscitation would limit the pressures and hence limit the lung distention.

Biotrauma

What I'd like to focus on now is a type of injury that is relatively new, that certainly wasn't contemplated a couple hundred years ago—the concept of biotrauma, a term we coined to describe biochemical injury or release of mediators that can be associated with mechanical ventilation.[12] We got interested in this topic about 10 years ago. Our hypothesis was that injurious ventilatory strategies—those strategies that allow either repeated recruitment/derecruitment of the lung and/or overdistention of the lung—could lead to a release of inflammatory mediators, such as cytokines. In our first set of studies, we used an isolated rat lung model. The movie I showed you a few minutes ago was of this model. The reason we used this model was because it allowed us to use relatively large volumes that could mimic the regional overdistention that occurs in patients (think back to that computed tomography scan of the patient with ARDS) (Fig. 4), without affecting hemodynamics. This was important because if one uses very high volumes in an in vivo situation, severe hypotension can occur; this by itself could potentially lead to an increase in mediators, which may not be strictly due to the mechanical forces on the lung.

We took the lungs, ventilated them for 2 hours, and used 4 different ventilatory strategies.[13] One strategy, which was the control, consisted of a relatively low level of PEEP (3 cm H_2O) and a V_T of 7 mL/kg—a relatively small V_T. The second group had a PEEP of 10 cm H_2O and V_T of 15 mL/kg. The third group had 0 PEEP and V_T of 15 mL/kg, and the final group had 0 PEEP and a very large V_T of 40 mL/kg, such that the end-inspiratory expansion was roughly the same in groups 2 and 4. Now, you might look at this last V_T and say, "Well, that's ridiculous. We would never use a V_T of 40 mL/kg in our patients," and that's certainly true. However, some patients have such bad disease that only about a quarter of their lung is available for ventilation (worse than the patient in Fig. 4). So, if a V_T of 10 mL/kg is applied to that patient, the regional overdistention in the quarter of the lung that's open is equivalent to the distention that would occur in a normal lung ventilated with 40 mL/kg.

At the end of 2 hours of ventilation, we measured a number of things, including concentrations of tumor necrosis factor alpha (TNF-alpha). This is a key cytokine that is a central mediator in the sepsis cascade. As shown in Figure 9, under control conditions very little TNF-alpha is found in the bronchoalveolar lavage fluid (BALF). With the medium-volume high-PEEP group there was a doubling or tripling of TNF-alpha, with a further doubling of TNF-alpha when we used 0 PEEP and V_T 15 mL/kg. Finally, with recruitment/derecruitment (0 PEEP) and overdistention (40 mL/kg), there was a 50–60 fold increase in TNF-alpha, compared to control.

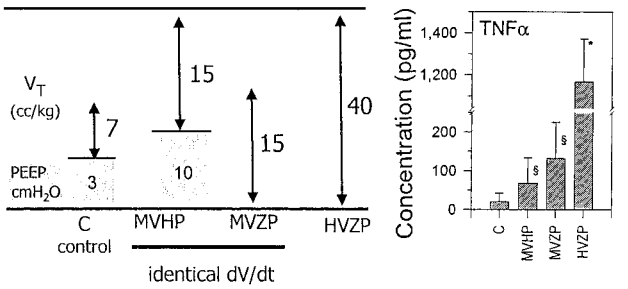

Fig. 9. Left panel: Schematic diagram of tidal volume and positive end-expiratory pressure (PEEP) levels used in the ex vivo ventilated lung model. The right panel demonstrates the values of tumor necrosis factor alpha (TNFα) versus the 4 different ventilatory strategies shown in the left panel. Note that there is a break in the axis at TNF-α value of about 250 pg/mL. C = control. MVHP = medium volume, high PEEP. MVZP = medium volume, zero PEEP. HVZP = high volume, zero PEEP. (From Reference 13, with permission.)

So, just 2 hours of ventilation is able to cause release of mediators that we know from other studies are important in sepsis and are critical in terms of organ dysfunction. Where do these cytokines come from? We obtained data a few years ago suggesting that the cytokines, to some extent or maybe to a large extent, come from the epithelial surface of the lung.[14] Remember, the epithelial surface area of the lung is huge. The cross-sectional area is the size of a tennis court and, if each one of the epithelial lining cells produces a little bit of TNF-alpha or other cytokines, such as interleukin 6 (IL-6), the total can be quite substantial. Figure 10 represents *in situ* hybridization for TNF-alpha, which looks at message levels of TNF-alpha. We also looked at the protein level within cells, using immunohistochemistry (see Fig. 10B). And in both cases it was the epithelial lining that lit up markedly, demonstrating that these cells were producing the cytokines. Other studies have addressed this issue, but I don't have time to discuss them. Most, but not all, studies are supportive of this concept that injurious ventilatory strategies can lead to release of mediators.

