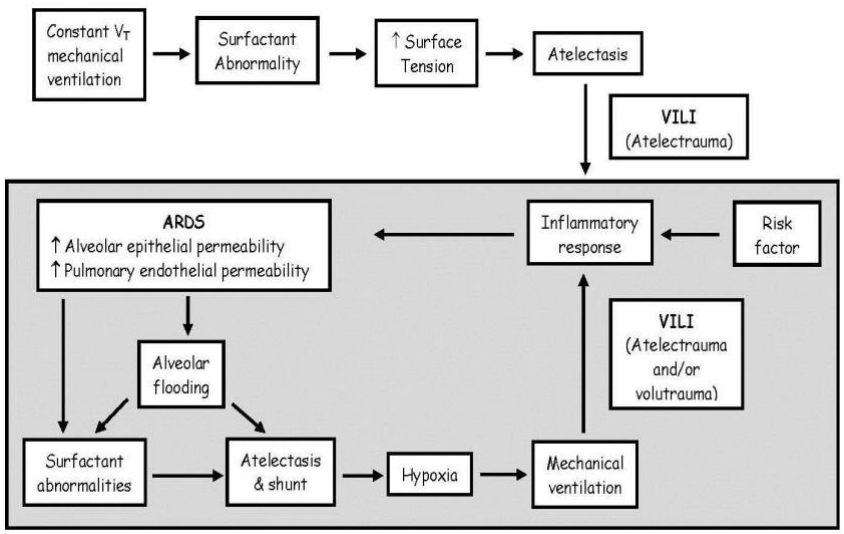
Sigh Ventilation to Increase Ventilator-Free Days in Victims of Trauma at Risk for the Acute Respiratory Distress Syndrome (SiVent)

Study PI: Dr. Richard K. Albert

Background

The current paradigm describing the pathophysiology of the acute respiratory distress syndrome (ARDS) begins with patients having one or more risk factors that predispose them to developing the syndrome (e.g., trauma, inhalation injury, sepsis, pneumonia) as depicted on the right-hand side of the shaded portion of Figure 1. These risk factors are thought to generate an inflammatory response that causes pulmonary endothelial and epithelial injury which, in turn, results in surfactant deficiency, alveolar flooding, atelectasis and shunt, and the resulting hypoxia necessitates the need for mechanical ventilation. Ventilator-induced lung injury (VILI) is thought to contribute to the pathophysiology by causing cyclical airspace opening and closing (termed atelectrauma) and/or overdistension (termed volutrauma) that produce additional, ongoing lung injury, as well as systemic effects that are termed biotrauma (Dos Santos, 2000; Ware, 2000).

Figure 1. Pathophysiology of ARDS



Interestingly, however, only ~20% of patients have ARDS at the time they are diagnosed with one or more of the predisposing risk factors. In the other ~ 80% the onset of ARDS is delayed by 1-4 days (median = 2 days) (Hudson, 1995; Hou, 2012). While this lag has been attributed to the inflammatory response taking time to develop it is also consistent with the hypothesis that, in perhaps as many as 80% of cases, ARDS might be occurring via a different pathophysiological pathway.

The following observations have led to the development of a <u>new paradigm for the pathophysiology of ARDS</u> as shown in the unshaded portion of Figure 1.

Constant tidal volume (V_T) ventilation inactivates and/or depletes surfactant and causes atelectasis.

Mechanical ventilation has been known to decrease lung compliance in humans since the 1950s (Wu, 1956; Butler, 1957, Ferris, 1960) and Mead and Collier (1959) were the first to link this change in compliance to the development of atelectasis. Greenfield and colleagues (1964) were the first to suggest that the compliance change and the atelectasis occurred because mechanical ventilation depleted, altered or interfered with surfactant. Subsequently, numerous investigators have confirmed that constant V_T ventilation for as little as 5 minutes (a) increases the surface tension of lung extracts, (b) increases lung elastic recoil and airway opening pressures and (c) causes atelectasis, and that these changes (d) are directly related to the size of the V_T, the duration of mechanical ventilation, and possibly the respiratory rate (Faridy, 1966; McClenahan, 1967; Forrest, 1972; Wyszogrodski, 1975). Wyszogrodski and colleagues (1975) and Bailey and colleagues (2008) found that large V_T ventilation released surfactant into the alveolar space but that it also increased the surface tension of lung extracts. Accordingly, they proposed that constant V_T ventilation inactivated, rather than depleted surfactant.

In a well-known and highly cited study, Webb and Tierney (1974) found that rats ventilated with large V_T and no PEEP developed severe hypoxemia, had a reduction in respiratory system compliance and developed alveolar edema and other pathologic changes. Although this study is frequently cited as being the first to demonstrate that mechanical ventilation injures the lung as a result of overdistension and/or cyclical airspace opening and closing (i.e., VILI), Webb and Tierney found no evidence of tissue disruption on histologic examination and concluded that overdistension was probably not the explanation for the abnormalities they observed. Cyclical airspace opening and closing was not mentioned in the manuscript. Webb and Tierney (1974) attributed their findings to surfactant depletion resulting from the large ventilatory excursions they employed, or to the absence of PEEP causing surfactant dysfunction from repeated compression of the fluid film as was first demonstrated by Clements (1957) nearly 20 years earlier. Accordingly, the findings of Webb and Tierney (1974), together with those cited above, suggest that the reduction in mortality in ARDS seen with low V_T ventilation does not occur because low V_Ts cause less overdistension, but rather because it causes less surfactant dysfunction which, in turn, results in less atelectasis and less cyclical airspace opening and closing.

Surfactant can be separated by centrifugation into large aggregates and small aggregates, with the latter having much less surface activity. Cycling surfactant ex-vivo or ventilating lungs in-vivo or in-situ with constant, large V_T converts large aggregates to small aggregates and impairs large aggregate function. Larger changes in surface area result in greater conversion (Veldhuizen, 1996; 2002), but compliance and surface tension decrease in as short a time as 15 minutes of ventilation even when V_T is low or normal, with accompanying increases in inflammatory cytokines and histologic evidence

of lung damage (Veldhuizen, 1996; Muscedere, 1994; Thet, 1979; D'Angelo, 2002; Chu, 2004; Myrianthefs, 2006; Bailey, 2008; Hauber, 2010; Hong, 2010; Vobruba, 2013).

Increased surface tension is *necessary and sufficient* to cause VILI.

Clements (1957), was the first to suggest that surfactant "might be an 'antiatelectasis factor'", that the "long-term stability of the lungs requires *periodic replenishment of surfactant*," (my emphasis) and that "the mechanism and speed with which the lungs *spontaneously decrease in compliance and become atelectatic* (my emphasis) probably depend significantly, and perhaps solely, on the viscoelastic parameters of the surface films" (Clements, 1957; 1961; 1963). Young and colleagues (1970) subsequently demonstrated that compliance decreased when lungs were held in inflation with air at 3 cm H_2O for 20 minutes with no V_T. They attributed the change to increases in surface tension that developed spontaneously because no change in compliance occurred when the lungs were distended with liquid to the same volume (see the explanation provided by Pattle discussed below).

