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Prophylactic Use of High-frequency Percussive Ventilation in Patients with Inhalation Injury

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Death and the incidence of pneumonia are significantly increased in burn patients with inhalation injury, despite application of conventional ventilatory support techniques. The effect of high-frequency percussive ventilation on mortality rate, incidence of pulmonary infection, and barotrauma were studied in 54 burn patients with documented inhalation injury admitted between March 1987 and September 1990 as compared to an historic cohort treated between 1980 and 1984. All patients satisfied clinical criteria for mechanical ventilation. High-frequency percussive ventilation was initiated within 24 hours of intubation. The patients' mean age and burn size were 32.2 years and 47.8%, respectively (ranges, 15 to 88 years; 0% to 90%). The mean number of ventilator days was 15.3 ± 16.7 (range, 1 to 150 days), with 26% of patients ventilated for more than 2 weeks. Fourteen patients (25.9%) developed pneumonia compared to an historic frequency of 45.8% ($p < 0.005$). Mortality rate was 18.5% (10 patients) with an expected historic number of deaths of 23 (95% confidence limits of 17 to 28 deaths). The documented improvement in survival rate and decrease in the incidence of pneumonia in patients treated with prophylactic high-frequency ventilation (HFV), as compared to a cohort of patients treated in the 7 years before the trial, indicates the importance of small airway patency in the pathogenesis of inhalation injury sequelae and supports further use and evaluation of HFV.

DURING THE PAST three decades, improvements in burn wound management, infection control, and metabolic support increased the survival of thermally injured patients. Inhalation injury, however, continues to be a significant comorbid factor in such patients, and its treatment has been improved little by the use of conventional means of pulmonary support. Bacterial pneumonia, which historically occurred in 38% of all patients with inhalation injury but in only 8% of those without such injury, continues to be the leading cause of morbidity and death. The combination of inhalation injury and pneumonia exert independent but additive effects on the age-related death attributable to burn size.[1]

Current treatment for inhalation injury is supportive and includes aggressive pulmonary toilet, mechanical ventilatory support when indicated, and aggressive treatment of pneumonia when diagnosed. In an ovine model, we showed that the major insult after smoke injury (as indexed by early postinjury ventilation/perfusion (VA/Q) mismatching and histopathologic findings) is the obstruction and collapse of small airways leading to distal atelectasis and subsequent pneumonia.[2] Experimental and clinical data suggest that high-frequency ventilation (HFV) may be beneficial in recruiting and stabilizing such collapsed diseased lung segments.[3-12] In addition some investigators reported improved clearance of secretions from the tracheobronchial tree with the use of HFV.[13] These observations support the hypothesis that HFV, by preventing alveolar collapse and improving secretion clearance, may be beneficial in patients with inhalation injury.

We previously reported a small cohort of 10 patients with inhalation injury requiring mechanical ventilatory support in whom the prophylactic use of high-frequency percussive ventilation (HFPV) appeared to reduce the incidence of pneumonia.[14] This report extends our observations to 54 patients in whom HFPV was used in a prophylactic manner in an attempt to decrease the incidence of pneumonia and improve survival rate.

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Methods

Patient Population

All adult patients admitted to the United States Army Institute of Surgical Research between March 1987 and September 1990 with a diagnosis of inhalation injury were eligible for enrollment in this study. Inhalation injury was confirmed in each patient by bronchoscopy and/or[133] Xenon ventilation–perfusion lung scan. The presence of carbonaceous debris beneath the true vocal cords, mucosal erythema, and ulceration were used to define moderate to severe inhalation injury. Patients with a positive[133] Xenon scan and negative bronchoscopy were determined to have mild inhalation injury. These criteria were established in our earlier review.[1] After meeting the entrance requirements listed in Table 1 and meeting the requirements for intubation and mechanical ventilatory support listed in Table 2, informed consent was obtained from each patient and HFPV initiated for pneumonia prophylaxis.

High-frequency Percussive Ventilation

Description of the high frequency percussive ventilator used in this study has been published.[14] Briefly, HFPV was delivered by a high-frequency pulse generator with gas from the high-frequency pulse generator delivered through a nongated sliding venturi to a standard endotracheal tube. The venturi entrains humidified gas from a fresh bias gas flow provided from the ventilator. The system combines serial high-frequency sub-dead space volume breaths with a variable inspiratory:expiratory (I:E) ratio. Periodic interruption of the high-frequency pulsatile flow is programmed to allow return of airway pressure to baseline continuous positive airway pressure (CPAP). The duration of the percussive phase and of the return to baseline phase are adjusted to manipulate oxygenation and CO_2 elimination. Peak airway pressure also can be varied independently to maintain CO_2 clearance. The frequency of sub-dead space breaths can range between 1.5 and 15 hertz. FIO_2 and PEEP are adjusted to maintain O_2 saturation greater than 90%.

All patients were placed initially on a conventional mechanical ventilator. In those patients intubated elsewhere, such support was of less than 24 hours duration, and all patients were converted to HFPV within 1 hour of admission. The patients intubated at our institution received conventional ventilation during admission processing but were converted to HFPV within 1 hour. After placing the patient on HFPV, standard ventilator settings were used as a baseline and then altered as indicated by arterial blood gas determinations, pulse oximetry, and end tidal CO_2 monitoring. The duration of the percussive phase was set at 2 seconds, with a rate of return to baseline approximately 2 less than the intermittant mandatory ventilation (IMV) setting required to maintain normal acid-base balance on conventional mechanical ventilation. Peak airway pressures were set at 5 cm H_2O less than those developed when a conventional volume-limited ventilator was set to deliver a tidal volume of 12 to 15 mL/kg. The FIO_2 and PEEP were maintained initially at the same levels as on conventional mechanical ventilation. The frequency of the sub-dead space tidal breaths was initially set at 10 hertz. After stabilization for approximately 30 minutes, arterial blood gas measurements were obtained and adjustments made as indicated. The goal of ventilator therapy was to maintain oxygenation and ventilation at the lowest possible peak airway pressure and fractional inspired oxygen concentration. Patients were weaned and extubated according to standard criteria.

TABLE 1. *Study Entrance Criteria*

Inhalation injury documented by bronchoscopy or Xenon lung scan
Clinical requirement for ventilatory support
Admission within 48 hours of injury
Older than 15 years

TABLE 2. *Requirements for Mechanical Ventilatory Support*

1. Respiratory rate > 35/min
2. Vital capacity < 15 mL/kg
3. Inspiratory force < 25 cm H_2O
4. $PAO_2/FIO_2 < 200$
5. $PCO_2 > 50$ mmHg
6. $Vd/Vt > 0.6$
7. Upper airway edema
8. $PCO_2 < 50$ mmHg but progressively increasing
9. Increased work of breathing

Diagnosis of Pneumonia

The diagnosis of pneumonia was based on standard criteria used in this institution for the past decade. Patients with sputum leukocytosis (more than 25 white blood cells per high-power field), lack of oropharyngeal contamination (less than 10 squamous cells per high-power field), a predominant organism on culture, and an infiltrate on chest roentgenograms were diagnosed as having pneumonia.