Systemic Consequences of Biotrauma

I'm not going to talk any more specifically about the lung. I'd like to now focus on what I think may be more important in terms of the outcomes of our patients—that is the systemic consequences of biotrauma. It's not just the

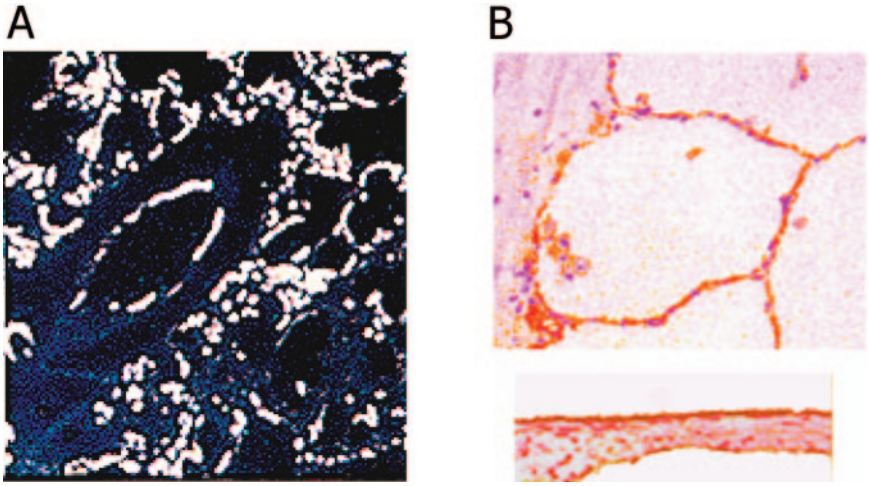

Fig. 10. Left: Dark-field image of in situ hybridization for tumor necrosis factor alpha (TNF-alpha) messenger ribonucleic acid (mRNA) with a ventilatory strategy using medium volumes and zero positive end-expiratory pressure (PEEP). The white denotes cells that are positive for TNF-alpha. Note that the message levels of TNF-alpha appears to be largely in epithelial cells. Right: Immunohistochemical staining for TNF-alpha protein in the lungs ventilated with the medium tidal volume and a zero-PEEP strategy. Note that the TNF-alpha protein (reddish color) appears localized largely to the alveolar epithelium. (From Reference 14, with permission.)

release of mediators in the lung. If these mediators can translocate from the lung and get into the systemic circulation, they can potentially cause damage to other end organs.[15]

The lung is unique in that virtually all of the systemic blood flow traverses the lung. It has a huge vascular bed and many neutrophils marginate or stick in the lung, waiting to be activated. It also has a huge surface area that is open to the environment and can be a portal of entry of many pathogens, such as bacteria. The lung is also a metabolically active organ. As I showed you, the epithelium produces TNF-alpha and IL-6, as well as other substances, and so does the endothelium. If these cells produce mediators that then are released into the systemic circulation, that can potentially cause problems.

We examined the hypothesis that ventilatory strategy could lead to the release of cytokines from the lung into the systemic circulation. We used an in vivo model of acute lung injury, in which intra-tracheal acid was injected into rats.[16] This is a pretty good model of what occurs in patients who aspirate—not an uncommon cause of ARDS. We then ventilated these animals with 4 different ventilatory strategies: V_T 16 mL/kg, 0 PEEP; V_T 16 mL/kg, PEEP 5 cm H_2O; and then a small V_T 5 mL/kg without and with PEEP. And then, in addition to measuring lung lavage cytokines, we measured serum cytokines. Figure 11 is a graph of serum TNF-alpha versus time. In most groups there is very little change in TNF-alpha over time. But in one group (large V_T, zero PEEP) there was a marked increase in TNF-alpha. Interestingly, PEEP was protective in this model: with PEEP in the large-V_T group there was no large increase in serum levels of TNF-alpha. So this study showed that mechanical ventilation can impact not

