

### **b3i. Indications**

#### **Indications:**

The SensorMedics 3100B is indicated for use in the ventilatory support and treatment of selected patients 35 kilograms and greater with acute respiratory failure.

#### **Contraindications:**

The SensorMedics 3100B Oscillatory Ventilator has no specific contraindications.

### **b3ii. Device Description**

The 3100B ventilator is based on the technology of the 3100A, but features slight changes to some of the subsystems to provide enhanced performance, safety and reliability for its intended application. Table 1 features the comparison of these system enhancements from the 3100A to the 3100B. Outlined below is a more in-depth discussion of each of these features.

#### **Differences between 3100A and 3100B**

<b>Specification</b>	<b>3100A</b>	<b>3100B</b>
Max Mean Airway Pressure (4B)(1)(2)	49 cmH2O	59 cmH2O
Bias Flow (2)	40 LPM	60 LPM
Max Delta-P (1)(2)	~ 105 cmH2O	~ 140 cmH2O
Safety Dump Pressure (1)(2)	50 cmH2O	60 cmH2O
Safety Dump Alarm Delay (1)	No Delay	1.5 Second Delay
Circuit Length (external)	25 inches	51 inches
Minimum Paw (1)	>20% High Paw Alarm Set	Fixed @ 5 cmH2O
Mean Airway Pressure Limit (1)	Manual (Approx. 10-45 cmH2O)	Automatic (Linked to Max Paw Alarm)
Piston Centering (4A)(5)	Manual	Automatic
Visual Set Max Paw Alarm (1)	Red LED (non-latching)	Red LED (latching)
Cooling Gas Flow (3)	10 lpm	25 lpm
Driver Setting, Amplitude (5)	42 v Pk to Pk	75 v Pk to Pk

**Table 1**

- (1) – Minor changes to Alarm Board (schematic beginning on page 607)
- (2) Minor changes to Pneumatics Assembly (drawings beginning on page 607)
- (3) Minor changes to Driver Cover Assembly (assembly diagram beginning on page 607)
- (4) Minor changes to Front Panel (assembly diagram beginning on page 607)
  - (4A) AutoCentering, DDI Board (schematic beginning on page 607)
  - (4B) Thumbwheel switch 49 to 59 (assembly diagram beginning on page 607)
- (5) Minor changes to the Driver Controller board (schematic beginning on page 607)

#### **MAXIMUM MEAN AIRWAY PRESSURE**

In consideration of the treatment of large patients whose body weight and chest wall compliance may represent significant barriers to adequate lung recruitment, the maximum mean airway pressure of the 3100B has been expanded from the 49 centimeters of water pressure used in neonates and pediatrics on the 3100A to 59 centimeters of water pressure. Although this pressure is the maximum capable, during operation of the oscillatory subsystem, typical mean airway pressures do not exceed 55 centimeters of water pressure.

Additionally, the typical use of an asymmetrical waveform (I:E ratio 1:2) causes the ventilator to contribute more towards expiratory pressure than inspiratory pressure. This results in the

distal mean airway pressure being less than the proximal airway pressure. This combination of higher oscillatory amplitudes and asymmetrical pressure waves may result in reductions in actual distal mean airway pressure; increasing the range to 59 cmH<sub>2</sub>O may compensate for this loss.

## **BIAS FLOW**

With the increased mean airway pressure capability of the 3100B, the maximum bias flow has been increased to 60 liters per minute. This was required to allow stable mean airway pressures to be maintained with the significantly larger tidal volumes achievable by the instrument. During normal operation the 3100B draws exhaled patient gases into the inspiratory limb of the patient breathing circuit. The additional flow enables the practitioner to increase bias flow to assure purging of carbon dioxide from the longer, higher volume, ventilator circuit utilized by the 3100B.

## **AMPLITUDE**

The 3100B is intended for use on patients 35 kilograms and larger. As such, the stroke volume of the linear motor has been increased to allow for adequate ventilation of this patient population. This increase in stroke volume results in a greater change in pressure within the patient breathing circuit, which is displayed as the oscillatory amplitude pressure.

## **SAFETY DUMP PRESSURE / DELAY**

Since the maximum achievable mean airway pressure of the instrument has been increased, the safety dump pressure has been increased to 60 centimeters of water pressure to match the instrument's performance.

Unlike the 3100A, the 3100B features a delay of approximately 1.5 seconds on the safety pressure dump. This delay has been incorporated to prevent the inadvertent triggering of the safety pressure dump system, which can occur with large oscillatory pressure amplitudes, and low ventilatory frequencies typically employed to treat this patient population. The pressure limit valve normally opens instantaneously when mean airway pressures exceed the set limit. The safety dump valve is a secondary safety system.

## **CIRCUIT LENGTH**

The length of the patient breathing circuit of the 3100B has been increased to facilitate patient movement and positioning without the need to relocate the instrument. Additionally, this circuit employs a heated wire to reduce the accumulation of condensate within the circuit.

## **MINIMUM MEAN AIRWAY PRESSURE**

The low-pressure alarm of 20% of Set Max (user setting) in the 3100A has been fixed to a level of 5 cmH<sub>2</sub>O. This change is related to the increase in oscillatory pressure amplitude of the 3100B. In clinical applications which employ a high oscillatory pressure amplitude and relatively low mean airway pressures, the sudden decrease in circuit pressure which occurs with activation of the oscillating linear motor may cause inadvertent activation of the low pressure dump valve, resulting in an inability to start the instrument.

Fixing activation of the low mean airway pressure dump valve at 5 centimeters of water pressure avoids this, while providing patient protection by not allowing the oscillating linear motor to start without supporting distending pressure and volume in the patient's lungs.

## **MEAN AIRWAY PRESSURE LIMIT / VISUAL SET MAX PAW ALARM**

The 3100A employs a operator set mean airway pressure limit which functions to provide patient protection in the event of an occlusion of the expiratory limb of the patient breathing circuit. This manual airway pressure limit includes no audible or visual indicators of activation.

The 3100B has linked the functions of the limit valve and maximum mean airway pressure alarms to provide enhanced patient safety as well as audible and visual indicators of activation.

During normal operation, the system pressurizes the patient breathing circuit limit valve to the dump valve seat pressure (i.e. 59 cmH<sub>2</sub>O). Should the maximum mean airway pressure alarm threshold be met, the ventilator will deliver an audible and visual signal and the limit valve will be depressurized to the control valve seat pressure (i.e. set mean airway pressure). Once the mean airway pressure has decreased to 80% of the maximum mean pressure alarm setting, the limit valve will re-pressurize to the dump valve pressure. Should alarm conditions continue, the valve will depressurize again and continue to cycle, providing audible and visual alarms until the fault is resolved.