Data Analysis

The incidence of pneumonia and death in the study patients was compared with predicted values based on two previous studies. The first predictor used relates burn size and age to death for all patients admitted to the Institute of Surgical Research between January 1980 and December 1986. The second predictor used as a basis for comparison relates burn size, age, the presence of inhalation injury and the occurrence of pneumonia to death

TABLE 3. *Burn Mortality Predictors*

$$\text{Predicted Mortality (PM)} = \frac{e^Y}{1 + e^Y}$$

I. Logistic equation relating burn size and age to mortality: 1980–1986

$$Y = -4.8216 + 0.10299\,(\text{PCTB}) - 0.18879\,(\text{Age}) + 0.50873\,(\text{Age}^2/100) - 0.27915\,(\text{Age}^3/10{,}000)$$

II. Logistic equation relating burn size, age, inhalation injury, and pneumonia to mortality: 1980–1984

$$Y = -3.4953 + 0.09589\,(\text{PCTB}) - 0.1988\,(\text{Age}) + 0.4478\,(\text{Age}^2/100) - 0.20314\,(\text{Age}^3/10{,}000) + 0.59056\,(\text{II}) + 0.92530\,(\text{PNeu})$$

PCTB, percentage of total body surface burned.
II = −1.0 if inhalation injury absent; +1.0 if inhalation injury present.
PNEU, −1.0 if pneumonia absent; +1.0 if pneumonia present.

in patients admitted between 1980 and 1984. The incidence of pneumonia in this latter patient population also was used for comparison purposes. Solution of the logistic equations listed in Table 3 provide the exponents for use in calculating the two values for predicted death.

Results

Patient Population

Fifty-four patients meeting the entrance criteria were enrolled in the study. Routine demographic data are included in Table 4. Ten patients died, for a mortality rate of 18.5%. The distribution of patients by burn size demonstrates that 50% of the patients had burns ranging between 30% and 60% of the body surface, which is the group of patients in whom inhalation injury has been reported to have its greatest impact on death (Fig. 1). Segregation of the patients by outcome revealed the expected differences between the two groups (Table 5); nonsurvivors were older and had larger burns and a greater incidence of pneumonia. Fifty-two of the fifty-four patients were diagnosed as having inhalation injury by bronchoscopy. The two patients with negative bronchoscopy but positive ^{133}Xenon scans developed severe adult respiratory distress syndrome (ARDS) in the first postburn week, necessitating mechanical ventilatory support.

TABLE 4. *Demographic Data*

Age	32.2 ± 1.8 (15–88)*
TBSB	47.8 ± 3.1 (0–90)
Sex	40 male, 14 female
Days on ventilator	15.3 ± 2.2 (1–150)
Bronchoscopy positive	96.3%
Incidence of pneumonia	25.9%
Mortality	10/54 (18.5%)

* X ± SEM (range).
TBSB, total body surface burn.

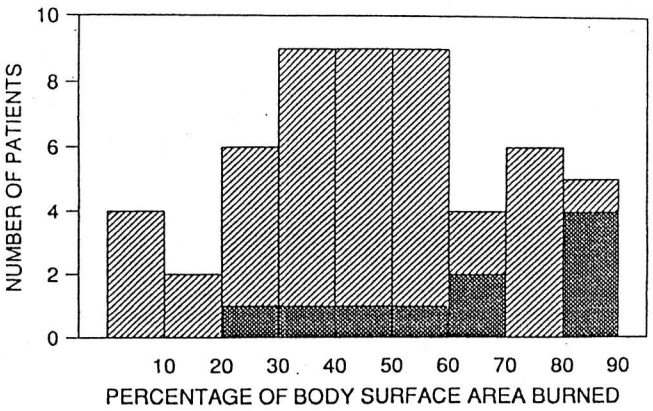

FIG. 1. Distribution of burn size for the 54 patients in the study. Of note is that 50% of the patient burn sizes are between 30% to 60% of the body surface area, which is the group of patients in whom inhalation injury exerts its greatest influence on mortality. Survivors are reported by the crossed bars, and nonsurvivors by the crosshatched bars.

Historically 45.8% of patients with positive bronchoscopy and 19.5% of patients with negative bronchoscopy but a positive ^{133}Xenon lung scan developed pneumonia. Based on that experience, 25 of the study patients would have been expected to develop pneumonia during hospitalization. Pneumonia was diagnosed in only 14 (26%) of the patients in this study, an incidence differing significantly from that of the comparison cohort ($p < 0.003$).

Actual Versus *Predicted Death*

Ten deaths occurred in this group of patients, for an observed mortality rate of 18.5%. To determine whether HFPV influenced outcome in this group of patients, we compared this observed mortality rate with two mortality predictions generated from patient data from this institution, as noted above. The first, based on burn size and age, related death in all patients admitted to this institution between January 1980 and December 1986, predicts the deaths of 19 patients (35%) in the study population, with a 95% confidence interval of 13 to 25 deaths. The second, based on burn size and age, related death in conjunction with the additive effects of inhalation injury and pneumonia and generated from patient data between January 1980 and December 1984, predicts 23 deaths (42.6%) with

TABLE 5. *Comparison of Survivors and Nonsurvivors*

	Survivors	Nonsurvivors	
Age (years)	29.6 ± 1.5*	43.3 ± 6.5	$p < 0.05$
TBSB	43.7 ± 3.2	65.3 ± 7.1	$p < 0.01$
Incidence of pneumonia	20.5%	50%	$p < 0.05$

* Mean ± SEM.
TBSB, total body surface burn.

a 95% confidence interval of 17 to 28 deaths. Thus the mortality rate in this cohort of patients was significantly less than that predicted by either technique ($p < 0.05$) (Table 6).

The causes of death in those patients who died are listed in Table 7. Of the 10 deaths, four were from pulmonary failure. One patient could not be ventilated and oxygenated and was changed to conventional ventilatory support with the same result. Three patients developed progressive pulmonary failure and died on postburn days 12, 43, and 50, respectively. Of the remaining 6 patients, 2 were resuscitation failures who died with severe inhalation injury, 1 patient extubated himself on postburn day 7 and died of cardiopulmonary arrest despite an emergency tracheostomy, and 1 patient was removed from the study by his attending surgeon. Two patients died from cerebrovascular accidents after they were extubated for 30 and 45 days, respectively.