Coker and colleagues (1992) and Taskar and colleagues (1997) both found that VILI only occurred in animal models when surfactant was inactivated. Bilek and colleagues (2003) developed an apparatus consisting of two glass plates that were coated with epithelial cells and separated by a distance that was similar to the diameter of small airways. Forcing fluid between these plates generated large pressure gradients that damaged the cells. When surfactant was added, however, fluid could be forced through the opposed surfaces at much lower pressures and the epithelial injury was prevented.

Increasing endogenous surfactant pools or intratracheal administration of exogenous surfactant protects against the hypoxia, the decrease in compliance, the protein leakage and the release of inflammatory cytokines that occur when animals are ventilated with large V_Ts and no PEEP (Verbrugge, 1998; Welk, 2001; D'Angelo, 2007; Maruscak, 2008; Yamashita, 2008) and Walker and colleagues (2009) confirmed this effect in mice ventilated with a small V_Ts (i.e., 5 ml/kg) and a PEEP of 3 cmH_2O.

In the most definitive study demonstrating that surfactant deficiency is necessary and sufficient to cause VILI Ikegami and colleagues (2005) developed mice that conditionally expressed normal levels of human surfactant-associated protein B (SP-B) when they were receiving doxycycline. When doxycycline was withdrawn in these spontaneously breathing mice, SP-B decreased, surface tension increased as did protein concentrations and inflammatory cells in bronchoalveolar lavage and IL-1β in lung tissue and 70% of the animals died from cyanosis and respiratory distress. If, after four days, doxycycline was reintroduced all of these changes reversed and none of the animals died.

Changes in surfactant and surface tension *precede* the onset of ARDS.

The current paradigm explaining the pathophysiology of ARDS indicates that surfactant abnormalities develop as a result of the endothelial and/or epithelial injury that occur in response to the inflammation induced by the predisposing risk factors (Figure 1). Hedley-Whyte and colleagues (1964), however, noted that lung compliance fell within 14 minutes of instituting large V_T ventilation in normal dogs, but that shunting and the alveolar-to-arterial oxygen tension difference did not increase until 30 minutes later. Finley and colleagues (1964) found that surface tension fell before the development of experimental atelectasis.

Large aggregate forms of surfactant decrease before increases in permeability occur or gas exchange abnormalities develop in animal models of acute lung injury (Lewis, 1990), and surfactant pool sizes and surface lowering activity are altered 1 hour before oxygen decreases after instituting high-stretch ventilation (Maruscak, 2008). Thammanomai and colleagues (2007) found that SP-B levels decreased after ventilating normal mice for only 20 minutes. Importantly, Greene and colleagues (1999) reported that SP-A and SP-B concentrations were reduced in bronchoalveolar lavage fluid of patients who were at risk for developing ARDS before the time they met roentgenographic or gas exchange criteria for ARDS.

Stretching alveolar type 2 cells in-vitro, or giving large tidal volumes (i.e., sigh breaths) in-vivo, causes secretion of surfactant into the alveolar space and prevents atelectasis and lung injury.

Cecil Drinker seems to be the first to recognize that intermittent delivery of large V_Ts decreased atelectasis (Drinker, 1945). In 1928, while observing the first subject being tested in the mechanical ventilator devised by his brother he noted that:

> "a more interesting matter relating to the comfort of the young man was his request that from time to time the respirator be made to give him a deep inspiration, a sort of prolonged yawn or sigh. This gave comfort to him and thought to me…if [man] has remained quiet for a long time, without the possibility of movement, he indulges often in a long breath, a sigh, or a yawn. The way to treat pulmonary stasis and atelectasis is to prevent their occurrence and, thereby, their eventual promotion of more serious conditions. This is accomplished by change in position and best by a few deep respirations" (Drinker, 1945).

The first report describing treatment of poliomyelitis with mechanical ventilation was published in 1930 by physicians who were using the Drinker respirator and included comments on the importance frequently administering deep breaths (Schambaugh, 1930). William Dock, in a 1944 paper entitled "The sequelae of complete bed rest" noted that: “patients with air hunger and deep respiration up to the final hour show

notably less collapse post mortem than do those with normal blood levels of hemoglobin and base…it is the acidosis and air hunger which prevent collapse" (Dock, 1944). Bernstein (1957), studying rabbits, was the first to demonstrate that ventilation-induced changes in lung pressure-volume curves could be prevented by periodically administrating large inflations. His observation was confirmed by Mead and Collier (1959) in dogs that were spontaneously breathing or receiving mechanical ventilation and subsequently by numerous other groups studying humans (Farris, 1960; Caro, 1960; Egbert, 1963; Bendixen, 1963; Laver 1964).

In 1965 Pattle (1965), one of the first biochemists to explore the physiology of surfactant, concluded that:

> "There thus exists a surface tension, γ_0, at which the free surface energy is at a minimum; if the surface tension is less than this, no recruitment of material to the lining film from the underlying complex can take place, and there will be a tendency for material to be desorbed from the surface film. Any desorption of the surface film will result in a decrease in the internal surface area; there will be a consequent fall in the volume at maximum pressure and in the compliance calculated from that volume. *Eventually collapse of some or all of the alveolar units will occur. If the ventilatory cycle is kept regular, therefore, decrease in compliance and slow collapse are to be expected…it follows that one of the functions of a yawn or deep breath is to recruit more material to the lining film. If such reactions are prevented slow collapse of the lining film, and eventually of the alveolar spaces, may be expected. If artificial respiratory is being used, the collapse might be prevented by giving the lungs an occasional maximal inflation"* (Pattle, 1965) (my emphasis).

The pool of surfactant in the alveolus is continuously depleted as a result of cellular uptake by type II alveolar epithelial cells and macrophages and by surfactant removal via the mucociliary escalator. The loss of surfactant is compensated for by secretion of surfactant from the type II cells. Accordingly, regulation of surfactant secretion is critical for homeostasis such that, if secretion is reduced, alveolar surface tension will increase thereby predisposing to atelectasis. Of the various chemical and physical stimuli that are known to regulate surfactant secretion lung distension, working through a calcium-dependent mechanism (Wirtz, 1990; Frick, 2004), is considered to be the most important physiologically (Dietl, 2005).

Tierney and Johnson (1965) also theorized that instability of surfactant would cause gradual atelectasis during shallow breathing and that "the alveolar surface film can be replenished by a single deep breath." A direct link between the effect of sighs and surfactant was subsequently demonstrated by numerous investigators who found that large V_T ventilation, large gasps in spontaneously breathing animals, single large inflations with air or liquid, or even single stretches of type II cells in-vitro all increased

the release of active surfactant (Nicholas, 1982; Nicholas, 1983; Massaro, 1983; Hildebran, 1981; Wirtz, 1990; Oyarzun, 1990).

Although the beneficial effect of sighs may seem inconsistent with the direct relationship between the size of the V_T and the resulting surfactant dysfunction noted above, the discrepancy is explained by the sizes of the V_Ts used and the frequencies and durations with which they were administered. Studies showing that larger V_Ts alter surfactant and increase surface tension used V_Ts ranging from 30% to 100% of the spontaneous V_T that were administered every breath for minutes to hours (Faridy, 1966; Forrest, 1972; Wyszogrodski , 1975; Oyarzun, 1977; Veldhuizen , 1996; Verbrugge , 1998; 1998a; Maruscak , 2008; Mascheroni, 1988; Davis, 1993). Studies showing that large V_Ts release surfactant and increase compliance used V_Ts ranging from 130% to 400% of the spontaneous V_T, with the sigh breaths given either intermittently or for brief periods of time (Mead, 1959; Egbert, 1963; Bendizen, 1963; Nicholas 1983; Oyarzun, 1991; Pelosi 1999; Patroniti, 2002).