Once the fault has been resolved, the ventilator will return to normal operation and the maximum mean airway pressure visual alarm will latch. The operator may clear this alarm by depressing the reset / power failure button.

## **PISTON CENTERING**

The 3100A features a manual piston centering control which requires the operator to read a visual indicator and adjust a baseline electromagnetic counter-force to offset the mean airway pressure load against the oscillating linear motor front plate. To avoid potential misapplication of this control at the higher mean airway pressures employed with the 3100B, this function is controlled internally by the instrument and requires no operator intervention.

## **COOLING GAS FLOW**

The higher stroke volumes delivered by the 3100B are the result of an increase in the drive voltage to the oscillating linear motor. This increased voltage produces an increase in the normal operation temperature. In order to maintain adequate cooling of the linear motor, the cooling gas flow has been increased from 10 to 25 liters per minute.

### **b3iii. Alternate Treatment Practices**

#### **Alternative Strategies for Managing ARDS**

Mechanical ventilation has many potential sequelae, but of particular concern in Acute Respiratory Distress Syndrome (ARDS) is its potential to further damage the already injured lung. Early in the history of mechanical ventilation this insult was recognized chiefly as “classical” barotrauma in the form of, for example, pneumothorax or pneumomediastinum.<sup>2</sup> Recently it has become increasingly apparent that in addition to “classical” barotrauma, mechanical ventilation may add to lung injury by a number of other mechanisms. These processes have become known collectively as Ventilator-induced Lung Injury (VILI).<sup>3</sup> They can, in turn, lead to a prolonged duration of mechanical ventilation and can cause both pulmonary and non-pulmonary morbidity, potentially including multiple organ failure.<sup>4</sup>

A number of mechanisms are thought to contribute in varying degrees to the development of VILI, which is histopathologically identical to ARDS: (1) oxygen toxicity; (2) overdistention injury (*volutrauma*); (3) shear injury (*atelectrauma*); and, (4) *biotrauma*.

The first mechanism recognized to contribute to VILI is exposure to high fractional inspired oxygen concentrations ( $F_{I}O_2$ ). This phenomenon has been well studied and has been generally accepted for many years. In addition to VILI, oxygen toxicity can cause absorption atelectasis, hypoventilation, systemic vasoconstriction and a decrease in cardiac output.<sup>5</sup>

Lung overdistention injury can occur when high tidal volumes and plateau pressures are delivered. Regional lung overdistention commonly occurs in ARDS because low lung compliance and significant hypoxemia prompt clinicians to raise pressures and tidal volumes. Additionally, because of the patchy nature of ARDS<sup>6</sup>, there are small areas of relatively normal lung which will receive the bulk of the tidal volume, and be at particular risk of *volutrauma*.<sup>7</sup> This effect will be magnified if “classical” tidal volumes (10-15 ml/kg) are used. Over the last 25 years numerous animal studies have been performed using both small and large animals, consistently showing that high peak inspiratory pressures can cause a clinical and histological picture similar to ARDS without any other noxious stimulus.<sup>8-13</sup> Additional data show that a low chest wall compliance is relatively protective against the hazards of high peak airway pressures, suggesting that end-expiratory stretch, related to transpulmonary pressure is the key factor for this mechanism of injury<sup>14</sup>

VILI can also be caused by repeated opening and closing of alveolar units. This has been termed *shearing injury* or more recently *atelectrauma*.<sup>15</sup> This repetitive opening and closing will occur whenever atelectatic lung regions are forced open with high pressures on inspiration and then allowed to close again with low expiratory pressures. There is a substantive body of animal evidence showing that efforts to limit lung unit closing on expiration by maintaining an adequate end-expiratory pressure are relatively protective against this shearing injury. This has been demonstrated using HFOV<sup>16,17</sup> and with the use of Positive End Expiratory Pressure (PEEP) in CMV.<sup>27,32,42-44</sup>

In addition to simple mechanical injury, both *volutrauma* and *atelectrauma* are thought to play a role in activating an inflammatory reaction, which can then progress autonomously, further injuring the lung. This phenomenon has recently been termed *biotrauma*.<sup>18</sup> This process is central to the theory that VILI can contribute to a systemic inflammatory response and multi-organ failure.<sup>4</sup> Studies comparing injurious with relatively safe ventilation strategies in CMV have found higher levels of inflammatory cytokines in the injured lungs.<sup>19,20</sup> Similarly, studies in animal models of lung injury have shown that initiating HFOV as a lung protective ventilatory strategy can lead to a decrease in inflammatory markers.<sup>21,22</sup> Indeed, animal evidence exists showing that HFOV produced less histological damage and lower cytokine levels when compared to a high PEEP and low stretch CMV strategy.<sup>23</sup> These studies suggest that, at the least, local inflammation can be attenuated by employing a lung-protective ventilation strategy. Newly available data, collected from human patients randomly assigned to a lung-protective (high PEEP, low stretch) or a conventional ventilation strategy, confirm these findings.<sup>24</sup> Importantly, Ranieri *et al* also found lower levels of inflammatory cytokines in the plasma of patients treated with the lung protective strategy, demonstrating that mechanical ventilation can cause a systemic inflammatory response which can be attenuated by manipulating ventilator settings.<sup>24</sup>

### **Strategies to Minimize VILI**

With an increased appreciation of the mechanisms of VILI, the next logical step is to employ ventilatory strategies that attempt to limit overdistention, repetitive opening and closing injury, and oxygen toxicity.<sup>1,25,26</sup> Clinicians can try and achieve the first goal by limiting inspiratory pressures and tidal volumes. Using conventional ventilation this frequently means accepting hypercapnea and respiratory acidosis along with their potential consequences.<sup>26-29</sup> In order to prevent repetitive opening and closing, the end-expiratory pressure must be kept above a critical closing volume. This is achieved with CMV through the use of PEEP, but again a potential problem exists because with higher PEEP and constant tidal volume comes a higher transpulmonary pressure and more risk for overdistention injury. The goals of mechanical ventilation in a patient at risk of VILI should be to ventilate and oxygenate the patient while staying within a “safe window”, avoiding both overdistention and derecruitment.<sup>30</sup>

### **Randomized Controlled Trials of Lung-protective Ventilation Strategies**

Four randomized controlled trials have been published examining whether ventilation strategies which attempted to limit VILI would reduce mortality. Three of these limited inspiratory pressures and tidal volumes in an effort to reduce overdistention injury.<sup>27-29</sup> None of their results showed any difference in mortality between the groups, and although they were all under-powered, the point estimates of treatment effect actually favoured the control group in all three trials. The fourth study, by Amato and colleagues, also used limited tidal volumes but these were employed in the setting of a multi-dimensional lung protective strategy.<sup>31</sup> The other components of this strategy were individual tailoring of PEEP above the lower inflection point of the pressure-volume curve and the use of frequent recruitment maneuvers (a sustained inflation at CPAP of 35-40 cm H<sub>2</sub>O for 40 seconds), both of which were designed to avoid atelectasis and derecruitment. These investigators found a striking increase in

8-day survival, demonstrating for the first time that ventilation strategies can affect mortality.