Ventilator complications were rare. Two patients developed severe necrotizing tracheobronchitis. It could not be determined whether this was secondary to the ventilator or the disease process itself. Barotrauma occurred in three patients. Two developed significant subcutaneous emphysema and one patient developed bilateral pneumothoraces requiring tube thoracostomies.

Discussion

The combination of cutaneous thermal injury and inhalation injury results in a significantly higher mortality rate than that attributable to cutaneous thermal injury alone. This additive effect of inhalation injury on death is most apparent in patients in whom predicted mortality attributable to age and burn size ranges from 40% to 60%. Inhalation injury also results in a marked increase in the incidence of bacterial pneumonia. As previously stated, only 8.8% of patients with thermal injury but without inhalation injury develop pneumonia during their course of treatment. The presence of inhalation injury, whether diagnosed by bronchoscopy or ^{133}Xenon scan, historically resulted in a 38% incidence of pneumonia, and the combination of inhalation injury and pneumonia has an even more drastic effect on outcome, increasing the mortality rate by as much as 60%.[1]

TABLE 6. *Actual* Versus *Predicted Outcome*

Predictor	Predicted Deaths	95% CL	Observed
#1 (1980–1986)	19	13–25	10
#2 (1980–1984)*	23	17–28	10

* This predictor includes the impact that inhalation injury and pneumonia have on outcome.
CL, confidence level.

TABLE 7. *Cause of Death*

TBSB (%)	Age (years)	PBD	Cause of Death
90	32	01	Resuscitation failure
85	25	03	Resuscitation failure
59	40	07	Accidental extubation
36	59	40	Removed from study
47	29	50	SBE, CVA, 30 days after extubation
65	60	80	CVA, 45 days following extubation
89	25	12	Pulmonary failure
30	88	43	Pneumonia (*Staph. aureus*), pulmonary failure
64	49	01	Unable to ventilate
86	29	50	Pneumonia, Aspergillus wound infection

TBSB, total body surface burn; PBD, postburn day.

Ideally the optimal treatment of any disease should reverse the pathophysiologic process without causing further injury. When inhalation injury is severe enough to require conventional mechanical ventilatory support, such an outcome is not achieved. The pathophysiologic response to inhalation injury includes extensive tracheobronchial injury, which results in sloughing of the mucosal lining of the respiratory tract and leads to obstruction of small- and moderate-sized airways. In addition, the mucociliary transport mechanism is impaired, resulting in impaired clearance of secretions and the sloughed debris. Distal airway obstruction results in atelectasis and, in conjunction with the disruption of the endothelial and epithelial integrity of the alveolus, produces foci for the development of bacterial overgrowth and subsequent pneumonia. The combination of atelectasis, pneumonia, and airway obstruction produces significant derangement of ventilation–perfusion relationships.

Conventional mechanical ventilatory support does not reverse these processes, is not characterized by improved clearance of secretions, and may actually compound the existing injury.[15] Conventional volume-limited ventilation in patients with inhalation injury normally is instituted at a tidal volume of 12 to 15 mL/kg. With such a ventilatory setting, peak inspiratory pressures often are elevated during the resuscitative and fluid mobilization phase of care. Recently Tsuno[16] reported adverse pulmonary effects of volume-limited mechanical ventilation when peak inspiratory pressures exceed 30 cm of water in paralyzed, anesthetized healthy sheep. Animals ventilated with an FIO_2 of 40% and a tidal volume of 10 mL/kg, with peak inspiratory pressure less than 18 cm of water, showed no measurable deleterious changes in lung function or histopathology after 48 hours of support. Animals ventilated with larger tidal volumes, resulting in peak inspiratory pressures greater than 30 cm H_2O, demonstrated progressive deterioration in static lung compliance, functional residual capacity, and arterial blood gases. Severe pul-

monary atelectasis, increased wet lung weight, and an increase in the minimum surface tension of saline lung lavage fluid were noted at autopsy. These data indicate that even in normal healthy lungs, prolonged elevation of inspiratory pressures may result in injury.

If pneumonia develops after resuscitation, the requirement for increased inspired oxygen concentrations to achieve normoxia may result in increased pulmonary damage when infection is present. Coalson et al.[17] recently reported a synergistic effect of hyperoxia and infection resulting in significant pulmonary dysfunction and damage. In a primate model, the combination of 80% O_2 and Pseudomonas pneumonia was as injurious as 100% oxygen during an 11-day period, while 80% O_2 or pneumonia alone resulted in minimal dysfunction.

The reported beneficial effects of HFV (ventilator frequency greater than 60 breaths/minute and tidal volumes of less than anatomic dead space) include lower peak airway pressures than those generated by conventional ventilation, positive endotracheal pressure throughout the ventilatory cycle, increased functional reserve capacity, and more efficient pulmonary gas distribution.[18] Unfortunately each of the advantages claimed for specific high-frequency ventilators has been refuted in various reports.[9,10,12] If, however, a form of HFV could achieve some of these advantages and maintain oxygenation and CO_2 clearance at lower inspiratory pressures and fractional inspired concentrations of oxygen, it might be possible to provide ventilatory support and avoid the deleterious side effects of conventional support.

In evaluating clinical reports of HFV, the physician must recognize that there are several types of high-frequency ventilators, all with different characteristics and different potentially adverse effects. Furthermore one must differentiate between prophylactic use of the ventilator, as in this study, and therapeutic or salvage use of the high-frequency device for patients in whom conventional mechanical ventilatory support has failed. Many reports documented the effectiveness of short-term salvage use of HFV in patients with ARDS.[7,8] Our own previously reported experience demonstrated that the ventilator used in these studies could oxygenate and ventilate patients at lower airway pressures and inspired oxygen concentrations, but all the patients died despite improved pulmonary performance.[14] Other reports also failed to identify a survival advantage with the use of HFV as a salvage mode of ventilatory support.

In this study we used HFPV prophylactically in an attempt to avoid the adverse effects of mechanical ventilatory support while reversing or minimizing some of the pathophysiologic changes that occur after inhalation injury. Our data indicate that, as compared to a recent historic cohort, the use of HFPV resulted in a significant decrease in the incidence of pneumonia and a decrease in the number of deaths.