If ventilation alters surfactant and causes atelectasis, and if surfactant secretion can prevent the atelectasis, why have the randomized trials of surfactant replacement in ARDS found no effect on mortality? Studies of surfactant replacement in ARDS are limited by concerns about differences in the composition of the various preparations used, the modes by which the surfactant is administered, the doses being given, the frequency of administration and the fact that a variety of proteins, lipids, proteases, and other substances can inactivate surfactant (summarized in Albert, 2012). In addition, all of the studies have been conducted in patients with established ARDS. The pathophysiology proposed in Figure 1 involves surfactant abnormalities developing before the onset of ARDS, prior to the time at which widespread alveolar filling with proteins, lipids, etc. occurs and alters gas exchange. In this sense, the new pathophysiology proposed more closely resembles that of the Respiratory Distress Syndrome in newborns in which surfactant production is inadequate as a result of type 2 pneumocyte immaturity. In this condition surfactant replacement is extremely effective (Einhorning, 1985; Hallman, 1985). In addition, increasing surfactant release into individual alveoli by incorporating sigh breaths should be a far more effective way of decreasing surface tension at the alveolar level than administering a variable dose of an exogenous surfactant into the airway and hoping it distributes to atelectatic airspaces.

Relevant clinical trials

Previous studies of sighs in humans utilized smaller volumes (e.g., two times the V_T), only administered sighs for a short period of time (e.g., 30-60 min) (Levine, 1972, Housley 1970), or gave sigh breaths more frequently than we propose but over an even shorter period of time (e.g., 3/min for one hour) (Pelosi, 1999). Bendixen and colleagues (1963) gave a series of three sigh breaths, each separated by four or five minutes, on one occasion to 15 patients undergoing general anesthesia for abdominal operations. The volume of the first sigh was that produced by a plateau pressure

(Pplat) of 20 cmH_2O and was held for 10 sec, the second was produced by a Pplat of 30 cmH_2O and was held for 15 sec and the third by a Pplat 40 cmH_2O and was held for 15 sec. Progressive improvements in gas exchange and respiratory system compliance were observed with each progressively larger breath (Bendixen, 1963).

Biologically variable ventilation (VV) is similar to sigh ventilation, but rather than delivering a sigh that is regularly interspersed among constant V_T breaths, VV delivers V_Ts that randomly vary in volume over time. The volume of the larger breaths is similar to those given by sighs. VV facilitates recruitment of atelectatic lung, prevents deterioration in gas exchange that occurs with constant V_T ventilation of animals with normal lungs, and improves mechanics and gas exchange in various animal models of acute lung injury and, in some but not all studies, reduced histological evidence of injury (Mutch, 2000; 2000a; 2000b; Arold, 2000a; Boker, 2002; Funk, 2004; Spieth, 2009). As was observed with sigh breaths, biologically variable ventilation also increases the release of surfactant into the alveolar space (Arold, 2000b). In animals with normal or injured lungs VV and sigh ventilation had similar effects on lung mechanics and gas exchange but IL-1β levels in bronchoalveolar lavage fluid of injured lungs were reduced more by VV than by sigh ventilation (Thammanomai, 2008). VV has been assessed in two human studies. In the first, Boker and colleagues (2004) randomized 41 patients undergoing abdominal aortic aneurysm repairs to controlled mechanical ventilation or VV, both of which were continued for six hours. Patients receiving VV had improvements in oxygenation, carbon dioxide partial pressure, dead space, respiratory system compliance and peak inspiratory pressure. In the second, Kowalski and colleagues (2013) administered VV for four hours in a cross-over study of eight patients with acute lung injury. Lung compliance, dead space fraction and the oxygen index improved slightly. No adverse effects were observed in either study.

Summary

The rationale for this proposal comes from an extensive basic science and clinical literature supporting a new pathway by which ARDS developed as depicted in Figure 1. If this paradigm were correct most instances of ARDS are actually VILI that occurs because constant V_T ventilation alters surfactant which, in turn, causes atelectasis and provide the setting in which atelectrauma occurs. Adding sigh breaths will augment surfactant secretion into the alveolar space and could interrupt this pathophysiologic process. If this study finds that sigh ventilation reduces ventilator-free days it will reduce the morbidity and possibly the mortality of victims of trauma who are at increased risk of developing ARDS.

Hypothesis and Specific Aim:

Hypothesis:

Adding sigh breaths to usual invasive mechanical ventilation of victims of trauma who are at risk of developing ARDS will decrease the number of days they require invasive mechanical ventilation.

Specific aim:

To determine if including sigh breaths in the usual care of victims of trauma who are at increased risk of developing ARDS will increase ventilator-free days.

Methods

Study Design:

Prospective, randomized, concurrently controlled clinical trial.

Inclusion criteria:

Patients in an intensive care unit (ICU) as a result of injuries from penetrating or non-penetrating trauma who are intubated and receiving invasive mechanical ventilation who also have one or more of the following:

1. Traumatic brain injury
2. > 1 long bone (femur, tibia, humerus) fractures
3. Shock on arrival in the Emergency Department (systolic BP < 90 mmHg)
4. Lung contusion (as diagnosed in the admission history and physical exam)
5. Receipt of > 6 units of any blood product in the first 24 hours

Exclusion criteria:

1. Inability to obtain consent from the patient or his/her legally authorized representative (LAR)
2. Unwillingness of the treating physician to use sigh ventilation as all treating physicians must have equipoise with respect to the intervention
3. Under 18 years of age
4. Undergoing invasive mechanical ventilation for > 24 hours, excluding any time during which the patient was being ventilated in the operating room, MRI, CT or IR, as this could represent too long a delay in instituting the intervention for it to have a chance of being effective
5. Presence of malignancy or other irreversible disease or condition for which the six month mortality is estimated to exceed 50% (e.g., chronic liver disease with a

Child-Pugh Score of 10-15, malignancy refractory to treatment) as this could affect the clinical course and cloud interpretation of the endpoints

6. Moribund, not expected to survive 48 hours as this could cloud interpretation of the endpoints
7. Women who are pregnant (negative pregnancy tests required on women of child-bearing age), per Human Subjects regulations
8. Prisoners, per Human Subjects regulations
9. Neurological condition that could impair spontaneous ventilation (e.g., C5 or higher spinal cord injury as this could affect the clinical course and cloud interpretation of the ventilator-free day endpoint
10. Lack of availability of Dräger Evita Infinity V500 ventilator as this is the only ventilator capable of delivering sigh breaths as described in the protocol
11. Burns > 40% of body surface area as this could affect the clinical course and cloud interpretation of the endpoints
12. Treating physicians being unwilling to use low V_T ventilation strategy when ARDS is diagnosed as low V_T ventilation is now considered standard of care for patients with ARDS
13. Patients on any ventilator mode that allows for spontaneous breathing, who are taking spontaneous breaths after intubation
14. Patient not expected to require mechanical ventilation > 24 hours (e.g., intubated for alcohol intoxication rather than pulmonary problem).
15. Patients enrolled in other studies should be reviewed with the study PI, Dr. Richard Albert, and the data coordinating center to assess eligibility for this study.