Very recently, a large multi-centre trial of tidal volume limitation in patients with ALI or ARDS was stopped early after an analysis of the first 800 patients showed a significant reduction in mortality for the treatment group (<http://www.hedwig.mgh.harvard.edu>). This trial was conducted under the auspices of the NIH/NHLBI ARDS Network, and its results were reported at the 1999 American Thoracic Society International Conference. The investigators compared tidal volumes of 6 ml/kg with 12 ml/kg and did not use a lung recruitment strategy in either group. They found a statistically significant 9% absolute risk reduction (ARR) in 28 day mortality rates favouring the treatment group (40% control, 31% low-stretch).

The results of all of these trials need to be taken in context. The negative results of the first three studies do not mean that one can use high inspiratory pressures and tidal volumes with impunity. It seems likely that these trials did not show any benefit either because the control groups were also relatively pressure-volume controlled and the incremental differences between groups were too small, or because the beneficial effects of limiting overdistention were counterbalanced by the adverse effects of increasing derecruitment. The preliminary results from the ARDS Network study confirm the fact that limiting overdistention is indeed important. These results do not, however, address the relative importance of avoiding derecruitment and atelectrauma. In fact, the possible creation of auto-PEEP and subsequent avoidance of derecruitment as a result of high respiratory rates in the treatment arm is one hypothesis explaining the difference in results between this and the other trials that only limited lung overdistention. Amato's results, while exciting and encouraging, should also be viewed with a critical eye. Concerns with this study include the high mortality rate in the control arm, the possibility of significant cointerventions, and a lack of generalization in both patients and maneuvers. This was a single, small randomized trial. Its results should not cause clinicians to think that the "correct" way to ventilate patients with ARDS is now certain, but rather should prompt further research into the use of ventilation strategies in ARDS.<sup>54</sup> Because of its size and multi-centered nature, the ARDS Network study will likely become the current standard against which other ventilatory strategies are measured. Its results are exciting because they reinforce the fact that ventilation strategies can positively influence mortality. It should be noted that the ARDS Network treatment strategy is not necessarily the best way to ventilate patients with acute lung injury, but simply a successful approach that has been well studied. While it is true that the mortality rate was quite low in the treatment group of this study, the mortality in the control group was also lower than in other studies, illustrating that caution must be exercised when comparing mortality rates across study populations. Replication of Amato's results using a similar treatment protocol and the exploration of new ventilatory modalities with similar physiologic goals such as HFOV<sup>32-33</sup>, are both needed and these should, at the current time, be compared with the treatment arm of the ARDS Network study.

• **References:**

1. Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. Chest 1993; 104:1833-1859.

2. Haake R, Schlichtig R, Ulstad DR, Henschen RR. Barotrauma. Pathophysiology, risk factors, and prevention. *Chest* 1987; 91:608-613.
3. Dreyfuss D, Saumon G. Ventilator-induced Lung Injury: Lessons from Experimental Studies. *American Journal of Respiratory & Critical Care Medicine* 1998; 157:294-323.
4. Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor?. *American Journal of Respiratory & Critical Care Medicine* 1998; 157:1721-1725.
5. Bryan CL, Jenkinson SG. Oxygen toxicity. *Clinics in Chest Medicine* 1988; 9:141-152.
6. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991; 74:15-23.
7. Roupie E, Dambrosio M, Servillo G, Mentec H, El Atrous S, Beydon L, et al. Titration of Tidal Volume and Induced Hypercapnia in Acute Respiratory Distress Syndrome. *American Journal of Respiratory & Critical Care Medicine* 1995; 152:121-128.
8. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *American Review of Respiratory Disease* 1974; 110:556-565.
9. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *American Review of Respiratory Disease* 1985; 132:880-884.
10. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *American Review of Respiratory Disease* 1987; 135:312-315.
11. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *American Review of Respiratory Disease* 1988; 137:1159-1164.
12. Parker JC, Hernandez LA, Longenecker GL, Peevy K, Johnson W. Lung edema caused by high peak inspiratory pressures in dogs. Role of increased microvascular filtration pressure and permeability. *American Review of Respiratory Disease* 1990; 142:321-328.
13. Tsuno K, Miura K, Takeya M, Kolobow T, Morioka T. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. *American Review of Respiratory Disease* 1991; 143:1115-1120.
14. Hernandez LA, Peevy KJ, Moise AA, Parker JC. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *Journal of Applied Physiology* 1989; 66:2364-2368.
15. Slutsky AS. Lung injury caused by mechanical ventilation. *American Journal of Respiratory & Critical Care Medicine* 1998; Supplement:In Press
16. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, et al. Comparison of conventional and high-frequency oscillatory ventilation. *Journal of Applied Physiology* 1983; 55:131-138.
17. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *American Review of Respiratory Disease* 1988; 137:1185-1192.
18. Tremblay LN, Slutsky AS. Ventilation-induced lung injury: from barotrauma to biotrauma. *Proceedings of the Association of American Physicians* 1998; 110:482-488.

19. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos mRNA expression in an isolated rat lung model. *Journal of Clinical Investigation* 1997; 99:944-952.
20. Tremblay L, Govindarajan A, Veldhuizen R, Slutsky AS. TNF levels are both time and ventilation strategy dependent in *ex vivo* rat lungs. *American Journal of Respiratory & Critical Care Medicine* 1998; 157:A213
21. Sugiura M, McCulloch PR, Wren S, Dawson RH, Froese AB. Ventilator pattern influences neutrophil influx and activation in atelectasis-prone rabbit lung. *Journal of Applied Physiology* 1994; 77:1355-1365.
22. Takata M, Abe J, Tanaka H, Kitano Y, Doi S, Kohsaka T, et al. Intraalveolar expression of tumor necrosis factor-alpha gene during conventional and high-frequency ventilation. *American Journal of Respiratory & Critical Care Medicine* 1997; 156:272-279.
23. Imai Y, Nakagawa S, Ito Y, Kawano T, Miyasaka K. Comparison of Lung Protection Strategies Using Conventional and High Frequency Oscillatory Ventilation. Submitted 2000;
24. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of Mechanical Ventilation on Inflammatory Mediators in Patients with Acute Respiratory Distress Syndrome. *JAMA* 1999; 282:54-61.
25. Stewart TE, Slutsky AS. Mechanical Ventilation: A shifting philosophy. *Current Science* 1995; 1:49-56.
26. Stewart TE. Lung Protection During Mechanical Ventilation. *Ontario Thoracic Reviews* 1997; 9:1-4.
27. Stewart TE, Meade MO, Cook DJ, Granton JT, Hodder RV, Lapinsky SE, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *New England Journal of Medicine* 1998; 338:355-361.
28. Brochard L, Roudot-Thoraval F, Roupie E, Delclaux C, Chastre J, Fernandez-Mondejar E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume reduction in ARDS. *American Journal of Respiratory & Critical Care Medicine* 1998; 158:1831-1838.
29. Brower R, Stanholtz C, Shade D, et al. Randomized trial of small tidal volume ventilation (STV) in ARDS. *American Journal of Respiratory & Critical Care Medicine* 1997; 155:A93
30. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time. *Critical Care Medicine* 1997; 25:906-908.
31. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *New England Journal of Medicine* 1998; 338:347-354.
32. Herridge MS, Slutsky AS, Colditz GA. Has high-frequency ventilation been inappropriately discarded in adult acute respiratory distress syndrome? *Critical Care Medicine* 1998; 26:2073-2077.
33. MacIntyre NR. High-frequency ventilation. *Critical Care Medicine* 1998; 26:1955-1956.

### **b3iv. Marketing History**

On March 29, 1991 SensorMedics received Premarket Approval for the Model 3100 High Frequency Oscillatory Ventilator for treatment of neonates with respiratory failure and barotrauma. Subsequently, SensorMedics received approval for the Model 3100A on June 27, 1991. The indications for use of the 3100A were expanded to include pediatric patients failing conventional ventilation on September 15, 1995. This instrument is currently in production and has demonstrated some success in the rescue treatment of large patients with acute respiratory failure.

In November of 1991 SensorMedics was granted an IDE for evaluation of a new version of ventilator, the Model 3100B Adult High Frequency Ventilator. This pilot clinical trial involved treatment of seventeen patients ranging from 16 to 83 years of age. The results of this trial demonstrated that HFOV was both safe and effective in adult patients with severe ARDS failing conventional ventilation. HFOV demonstrated improvements in oxygenation and reduced the mean airway pressure cost of oxygenation. Overall survival was 37% which is consistent with prior studies in similar patients.

The results of this clinical trial were supportive of further research and subsequently a second IDE was received for a prospective randomized controlled trial of high frequency oscillatory ventilation in adults with ARDS in 1996. This clinical trial, known as MOAT 2, had its final patient enrolled in December 2000.

The model 3100A has been in International Commercial distribution since 1991. More than 3,000 units have been built and shipped to date.

The model 3100B, has been shipped to countries outside of the United States since 1993. Approximately 100 units have been shipped internationally. Prior to June 1998 units were shipped freely to Europe; since June 1998, all units shipped to the European Union have been marked with the CE-Mark of conformity. SensorMedics maintains a certificate to export an un-approved product under section 802 of the exporting regulations.

3100B units have been shipped to the following countries:

Austria  
Belgium  
France  
Germany  
Italy  
Norway  
Qatar  
Saudi Arabia  
South Africa  
Spain  
Sweden  
Switzerland  
Netherlands  
UK

## **b3v. Summary of Studies**

### **b3vA. Nonclinical Studies**

The following nonclinical studies were performed to ensure that the minor physical changes and the increased work load applied to the 3100B did not adversely affect the safety and efficacy of the function of the device.

- 1) A set of tests was performed on the driver assembly to ensure that the increased tidal volume being demanded could be provided reliably.
- 2) Tests were performed to validate each of the minor physical changes to the 3100A that allowed it to become and function as a 3100B.
- 3) FMEA analysis was performed to identify and ensure adequate mitigation of potential risks and hazards.
- 4) Tests were performed to ensure that none of the minor changes adversely affected the electrical safety or EMC of the 3100B. These tests (IEC 601-1 and IEC 601-2-12) were performed by ETL Laboratories.

Details of each of these three tests are included beginning with page 43.

## **b3vB. Summary of clinical investigations**

Pivotal Trial (MOAT2)

PROSPECTIVE RANDOMIZED MULTICENTER OSCILLATOR ARDS TRIAL (MOAT2) (IDE G960017)

### ***STUDY DESIGN***

MOAT2 was designed as a prospective multicenter randomized trial to compare the model 3100B High Frequency Oscillatory Ventilator (HFOV) and conventional mechanical ventilation (CMV) for the respiratory management of patients with acute respiratory distress syndrome (ARDS). While many patients were likely to have exposure to both ventilators, the study design did not include crossover treatment and all analyses were to be based on the intention to treat. Both ventilator strategies were aimed at establishing and maintaining a normalized lung volume and minimizing peak lung pressures.

Patients 16 years or older, and weighing at least 35 kilograms were eligible for enrollment if they meet the American-European Consensus definition of ARDS (i.e., PaO<sub>2</sub>/FiO<sub>2</sub> < 200, bilateral pulmonary infiltrates not resulting from left atrial hypertension), with a positive end expiratory pressure of at least 10 cm H<sub>2</sub>O. Patients otherwise eligible for enrollment were excluded for any of the following reasons: 1) lack of informed consent, 2) FiO<sub>2</sub> greater than .80 for 48 hours, 3) severe persistent air leak, 4) non pulmonary terminal prognosis, 5) severe chronic obstructive pulmonary disease, or asthma, 6) or recent enrollment in another ARDS or septic shock investigation.

The aim of the study was to show HFOV treatment was at least comparable to CMV treatment. Four primary end points were prospectively identified, 1) death or continued respiratory support at 30 days, 2) death at 30 days, 3) development of acute intractable hypotension, and 4) development of new air leak. A power analysis suggested this could be accomplished with an enrollment of 148 patients.