There are several problems inherent to the use of historic controls. The development of more sensitive diagnostic techniques resulting in the diagnosis of less severe injury could favorably bias the results of recent studies, although the diagnostic modalities and criteria have remained constant since 1976. It is generally accepted that during the past three decades, survival of all patients with thermal injury has improved. Even so the effects of inhalation injury and pneumonia on outcome have remained refractory to standard treatment, as indicated by the mortality predictor used at this institution. Furthermore the predictors used in this study introduce some bias against finding an improvement in outcome in the current study population as compared to the populations on which the predictors were based. The predictor that account for the effects of both burn size and age as well as pneumonia and inhalation injury on death was based on all patients with inhalation injury admitted during the years 1980 to 1984, regardless of whether they required mechanical ventilatory support. The present study population includes only the sickest patients with the most significant injuries, all requiring ventilatory support. Demonstration of a survival advantage in this group of patients compared to a group that included patients with less severe injury supports the hypothesis that HFPV has a significant, beneficial effect. In short it seems reasonable to assign a major portion of the decrease in incidence of pneumonia and improvement in outcome of the study patients to the ventilatory support used.

Only two other published studies in the literature evaluated the prophylactic use of HFV in patients requiring ventilatory support as prophylaxis against ARDS. In 1986 Carlon[18] reported a study of 309 patients who were randomized to high-frequency jet ventilation or conventional ventilatory support. All patients who were admitted to the intensive care unit and who were at risk for the development of pulmonary failure were entered into the study. The use of high-frequency jet ventilation resulted in lower peak airway pressures but did not decrease the 4% incidence of barotrauma or improve the overall outcome as compared to conventional support. In 1990 Hurst et al.[19] reported a study of 113 patients at risk for the development of ARDS who were randomized to receive ventilatory support with HFPV or conventional mechanical ventilation before the onset of ARDS. Changes in ventilator settings were made to achieve the same therapeutic endpoints in both groups of patients. There was no difference in the percentage of patients who developed ARDS in either group. In the patients who developed ARDS, HFV achieved therapeutic endpoints at lower peak airway pressures, lower positive end expiratory pressures,

and an increased inspiratory time as compared to the conventional group. There was, however, no difference in the incidence of barotrauma or outcome in those patients. Both of these studies involved heterogeneous patient populations, in which the etiology of respiratory failure was diverse, usually a consequence of a systemic insult that resulted in diffuse parenchymal disease and dysfunction. This type of insult is quite distinct from that seen after smoke inhalation in both humans and animal models, in which edema resolves rapidly after resuscitation and repair of the airway mucosa typically occurs within 14 to 21 days.

The exact mechanism by which HFPV achieved the results reported in this study is not known. We hypothesize that the ability to maintain ventilation and oxygenation at lower peak airway pressures and inspired oxygen concentrations may decrease the iatrogenic injury that occurs with conventional mechanical ventilatory support. Extrapolation of the data reported by Tsuno[16] to humans would indicate that ventilation at lower peak airway pressures offers significant advantage, especially in lungs that have already been injured. In addition several studies now suggest that asymmetric high-frequency breaths improve clearance of secretions, results that have been obtained with high-frequency jet ventilators and high-frequency oscillators, both *in vitro* and *in vivo*.[13,20–22] Our clinical experience supports this finding. Patients with severe inhalation injury treated prophylactically with high-frequency percussive ventilation typically are found, by bronchoscopic examination, to have large deposits of secretions at the tip of the endotracheal tube. After removal of these secretions, the main stem bronchi and distal airways often are patent and free of pathologic secretions. The documented improvement in survival and the decrease in the incidence of pneumonia in patients treated with prophylactic HFPV, as compared to the recent historic cohort, indicate the importance of maintaining small airway patency in reducing the sequela of inhalation injury. The beneficial effects reported here and the paucity of ventilator complications support continued use and further evaluation of HFV in patients with inhalation injury.

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Discussions

DR. HARVEY SUGERMAN (Richmond, Virginia): In this study, high-frequency percussive ventilation from 1987 through 1990 was associated with a significant decrease in, one, the incidence of pneumonia and, two, the mortality rate when compared, as mentioned, to historical controls for inhalational injury from 1980 through 1984 and mortality rate from 1980 through 1986.

As discussed in their paper, this is one of the only studies in which high-frequency ventilation has shown a significant decrease in mortality rate. It has been my experience and that of the literature that you can significantly, but only temporarily, improve blood gas parameters in ARDS patients with high-frequency ventilation. It prolongs death rather than improving survival.

The hypothesis proposed by Dr. Cioffi and his colleagues and supported by sheep inhalational injury studies in their laboratory is that high-frequency percussive ventilation improves bronchiopulmonary toilet of the small airways, which are plugged with soot and debris, with an increased alveolar recruitment and ventilation at lower peak airway pressures when high-frequency ventilation is provided early or prophylactically before the development of severe ARDS.

This has not been the case in nonburn septic patients in randomized prospective trials. Dr. Cioffi's study suffers from all of the potential weaknesses of a nonrandomized trial. In comparing inhalational injury and the risk of pneumonia, why did the authors compare data from 1980 to 1984 with 1987 to 1990?

What happened to the missing 3 years? Were other treatment modalities that could influence the development of pneumonia during these two time intervals changed, such as the use of H2 blockers *versus* carafate for the prevention of stress ulcers or TPN *versus* enteral feedings vis-a-vis the issue of bacterial translocation, and so on?

Were the methods of providing pulmonary toilet in the two groups, such as the nursing staff and inhalational therapists, unchanged during these two time periods?

Could prejudice have been inadvertently present in roentgenographic interpretation or were so-called blinded radiologists used to describe the presence or absence of pulmonary infiltrates?

Finally, using historical controls, were there any differences in the duration of mechanical ventilation *versus* duration of ventilation with high-frequency ventilation present?

We heard the duration of ventilation for high-frequency ventilation but not for the mechanical ventilatory group.

In 1988 this group reported their first positive experience with high-frequency percussive ventilation in 14 patients before the American Association for the Surgery of Trauma. Today we have heard more suggestive data in an additional 40 patients.

High-frequency ventilation has been a technique in search of documented therapeutic efficacy. Now is the time for a truly randomized prospective, perhaps multi-center trial for the study of high-frequency ventilation in burn inhalational injury patients.

DR. DAVID HERNDON (Galveston, Texas): Dr. Cioffi and Dr. Pruitt and their group must be commended on their impressive mortality statistics. A mortality rate as low as 18.5% in a group of patients with significant inhalation and burn injury requiring prolonged ventilatory support has never been reported in the United States before.

The usual mortality rates quoted are from 40% to 50%. This in respect to nationally reported mortality rates is clearly a great advance and allows Brooke still to be called the world's most famous burn unit.

However demonstration of a treatment effect in a patient population with this high rate of mortality is extremely difficult. Comparison to an historic cohort from 1980 to 1984 or 1986 is somewhat misleading. The investigators have admitted that.