Patients meeting enrollment criteria will be randomized to one of two groups:

1. Those receiving "usual care", meaning that their treating physician will be free to treat the patient in any way he or she sees fit, including utilizing invasive mechanical ventilation as they wish (with the exception that, if the patient has ARDS of any severity, low V_T ventilation will be employed as this is now the standard of care), or

2. Those receiving "usual care" as described above but with the addition of sigh breaths given once every 6 minutes.

Patients will be followed on a daily basis for 28 days or until they leave the intensive care unit or die. If a patient is transferred to a progressive care or step-down unit and continues to receive ventilation, the patient will be followed on a daily basis until the patient is extubated or dies or until day 28. If a patient is extubated and reintubated before day 28, the patient will continue to receive ventilation according to the group to which the patient was originally randomized.

Intervention to be tested

The intervention we will test is adding sigh breaths, consisting of an increase in PEEP that produces a plateau pressure (Pplat) of 35 cmH_2O (or 40 cmH_2O in patients with BMIs > 35, in patients with moderate or severe abdominal distension from ascites, blood and/or ileus, or prone patients). The sigh breaths will be delivered once every 6 minutes, as part of usual invasive mechanical ventilation.

The rate of delivery of these sigh breaths was selected on the basis of several studies. Bendixen and colleagues (1964) documented that the rate at which sighs occurred in normal humans was approximately 10/hour. Mead and Collier (7) showed that sighs given only six times/hour prevented the reduction in compliance that occurred with constant V_T ventilation in animals with normal lungs and Reiss and colleagues (2011) found that a single sigh given once every 5 min improved mechanics, gas exchange and inflammatory cytokines in normal mice. Frick and colleagues (2004) reported that lamellar body fusion preceding surfactant secretion that was increased by applying a single stretch of isolated type II cells abated by 5 min and Steimback and colleagues (2009) found that delivering one sigh every 6 min reduced epithelial cell apoptosis and procollagen III expression and improved respiratory mechanics in rats with experimental lung injury compared with animals not receiving sighs and those receiving three sighs/min.

The plateau change resulting from increasing PEEP producing a Pplat of 35 or 40 cmH_2O was selected for two reasons. First, it produces an end-inspiratory lung volume that approximates total lung capacity in patients with normal chest wall and lung compliances, thereby facilitating secretion of surfactant. Second, a Pplat of 40 cmH_2O has been utilized in numerous short-term studies of recruitment maneuvers in patients with ARDS without any evidence that it caused barotrauma or volutrauma (Pelosi, 1999; Oczenski, 2005; Grasso, 2002; Lim, 2003; Antonaglia, 2006). In patients with clinically evident abdominal distension graded moderate or severe, in those with BMI's exceeding 35, and in those who are prone the volume of the sigh breath will be determined on the basis of a Pplat of 40 cmH_2O given the decrease in chest wall compliance that will be present in these situations. Patients who have reached maximum PEEP and cannot obtain goal Pplat will not be considered deviations and the reasons for not reaching goal will be recorded by study personnel.

At present there is only one mechanical ventilator available in the U.S. that is configured to provide sigh breaths as designed, the Drager Evita Infinity V500.

For patients receiving invasive mechanical ventilation prior to admission to the ICU, the intervention will begin as soon as possible, but not longer than 24 hours after the patient was placed on mechanical ventilation. For patients who are intubated and placed on invasive mechanical ventilation at some time after admission to the ICU, the

intervention will begin as soon as possible, but within 24 hours of starting invasive mechanical ventilation.

If a patient is randomized to receive sigh breaths and is transported to the operating room, CT, IR or other hospital department after randomization, the patient should be ventilated according to usual practice, i.e., they need not continue to receive sigh breaths during the time they are away from the ICU. Sigh breaths should be restarted on their return.

Endpoints

1. The primary endpoint in this study is the number of ventilator-free days (VFDs) to day 28 after enrollment. VFDs will be counted in the following fashion:

    a. VFD to day 28 is defined as the number of days of unassisted breathing to day 28 after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28 unless a period of assisted breathing was less than 24 hours and the purpose of assisted breathing was a surgical procedure.

    b. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFD will be 0.

    c. Any VFDs before patients are placed on comfort care will be counted.

    d. Unassisted breathing is defined as the patient breathing spontaneously with a face mask, nasal prong oxygen, or on room air, T-tube breathing, tracheostomy mask breathing, or CPAP < 5 without pressure-support or intermittent mandatory ventilation, or with the use of noninvasive ventilation solely for sleep-disordered breathing. Assisted breathing is defined as any level of ventilatory support at pressures higher that the unassisted breathing thresholds.

2. Secondary endpoints will include the following:

    a. All-cause 28-day mortality.
    b. The number ICU-free days to day 28 after enrollment
    c. The occurrence of complications of treatment (specifically pneumothorax, ventilator-associated pneumonia, hypotension requiring pressors, pneumatocele).

d. Percentage of patients discharged to extended care facilities, on mechanical ventilation, or to in-patient or home hospice.
e. Newly requiring continuous oxygen therapy at discharge

Recruitment process

Research personnel (e.g., study physicians, research coordinators, research assistants) will seek out the senior treating physician for patients meeting study inclusion criteria to request permission to seek consent from the patient or, if the patient cannot participate in the consent process, from the patient's legally recognized representative (LAR) or proxy decision maker for participation in the study. If the senior treating physician agrees, the research personnel will pursue obtaining consent.

Informed consent process

Written informed consent will be obtained from each patient, or from their LAR, by having the patient or their LAR sign a consent form that is approved by the institution's IRB after the research personnel reviews each item in the consent form with the patient or their LAR, answers questions and allows the patient or their LAR time to consider the request if they wish. If a patient is unable to consent and their LAR is not physically present at the hospital but reachable by phone, verbal consent may be obtained by telephone. The LAR for all subjects for whom telephone consent is obtained will be asked to sign a paper consent upon arrival at the hospital and will be given the opportunity to withdraw from the study if they do not reaffirm consent to continue participating.

Patients will be randomized to one of the two study arms as soon as possible, but not longer than 24 hours, after initiation of invasive mechanical ventilation.

All patients meeting the inclusion criteria will be entered in the eligibility form. If the patient is not enrolled, the eligibility form will include information explaining why enrollment did not occur (e.g., exclusion criteria, attending physician denial, patient refusal, etc.).

Research personnel (described above) will be responsible for explaining the study, answering questions and obtaining consent. If patients still have questions the site PI will be contacted to assist with providing the requested information. The research personnel will be responsible for obtaining consent and the Site-Principal Investigator will be responsible for cosigning the consent form.

The consenting process will occur either in the ICU or in family counseling rooms adjacent to the ICU.

In the event that research personnel or the treating physician believes the patient is not competent, either because of the condition requiring treatment (e.g., traumatic brain injury) or the medications being used to treat anxiety or pain (e.g., sedatives and/or narcotics) consent will be sought from the patient's legally authorized representative (LAR). All subjects for whom LAR or proxy consent is obtained will be asked to provide consent if decisional capacity is regained and will be given the opportunity to withdraw from the study if they do not give consent to continue participating. If decisional capacity is not regained on or before day 28, re-consent is not required. If decisional capacity is regained on or before day 28 and the patient is still hospitalized, they will be re-consented as soon as decisional capacity is regained.

