

June 11, 2001

Document Mail Center (HFZ-401)
Center for Devices & Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Re: Supplement 14 to PMA P890057
Amendment 4
Model 3100B High Frequency Oscillatory Ventilator

Dear Sir or Madam:

Enclosed are 6 copies of Amendment 4 to Supplement 14 of PMA 890057. This amendment is being submitted in response to information requested by e-mail from Joanna Weitershausen to Alex Stenzler. The e-mail is titled (FW: Panel Meeting) and is dated (6/5/01).

The first 28 pages provide additional information that was specifically requested. The last 7 pages include additional information that SensorMedics feels would benefit the panel members. The following page includes a table of contents describing the contents of this amendment.

The information contained in this amendment is not considered to be confidential and may be released under FOI.

If you have any questions regarding this submission, please contact me at telephone number (714) 283-2228 x8461, or at fax number (714) 283-8426. Additional contacts are Paul Kittinger at x8351 and Alex Stenzler at x8327.

Sincerely,

Earl W. Draper
Director of Quality Systems

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Table 2. Daily Ventilator and Physiologic Variables for the HFOV and Conventional Ventilation arms during the first three days taken at approximately 8-hour intervals

	HFOV			CV		
	n	mean	stdev	n	mean	stdev
FiO2						
Day1	60	.51	.15	57	.60	.19
Day 2	55	.52	.17	54	.54	.18
Day 3	45	.51	.15	48	.51	.17
PIP						
Day1	60			57	37	8
Day 2	55			54	38	9
Day 3	45			48	37	9
PEEP						
Day1	60			57	13	3
Day 2	55			54	13	4
Day 3	45			48	13	4
TV/kg						
Day1	60			57	8	2
Day 2	55			54	8	3
Day 3	45			48	8	2
Mean Paw						
Day1	60	29	6	57	23	7
Day 2	55	28	6	54	23	8
Day 3	45	28	6	48	22	8
Delta-P						
Day1	60	66	14	57		
Day 2	55	65	13	54		
Day 3	45	66	17	48		

PaCO2

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	72	44.93	13.43	70	44.96	13.10
	1	72	49.68	16.63	65	43.83	10.33
	2	66	48.06	13.33	65	41.57	9.79
	3	62	47.73	14.20	56	42.46	10.51
Day 2	1	62	46.85	12.83	56	42.91	10.11
	2	60	48.18	12.66	54	42.50	12.03
	3	56	47.27	12.91	50	43.58	14.91
Day 3	1	54	48.33	12.50	54	43.02	13.53
	2	47	49.23	14.30	49	42.78	10.63
	3	42	52.14	14.29	44	44.59	11.94

pH

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	73	7.37	0.10	71	7.34	0.11
	1	72	7.34	0.13	66	7.36	0.11
	2	67	7.35	0.11	66	7.36	0.11
	3	62	7.35	0.09	56	7.36	0.10
Day 2	1	62	7.36	0.09	56	7.37	0.18
	2	59	7.36	0.08	54	7.37	0.10
	3	56	7.37	0.09	52	7.38	0.11
Day 3	1	54	7.36	0.08	54	7.37	0.11
	2	47	7.37	0.07	48	7.39	0.09
	3	42	7.34	0.08	44	7.37	0.09

PO2/FiO2

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	73	110.88	36.98	71	109.92	41.66
	1	72	141.63	61.14	64	127.34	58.54
	2	65	177.87	126.69	64	131.20	51.55
	3	61	205.68	165.16	56	143.14	57.05
Day 2	1	59	172.20	88.12	54	149.80	65.68
	2	58	181.59	107.53	54	162.80	69.17
	3	55	169.45	73.97	50	153.98	63.80
Day 3	1	53	166.00	73.34	54	166.94	93.75
	2	46	177.31	65.61	48	163.96	73.94
	3	41	173.72	75.45	44	162.77	79.74

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	68	24.04	15.48	69	26.36	17.24
	1	72	26.19	13.19	61	25.06	20.13
	2	66	23.15	11.41	61	21.46	13.54
	3	59	19.33	10.32	55	19.18	11.65
Day 2	1	58	19.98	9.79	54	19.28	12.98
	2	56	20.81	11.56	53	17.38	11.72
	3	55	21.19	13.57	48	21.20	23.67
Day 3	1	52	19.57	11.22	52	19.58	20.13
	2	44	18.44	8.65	48	18.16	18.51
	3	41	19.21	9.71	44	18.90	18.76