I would like to know if more aggressive early surgical removal of the burn wound in a later period may have contributed to a decrease in the incidence of pneumonia by decreasing burn wound bacteremia as a source of hematogenous pneumonia. Has there been any effect of the more recently developed antibiotics?

The H2 blockers have been mentioned.

You have noted also that a wide variety of high-frequency ventilators are available, and varying reports of efficacy in the literature have been received. The incidence of barotrauma, specifically pneumothoraces due to gas trapped behind inspissated mucosal casts, has been discouraging in inhalation injury patients. However the ventilator you used is very specific and seems to overcome many of these adverse effects with a very low incidence of barotrauma.

My major question is, is this complicated ventilator commercially available or will it become commercially available? I'm not aware of it being so. If it is, then I think, as Dr. Sugerman did, concurrent multicenter studies based on your encouraging preliminary results might be warranted to determine mortality effects, whether specific for this machine or specific for this excellent treatment team.

I would also like the authors to speculate as to whether our general level of burn care has improved to such an extent that we might also recontemplate randomized studies that would treat barotrauma by use of extracorporeal membrane oxygenation.

Previous attempts in the 1970s, when burn wound sepsis was rampant, were unsuccessful, but mortality statistics are sufficiently decreased, and early excision of the wound would prevent many of the septic complications that were seen before. Or perhaps the new technique of intravenacava filamentous O_2–CO_2 exchange rods being tested in multiple centers for support of adult respiratory distress syndrome might make more sense than a jet ventilator.

DR. EDWIN DEITCH (Shreveport, Louisiana): I will limit my remarks to a few questions, some of which have been covered before but, nonetheless, I think they need to be stated again.

I wonder whether the authors are now ready to carry out a prospective randomized study to verify these results. There are several reasons to do so. The first is that this high-frequency ventilator technique that they are proposing is much more time consuming, technically demanding and more expensive than conventional mechanical ventilation.

And second, and perhaps more important, all too often in the past studies carried out using historical controls, even one as well defined as this one, fail to verify the encouraging results of the initial study.

There are many reasons why this phenomenon occurs, not the least of which is the special attention directed toward these patients by a highly motivated investigational team. Perhaps the fact that Dr. Cioffi and his coworkers were performing bronchoscopy on these patients to remove debris may have made this a study of repeated bronchoscopy as much as ventilatory support.

I have two other related questions. One is that it has become apparent in the last several years that the intubated patients receiving antacids or H2 blockers for stress ulcer have an increased incidence of gram-negative pneumonia and even death.

Therefore I wonder whether the authors are still using H2 blockers, what they're using, and whether they have changed their therapy to use sucralfate to prevent colonization of the stomach with potential pathogens.

Related to that, do you have any data on the bacteriology in these patients and if so was it different from the historical controls? I ask this question because pneumonia due to gram-negative enteric bacilli or pseudomonas is associated with a higher mortality rate than pneumonias caused by gram-positive organisms.

Therefore, if you are shifting your flora due to changes in therapy, you may also be shifting your results.

DR. ANTHONY MEYER (Chapel Hill, North Carolina): I would like to compliment the authors on their continued evaluation of this alternate method of ventilation for inhalation injury. I have a few questions.

You had a relatively low incidence of necrotizing tracheobronchitis and barotrauma. Is this consistent with the incidence in your conventionally ventilated patients?

Is there any evidence or data on pulmonary compliance in these patients? Obviously it is difficult to measure using this mode of ventilation, but if pulmonary fibrosis is one of the key hallmarks of ARDS and late pulmonary problems, and if this is indeed triggered by the barotrauma of conventional ventilation, this might be a significant physiologic alteration using this type of support.

There is a relatively high incidence of pneumonia in the historical series. And because of this and many of the other reasons, I would like to join the chorus in suggesting that a true prospective randomized study should be carried out to evaluation further the technique.

I think it is interesting that this sophisticated pulmonary management is being discussed before a surgical society rather than something that is only discussed before pulmonary medicine groups.

DR. WILLIAM CIOFFI (Closing discussion): First I would like to address the recurring question of why we did not perform a randomized trial.

When we started this study, we did a trial in which we enrolled 20 patients to see if we could see a decrease in the incidence of pneumonia or change in mortality rate, and indeed we did. We entertained the thought of a prospective randomized trial at that time. By doing the calculations, we discovered that it would require more than 230 patients to have satisfactory type one and type two errors. It took us almost 4 years to enroll 54 patients in this trial, so we were looking at more than a decade to complete the study with all the problems that would occur in treatment changes in 10 years or more.

Second we have used these predictors for at least one decade in our institute, if not longer, and in other studies have found them to be entirely reliable in predicting results from other types of studies, not just including the ventilator study discussed here today.

Third because doing this randomized trial will be difficult in a period of time that is reasonable, we have begun a study in primates looking at high-frequency ventilation in two forms, high-frequency percussive ventilation discussed here today and high-frequency oscillation as compared to conventional ventilation in a long-term support model in which we ought to be able to discern whether the differences we see in patients will hold out in the primate model. That trial is now underway.

To continue with Dr. Sugerman's questions, other treatment modalities have not changed significantly in our unit in the past 10 years.

Our mode of nutritional support is enteral and has remained enteral for 10 years, with TPN being used in less than 5% of patients.

Our diagnosis and treatment of pneumonia also has remained the same in the studied period of 10 years.

Respiratory therapy has not changed significantly. Frequent bronchoscopy for pulmonary toilet in patients with severe inhalation injury has been the standard in the unit for approximately 10 to 15 years.

Dr. Sugerman also asked whether the duration of ventilatory support was similar in the high-frequency patients as compared to the conventional patients. Unfortunately I do not have that data for the 1980–1984 patients. But I would say that 15 days of support in these patients indicates a rather severe insult. The patients are weaned as quickly as possible from this ventilator, and it has been my experience in patients who have not been placed in the trial for other reasons that it is easier to wean the patients from high-frequency ventilation than conventional support.

Dr. Herndon asked about our excision practices. In the past decade, our day of first excision has decreased by about 3 days in patients with burn size discussed in this paper. He also asked whether the incidence of hematogenous *versus* bronchopneumonia or airway pneumonia has changed. Hematogenous pneumonia has been relatively infrequent in the past decade, and bronchopneumonia is responsible for almost all our pneumonias. I don't think that later excision in the earlier group had much to do with the incidence of pneumonia.

Our antibiotic therapy has been relatively unchanged. The standard antibiotic therapy in our unit is Amicacin and Vancomycin and has been that way for almost the entire period of the 1980s.