The consent form specifically states that the patients do not have to decide whether they want to participate at the point in time when consent is being discussed. It also states that the patients are free to consider the decision and/or to discuss it with others in private, without any study personnel or physicians involved in their care being present. The consent form also notes, however, that the patient must decide whether they wish to participate before they have been receiving mechanical ventilation for 24 hours as receiving ventilation for longer than 24 hours is one of the exclusion criteria.

The proposed study will be conducted in eight states in the U.S. Each site may have different local or regional regulations regarding who can serve as a LAR and when an LAR is considered necessary. The consent form specific to each site will be modified to include the regulations regarding LARs for each site prior to submitting it for individual IRB approval.

If a patient is deemed incompetent or cannot otherwise participate in the consent process the same process described for seeking consent from the patient will be used to seek consent from the LAR.

Patient Follow-up Process

Research personnel will see patients enrolled in the study daily until day 28 or until the patient is discharged from the ICU, either to another floor in the hospital or home. If a patient is transferred to a progressive care or step-down unit and continues to receive ventilation, the patient will be followed on a daily basis until the patient is extubated or dies or until day 28.

If the patient is discharged from the ICU before day 28 and is no longer receiving mechanical ventilation, research personnel will review medical records and/or contact the patient on day 28 (or the Friday before or Monday after if day 28 occurs on a weekend) to determine if the patient is still alive, discharged from the hospital (and if so, when), and whether the patient has experienced any adverse events (see the risk management and emergency response section) between the day the patient was discharged from the ICU and day 28.

If a patient is extubated and reintubated before day 28, the patient will continue to receive ventilation according to the group to which the patient was originally randomized.

If a patient is randomized to receive sigh breaths and is transported to the operating room, CT, IR or other hospital department after randomization, the patient should be ventilated according to usual practice, i.e., they need not continue to receive sigh breaths during the time they are away from the ICU. Sigh breaths should be restarted on their return.

Data collection

1. Assessment on enrollment

    a. Demographics (age, gender, self-reported race)
    b. Pregnancy test (serum or urine) for women of child-bearing potential (this is part of usual care and does not represent a study-related expense)
    c. Co-existing medical conditions
    d. Evidence of previous thoracic surgery
    e. Height, weight, BMI and calculated predicted body weight
    f. Date and time of injury
    g. Date and time of admission to ED
    h. Date and time patient was admitted to ICU
    i. Description of any operations done between ED and ICU admission
    j. Blood alcohol level (if recorded)
    k. Smoking status
    l. Initial BP in ED
    m. Initial Glascow Coma Scale in ED

2. Initial assessment

    a. Date and time patient was intubated and started on invasive mechanical ventilation
    b. Ventilator used, ventilator mode, tidal volume, F_IO_2, PEEP, peak and plateau pressures, whether prone positioning was utilized
    c. The latest arterial blood gas prior to the ventilator settings recorded, indicating pH, the $PaCO_2$, the PaO_2, the HCO3, the F_IO_2, the SaO_2 and the PEEP level and the time the sample was obtained
    d. If the patient has been randomized to sigh ventilation:

        i. Is the patient's BMI > 35?
        ii. If yes, is the Pplat for the sigh breath 40 cmH_2O?
        iii. If no, is the Pplat for the sigh breath 35 cmH_2O?

e. Level of PEEP applied during sighs to produce a Pplat of 35 or 40 cmH_2O
f. Transfusions of any blood products (in units, includes red blood cells, fresh frozen plasma, platelets and/or whole blood)
g. Does the patient have an abdominal distention (yes/no)? If yes, is it mild, moderate or severe?
h. Whether the patient is receiving any of the following medications (yes/no)

    i. Vasopressors (includes norepinephrine, vasopressin, epinephrine, phenylephrine, isoproterenol and dopamine). Indicate all that were administered
    ii. Inotropic agents (includes dobutamine, milrinone, amrinone).
    iii. Paralytics If yes, indicate reason (ventilator dyssynchrony, other)
    iv. Benzodiazapine (diazepam, lorazepam, midazolam)
    v. Dexmetatomidine
    vi. Propofol
    vii. Other (haloperidol, phenobarbital, droperidol, quetiapine)

i. Most recent Richmond Agitation-Sedation Scale (RASS) score before randomization
j. Does the patient have a tube thoracostomy?

    i. If yes, what was the timing (on admission, after admission but within the first 24 hours or before the initial assessment)?
    ii. Reason for the tube thoracostomy (pneumothorax, hemothorax, both)

k. Did the patient undergo an operation after admission but within the first 24 hours or before the initial assessment? If yes, provide date/time for each operation and a description of the operation.
l. Were any infiltrates identified? If yes, indicate which area or areas:
    i. Left upper (including left middle area)
    ii. Left lower
    iii. Right upper (including right middle area)
    iv. Right lower

3. Daily Assessments

a. Use of continuous invasive mechanical ventilation
b. Ventilator used, ventilator mode, tidal volume, F_IO_2, PEEP, peak and plateau pressures, prone positioning
c. The latest arterial blood gas prior to the ventilator settings recorded, indicating pH, the PaCO2, the PaO2, the HCO3, the FIO2, the SaO2 and the PEEP level and the time the sample was obtained
d. Were any infiltrates identified? If yes, indicate area:

i. Left upper (including left middle area)
ii. Left lower
iii. Right upper (including right middle area)
iv. Right lower

e. Are the infiltrates:

i. Unchanged from previous film
ii. Worse or more extensive than on previous film
iii. Better than on previous film

f. Ejection Fraction (EF) if echocardiogram was obtained.
g. Whether the patient is receiving any of the following medications (yes/no)

i. Vasopressors (includes norepinephrine, vasopressin, epinephrine, phenylephrine, isoproterenol and dopamine). Indicate all that were administered
ii. Inotropic agents (includes dobutamine, milrinone, amrinone).
iii. Paralytics If yes, indicate reason (ventilator dssynchrony, other)
iv Benzodiazapine (diazepam, lorazepam, midazolam)
v. Dexmetatomidine
vi. Propofol
vii. Other (haloperidol, phenobarbital, droperidol, quetiapine)

h. Most recent Richmond Agitation-Sedation Scale (RASS) score
i. Use of prone positioning or inhaled NO > 12 hr in last 24 hrs (y/n)
j. Date and time of discontinuation of invasive mechanical ventilation
k. Did patient receive non-invasive mechanical ventilation (CPAP > 5 cmH2O, BiPAP other than for OSA)
l. Date and time of reinstitution of invasive mechanical ventilation (if necessary)
m. Date and time of transfer out of ICU to day 28 (if occurred)
n. Date of hospital discharge to day 28 (if occurred)
o. Date and cause of death to day 28 (if occurred)
p. Assessment of abdominal distension (mild, moderate, severe)
q. Did the patient undergo an operation in the previous 24 hours (laparotomy, thoracotomy, craniotomy, rib plating, ORIF, other)
r. Presence of pneumothorax or pneumatocele
s. Tracheostomy in the past 24 hours?
t. BAL or mini-BAL with colony counts if available
u. Is alcohol withdraw affecting management
v. Occurrence of complications (e.g., cardiac arrest, stroke, MI, PE, AKI, pneumonia, ICP related to the vent mode)

4. Closeout assessments

    a. Final 28-day disposition (e.g., discharged or transferred to home or elsewhere if alive)
    b. Discharge diagnoses (ICD9 or ICD10 codes)
    c. Procedures (CPT codes)
    d. Chest AIS
    e. Description of trauma
    f. ISS
    g. Mechanism of injury
    h. Rib plates
    i. Discharged on new continuous home oxygen

Statistical plan

Sample size estimate

We initially estimated a need to enroll 916 patients in SiVent. This was based on the assumption that the number of ventilator-free days (VFDs) in the control arm of the study would be 11.75 days, with a standard deviation (SD) of 10.5 days. These assumptions were taken from a study by Wiedemann et al, (N Engl J Med, 2006) that also used VFDs as a primary endpoint in a study of ARDS patients.