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	33	7.41	2.33	34	7.94	3.46
	1	31	6.98	2.01	26	7.41	3.42
	2	34	6.83	2.75	27	7.71	3.26
	3	31	6.69	2.33	25	7.12	2.86
Day 2	1	26	6.44	2.13	19	8.25	5.06
	2	28	6.32	2.45	24	7.22	3.19
	3	28	6.44	2.75	24	6.80	2.70
Day 3	1	25	6.53	2.60	21	6.98	2.86
	2	24	6.74	2.81	20	7.95	2.98
	3	18	7.44	2.66	17	7.47	2.31

		HFOV			CV		
		n	mean	stdev	n	mean	stdev
Day 1	pre	34	16.18	3.72	30	17.20	4.46
	1	30	18.43	2.96	28	18.32	4.70
	2	29	20.07	3.99	22	18.59	4.53
	3	26	20.42	6.34	20	19.50	4.07
Day 2	1	24	20.21	5.81	19	18.58	3.76
	2	24	20.17	5.17	25	18.88	4.56
	3	23	20.22	5.12	24	19.04	4.36
Day 3	1	23	20.91	7.22	21	18.52	3.50
	2	21	19.14	5.42	17	19.12	3.69
	3	15	19.53	4.53	18	17.56	2.81

Patients In- Study		HFOV n	CV n
Day 1	pre	75	73
	1	74	71
	2	73	68
	3	68	65
Day 2	1	66	65
	2	64	60
	3	60	59
Day 3	1	58	56
	2	50	52
	3	46	51

The In-Study Table identifies the number of patients who had not exited the study at each measurement time. The difference between this number and the n for the measurements represents data that was not available for an enrolled patient at that measurement time.

As indicated elsewhere a repeated measures analysis of variance identified statistically significant differences between ventilators for only PaCO₂, PaO₂/FiO₂ and pulmonary capillary wedge pressure (PCWP).

Poolability and Discontinuance of Treatment Analysis

The statistical review of the data submitted with the PMA reflected two questions relative to the analyses performed for the data submitted. These two comments questioned evidence to support the poolability of data, and interest in a discussion and statistical review of the effects of discontinuation of therapy on the interpretation of the data. The following addresses both these questions.

Poolability

Table 1 below is a tabulation of the enrollment and outcome by ventilator from each of the 10 centers that recruited patients. The two outcomes included are death within 30 days and the combined variable, death or chronic lung disease (D.CLD) at 30 days. Some variation in overall outcome between the centers would be expected due to chance and patient population (e.g., medical vs. trauma). Statistical analysis reveals that there is no significant difference in the overall rate of death (chi-squared $p= 0.432$) or D.CLD. (chi-squared $p= 0.097$) among centers.

Site	HFOV			CV			% Risk	% Risk	RR (H/C)	RR (H/C)
	n	Death	D.CLD	n	Death	D.CLD	Death	D.CLD	Death	D.CLD
1	10	4	8	10	6	9	50%	85%	0.67	0.89
2	11	5	11	10	3	6	38%	81%	1.52	1.67
3	9	5	7	10	8	10	68%	89%	0.69	0.78
4	8	3	6	7	4	6	47%	80%	0.66	0.88
5	1	0	0	0	0	0	0	0		
6	6	1	5	5	3	3	36%	73%	0.28	1.39
7	7	2	5	10	5	6	41%	65%	0.57	1.19
8	4	0	2	3	1	2	14%	57%	0	0.75
9	14	6	10	13	5	7	41%	63%	1.11	1.33
10	5	2	5	5	3	5	50%	100%	0.67	1.0

Table 1. D.CLD is the combined variable, death or continued respiratory support at 30 days. Died is also the outcome at 30 days. RR is the relative risk of HFOV/CMV (H/C)