The study protocol is included beginning on page 105. The study was approved for use in 1997 as IDE #G960017. There were two minor changes made to the protocol after the study began, both affected the enrollment criteria. First, the enrollment criteria requiring a PEEP of at least 10 was included at the first investigators meeting on February 6, 1998 shortly after the study began. Only 4 patients had previously been enrolled with initial PEEP's less than 10. In January 1999, after enrollment of 39 patients, the enrollment exclusion for extended high FiO<sub>2</sub>'s was increased from 24 to 48 hours to improve enrollment by facilitating informed consent.

### ***STUDY CENTERS AND ENROLLMENT***

The first of 148 patients was enrolled on 10/26/97 and the last on 12/7/00. Enrollment for the 4 years was as follow: 1997 - 6, 1998 - 31, 1999 - 65, 2000 -46.

The patients were enrolled from 10 centers, as shown in the Table 1 below. Three centers gained IRB approval, but found it impractical to enroll patients and were dropped from participation. One of these three centers enrolled one patient, the other two none. Three of the 10 enrolling centers were located in Toronto Canada. Each received approval from their respective institutional ethics and research committees and agreed to participate in accordance with USA Investigational Device regulations 21CFR part 812, which was not inconsistent with Canadian patient protection requirements. Details of the IRB approvals and site participation are included on page 153. Two of the centers represented multiple sites, each with corresponding institutional approval for each site and with the same Principal Investigator. The Wilford Hall Medical Center included Brook Army Medical Center, with one patient being enrolled at the latter site. Mt Sinai Hospital included Wellesley Hospital, the later having enrolled 5 patients. In this case, as originally anticipated, the ICU at Wellesley was closed and the staff transferred to Mt Sinai where the study continued. The study was conducted, to the best of our knowledge, according to CFR Part 812, with the exception that written informed consent was not received at the time of enrollment of one patient. (4/26/99 patient 8.02). The Principal Investigator reported this to his IRB, once discovered. This event is identified in a Table on page 159.

Table 1

	HFOV	CV	Total	Rate #/m
Wilford Hall / BAMC	10	10	20	.53
Toronto General	11	10	21	.62
Wellselley / Mt Sinai	9	10	19	.79
Maine Medical Center	7	8	15	.48
Bronson Methodist	1		1	
Loma Linda	6	5	11	.44
University Virginia	7	10	17	.85
Allegheny General	4	3	7	.30
Barnes Jewish	14	13	27	1.50
Sunnybrook	5	5	10	.83

### STUDY POPULATION

Seventy-five patients were assigned to HFOV treatment and 73 to CMV treatment. The four tables that follow describe the patients enrolled in the CMV and HFOV treatment arms of the study. They are quite similar. Statistical evaluation of specific differences between the treatment groups using chi-square and t-test found none that reached significance ( $p=0.05$ ). In cases where the n does not equal the enrollment, data was unavailable from the site.

Table 2: Demographics

	#	HFOV	#	CMV
Age (years)	75	48 (17)	72	51 (18)
Weight (kg)	75	78 (25)	72	81 (26)
Gender (% male)	75	52%	73	64%

Continuous data presented as mean (stdev).

Table 3: Pre Enrollment Ventilator Settings

	#	HFOV	#	CMV
PIP	75	39 (7)	73	38 (8)
PEEP	75	13 (3)	73	14 (3)
mPaw	71	22 (5)	71	24 (7)
TV/KG	72	8.2 (3)	69	7.8 (3)
FiO2	75	.71 (.19)	73	.72 (.19)

Continuous data present as mean (stdev). PIP is peak inspiratory pressure, PEEP is positive end expiratory pressure, mPaw is mean airway pressure, all presented as centimeters of water. TV/KG is the tidal volume (milliliters) divided by the body weight in kilograms.

Table 4: Pre-Enrollment Clinical indicators

	#	HFOV	#	CMV
PaO2	75	76 (20)	73	73 (18)
PaCO2	75	44 (12)	73	45 (12)
pH	73	7.37 (.09)	73	7.34 (.11)
PaO2/FiO2	75	114 (37)	73	111 (42)
Oxygenation Index	71	24 (15)	71	27 (19)
Mean Blood Pressure	65	80 (14)	61	76 (12)

Cardiac Output	36	7 (2)	37	7 (3)
APACHE II	68	22 (6)	65	22 (9)

Continuous data present as mean (stdev). PaO2 is the partial pressure of arterial oxygen, PaCO2 is the partial pressure of arterial carbon dioxide, both presented in millimeters of Hg. FiO2 is the fraction of inspired oxygen. Oxygenation Index is the mPaw x100/PaO2/FiO2. Mean blood pressure is presented in millimeters of Hg, and cardiac output in liters per minute. APACHE II is a disease severity score.

Table 5: Pre-Enrollment Diagnoses

	#	HFOV	#	CMV
Primary ARDS Trigger:	75		73	
Sepsis Syndrome		47%		47%
Pulmonary Infection		19%		16%
Trauma		21%		18%
other		13%		19%
Confounding Dx				
Air leak	75	16%	73	19%
Immune compromise	61	12%	62	14%
>4 days mech. vent	74	22%	73	36%

Incidences rounded to nearest percent

Table 6 below details the reasons for exit from the study. A chi-squared test suggests the patterns of exit are different for the two ventilator treatments, (p=0.015). The data suggests that HFOV patients were less likely to exit as a result of death, more likely to exit after being weaned from mechanical ventilation, and more likely to still be on mechanical ventilation at 30 days. Exit data was available for all 148 patients enrolled in the study.

Details on the 56 patients who exited the study because of death can be found beginning on page 170. Twenty patients exited the study prematurely, either because of Withdrawal of Informed Consent, HFO Treatment Failure or “Other”. Details of these patients can be found on page 344. The exit for 6 patients are identified as “Other”, a category not prospectively defined. One of these patients was exited in the first day after a decision was made that bilateral infiltrates had not been present on the radiograph, and thus the patient had not been eligible for enrollment. Two exited because they were transferred to other facilities while still on mechanical ventilation. The other 3 patients were withdrawn by the attending physician so that therapy could be modified. These last three identified as “Other”, could also have been treated as Withdrawal of Consent.

Table 6: Study Exit

	HFOV	CMV
number	75	73
Withdrawal of consent	3 %	11 %
Weaned from mechanical ventilation	37 %	27 %
30 days from entry	21%	11 %
TX failure, stop HFO	5 %	0 %
Died	31 %	45 %
Other	3%	6 %
P= 0.015		

Incidences rounded to nearest percent

The average mortality rate varied among centers. This was expected, considering differences in patient populations (trauma vs. medical) and referral basin. Overall, mortality was consistent with differences in pre enrollment length of ventilation and APACHE II scores. Importantly, only one center experienced a higher mortality in the HFOV patients. Therefore as planned the data from all the sites were pooled.