The actual number of VFDs and SD for patients enrolled in the control arm calculated by the DCC at the time of the first interim analysis were 15 days and 9.9 days, respectively. Using these actual numbers, a power of 80%, and an observed withdrawal rate of 1% (which we did not account for in the initial sample size estimate but was observed in the first 300 patients enrolled), we determined that we would be able to meet acceptable statistical goals by enrolling 544 patients.

Data Analysis

The primary endpoint for the SiVent study is VFDs in the first 28 days following randomization, with the convention that mortality prior to day 28, regardless of when it occurs, is equated to 0 ventilator-free days. This composite outcome, abbreviated as VFD28 in the following, has been used in previous studies of ARDS and is recommended by data analysts in the ARDS Network [Schoenfeld D, Bernard G (2002), Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med 30: 1772-1777.]

Because the statistical distribution of VFD28 is usually not close to normal, the primary analysis of the difference between the ‘Sigh’ group and the control group can be based on the Wilcoxon rank-sum statistic. Additional analyses, taking into account

covariates such as age, gender, smoking history, and characteristics of the trauma which resulted in the patient being put on mechanical ventilation, in addition to treatment group, will be carried out using least-squares regression. Non-normality of the outcome is unlikely to influence the results of such analyses because the sample size is expected to be in the 300-1000 range (for interim and final analyses).

Mortality will be analyzed separately as a secondary endpoint. ICU-free days (up to day 28, with deaths prior to day 28 classified as having ICU28 = 0) will be analyzed as just described for VFD28. Occurrences of complications of treatment (adverse effects) prior to day 28 will be analyzed using logistic regression.

Interim Analyses; Early Termination

A Data and Safety Monitoring Board (DSMB) will be appointed to oversee the progress of the SiVent trial and to review adverse events and efficacy. The DSMB will be comprised of 3 members: one pulmonary physicians, a surgeon who treats ARDS, and a statistician. The members will be independent of the institutions where the clinical sites are located. The DSMB will meet approximately every 6 months (alternately in-person and by conference call). The DCC will prepare a complete summary of data on recruitment, adherence to protocol, protocol violations, withdrawal rates, adverse events, deaths, and the primary and secondary outcomes. One of the responsibilities of the DSMB at each of its meetings is to make recommendations concerning continuation, revision, or termination of the clinical trial. Here we describe guidelines for interim analysis of results, with the goal of providing 'stopping boundaries' for the primary outcome (VFD28).

Our expectation is that three formal interim analyses will be conducted: the first when approximately 1/3 of the total patients have been evaluated, the second when about 2/3 have been evaluated, and the third when all patients have been evaluated. The monitoring boundaries for these 'looks' at the data are based on the Lan-DeMets 'alpha spending function' approach. This yields an overall significance level of approximately 0.05. We have chosen monitoring boundaries in the 'Pocock' family [Pocock S (1977), Group sequential methods in the design and analysis of clinical trials. *Biometrika* 64: 191-199]. The software is 'ld98', an interactive program based on the research of K.K. Gordon Lan and David DeMets:

[https://www.biostat.wisc.edu/content/lan-demets-method-statistical-programs-clinical-trials]

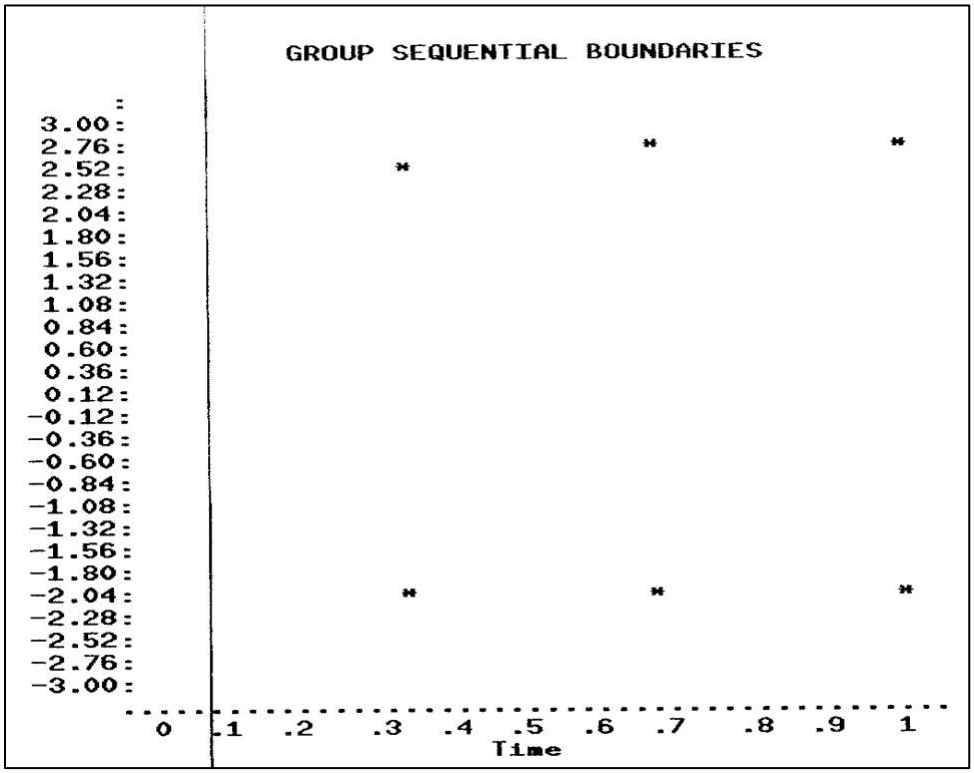
See also Lan KKG, DeMets DL (1983) Discrete sequential boundaries for clinical trials. *Biometrika* 70: 659-663. The boundaries are shown in the Figure below. Boundary values are expressed in terms of 'Z' statistics. The upper boundary corresponds to stopping for a benefit to the Sigh group; the lower boundary would be crossed if there is relative evidence of harm in the Sigh group. We have chosen to use asymmetric boundaries, with the lower boundary more likely to be crossed, because we

feel that if there is evidence that the 'Sigh' group has more bad outcomes, we do not want the trial to continue. Note also that, if the lower boundary is crossed at some point, it is highly unlikely that at a future 'look', the upper boundary will be crossed. That is, crossing the lower boundary corresponds to 'futility' for the Sigh treatment group.