The relative risk for the two outcomes (HFOV/CMV) is also included in the table. Statistical analysis reveals that there is no significant difference in the odds ratio of Death or D.CLD among centers. (Mantel-Haentzel $p= 0.142$, and $=0.513$). The risk of death was greater for HFOV treatment than for CMV treatment at only two of the 10 centers, which is consistent with the trend toward a survival benefit for HFOV in the pooled data. The risk of D.CLD among the centers is evenly balanced, consistent with no statistical trend in the pooled data. The two centers that enrolled the most patients (48 patients) had the worst HFOV outcomes relative to CMV. However at the next 2 highest enrolling centers (39 patients) the HFOV outcomes are quite favorable. The trend toward reduced mortality with HFOV and comparable D.CLD is also reflected in the results from the smaller centers.

One third of the patients were enrolled at three centers outside the US. These three centers in Toronto are all University affiliated hospitals with a standard of care similar to the US. The studies were conducted at these sites consistent with the protocol and US Investigational Device Regulations.

There being no statistically identified site inhomogeneity, no subjectively observable site bias, or inconsistency of standard of care in the foreign data we can see no reason not to pool the data for analysis

Patient Discontinuation

A small percent of the patients (14%) exited the study early, prior to the primary anticipated exits (death, weaned from mechanical ventilation, or 30 days on study). Only 3 of these 20 patients were alive without respiratory support at 30 days (2/8 HFOV, 1/12 CMV). An additional 8 still required respiratory support at 30 days (2/8 HFOV, 6/12 CMV). The 30 day mortality in these CMV patients was 42% (5/12) slightly lower than the 52% seen in all CMV patients. In contrast, the 30 day mortality seen in these HFOV patients was 50% (4/8) slightly higher than the 37% seen in all HFOV patients.

This study was designed with the outcomes to be analyzed based on an intention to treat. The protocol did permit patients in the experimental HFOV arm, who meet specific treatment failure criteria to be returned to conventional ventilation if the attending physician thought it was in the patient's interest. This occurred in 4 of the 8 cases (mortality 2/4). Interestingly, many of the early exits from the CMV arm (7/12) went on to receive high frequency ventilation (mortality 3/7). One conservative approach to dealing with early discontinuations is to treat them as deaths (failures). In the intention to treat analysis the mortality in the HFOV group was 37% (28/75) and 52% (38/73). If the discontinued patients were pooled with the deaths the outcome would be 48% (36/75) for HFOV and 68% (50/73) for CMV. The later proportions are significantly different ($p = 0.012$). An alternative approach would be to discard all early discontinuations from the analysis. This approach also results in a significant difference. (HFOV 24/67, CMV 33/61, $p=0.047$). There was a strong trend toward reduced mortality in the HFOV treatment that approached significance ($p= 0.072$).

The two approaches to making adjustments for patients that discontinued the study early each reflect an improvement in the statistical significance of improved mortality from HFOV treatment. This suggests that there was some bias in the study as a result of early discontinuation, and speculatively, that bias might have been a result of successful HFOV rescue of CMV assigned patients. This observation further supports the overall conclusion that HFOV is at least as effective as CMV.

Diaphragm Rupture Analysis

Statement:

SensorMedics was requested to explain why failure of the driver diaphragm does not affect the safety and effectiveness of this device, and describe how the risk to the patient from an intra-procedure failure of the device is mitigated. SensorMedics was also asked to comment regarding the MTBF of the driver and the subsequent rebuilding frequency.

Response:

Failure (rupture) of the driver diaphragm does not occur catastrophically nor has our experience indicated that a diaphragm rupture causes the 3100B to fail catastrophically or to instantaneously cause a detriment in its ability to deliver the specified tidal volume. Diaphragm ruptures occur directly from wear over long periods of operation, not suddenly. In the 3100B clinical trials all of the reported diaphragm ruptures were observed after patient treatment had been concluded, when replacing patient circuit/bellows assemblies or in setting up and verifying correct performance before placing another patient on the 3100B. During these clinical trials, there were no reports of actual intra-procedure failures of the 3100B caused by driver diaphragm ruptures, nor, based on our experience and life testing, is it likely that a driver diaphragm rupture would/cause an intra-procedure device failure. SensorMedics, throughout supplement 14, has utilized torn diaphragms as a measure of MTBF. It should be noted, however, that the torn diaphragm did not cause a device failure. While the driver should be replaced once a torn diaphragm is discovered, the ventilator can continue to perform adequately for quite some time. SensorMedics has conducted driver reliability tests and has found the average mean time between diaphragm tears to be in excess of 2000 hours, and has therefore included a recommended driver rebuild frequency of 2000 hours.