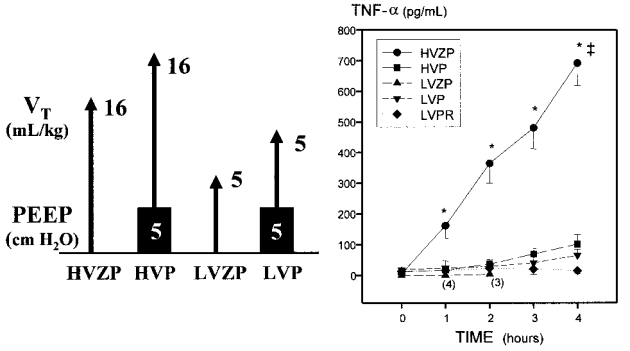

Fig. 11. Left panel: Four ventilatory strategies were used to ventilate rats following intratracheal acid aspiration: HVZP = high volume, zero positive end-expiratory pressure (PEEP); HVP = high volume, 5 cm H_2O PEEP; LVZP = low volume, zero PEEP; and LVP = low volume, 5 cm H_2O PEEP. Tidal volume (V_T) was 16 mL/kg. Right panel: Serum levels of tumor necrosis factor alpha (TNF-α) versus time for the different ventilatory strategies. Note the marked increase in TNF-α with time in the strategy with high volume and zero PEEP. (From Reference 16, with permission.)

only the lung, but could possibly impact other organs by release of various mediators into the circulation.

We were interested in studying the mechanisms by which mediator release could lead to organ dysfunction in other organs. Last year we published an article in *JAMA*,[17] in a new section called "Translational Medical Research."[18] We used the acid aspiration model in anesthetized rabbits. The animals were then randomized and ventilated for 8 hours. One group received an injurious ventilatory strategy, with high V_T and 0 PEEP; other animals received a relatively noninjurious ventilatory strategy, with relatively low V_T and higher PEEP levels. We measured a number of

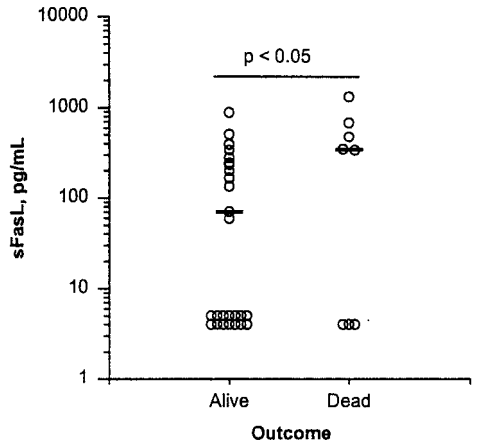

Fig. 12. Plot of soluble Fas ligand (sFasL) in patients with acute respiratory distress syndrome who went on to live or die. (From Reference 19, with permission.)

factors, including hemodynamics, enzymes, and blood gases, but we focused on something called apoptosis using TUNEL (terminal deoxyribonucleotidyl transferase-mediated deoxyuridine 5-triphosphate-digoxigenin nick end labeling) assay, and electron microscopy.

Now I'm going to take a bit of a tangent to tell you a little bit about apoptosis, because I know that that's something that many of you may not be familiar with. Cells can die in a couple of ways. They can die by necrosis, with a breakdown of the cell's plasma membrane and release of the cell's contents—a process that causes an inflammatory reaction. The other way that cells can die is by apoptosis—also known as programmed cell death. This an orderly way for cells to die. Key mediators here are caspases, which can be triggered by chemicals or substances called Fas and Fas ligand.

Well, are apoptosis and Fas important in ARDS? Figure 12 presents data from a group in Seattle, which suggest that they may be important. Patients with ARDS who went on to live had lower levels of soluble Fas ligand than those who died.[19] It certainly doesn't prove that this is an important molecule in ARDS, but it certainly indicates that there is some relationship between soluble Fas ligand and clinical outcomes. Other studies from this group have shown that the BALF from ARDS patients triggers apoptosis, and the apoptosis can be blocked by molecules that block Fas.[20]

Now let's get back to our animal study. Blood pressure was identical for the injurious group and the noninjurious groups, so what I'm going to show you here in terms of kidney function, in terms of kidney apoptosis, is not due to changes in blood pressure. Figure 13 presents the results of a TUNEL assay in kidney and gut from animals in the injurious and noninjurious groups. The apoptotic-positive cells are stained yellow-green. The results in the 2 groups were quantified in a blinded fashion (right of Fig. 13); the injurious group had a much higher apoptotic index in kidney and the villi of the gut in the animals ventilated with the injurious strategy.