Several discussants asked about stress ulcer prophylaxis and whether we use H2 blockers. Until 5 or 6 months ago the standard of care was H2 blockers and antacids titrated to keep the gastric pH above 4.5.

We just started a trial comparing sucralfate to standard therapy, but of the patients reported in this study, only two of the last five patients were enrolled in that study. So all patients were on H2 blockers, and the idea of nonacid neutralizing therapy to decrease pneumonia does not enter into play.

The barotrauma reported in our series is low. It is lower than it has been in the past. The incidence of significant barotrauma as far as pneumothoraces was one patient of 54. Most ICUs report incidence of barotrauma approximately 4%. Two patients did have significant subcutaneous emphysema but never developed a pneumothorax.

Dr. Herndon asked whether this device was commercially available. It was approved by the FDA approximately 1 year ago and is now commercially available through Percussion Air Corporation, which is a company owned by Dr. Bird, who developed this form of ventilation.

Dr. Herndon also asked us to speculate whether other forms of support, total rest of the lungs using either ECCOR or the new intravenacaval device, the IVOX, might be of more benefit. In those studies it is still a requirement that the patient be kept on high mean airway, low peak pressure ventilation to splint the lung. And it might be that some high-frequency ventilation in combination with extracorporeal support might be the answer. The studies that are using that form of therapy, however, are all on ARDS patients.

Dr. Deitch asked not only about why not a prospective study, which I've already covered, but also about the costs. The cost of this ventilator is approximately one fifth of a 7200 ventilator. So cost is not really an issue.

The first two forms of this ventilator were exceptionally hard to use, as we reported in our early review; however the VDR for the most current form of this ventilation is very easy to use. We have residents who rotate 1 month from multiple institutions. And by the end of 1 month, most residents are capable of using this ventilator and are able to support the patients at night on their own.

Dr. Deitch also asked about the etiology of our pneumonia, our gram negatives *versus* gram positives. We have had a predominance of gram-positive pneumonias at our institute for more than a decade, and that incidence has not changed.

He also asked about comparing it to a population from 1980 to 1984 and 1987 to 1990. We are just starting to look at the data in the intervening years. And the incidence of pneumonia before use of this ventilation from 1985 to 1987 had not changed in patients with inhalation injury compared to the 1980 to 1984 group.

Finally Dr. Meyers asked about necrotizing tracheobronchitis. It is our impression that it has been significantly decreased with the use of this ventilator, despite the fact that there are reports in the literature using this form of ventilation in neonates, in which that incidence approaches one third to one half of patients.

However we only had two patients, the very first patient and a latter patient entered in the trial, both of whom survived. And it appeared to be more an indication of the severity of their insult.

Finally, Dr. Meyers, we have not done compliance measurements to indicate the severity of the insult.

In closing I would like to add that many discussants compared this form of support in patients with inhalation injury to those studies in the literature that deal with ARDS patients. I would emphasize that the insult in our patients is distinctly different from ARDS. It is a self-limiting disease process, which, if it can be left to heal on its own, should do so in 10 to 14 days. We feel strongly that conventional mechanical ventilatory support impairs that healing process and that the use of low-pressure ventilation by the use of this device or other high-frequency devices may just allow the natural process of healing to occur.

火傷患者は，吸入傷害を伴うと，現行の換気サポート技法を適用しても死亡と肺炎の発症は著しく増加します．1987年３月～1990年９月の間に取扱った吸入傷害を伴った54名の火傷患者について，高頻度パーカッションベンチレーションを行い，死亡率，肺炎感染の発症，圧損傷に及ぼす効果について，過去1980～1984年の患者群の成績と比較研究を行いました．高頻度パーカッションベンチレーションは，挿管後24時間以内に施行されました．患者の平均年令と火傷の範囲は，夫々32.2才，48%です．（年令範囲：15～88才，火傷範囲：０～90%）．平均の換気日数は15.3±16.7日（範囲：１～150 日）で，26%の患者は２週間以上の換気を受けました．過去の例での肺炎の発生頻度の予想は45.8%(P<0.005)ですが，これと比べて，本研究のケースでは患者の肺炎の発症は14名（25.9%）でした．本ケースでは死亡者は10名（18.5%）です．過去の例からの予想死亡者数は23名（95%の信頼限界で17～28名死亡）でした．

本研究の７年前の，過去の患者群の成績と比較して，高頻度換気を予防的に行うと患者の生存率が向上し，肺炎の発症が減少することが実証されました．これらのことは　吸入傷害から直接あるいは間接的に生じる疾病の発生に関し，小気道が開口しているかどうかが重要であるかを示すもので，ＨＦＶの更なる使用とその評価を行うことが求められます．

過去30年の間に，火傷の処置が向上し感染のコントロールや代謝のサポートで熱傷患者の生存率は向上しています．しかし吸入傷害（inhalation injury:気道熱傷）は関連の病気をひきおこす重要な因子となります．現行の肺補助の手段では，その処置に向上が余り見られません．バクテリア性の肺炎は，煙吸入傷害患者の38%で生じ，この傷害のない患者でも８%の発症がみられ，死に至る要因となっています．吸入傷害と肺炎が共に生じると，それぞれの影響に加えて火傷のサイズによりますが，年令に関係する死亡に影響をおよぼします．現行の吸入傷害に対する処置は，対症療法で肺の強力な清浄化とメカニカル換気補助を行い，もし肺炎と診断されれば，強力な肺炎の処置を行います．羊をモデルにして私達は吸入傷害を受けたあとの，主たる現象（初期の傷害後の，換気／パーフュージョン(VA/Q)のミスマッチと病理組織学的な所見で示される）は，小気管支の閉塞と虚脱で，これが原因となって遠位の無気肺，更に肺炎の発症に至ることを示しました．実験的な臨床データでは高頻度換気（ＨＦＶ）が，このような肺の虚脱の部分を再生し，安定化させるために有効であることを示唆しています．若干の研究者らは，ＨＦＶの使用によって気管・気管支分岐の分泌物の清浄化を改善したと報告しています．これらの観察は，ＨＦＶは肺胞の虚脱化を防ぎ，分泌物の清浄化を改善し，吸入傷害の患者に有益であるという説を支持します．我々は以前に，メカニカル人工呼吸が必要な少人数（10人）グループの吸入傷害患者に，高頻度パーカッションベンチレーション（ＨＦＰＶ）を用いて，肺炎の発症を抑えることが出来ると報告しました．本報告は，引き続いて肺炎の発症を減らし，生存率を高めるために予防的にＨＦＰＶを使用した54名の患者についての報告です．

方法

患者群

米国陸軍外科学研究所（United States Army Institute of Surgical Reserch）で，1987～1990年に吸入傷害と診断されて入院したすべての成人患者を本研究の対象としました．