To ensure continued performance of the Ventilator in the event of a diaphragm tear, SensorMedics has conducted tests on a driver having a typical rupture; its performance (tidal volume versus frequency and power setting) was no different than that of a new driver as tested in a new 3100B. A driver with a diaphragm rupture can operate completely normally for a lengthy period, many hours if not several days, allowing operators more than adequate time to both discover the rupture and, as necessary, switch to another 3100B or alternate method to continue patient treatment.

Nevertheless, if a major intra-procedure driver failure from a diaphragm rupture were to occur, it would be preceded by a period in which the operating temperature of the driver would increase to higher levels, thus activating over-temperature indicators to alert operators. Also, other alarms would be activated as the driver's performance began to slowly reduce. This reduced performance would result in decreases in mean airway and/or oscillatory pressures.

Site #		HFOV	CV	Total	Rate/month
1	Wilford Hall / BAMC	10	10	20	.53
2	Toronto Hospital	11	10	21	.62
3	Wellselley / Mt Sinai	9	10	19	.79
4	Maine Medical Center	8	7	15	.48
5	Bronson Methodist	1		1	
6	Loma Linda	6	5	11	.44
7	University Virginia	7	10	17	.85
8	Alleghany General	4	3	7	.30
9	Barnes Jewish-Washington Univ	14	13	27	1.50
10	Sunnybrook	5	5	10	.83
	Total	75	73	148	

Table 1

In the original submission (page 162), the patients from Maine Medical Center were switched in the above columns and the single patient from Bronson Methodist was not included in the total column.

6. Study Site Information

SITES:

IRB's:

Key Dates/Info:

1.

Wilford Hall Medical Center
Lackland AFB, TX
78236-5300

PI

Stephen Derdak DO

Darlene Castro
Clinical Research Div.
AF Medical Operations
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Bolling AFB,DC 20332

IRB Approval: 8/5/97
First subject: 10/26/97
Patients enrolled: 20

2.

The Toronto Hospital
200 Elizabeth Street
Toronto, Ontario
M5G2C4/Canada

PI

John Granton, MD

M Elvis
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CCRW 2-814
The Toronto Hospital
200 Elizabeth Street
Toronto, Ontario
M5G2C4, Canada

IRB approval: 7/7/97
First subject: 12/11/97
Patients enrolled: 21

3a.

The Wellesley Hospital
160 Wellesley St. East
Toronto, Ontario
M4Y1J3, Canada

PI

Thomas Stewart MD

E Keystone
Research Institute
The Wellesley Hospital
160 Wellesley St. East
Toronto, Ontario
M4Y1J3, Canada

IRB approval: 8/28/97
First subject: 12/4/97
Patients enrolled: 5
ICU closed and study
terminated: 6/1/98

3b.

Mount Sinai Hospital
600 University Avenue
Toronto, Ontario
M5G1X6/Canada

PI

Thomas Stewart, MD

Bill Wilson
Mount Sinai Hospital
600 University Avenue
Toronto, Ontario
M5G1X6/Canada

IRB approval: 10/13/98
First subject: 8/25/98
Patients enrolled: 14

4.

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04102

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Sandy Bagwell, MD

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S. Portland, ME 04106

IRB approval: 6/25/97
First subject: 1/28/98
Patients enrolled: 15

5.

Bronson Medical Center
252 E. Lovell Street
Kalamazoo, MI
49007-5345

PI

Bill Shillingwall DO

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252 E. Lovell Street
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IRB approval: 8/14/97
First subject: 3/14/98
Patients enrolled: 1
Study terminated:
10/30/98

SITES:**6.**

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 92354

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7.