To summarize, cells in the kidney are dying from apoptosis in the group ventilated with the injurious ventilatory strategy. I don't have time to give you details here, but in this study we also suggested that it was Fas ligand that was important. We took serum from the rabbits and applied this serum to cell culture and showed that we could block Fas ligand and could block the increased apoptosis.

Clinical Relevance of Biotrauma

At this point you might be saying to yourself, "Well, all this is very nice, but in my intensive care unit we don't ventilate rats. We don't ventilate rabbits. We take care of humans." So does any of this have any relevance at the bedside to our patients? Is this of any relevance to patients with ARDS? Well, I think that there are increasing data suggesting that these concepts do have clinical relevance.

About 5 years ago, in collaboration with Marco Ranieri, we published a paper in *JAMA* in which we performed a randomized controlled trial in patients with ARDS, comparing a minimal-stress ventilatory strategy to a conventional ventilation strategy, and measured cytokines in these patients.[21] Some results are shown in Figure 14. The group treated with the minimal-stress ventilatory strategy had markedly lower BALF cytokines, and lower serum cytokines at 24 and 36 hours, compared to the conventional group. These data are very reminiscent of the animal data that I showed you earlier, demonstrating that a ventilatory strategy that minimized VILI was associated with decreased cytokine concentrations. In fact, ventilatory strategy can impact cytokine levels within a very short time frame. Figure 15 is from a study by Stuber et al, in which they ventilated patients with ARDS with a lung-protective strategy for a period of time, then changed to a lower PEEP/higher-V_T strategy for a few hours.[22] When the more injurious strategy was used, there was an increase in concentration of cytokines; this occurred within an hour of changing ventilatory strategy. When they changed back to the lung-protective strategy, there was a rapid decrease in these cytokines. The fact that these mediators can be released relatively quickly after a change in strategy brings up an interesting possibility. Maybe we can use some of these markers to decide when we have optimized ventilatory strategy in a patient with ARDS. Perhaps in the future we will titrate ventilatory strategy to serum mediator release.

Other evidence suggesting that these concepts may be relevant to patients is based on the results from the ARDSNet study I mentioned previously, which demonstrated a 22% relative decrease in mortality in the group treated with a V_T of 6 mL/kg predicted body weight, ver-