**PATIENT COMPLAINTS**

No patient complaints were reported through the course of the study. Considering the general health and other vital statistics attributed to the patient population complaints were not anticipated nor were they reported.

**PRIMARY OUTCOMES**

Table 7 below includes the results for the four primary safety and effectiveness outcomes. This outcome data was available for all 148 patients enrolled in the study. The results are shown as percent incidence with a corresponding 95% confidence limit of the difference in the incidences (corrected for continuity). None of the differences reached statistical significance.

Table 7: Primary Outcomes

	HFOV	CMV	95% CL Difference
number	75	73	
Status @ 30 days			
Death or respiratory support	79%	74%	-10% to +20%
Death	37%	52%	-32% to +3%
On Study			
Intractable hypotension	0%	3%	-8% to +2%
Develop new air leak	8%	8%	-12% to +11%

Incidences rounded to nearest percent

The primary effectiveness measure in this study was death or continuing respiratory support at 30 days. Because the goal of this study was to determine if HFOV treatment was at least comparable to CMV treatment, the hypothesis was that HFOV was not more than 10% worse than CMV. As can be seen, HFOV was approximately 5% worse (59/75 and 54/73), with a 95% confidence of being between 10% better and 20% worse. Interestingly, a post-hoc analysis looking at death or continued mechanical ventilation at 30 days (as compared to including supplement oxygen as “respiratory support”), identified a 7% difference (47/75 & 51/73), with a 95% confidence that HFOV is between 34% better and 9% worse.

**SECONDARY OUTCOMES**

The status of the patients at 1 month (30 days) and 6 months is shown in Table 8. Data is available for all 148 patients. The status for patients discharged without respiratory support is based on discharge status. Follow up on all patients discharged or transferred while still on respiratory support was completed. Chi-squared analysis of the status at 1 month (30 days) and 6 months suggests the HFOV assigned patients had different outcomes than the CMV assigned patients. (p= 0.038 @ 1 month, 0.086 @ 6 months )

Table 8: Status at 1 month and 6 months

	HFO	HFO	CMV	CMV
number	75	75	73	73
End Points	1 M	6 M	1 M	6 M
Died	37 %	47 %	52 %	59 %
Survived (resp. support)	41 %	0 %	21 %	3 %
Survived	21%	53 %	26 %	38 %
1 month p= 0.038 6 months p=0.086				

Incidences rounded to nearest percent

Table 9 below describes the incidence of four prospectively defined secondary outcome parameters. Data for these parameters was available for all of the patients for these variables.

Table 9: Secondary Treatment Failures

	HFO	CMV	95% CL Diff
number	75	73	
Oxygenation	5%	8%	-12% to +7%
Respiratory Acidosis	5%	8%	-12% to +7%
Develop new or worsening ALS	9%	12%	-14% to +8%
Mucous Plugged ET Tube	3%	1%	-5% to +7%

Incidences rounded to nearest percent. ALS is air leak syndrome.

### **ADVERSE EFFECTS**

As anticipated in this treatment population, and reflected in Table 6, death was a common reason for exit from the study. Table 10 below summarizes the causes of death for the 56 patients who died on study, tabulated with regard to whether life support was withdrawn. Details of each case are listed on page 172. Note the causes of death were often multifactorial.

Reported unanticipated adverse effects were infrequent. The most common event was a mucous plug of the ET Tube that required suctioning, which was reported twice for each ventilator group. All the reported Adverse Effects, protocol violations and investigational device failures are listed on page 159. Four HFOV failures were reported. There were no reports of complaints from patients or their families.

No new Precautions or Warnings were identified, other than those included in the Operating Instructions, in the Appendix pages 497 through 502.

Table 10: On Study Deaths

Cause of Deaths when Study Exit	Support withdrawn	<b>Not</b> withdrawn
	HFO/CMV	HFO/CMV
Total number	16 / 22	9 / 14
Cardiac Arrhythmia	2 / 0	2 / 6
Multiple Organ Failure	10 / 14	4 / 4
Sepsis	6 / 6	4 / 5
Profound Hypoxemia	2 / 2	2 / 6
other	2 / 2	2 / 2

### **TREATMENT COURSE**

The length of mechanical ventilation in the two treatment groups was quite similar. In the CMV control group the average was 20 days (stdev 31) for all patients and 33 days (stdev 45) for survivors. The HFOV treatment strategy included transition to conventional ventilation during recovery and then weaning from conventional ventilation. The average total length of mechanical ventilation for the HFOV patients was 22 days (stdev 21), 6 of these were on HFOV (stdev 5). The average length of mechanical ventilation for HFOV survivors was 29 days (stdev 25).

Multivariate repeated measures analysis of variance was used to identify differences in the course of clinical indicators during the first 3 days of treatment course of the two ventilator groups. Data was collected at initiation of the treatment and then every 8 hours. In addition to ventilator, the model included outcome and time trend. The clinical indicators evaluated were: mean airway pressure, PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, Oxygenation Index, PaO<sub>2</sub>/FiO<sub>2</sub>, mean arterial blood pressure, pulmonary capillary wedge pressure and cardiac output. Because of the likelihood of a type 1 error with so many comparisons, differences were only considered significant if they reached a p < 0.01.

As anticipated as a result of the treatment strategy, the mean airway pressure was significantly higher in the HFOV treated patients (average 28.9 vs. 22.7,  $p < 0.0001$ ). It was further expected that this higher airway pressure would result in improved lung recruitment, which was in fact reflected in an improved and significantly higher PaO<sub>2</sub>/FiO<sub>2</sub> status for the HFOV patients during this period. (average 167 vs. 147,  $p < 0.001$ ). The pulmonary capillary wedge pressure was also found to be slightly higher in the HFOV patients (average 19.5 vs. 18.5,  $p < 0.01$ ). The PaCO<sub>2</sub> in the HFOV patients was also slightly higher (average 48 vs. 43,  $p < 0.01$ ). There were no ventilator-outcome interactions or ventilator-time interactions that were identified that were statistically significant. There was a significant association of higher Oxygenation Index with poor outcome ( $p < 0.001$ ), but this effect was independent of ventilator group.

This study design did not include crossover. However, patients in the investigational arm (HFOV) were permitted to be exited and treated with conventional ventilation if the patient met specific treatment failure criteria and the attending physician felt conventional ventilation might be advantageous for the patient. This situation occurred 4 times. Two of these four patients died. While not the intent of the study design, nine patients assigned to CMV, were treated with HFOV at the direction of the attending physician. Only two of these nine patients survived.