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Key Dates/Info:

IRB Approval: 7/8/98
 First subject: 10/8/98
 Patients enrolled: 11

IRB approval: 10/13/98
 First subject: 3/16/99
 Patients enrolled: 17

IRB approval: 8/21/98
 First subject: 3/30/99
 Patients enrolled: 7

IRB approval: 8/7/99
 First subject: 5/20/99
 Patients enrolled: 27

IRB approval: 1/27/99
 First subject: 11/1/99
 Patients enrolled: 10

In the original submission (pages 153-154), The Wellesley Hospital and Mount Sinai Hospital in Toronto were listed separately. The two ICU's data were treated as a single center when The Wellesley Hospital closed and the personnel and PI transferred to Mt. Sinai. The data for these units was combined in the analysis. There were also two institutions incorrectly labeled by their identified number.

Table 8: Status at 1 month and 6 months

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

In the original submission (page 164) the percentage for survival in the CMV group at 6 months was entered as 26%. The correct number is 38%.

Conclusions Drawn From Comparisons of ARDS Studies with MOAT2

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 determine the benefit of HFOV in the management of ARDS, the data from the HFOV treated patients must be considered both in comparison with the control subjects as well as compared with other published ventilator trials in similar patient populations. Specific characteristics associated with higher risk of mortality include patient age^{1,3,10}, specific ARDS triggering etiologies^{3,8-11}, severity of hypoxemia^{3,10-13}, existing air leaks¹⁴, immune compromised⁴, and ventilator strategies that use high volumes and pressures^{5,6}.

The two populations for the treatment and control arms in this study were very well balanced (tables 1a and 1 b) and contained no statistically significant differences.

Table 1a. Baseline Patient Characteristics		
	HFOV	CMV
Number	75	73
Age (years)	48 (17)	51 (18)
Percent > 70 years age	15%	16%
Weight (kg)	78 (25)	81 (26)
Gender (% male)	52%	64%
Apache II Score	22 (6)	22 (9)
ARDS Trigger:		
Sepsis Syndrome	47%	47%
Pulmonary Infection	19%	16%
Trauma	21%	18%
other	13%	19%
Confounding Dx		
Air leak	16%	19%
Immune compromise	12%	14%
5 or more days preCMV	22%	36%

Continuous data presented as mean std dev). Discrete data presented as %. PaO₂ denotes the partial pressure of arterial oxygen (mm Hg) and FiO₂ the fraction of inspired oxygen. Oxygenation Index is the mean airway pressure x FiO₂ x 100 divided by the PaO₂. None of the differences between the groups was statistically significant. APACHE II score is a multivariate assessment of patient severity.

Table 1b. Baseline Physiological Parameters

	HFOV	CMV
number	75	73
PIP (cm H ₂ O)	39 (7)	38 (8)
Mean Paw (cm H ₂ O)	22 (5)	23 (6)
PEEP (cm H ₂ O)	13 (3)	14 (3)
Respiratory rate (/min.)	18 (5)	20 (6)
Tidal Volume (cc/kg)	8.2 (3)	7.8 (3)
FiO ₂	.71 (.19)	.72 (.19)
PaO ₂	76 (20)	73 (18)
PaCO ₂	44 (12)	45 (12)
PH	7.37 (.09)	7.34 (.11)
PaO ₂ /FiO ₂	114 (37)	111 (42)
Oxygenation Index	24 (15)	27 (19)
Apache 2	22 (6)	22 (9)

Continuous data presented as mean (stdev). PIP denotes the peak inspiratory pressure, PEEP the positive end expiratory pressure. PaO₂ denotes the partial pressure of arterial oxygen and FiO₂ the fraction of inspired oxygen. PaCO₂ the partial pressure of arterial carbon dioxide. Oxygenation Index is the mean airway pressure x FiO₂ x 100 divided by the PaO₂. None of the differences between the groups was statistically significant.

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 relative 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 only 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. None of these differences reached statistical significance.