患者の吸入傷害は，気管支鏡とキセノン換気―灌流肺走査によって確認されました．

声帯の下部の炭化汚物，粘膜紅斑，潰瘍化の存在等を吸入傷害の程度（中程度から重程度）を決めるのに用いました．

キセノン走査と気管支鏡で陰性のものは軽度（mild）としました．これらの規準は前報で確率されています．Table 1 に示された研究に参入する適合条件を満たし，Table 2 に示された挿管とメカニカルベンチレーターへの適合条件に合った患者から，肺炎予防を目的としてＨＦＰＶを始めることに対してインフォームドコンセントがとられました．

TABLE 1. *Study Entrance Criteria*

Inhalation injury documented by bronchoscopy or Xenon lung scan
Clinical requirement for ventilatory support
Admission within 48 hours of injury
Older than 15 years

Table 1.　研究導入規準

気管支鏡又はキセノン肺スキャニングで吸入傷害がある
臨床上ベンチレーターサポートが必要
傷害発生後48時間以内に手当
年令15才以上

TABLE 2. *Requirements for Mechanical Ventilatory Support*

1. Respiratory rate > 35/min
2. Vital capacity < 15 mL/kg
3. Inspiratory force < 25 cm H_2O
4. PAO_2/FIO_2 < 200
5. PCO_2 > 50 mmHg
6. Vd/Vt > 0.6
7. Upper airway edema
8. PCO_2 < 50 mmHg but progressively increasing
9. Increased work of breathing

Table 2.　メカニカルベンチレーターサポートを受ける必要性

1．呼吸数＞35／min
2．肺活量＜15㎖／kg
3．吸気圧＜15cm H_2O
4．PAO_2／FiO_2＜200
5．PCO_2＞50mmHg
6．Vd／Vt＞0.6
7．気道上部の浮腫
8．PCO_2＞50mmHg　けれども増加しつつある
9．呼吸の仕事の増加

頻度パーカッションベンチレーション

本研究に用いた高頻度パーカッションベンチレーターについてはすでに報告されています．簡潔にいえば，ＨＦＰＶはスライド式ベンチュリー管によって生ずる高頻度の拍動ガスを標準的なＥＴチューブに導入するものです．ベンチュリー管には，ベンチレーターから供給される新鮮なガスに加湿したガスが加わります．このシステムは，種々な吸気：呼気(I:E) 比で，一連の準死腔量（小換気団）の呼吸の組合せといえます．高頻度拍動流が休止している間に，気道圧が持続的気道内陽圧気（CPAP）のベースラインにもどるようにプログラムされています．パーカッションの持続時間相とベースラインにもどる時間相は，酸素化とCO_2 除去のために操作することが出来ます．

最大気道圧も CO_2クレアランスを保つように，独立して変えることが出来ます．小換気団（準死腔スペース量）の頻度は 1.5～15ヘルツの範囲で調節出来ます．FiO_2とPEEPも，O_2飽和度を90%以上になるように調節出来ます．すべての患者は，当初は現行のメカニカルベンチレーターに依存していました．別施設で挿管された患者のメカニカルベンチレーターの呼吸補助は24時間以内で，我々の施設で挿管した患者は，院内で現行の人工呼吸を受けましたが，すべて１時間以内にＨＦＰＶに移行しました．

患者はＨＦＰＶに移行したあと，基礎規準としてベンチレーターの標準の設定を用い，その後動脈血ガス分析値，パルスオキシメトリー，そして終末換気CO_2 のモニターのデータで変更されました．パーカッション相の持続時間は２秒にセットし，ベースラインに戻る速さ（rate）は，現行メカニカル人工呼吸で正常な酸－塩基バランスを保つために必要であった間歇的強制換気（ＩＭＶ）の設定より約２低くしました．最大気道圧は，現行の従量式ベンチレーターで１回換気量12～15mℓ／kgを送気するためのセット値より５cmH_2O 少なくなるように設定しました．小換気団の頻度は最初10ヘルツに設定されました．約30分間続けて安定したところで，動脈血ガスの測定を行い，それに従って調節を行いました．ベンチレーター療法のゴール（目標）は，酸素化を維持し，最大気道圧と，吸気酸素濃度を出来るだけ低くすることです．患者は標準のクリテリア（規準値）にしたがって，ウィーニングし，抜管しました．

肺炎の診断

肺炎の診断は当施設で，過去10年間にわたって用いている規準によりました．喀痰白血球増加症（ハイパワーフィールド当り25白血球症以上），口，咽頭の病原菌による汚染の欠如（ハイパワーフィールド当り10以下の鱗状細胞），培養で大量の微生物存在，胸部レントゲンでの浸潤ななどで肺炎であると診断されました．

データ解析

本研究での患者の肺炎の発症と死とは，前に行った２つの研究に基づいて予想値と比較しました．

最初の予想値は，1980年１月～1986年12月に当外科学研究所で取扱ったすべての患者に対する火傷サイズと年令別の死亡に関係するものです．２番目の予想値は，比較のベースとして用いたもので，1980年～1984年の間に取扱った患者の死亡数，火傷のサイズ，年令，吸入傷害の有無，肺炎の発症で死に至ったものに関係しています．後者の患者群の肺炎の発症は，比較のために使用しました．Table 3 に示す計算式は，予想される死亡に対する２つの値の計算に用いたベキ指数を提供します．

TABLE 3. *Burn Mortality Predictors*

$$\text{Predicted Mortality (PM)} = \frac{e^{Y}}{1 + e^{Y}}$$

I. Logistic equation relating burn size and age to mortality: 1980–1986

$$Y = -4.8216 + 0.10299\,(PCTB) - 0.18879\,(Age) + 0.50873\,(Age^2/100) - 0.27915\,(Age^3/10{,}000)$$

II. Logistic equation relating burn size, age, inhalation injury, and pneumonia to mortality: 1980–1984

$$Y = -3.4953 + 0.09589\,(PCTB) - 0.1988\,(Age) + 0.4478\,(Age^2/100) - 0.20314\,(Age^3/10{,}000) + 0.59056\,(II) + 0.92530\,(PNeu)$$

PCTB, percentage of total body surface burned.
II = −1.0 if inhalation injury absent; +1.0 if inhalation injury present.
PNEU, −1.0 if pneumonia absent; +1.0 if pneumonia present.