### ***LIMITS OF EFFECTIVENESS***

The therapeutic role of mechanical ventilation is to provide adequate oxygenation and ventilation while minimizing trauma from ventilator airway pressures. Excessive pressure usually manifests acutely as pulmonary air leaks or compromise of the cardiovascular system (hypotension). The study was designed with prospective criteria for oxygenation, ventilation (respiratory acidosis) and hypotensive failures as well as development of pulmonary air leaks. As can be seen in Table 11 these failures were infrequent in both treatment groups and do not appear to be more frequent in the HFOV treated patients. No limits of effectiveness were identified in this study.

Table 11: Limit of Effectiveness Treatment Failures

	HFO	CMV	95% CL Diff
Oxygenation	5%	8%	-12% to +7%
Respiratory Acidosis	5%	8%	-12% to +7%
Develop new Air leak	8%	8%	-12% to +11%
Intractable hypotension	0%	3%	-8% to +2%

### ***DEVICE FAILURE AND REPLACEMENTS***

The majority of the device failures were routine in nature. In each case, the study device was able to be repaired back to original factory specifications. The following list indicates the particular failures that were reported during the study.

## SUMMARY OF 3100B SERVICE HISTORY

### S/N 31B004

Date: 18 May 1999

C/D #: 40035

Problem: Torn driver diaphragms

Solution: Sent replacement driver diaphragms; Krytox lubricant useage

Date: 9 July 1999

C/D #: 44500

Problem: Machine not working right

Solution: Unknown ("resolved by Terry Blansfield")

### S/N 31B011

Date: 2 July 1999

C/D #: 43953

Problem: Not stated

Solution: "Steve on site, problem take care of."

### S/N 31B014

Date: 7 May 1998

C/D #: 5361

Problem: Source Gas Low LED on

Solution: Replaced leaking pressure switch

Date: 8 May 2000

C/D #: 75488

Problem: Torn diaphragm

Solution: Send new 3-ohm driver

Date: 31 Oct 2000

C/D #: 96911

Problem: MAP fluctuating by 10 cm on patient

Solution: Replaced Alarm board

### S/N 31B019

Date: 7 July 2000

C/D #: 82852

Problem: Driver over-heated after a few hours on patient

Solution: Installed 3-ohm driver and Auto-Limit pneumatic

**S/N 31B020**

Date: 27 Nov 2000  
C/D #: 100065/100078  
Problem: Burning smell  
Solution: Replaced alarm board (burnt capacitor C30).

**S/N 31B023**

Date: 20 Nov 2000  
C/D #: 99276  
Problem: Power ON/OFF switch (circuit breaker) intermittently trips  
Solution: Installed new circuit breaker

**S/N 31B024**

Date: 4 Dec 1998  
C/D #: 26030  
Problem: Low MAP during Performance checks  
Solution: Adjusted pneumatics

Date: 6 May 1999  
C/D #: 38992  
Problem: Low Delta-P during performance checks  
Solution: Replaced PR8 with new style, adjusted pneumatic functions and driver control.

Date: 4 June 1999  
C/D #: 40899  
Problem: Pressure bad  
Solution: Replaced driver and driver power module.

Date: 5 July 2000  
C/D #: 82745  
Problem: Driver began to "miss a beat"  
Solution: Installed 3-ohm driver, Auto-Limit pneumatics and Driver Power Module.

Date: 30 Oct 2000  
C/D #: 96748  
Problem: Delta-P low during Performance checks  
Solution: Replaced Alarm board, calibrated all electrical/pneumatic functions

**S/N 31B025**

Date: 13 Sep 2000  
C/D #: 90810  
Problem: Leaking/hissing pressure switch in pneumatics  
Solution: Replaced pressure switch

**S/N 31B030**

Date: 14 Jan 2000

C/D #: 62632

Problem: Would not pass Patient Circuit Calibration

Solution: Repaired possibly bad electrical connection at dump valve solenoid, replace regulator PR3, and replaced dump valve solenoid.

**S/N 31B032**

Date: 20 June 2000

C/D #: 80702

Problem: Driver diaphragm ruptured

Solution: Replaced driver

Date: 30 Nov 2000

C/D #: 100360

Problem: Torn driver diaphragm

Solution: Replaced driver

**S/N 31B033**

Date: 12 Sep 2000

C/D #: 90725

Problem: Torn driver diaphragm (after 362 hours useage)

Solution: Replaced driver

**S/N 31B036**

Date: 16 Dec 1998

C/D #: 27070

Problem: Low MAP

Solution: Adjusted pneumatic functions

**S/N TMA03488**

Date: 26 May 2000

C/D #: 81090

Problem: Torn driver diaphragm

Solution: Replaced driver with 3-ohm one; upgrade with Auto Limit

***CONTRAINDICATIONS AND PRECAUTIONS***

The 3100B Oscillatory Ventilator has no specific contraindications.

### **b3vi. Conclusions drawn from the study**

MOAT2 was a prospective randomized multicenter comparison of the SensorMedics 3100B HFOV and conventional mechanical ventilation for the treatment of ARDS. Both ventilators used a strategy aimed at normalization of lung volumes and minimization of peak ventilatory pressures. Patients were exited from the study at 30 days, death or upon successful weaning from mechanical ventilation. The primary endpoint was status at 30 days, however secondary endpoints included status at 6 months and the incidence of specific adverse events while on study.

To explore the potential benefit of HFOV the data from the HFOV treated patients must be considered both in comparison with the control patients as well as compared with other published ventilator trials in similar patient populations. Specific characteristics associated with higher risk of mortality include patient age<sup>1,3,10</sup>, specific ARDS triggering etiologies<sup>3,8-11</sup>, severity of hypoxemia<sup>3,10-13</sup>, existing air leaks<sup>14</sup>, immune compromised<sup>4</sup>, and ventilator strategies that use high volumes and pressures<sup>5,6</sup>. To evaluate any benefit from the use of HFOV, adverse effects that might pose excessive risk to the patient with its use must also be taken into consideration.

The two populations for the treatment and control arms in this study were very well balanced and contained no statistically significant differences in any of the identified characteristics of increased mortality. At 30 days of study entry, the mortality in the conventionally ventilated patients was 52 percent while in the HFOV group the mortality was 37 percent, a 29 percent lower mortality. While there were more patients on some form of respiratory support in the HFOV group at 30 days, fewer of them required mechanical ventilation versus supplemental oxygen than in the control group (61% vs. 73%). At six months, although the mortality differences narrowed, there was still a 20 percent mortality benefit for patients in the HFOV group. There was no residual need for respiratory support in the HFOV treated patients at six months.