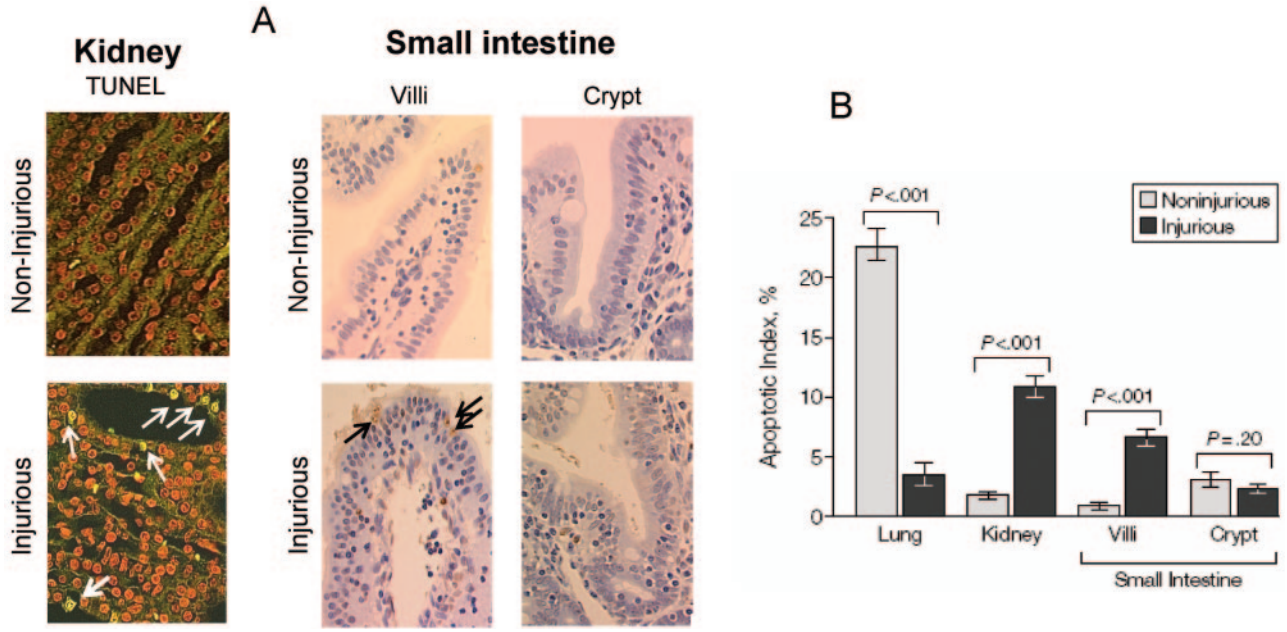

Fig. 13. Left: Terminal deoxyribonucleotidyl transferase-mediated deoxyuridine 5-triphosphate-digoxigenin nick end labeling (TUNEL) staining of kidney and small intestine from rabbits ventilated with a noninjurious strategy (low tidal volume, relatively high positive end-expiratory pressure [PEEP]) and an injurious ventilatory strategy (large tidal volume, zero PEEP). Note that there were many more TUNEL positive cells (indicated by the arrows) in the kidney and in the villi of the small intestine in the injurious ventilatory strategy. Right: The apoptotic index was calculated for each of the organs shown on the left, as well as the lung. There was decreased apoptosis in the lungs of animals ventilated with the injurious ventilatory strategy, but an increase in apoptosis in the kidney and the villi. (From Reference 17, with permission.)

sus 12 mL/kg.[1] We don't know the mechanism for the decreased mortality in the smaller-V_T group, but it was not due to reduced barotrauma, as the incidence of barotrauma was essentially identical in both groups. It was not due to differences in oxygenation; in fact, the lower-V_T group, which had the better survival, had *lower* P_{aO_2}/fraction of inspired oxygen ratios for the first couple of days than did the higher-V_T group. The ARDSNet investigators suggested that this difference in mortality may be related to differences in mediator release; levels of IL-6 decreased significantly more quickly over time in the lower-V_T group.[1,23] So maybe the biotrauma hypothesis explains the decrease in mortality in this study.

Implications of the Biotrauma Hypothesis for Novel Treatments of Ventilated Patients

Does the biotrauma hypothesis suggest any novel nonventilatory approaches to mitigate VILI? A reasonable first question to ask is, why do we need novel nonventilatory therapies? One could argue that we have the ARDSNet study that demonstrated a decrease in mortality. Let's just optimize the ventilatory strategy and we won't need anything else. In fact, this would be ideal, but the problem is that it's going to be difficult to obtain a completely noninjurious ventilatory strategy in every patient. The reason I say that is the tremendous spatial heterogeneity of the lung disease that exists in patients with ARDS. Figure 16 is taken from a study by Gattinoni et al.[24] The X axis is PEEP level, and the Y axis represents gas tissue ratio. The upper panel represents the nondependent region; the lower panel is the dependent region; and the middle panel is the mid-lung region. If one were to set the PEEP level to minimize VILI and optimize oxygenation for the middle region, one might pick a value of PEEP somewhat above the inflection point—about 16 or 18 cm H_2O. This might be adequate for this region, but if one examines what this would mean for the other 2 regions, one can see the problem. For the dependent region the lung is essentially still collapsed. Examination of the nondependent region suggests that this level of PEEP might lead to over-distention of this portion of the lung. So, based on these and other data, I think in some patients it will not be possible to develop a ventilatory strategy that is noninjurious in all lung regions. There are other approaches than simply changing PEEP, but whether one uses the prone position or uses high frequency or whatever, in patients with very severe ARDS, VILI will still occur in some lung regions.

So in these patients with severe lung injury we might think about targeting mediators, since the patients are dying of multiple-system organ failure, perhaps due to a release of mediators. Could this approach be effective?