Stopping boundaries in terms of the Z statistic:

Information time	Lower Bound	Upper Bound	Cumulative alpha
0.33	-2.09	+2.61	0.023
0.66	-2.09	+2.65	0.016
1.00	-2.09	+2.66	0.050

Figure: Sequential Monitoring Boundaries



The 'stopping boundaries' are intended as statistical guidelines for the DSMB; the DSMB needs to review the sequential monitoring scheme and the boundaries as described above, and approve this plan prior to initiating the trial. Further, the DSMB is free at any time to make recommendations that disagree with these guidelines, i.e., they may recommend that the trial continue even though the 'stopping boundaries' have been crossed, or to recommend termination of the trial even though the primary outcome data are strictly between the upper and lower boundaries.

Data management

Identifiers

Research personnel at each site will prepare a separate paper file for each patient. Patients will be identified by name, date of birth and medical record number. When data are transmitted to the DCC the research personnel at each site will access a password-protected website. On doing so, and indicating they are registering a new patient, the system will assign a site designation (A through J) and a number to uniquely identify that patient.

Confidentiality

1. Protecting privacy and maintaining confidentiality

All data transmitted to or from the DCC, whether through the password-secured website or by e-mail, will be fully encrypted. Each patient's file will contain information linking the letter and number with that patient but the patients' name, date of birth and medical record number will not be transmitted to the DCC. Individual patient files will be kept under locked access at each site until notified by the DCC that the files can be destroyed.

2. Access to study records

Research personnel at each site (i.e., site- Principal Investigator, research coordinators or research assistants) will have access to the study data collected for each specific patient enrolled from that site and will be able to link these data to each specific patient. DCC personnel will have access to all study data collected from all patients but will not be able to link those data to any specific patient.

Representatives of the Representatives of the USAMRMC (US ARMY Medical & Materiel Command) will be eligible to review all study records.

Data capture, verification and disposition

Data from screening and monitoring will be collected on printed paper forms and kept in these files. Copies of radiological reports will be collected and kept in the same files. After forms have been completed research personnel at each site will enter data by accessing a password-protected web site. Clinic personnel can enter and access

patient data from their site only. User names are unique and protected by a strong password. Only de-identified data will be entered.

Data are double entered (entered twice) to ensure data accuracy. Data will be edited in real time and personnel get immediate feedback if data edits are triggered. The data entry program inserts data directly into the database at the DCC. An additional and more comprehensive edit will take place nightly at the DCC, which automatically generates data queries. Data queries are posted on the study website and personnel respond to queries via the website user interface.

Data management at the DCC uses Oracle Application Server for the website software, with an Oracle database to store study data, running on a UNIX network. All files are automatically backed up nightly, with backup files stored off-site on a twice weekly basis.

The DCC will make available current reports on recruitment, randomization, study completion rates, form completion and accuracy, adherence to protocol, compliance, serious adverse events and other information, both by site and for all sites combined. These reports display real-time data with no time lag data that has been entered and data displayed in the reports.

Data quality

Each center participating in this study has prior experience with clinical trials in critical care. While the screening, monitoring, intervention and endpoints of the proposed trial are simple we plan an in-person training session that will be conducted in conjunction with the DCC involving the research personnel and site-investigators at all centers.

Data quality will be facilitated by training site personnel on:

1. The design and rationale of the study
2. The target population and recruitment
3. Inclusion and exclusion criteria
4. Informed consent procedures
5. Randomization
6. Baseline data collection
7. Daily monitoring
8. Data entry, transmission and error correction
9. Reporting adverse events
10. Reporting protocol violations
11. Closeout of the study for the participants

In addition, the DCC will prepare a comprehensive Manual of Procedures that will be available on-line, will design structured data collection forms, will be involved in interactive editing at the time of data entry and will subsequently do comprehensive editing, will regularly and frequently prepare monitoring reports and review of these reports with site personnel on monthly conference calls involving all sites. The DSMB will review data on safety, efficacy and study operation.

Interim reports to the DSMB will be carried out at monthly and 6-monthly intervals. Monthly reports will include a graphical comparison of actual and target enrollments. Six-monthly reports will include completion rates, adverse events, mortality, levels of compliance, losses to follow-up and data on the primary and secondary outcomes.

Clinical trial monitoring

Each center will be visited during the conduct of the trial by a team assembled by the DCC. Site visitors will review the following aspects at each site:

1. Organizational structure
2. Recruiting methods and strategies
3. Adherence to protocol
4. Study completion rate
5. Error rates and timeliness of corrections in data entry
6. Handling of adverse events
7. Compliance with protocol
8. Agreement of entered data with raw source documents (i.e., a review of records)
9. Data transmission to DCC
10. Exit interview with site-PI and other research personnel

A brief written report will be prepared by the DCC after each site visit and sent to the site-PI, to all research personnel at the site, to the study PI and to the Department of Defense. If any corrective actions are needed these will be specifically outlined in these reports. If corrective actions are needed the site-PI will be expected to prepare a written response outlining how he/she plans to address the concerns. These responses will be reviewed by the DCC and the study PI and a monitoring plan will be developed to be carried out within the three months subsequent to the report.

Risk/Benefits Assessment

1. Foreseeable risks

We could find no human studies reporting the effects of administering sighs in a fashion similar to what we are proposing that would allow us to categorize foreseeable risks as previous studies of sighs have utilized smaller volumes [e.g., two times the V_T (Housley, 1970; Levine, 2002)], sighs only given for a short period of time [e.g., 30-60

min, Housley, 1970; Levine, 2002)] or sighs given more frequently than we propose but for a shorter period of time [e.g., 3/min for one hour (Pelosi, 1999)]. In addition, the largest study we could find only enrolled 18 patients (Bendixen, 1964). On the basis of physiology, however, we can conceive of the following foreseeable risks.

a. Baro- or volutrauma

A systematic review identified 40 studies that evaluated the effects of various types of recruitment maneuvers in patients with ARDS (Hodgson, 2012). While the majority of these studies utilized sustained inflations, high pressure-controlled ventilation, or incremental PEEP to achieve recruitment five utilized sighs as the mechanism of achieving recruitment (Fan, 2008). These can be examined with respect to safety.

In the first of these, Pelosi and colleagues (1999) delivered three consecutive sigh breaths/min to a Pplat of 45 cmH_2O for one hour to 10 patients with ARDS. Prior to instituting the sighs the patients were receiving a mean V_T of 0.56 ± 0.11 L and a PEEP of 14 cmH_2O. Accordingly, the patients had more severe lung injury that those we are planning to study. During the period when sigh breaths were delivered the V_T's increased to 1.1 ± 0.45 L. Pulmonary arterial pressure decreased 2.5 ± 1.9 mmHg and pulmonary vascular resistance decreased 30.8 ± 27.8 $dyne \bullet sec \bullet cm^{-5} \bullet m^{-2}$ and both returned to control values after the sighs were discontinued. No instances of barotrauma were reported. These small but significant hemodynamic changes are not likely to be encountered in the study we propose as they were seen when three sighs were administered each minute whereas we are proposing to deliver one sigh every 6 minutes.