The identified risks associated with HFOV are similar to the risks associated with conventional ventilation. These include developing or worsening of air leaks, mucous plugging of the endotracheal tube or airways, and hypotension. In this study, incidences of these events, as well as unanticipated adverse events, were low in both arms and there were no statistical differences in these occurrences. This suggests that HFOV is at least as safe as conventional ventilation and poses no significant additional risk.

The only large multicenter prospective randomized ventilator trial in ARDS that has demonstrated a statistically significant benefit with use of a specific management approach has been the NIH lower tidal volume as compared with higher tidal volume study.<sup>5</sup> This study compared patients managed with 6 ml/kg tidal volume as compared with patients managed with 12 ml/kg. They reported a lower mortality of 31 percent in the patients treated with 6 ml/kg tidal volume as compared with the 39.8 percent mortality in the control group (reduction of 22%). A comparison of the patients in the MOAT2 study with the NIH patients may be important when considering the effectiveness of HFOV.

The NIH trial enrolled patients with less severe respiratory failure, as the entrance criteria included patients who had acute lung injury as defined by a PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio <300 torr.<sup>5</sup> There was also no minimum level of end expiratory pressure (PEEP) required for entry. Entrance in the MOAT2 trial required a P/F <200 on a minimum PEEP of 10 cmH<sub>2</sub>O. As a result, the severity of the patients in the MOAT2 trial was very different than in the NIH trial. The average P/F in the NIH trial was 136 and in the MOAT2 trial it was 112. The MOAT2 patients had significantly worse oxygenation with PEEP levels approximately 50% higher. A prior publication evaluating the influence of a P/F <150 with a PEEP of 5 cmH<sub>2</sub>O on mortality reported that if the P/F was >150, the mortality was 23%.<sup>3</sup> However, if the P/F on 5 cmH<sub>2</sub>O was <150, the mortality rose to 68%. Similar increases in mortality have been reported with P/F's less than 100.<sup>7</sup>

Sepsis syndrome was the triggering mechanism for ARDS in 47% of both groups in the MOAT2 trial, while it accounted for only 27% of the NIH patients. Analysis of prior HFOV data and consistent with other conventional ventilation data, the presence of sepsis has a negative impact on survival and/or morbidity.<sup>4,8-11</sup> This alone could account for the outcome differences seen between these trials.

When the MOAT2 trial was designed, there was no evidence that low tidal volumes during mechanical ventilation would be beneficial. The MOAT2 strategy for conventional ventilation was not a high stretch as was used in the control arm of the NIH trial. The targeted tidal volume was at 6-10 ml/kg of actual body weight. However, as a

result of the NIH report, a post-hoc analysis of the mortality in the control arm was performed with recalculation of actual tidal volume per kilogram of ideal body weight. The mortality in the conventionally ventilated patients in MOAT2, stratified by ideal body weight follows in table 1.

TV/kg (IBW)	Mortality	N	Average VT	Std Dev
< 8 ml/kg	0.67	6	7.13	0.62
8 to 10 ml/kg	0.44	25	9.15	0.58
> 10 ml/kg	0.46	28	11.54	0.66

Table 1. Mortality by ideal body weight (IBW)

The analysis demonstrated that while the mortality in the MOAT2 patients treated with conventional ventilation was higher than the patients from the NIH trial, actual tidal volume appeared to have no impact on outcome. It is evident that there may be other differences in the patient population that resulted in the difference in outcome (e.g. sepsis syndrome, derangement of oxygenation, etc.).

While the large differences in mortality at 30 days (29%) did not reach statistical significance, the status (died or alive requiring respiratory support or alive requiring no respiratory support) does reflect a statistically significantly difference ( $p < 0.05$ ) at 30 days. Additionally, considering the persistence of a trend toward reduced mortality at 6 months, the 30 day status can be interpreted as supporting HFOV effectiveness.

We conclude that use of the 3100B HFOV for treating patients with acute respiratory failure is at least as effective as conventional ventilation and that there are no increased risks that outweigh any potential benefit.

#### References

1. Suchyta MR. Clemmer TP. Elliott CG. Orme JF. Morris AH. Jacobson J. Menlove R. Increased mortality of older patients with acute respiratory distress syndrome. *Chest* 1997; 111:1334-9
2. Zilberberg MD. Epstein SK. Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. *Amer J Respir and Crit Care Med* 1998; (4 Pt 1):1159-64
3. Villar J, Perez-Mendez L, Kacmarek RM. Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome. *Intensive Care Med* 1999; 25:930-935.
4. Arnold JH, Anas NG, Luckett P, et al. High Frequency Oscillatory Ventilation in pediatric respiratory failure: A multicenter experience. *Critical Care Med* 2000; 28(12):3913-3942
5. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301-8
6. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998; 338:347-54
7. Esteban. Survey of 15,000 ICU patients in Europe. Personal Communication
8. Ferring M. Vincent JL. Is outcome from ARDS related to severity of respiratory failure? *Euro Resp J* 1997; 10(6):1297-300
9. Headley AS. Tolley E. Meduri GU. Infections and the inflammatory response in acute respiratory distress syndrome. *Chest* 1997; 111:1305-21
10. Abel SJ. Finney SJ. Brett SJ. Keogh BF. Morgan CJ. Evans TW. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax* 1998; 53:292-4
11. Vieillard BA. Girou E. Valente E. Brun-Buisson C. Jardin F. Lemaire F. Brouchard L. Predictors of mortality in acute respiratory distress syndrome.

- Focus on the role of right heart catheterization. *Amer J Resp Crit Care Med* 2000; 161:1597-601
12. Roupie E. Lepage E. Wysocki M. Fagon JY. Chastre J. Dreyfuss D. Mentec H. Carlet J. Brun-Buisson C. Lemaire F. Bouchard L. Prevalence, etiologies and outcomes of the acute respiratory distress syndrome among hypoxemic ventilated patients. SRLF Collaborative Group on Mechanical Ventilation. *Intensive Care Med* 1999; 25:920-9
  13. Monchi M. Bellenfant F. Cariou A. Joly LM. Thebert D. Laurent I. Dhainaut JF. Brunet F. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Amer J Respir and Crit Care Med*. 1988; 158:1076-81
  14. Briassoulis GC. Venkataraman ST. Vasilopoulos AG. Sianidou LC. Papadatos JH. Air leaks from the respiratory tract in mechanically ventilated children with severe respiratory disease. *Pediatric Pulmonology*. 2000; 29(2):127-34