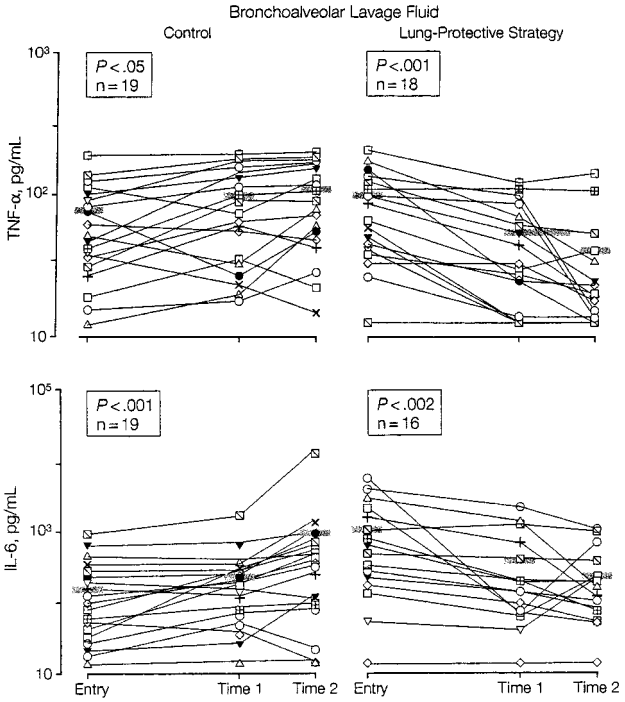

Fig. 14. Cytokine levels in patients ventilated with either a protective or a conventional ventilatory strategy (control patients) versus time (Entry = time of entry into study; Time 1 is approximately 24 h after entry; Time 2 is approximately 36 h after entry into the study). Top: Bronchoalveolar lavage fluid levels of tumor necrosis factor alpha (TNF-α) in the control patients (left panel) and the patients ventilated with the lung-protective strategy (right panel). There was an increase in bronchoalveolar lavage fluid TNF-α in the control patients, and a decrease in the patients ventilated with the lung-protective strategy. Bottom: Interleukin 6 (IL-6) concentrations in the plasma of the control patients and the patients ventilated with the lung-protective strategy. There was an increase in plasma IL-6 levels in the control patients, and a decrease in IL-6 in the patients ventilated with the protective ventilatory strategy. (From Reference 21, with permission.)

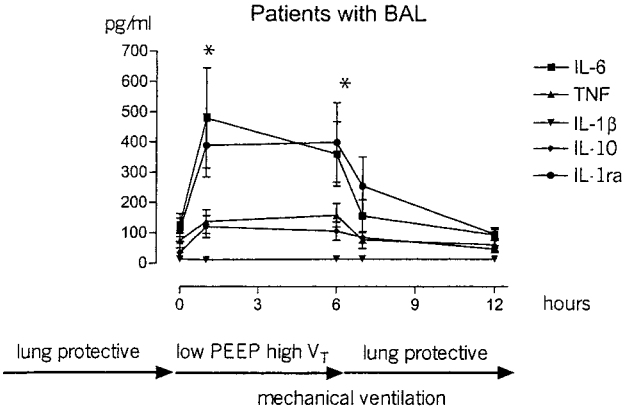

Fig. 15. Plot of cytokine levels on the Y axis versus time on the X axis. Patients were ventilated initially with a lung-protective strategy, then a low-positive-end-expiratory-pressure (PEEP)/high-tidal-volume (V_T) strategy, and then with a lung-protective strategy again. Note that when the strategy was changed to the low-PEEP/high-V_T strategy that levels of most cytokines increased. Similarly, when the ventilatory strategy was changed back to the lung-protective strategy there was a decrease in most cytokines. IL = interleukin. TNF tumor necrosis factor. (From Reference 22, with permission.)

Figure 17 is from a study by Imai et al in which they used intratracheal anti-TNF antibodies to see whether they might attenuate VILI.[25] They used the lung lavage model—a commonly used model of infant respiratory distress syndrome. In the control groups there was a marked decrease in P_{aO_2} after lavage. When they used a low dose of an anti-TNF antibody, there was attenuation of the decrease in oxygenation; and when they used a higher dose of anti-TNF antibody, you can see that there was a marked increase in P_{aO_2}, almost toward normal levels.

These data suggest that TNF-alpha is pretty important in VILI—it's not just an innocent bystander. What about targeting end-organ dysfunction? Guery et al addressed this issue using a rat VILI model.[26] They gave rats a neutralizing anti-TNF antibody or a control antibody 2 hours prior to ventilation with low (10 mL/kg) or high (20 mL/kg) V_T, and then measured various lung parameters and

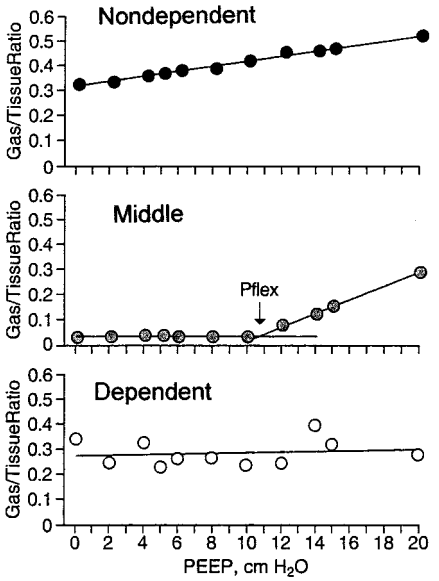

Fig. 16. Plots of gas/tissue ratio versus positive end-expiratory pressure (PEEP) levels for 3 regions of the lung (nondependent, middle, and dependent). The data were obtained from computed tomography scans and demonstrate the tremendous heterogeneity in aeration that can occur in patients with acute respiratory distress syndrome. In this patient there was no recruitment with increasing positive end-expiratory pressure in the dependent regions, and there was an inflection point in the middle zone, with increasing recruitment of the lung as PEEP level increased above approximately 10 cm H_2O, and continuing inflation of the lung with increasing PEEP levels in the nondependent regions. (From Reference 24, with permission.)