In the second, Foti and colleagues (2000) raised PEEP from 9.4 ± 3 to 16 ± 2 cmH_2O for two breaths separated by 30 sec, twice a minute for 30 minutes in 15 patients with ARDS. Peak inspiratory pressure averaged 35.5 ± 5.4 cmH_2O during the period in which sighs were instituted. Cardiac out, mean arterial blood pressure, pulmonary arterial pressure, pulmonary arterial wedge pressure, central venous pressures and oxygen delivery did not change. No instances of barotrauma were reported.

Patroniti and colleagues (2002) utilized one sigh breath/min, each lasting 3 to 5 seconds by intermittently raising PEEP to produce a Pplat that was 20% higher than the Pplat under the control condition or 35 cmH_2O, whichever was higher, for one hour in 13 patients with ARDS. Pplat averaged 38 ± 3.2 cmH_2O during the period when sighs were applied corresponding to V_T's of 1.15 ± 0.3 L that were delivered on top of PEEP levels that averaged 10 ± 4 cmH_2O. Heart rate, systolic and diastolic blood pressure did not change. No instances of barotrauma were reported. This study indicates that limiting our Pplat to 40 cmH_2O (45 cmH_2O in those with a BMI > 30) will allow us to achieve increases in V_Ts that are sufficient to cause surfactant release.

In a second study, Pelosi and colleagues (2003) delivered three consecutive sigh breaths/min to a Pplat of 45 cmH_2O (that corresponded to a V_T of 947 ± 321 mL) for one hour to 10 patients with ARDS. Prior to administering sigh breaths the patients were being ventilated with a V_T of 590 ± 138 mL and a PEEP of 14 ± 3 cmH_2O. No change in hemodynamics occurred and no instances of barotrauma were reported.

Accordingly, although the number of patients studied is small but the literature contains no suggestion that the sigh breaths in volumes that we propose to deliver will cause any hemodynamic compromise. In addition, using a Pplat of 35 or 40 cmH_2O is below that used by other investigators in patients who had more severe lung injury than those we will be studying and no instances of barotrauma were observed.

b. Ventilator-induced lung injury (VILI)

VILI is attributed to overdistension and/or to cyclical airspace opening and closing. Low V_T ventilation is now the standard of care for patients with ARDS and is thought to reduce VILI by reducing overdistension. The lung volume produced by a Pplat of 35 or 40 cmH_2O could result in overdistension in some areas of the lung in some patients. It seems unlikely, however, that VILI could occur from this degree of overdistension occurring only 10 times/hour, and studies in animal models of lung injury indicate that such a strategy is protective rather than injurious (Oyarzun, 1977; Mascheroni; 1988; Oyarzun, 1991; Pelosi, 1999; Patroniti, 2002). Nonetheless, VILI remains a potential adverse effect. Nonetheless, we will perform two interim analyses of the data looking for evidence that there might be *fewer* VFDs in the intervention arm of the study than in the control (i.e., a result opposite to the one hypothesized) and the stopping rules for harm are less stringent than those for documenting benefit (see above). In addition, respiratory therapists will, on at least a daily basis, confirm that the sigh breaths being delivered do not result in a Pplat that exceeds 40 cmH_2O (45 cmH_2O in patients with decreased chest wall compliance as described above). Adjustments in the volumes or Pplat will be made as needed. In addition these pressures will be rechecked whenever the treating physician is concerned about a change in the patient's clinical status. The frequency with which these adjustments are needed will be recorded.

c. Patient-ventilator dyssynchrony

Although people take sigh breaths approximately 10 times/hour under normal circumstances (Bendixen, 1964) and intermittent sighs for short periods of time have been used in patients with ARDS without apparently causing any dyspnea or respiratory discomfort, sigh breaths could conceivably result in patient-ventilator dyssynchrony.

Patient-ventilator dyssynchrony is common in patients with ARDS because they are receiving low V_T ventilation. This dyssynchrony is frequently managed by increasing

sedation or even resulting to use of paralytics. Accordingly, it is equally conceivable, that sigh ventilation could decrease patient-ventilator dyssynchrony. If patient-ventilator dyssynchrony is occurring at an increased frequency in the intervention arm of this study it will be manifested by an increased need to administer sedation and/or analgesics and we will monitor the use of these two medication classes on a daily basis with the results being made available to the DSMB for their periodic reviews.

We can think of no other psychological, legal, social, economic or physical risk that might be associated with receiving sigh breaths once every six minutes.

Risk management and emergency response

a. Research Monitor

Dr. Jesse Hall, Professor of Medicine, Anesthesia and Critical Care at the University of Chicago Biological Sciences will serve as both the chair of the Data Safety Monitoring Board (DSMB) and the research monitor. Dr. Hall's role may include observing recruitment, enrollment, and consent as well as study interactions with subjects. In addition, he may work with the DCC to review monitoring plans, data collection, and analysis. As research monitor, he has the authority to discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. Dr. Hall will also have the authority to take any steps necessary to protect the well-being of human subjects until the IRB(s) can assess his concerns, including stopping the study or removing individual human subjects from the study. Dr. Hall will be required to promptly report any observations and findings to the IRB or other designated official and the HRPO.

b. Surveillance and reporting

Each patient will be seen daily by research personnel from the time each patient is enrolled until day 28 or until the patient is discharged from the ICU, either to another floor in the hospital or home or dies. If a patient is transferred to a progressive care or step-down unit and continues to receive ventilation, the patient will be followed on a daily basis until the patient is extubated or dies or until day 28.

These daily visits will seek evidence of adverse events or complications per the study manual of procedure. If adverse events or complications have occurred they will be recorded on the adverse event case report form. Whether a patient experiencing an adverse event continues on the study or is withdrawn will be decided by the treating physician.

If the patient is discharged from the ICU before day 28 and is no longer receiving mechanical ventilation, research personnel will review medical records and/or contact

the patient on day 28 to determine whether the patient has experienced any adverse events between the day the patient was discharged from the ICU and day 28.

The investigator will report all adverse events to the DCC within 24 hours of their occurrence. The local Institutional Review Board (IRB) will also be informed in a timely manner. The investigator will then submit a detailed, written report to the DCC and to the IRB no later than five days after the investigator discovers the event.

The DCC will report all serious, unexpected and study-related adverse events to the DSMB by fax or telephone within seven calendar days. A written report will be sent to the DSMB within 15 calendar days and these reports will be sent to investigators for submission to their respective IRBs. The DSMB will also review all adverse events during each scheduled interim analysis. The DCC will distribute the written summary of the DSMB's periodic review of adverse events to investigators for submission to their respective IRBs.

All patients in this study will be hospitalized in an intensive care unit. Accordingly, emergency care will be readily available at all times. The cost of treatment for all study-related adverse events will be covered by each individual hospital.

Potential benefits

Numerous studies in the literature document that (a) constant V_T ventilation depletes and/or inactivates surfactant, (b) loss of surfactant increases surface tension and predisposes to airspace collapse, (c) having airspace collapse predisposes the lung to VILI as a result of cyclical airspace opening and closing, (d) VILI increases the mortality of patients with ARDS and (e) sigh breaths are known to cause surfactant secretion from type 2 alveolar epithelial cells and protect against VILI. Accordingly, adding sigh breaths should decrease VILI and increase the number of VFDs. If this occurs, the incidence, severity and mortality of ARDS should all decrease.

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