The largest 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.⁵ This study compared patients managed with 6 ml/kg tidal volume as compared with patients managed with 12 ml/kg. They reported a 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 (a 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 define by a PaO₂/FiO₂ (P/F) ratio <300 torr.⁵ 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 cmH₂O. As a result, the severity of the patients in the MOAT2 trial overall was very different than in the NIH trial. The mean P/F in the NIH trial was 136 and in the MOAT2 trial it was 112. In support of the differences in severity of disease, the MOAT2 patients had P/F values recorded on a minimum PEEP of 10 cmH₂O. A prior

publication evaluating the influence of a P/F <150 with a PEEP of 5 cmH2O on mortality in ARDS reported that if the P/F was >150, the mortality was 23%.³ However, if the P/F on 5 cmH2O was <150, the mortality rose to 68%. Similar increases in mortality have been reported with P/F's less than 100.⁷ Additionally, the mean Oxygenation Index in the NIH trial was 12 versus 25 in MOAT2.

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. Our own analysis of prior HFOV data and consistent with other conventional ventilation data, presence of sepsis has a negative impact on survival and/or morbidity.^{4,8-11} 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. However, the MOAT2 strategy for conventional ventilation was not as high a volume target as was used in the control arm of the NIH trial. The targeted tidal volume in MOAT2 was at 6-10 ml/kg of actual body weight. As a result though of the NIH report, a post-hoc analysis of the mortality in the control arm was performed with recalculation of delivered tidal volume per kilogram of *ideal body weight*. Analysis of the mortality in the conventionally ventilated patients, stratified by ideal body weight follows in table 2.

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 2. MOAT2 Control Arm mortality by ideal body weight (IBW)

This analysis was limited by the small number of patients in the groups. However, the trend tended to demonstrate 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, duration of pre-entry mechanical ventilation, etc.).

With the assistance of the ARDSnet data group, we further explored their data to understand the differences between their outcomes and the MOAT2 control group. We were able to select patients from both the low and high stretch groups who entered the NIH trial with PEEP's greater than or equal to 10 cmH2O, with group average incidences of sepsis at 47% and median P/F ratios in both groups at 112 so as to match the MOAT2 control group for those parameters. The 28 day mortality from these two sicker groups of patients rose slightly to 34.9 and 40.9 percent respectively.

To further explore the mortality in the control arm, we additionally reviewed several other ARDS trials from the literature where there was no difference in outcome. These included studies by Stewart¹⁵, Brochard¹⁶, and Brower¹⁷. Table 3 reflects the data from these trials.

	NIH Control	Stewart Control	Brower Control	Brochard Control	MOAT2 Control	Stewart Study	Brower Study	Brochard Study
Vt/kg IBW	11.8	10.7	10.2	10.3	10.2	7	7.3	7.1
PEEP	8.6	7.2	8.3	10.7	14	8.6	9.5	10.7
Apache 2		22		17	22	22		19
Apache 3	84		85				91	
PaO2/FiO2	134	145	150	155	111	123	129	144
Pre-Vent Days	36 hrs ARDS	<1	24 hrs ARDS	2.7	4.4	<1	24 hrs ARDS	2
Mortality	40	47	46	38	52	50	50	47

Table 3. Comparison of ARDS trials

In reviewing this data so as to understand possible causes of the differences in outcomes between trials, it is evident that the patients in the MOAT2 trial were on conventional ventilation for a longer period prior to entry into the trial and had lower P/F's than any other trial.

The mortality in the MOAT2 conventional ventilation arm was not largely different from the mortality in other ARDS trials. Of interest when taken to an extreme of the trends from table 3, considering that the NIH control arm had a mortality of only 40% at a tidal volume of 12 ml/kg, and that all of the other trials also had the lowest mortalities in their control (higher tidal volume) arms, one could hypothesize that either large or small tidal volumes are protective and only moderate tidal volumes are harmful. There is no evidence to support this argument so that other mechanisms and/or patient populations selection most likely explain these differences. This data is only one more reason why comparisons of trials are extremely difficult and that the data for each trial must stand on its own.

To further explore the possibility of differences in treatment effect of HFOV in patients of varying initial severity of oxygenation, we conducted a retrospective analysis of PaO2/FiO2, oxygenation index (OI), and peak inspiratory pressure at entry, stratified at their median levels. Interestingly, this post-hoc stratification of patients based on initial peak airway pressure at enrollment, but not PaO2/FiO2 or OI, showed a significant difference in mortality outcome between HFOV and CV.