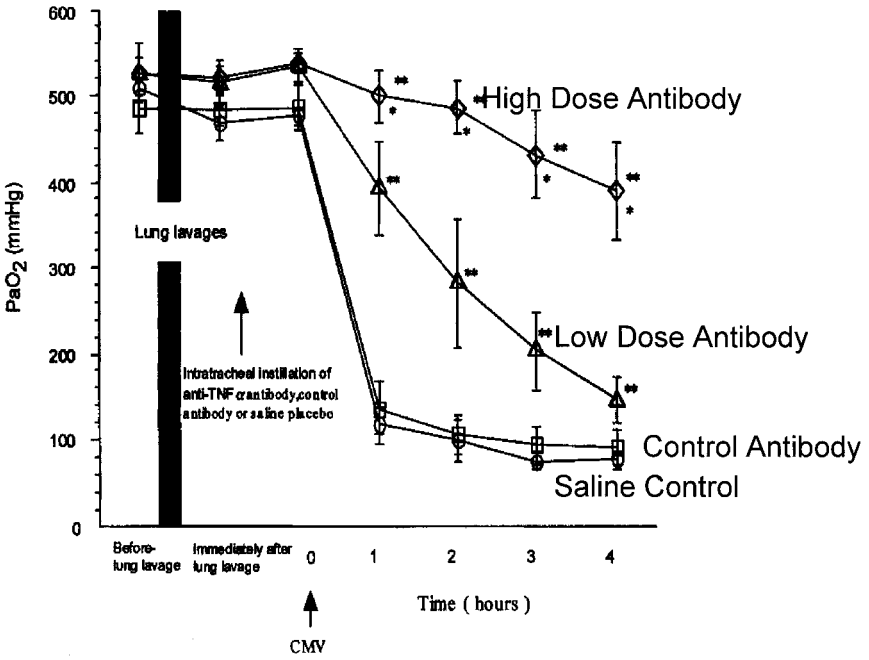

Fig. 17. Plot of P_{aO_2} versus time in rabbits when lung injury was induced by lung lavage. Just before time zero there was intratracheal instillation of anti-tumor-necrosis-factor-alpha (anti-TNF-α) antibody (high or low doses), control antibody, or saline placebo. The P_{aO_2} in the low-dose antibody group was greater than the control antibody or saline control. The P_{aO_2} was greater in the high-dose antibody group. CMV = continuous mandatory ventilation. (From Reference 25, with permission.)

various indices of end-organ permeability. They found that the high-volume ventilation increased TNF-alpha to 3,758 ± 1,459 pg/mL from 581 ± 188 pg/mL in the low V_T group. In the high-V_T group the anti-TNF antibody significantly decreased the gut permeability index by about 75%. These data provide hope that an anti-inflammatory mediator may mitigate end-organ failure.

Summary and Concluding Remarks

In summary, we've known for a long time that mechanical ventilation can lead to biophysical injury (Fig. 18);[15] there's shear injury, and there's overdistention of lung units. There are changes in intrathoracic pressure that can have a number of effects, including an increase in alveolar-capillary permeability, a decrease in cardiac output, and a decrease in organ perfusion. These can all lead to end organ dysfunction. We've known this for many years. Over the last few years we've begun to realize that mechanical ventilation can cause much more subtle injury—biochemical injury—something that we've called biotrauma—release of mediators from the lung. These mediators can attract neutrophils and other inflammatory cells that could then worsen the lung injury. And if there's spillover of these mediators from the lung into the systemic circulation, this could potentially lead to distal organ dysfunction and eventually lead to death. If this hypothesis is correct, it could explain the puzzle that I posed earlier: *why is it that patients with ARDS who go on to die, die of multiple-system organ failure rather than respiratory failure?*

I think the main message is that the way we ventilate patients is critical to their outcomes. It's not just a matter of putting the patient on the ventilator, improving oxygenation, and now the patient's going to live—thanks to us. The ventilatory strategy we use can also injure them, and it's very important for us to think about using gentle ventilatory strategies to minimize VILI. Maybe some time in the future we'll be looking at anti-mediator therapy. I don't expect this to happen for a long time, quite frankly. It'll be many years. And one might ask, "Well, is there really a chance that this mediator therapy is going to be useful?" We know that in sepsis, for example, we've tried anti-TNF antibodies, and they haven't been very successful. I think there's hope that this approach might be more successful for VILI and biotrauma. We're in a terrific position compared to the therapy of sepsis. In the animal models of sepsis, anti-TNF therapy is very effective when given prior to the start of the septic process. The problem in patients is that by the time one makes the diagnosis of sepsis, the patient has had an ongoing process for many, many hours and maybe many days, so when treating sepsis with anti-TNF therapy, we're always treating after the disease process has been ongoing for some time. With VILI we're in

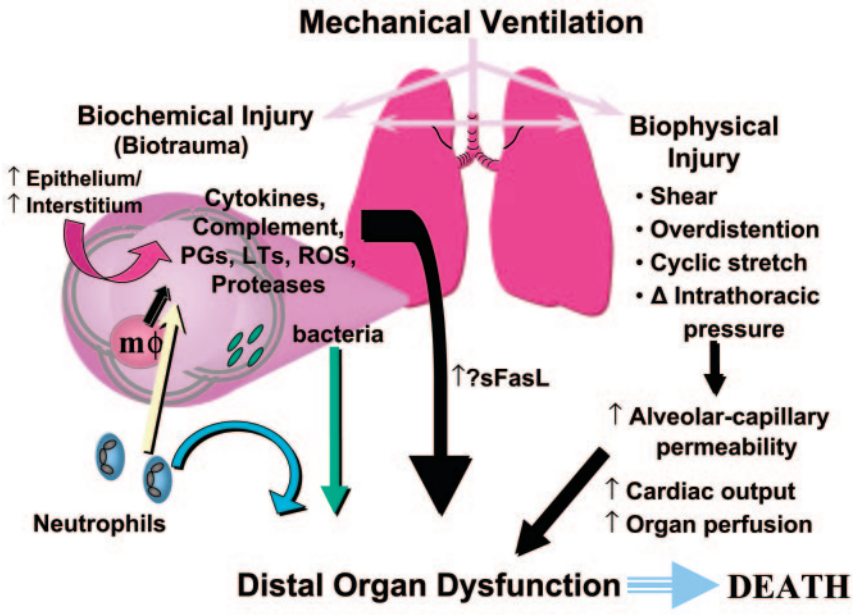

Fig. 18. Schematic diagram of the impact of mechanical ventilation on distal organ dysfunction. Mechanical ventilation can lead to biophysical injury by a number of mechanisms, as shown on the right, as well as more subtle biochemical injury (biotrauma), with release of a number of mediators into the lung. The mediators can lead to recruitment of a number of cells, including neutrophils, and if some of these mediators are translocated from the lung into the systemic circulation they may lead to distal organ dysfunction and death. This hypothesis would explain the development of multisystem organ dysfunction in patients with acute respiratory distress syndrome who are being ventilated. One such mediator is soluble Fas ligand (sFasL), which may be a target for future therapy. PG = prostaglandins. LT = leukotrienes. ROS = reactive oxygen species. (From Reference 15, with permission.)

the lucky position that we know exactly when VILI will start—it's going to start after the patient is intubated and mechanical ventilation is started. So we could pretreat patients. Perhaps 10 years from now as we intubate patients we'll be squirting in some anti-Fas therapy or other anti-mediator therapy to try to mitigate what's going to happen later on in terms of organ failure.

So the main message I want to give is that the ventilatory strategy we use to ventilate our patients is critical. I think that research into mechanical ventilation is having an impact—not just on the number of papers published—but the translation of concepts developed in the basic science laboratory is having a huge impact on the clinical outcomes of our patients. It has led to a marked decrease in mortality in ARDS over recent years. Respiratory therapists have been and will continue to be critical to this process. You are at the bedside and what you do impacts our patients on a breath-by-breath basis. Keep up the great work!

I'd like to thank the organizers for inviting me, and I'd like to thank you for your attention.

ACKNOWLEDGMENTS

I would like to thank all of my colleagues and fellows who contributed to so much of the work which I presented, and to George Volgyesi and Dr Tom Whitehead for their help in creating the movie of ex vivo ventilated lung (Figure 6).

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