	HFOV	CV
N	38	42
PIP	33	32
PEEP	13	13
Vt (ml/kg)	8.5	7.9
PaO2/FiO2	115	120
Sepsis	45%	45%
Median pre-CV days	1.5	1.9
Mortality 30 days	26%	52% (p < 0.018)
Mortality 6 months	39%	62% (p < 0.045)

Table 4. Patients stratified by median peak airway pressure (≤ 38 cm H2O) at time of enrollment.

A post-hoc subgroup analysis of patients (table 4) stratified by median enrollment peak airway pressure was then performed. There were no differences between the groups

as related to entry data, however the analysis revealed a statistically significant reduction in 30-day mortality in the HFOV treatment group compared with the CV group (26% versus 52%; $p=0.018$), which persisted at 6 months (39% versus 62%; $p=0.045$). The mortality in this group of patients was 16 percent relatively lower than the overall NIH low stretch arm mortality (31%) and 26 percent relatively lower than the matched population (34.9%). In contrast, there was no subsequent mortality difference between treatment groups if baseline peak inspiratory pressure was greater than the median. The groups in the higher peak inspiratory pressure groups were not evenly matched and therefore no interpretation of that data is meaningful.

Survival curves showing the proportion of survivors for all patients enrolled (1a) and the patients with PIP 38 or lower prior to enrollment (1b) are in the following graphs. Dark Black lines represent HFOV patients and Light Grey lines CV patients. No enrolled patients died after 89 days. The difference in survival rate in 1a did not reach significance censored at 30 days or at 90 days ($p=0.057, 0.078$ respectively). However both were significantly different in 1b ($p=0.019, 0.026, 30$ days and 90 days respectively)

Figure 1a

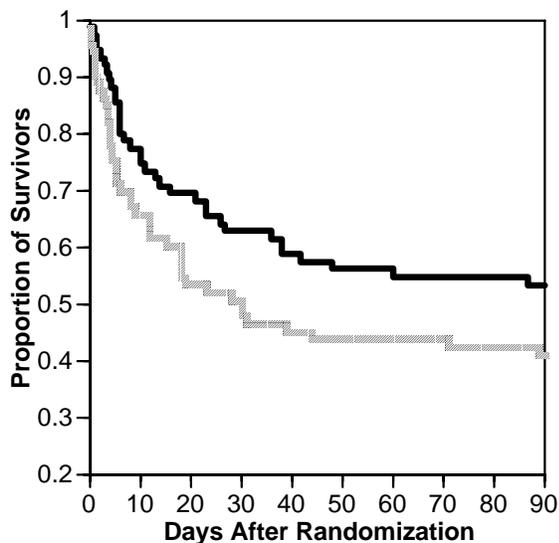
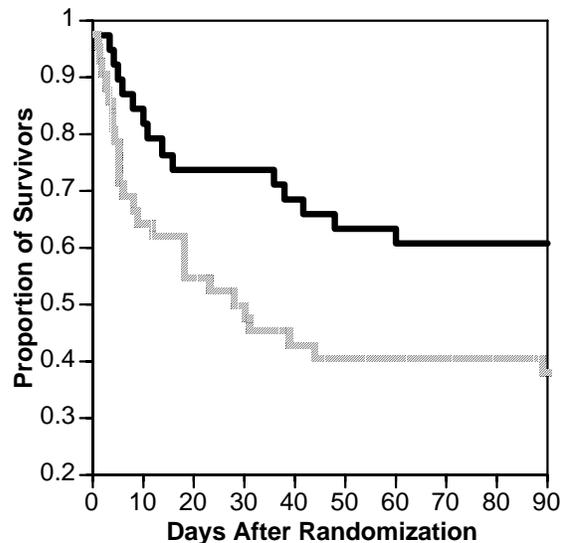


Figure 1b



Conclusions:

We believe that comparisons between trials are very difficult to interpret; that each randomized controlled trial must be interpreted within the patient populations from each trial; that multiple factors can explain differences in outcomes between trials; and while the differences in mortality at 30 days (29%) did not reach statistical significance, considering the 6 month status, this may be interpreted as supporting HFOV effectiveness. This is further supported by the post-hoc analyses which do show significant differences ($p < 0.018$). We submit 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.

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