Table 3.　火傷死亡率の予想値

$$\text{予想死亡率(PM)} = \frac{e^{Y}}{1 + e^{Y}}$$

火傷サイズと年令の死亡率に関する計算式

$$Y = -4.8216 + 0.10299\,(PCTB) - 0.18879\,(Age) + 0.50873\,(Age^2/100) - 0.27915\,(Age^3/1{,}000)$$

火傷，年令，合併肺炎の死亡率に関する計算式

$$Y = -3.4953 + 0.09589\,(PCTB) - 0.1988\,(Age) + 0.4478\,(Age^2/100) - 0.20314\,(Age^3/1{,}000) + 0.59056\,(II) + 0.92530\,(PNeu)$$

PCTB，火傷サイズの全体に対するパーセント
II＝−1.0 吸入傷害の無い場合；＋1.0 吸入傷害のあるとき
PNeu，−1.0 肺炎のないとき；＋1.0 肺炎がある場合

結果

患者群

試験への導入規準に適合した54人の患者が本研究に加わりました．ルーチンの人口統計データーは Table 4 に示されています．10名の患者が死亡し，死亡率は18.5%でした．火傷のサイズによる患者の分布は，患者の50%が30%～60%の範囲で火傷しています．これらの患者は，吸入傷害が死に至る最大のインパクトになるとされている患者群です．成績によって患者を分けると，２つのグループの間で差が示されます．(Table 5).

死亡者は，より年長で火傷がひどく，肺炎の発症も多くなっています．54名中52名は気管支鏡で吸入傷害があると診断されました．気管支鏡で陰性を示したけれどキセノン走査で陽性であった２名の患者は，重篤な成人呼吸切迫症候群（ＡＲＤＳ）を火傷後の第一週に発症し，メカニカル人工呼吸器が必要となりました．過去の例によりますと，気管支鏡で陽性であった45.8%，気管支鏡で陰性であったけれどもキセノン^{133} 肺走査で陽性であった患者の19.5%が肺炎を発症しています．我々の経験からは本研究の患者のうち25人の肺炎発症があると予想されていました．本研究で肺炎と診断されたのはわずか14名（26%）で比較グループの発症とは顕著に異なっています．

予想の死亡と実際

本患者のグループで死亡例は10例で死亡率は18.5%です．ＨＦＰＶがこの患者グループの成績に影響を及ぼしているかどうかを結論する目的で，患者データから得られる２つの死亡率の予想値と比較しました．

第１は1980年１月～1986年12月までの本施設で扱ったすべての患者に関して，火傷のサイズと年令を基礎に比較したもので，本研究の患者人口では19人の死亡（死亡率35%）が予想され，95%の信頼区間で13～25人の死亡が予想されました．

第２は1980年１月～1984年の間の患者データから得られたもので，肺炎に加えて吸入傷害を伴っているもので火傷サイズと年令に基づいたものです．

予想は23人の死亡（42.6%）で，95%の信頼区間，17-28名の死亡が予想されていました．本患者グループでの死亡率はTable 6 に示すように，どちらの方法でも（Ｐ＜0.05）有意に減少しています．

TABLE 4. *Demographic Data*

Age	32.2 ± 1.8 (15–88)*
TBSB	47.8 ± 3.1 (0–90)
Sex	40 male, 14 female
Days on ventilator	15.3 ± 2.2 (1–150)
Bronchoscopy positive	96.3%
Incidence of pneumonia	25.9%
Mortality	10/54 (18.5%)

* X ± SEM (range).
TBSB, total body surface burn.

Table 4.　統計的データ

年令	32.2±1.8(15-88)*
TBSB	47.8±3.1(0-90)
性	40male, 14female
換気日数	15.3±2.2(1-150)
気管支鏡陽性	96.3%
肺炎の発症	25.9%
死亡率	10/54(18.5%)

* X±SEM(range).
TBSB, total body surfase burn.(火傷の全サイズ)

TABLE 5. *Comparison of Survivors and Nonsurvivors*

	Survivors	Nonsurvivors	
Age (years)	29.6 ± 1.5*	43.3 ± 6.5	$p < 0.05$
TBSB	43.7 ± 3.2	65.3 ± 7.1	$p < 0.01$
Incidence of pneumonia	20.5%	50%	$p < 0.05$

* Mean ± SEM.
TBSB, total body surface burn.

Table 5.　生存者と死亡者の比較

	Survivors	Nonsurvivors	
Age(years)年令	29.6± 1.5*	43.3±6.5	p<0.05
TBSB	43.7± 3.2	65.3±7.1	p<0.01
肺炎の発症	20.5%	50%	p<0.05

* Mean±SEM.
TBSB, total body surfase burn.(火傷の全サイズ)

TABLE 6. *Actual* Versus *Predicted Outcome*

Predictor	Predicted Deaths	95% CL	Observed
#1 (1980–1986)	19	13–25	10
#2 (1980–1984)*	23	17–28	10

* This predictor includes the impact that inhalation injury and pneumonia have on outcome.
CL, confidence level.

Table 6.　事実と予想の比較

Predictor	予想の死亡率 Predicted Deaths	95%CL	実際 Observed
#1(1980-1986)	19	13-25	10
#2(1980-1984)*	23	17-28	10

* この予想値には吸入傷害と肺炎の成績も含まれている
CL, confidence level.

死亡した患者の死因はTable 7 に示しました．一人は換気と酸素化が出来ず，通常の人工呼吸サポートに移行しましたが結果は同じでした．３名は，進行性の肺不全となり，火傷後夫々 12,13,15 日後に亡くなりました．残りの６名のうち２人はきびしい吸入傷害を伴い蘇生法がうまく効きませんでした．１名は火傷後７日で患者自身が抜管し，緊急の気管開口術を行ったにもかかわらず心肺機能停止で死亡しました．１名は主治医によって本研究から除外されました．２名の患者は夫々抜管して30日，45日後に脳血管の異常のために死亡しました．換気による副作用はまれでした．２名の患者は重篤な壊死を伴う気管・気管支炎を発症しました．これが換気法の２次的な発症なのか，病気そのもののプロセスによるのかはわかりませんでした．
バロトロウマは３名の患者にみられました．２人は皮下の肺気腫を見，１名は両肺に気胸が生じ胸部開口術が必要となりました．

TABLE 7. *Cause of Death*

TBSB (%)	Age (years)	PBD	Cause of Death
90	32	01	Resuscitation failure
85	25	03	Resuscitation failure
59	40	07	Accidental extubation
36	59	40	Removed from study
47	29	50	SBE, CVA, 30 days after extubation
65	60	80	CVA, 45 days following extubation
89	25	12	Pulmonary failure
30	88	43	Pneumonia (*Staph. aureus*), pulmonary failure
64	49	01	Unable to ventilate
86	29	50	Pneumonia, Aspergillus wound infection

TBSB, total body surface burn; PBD, postburn day.

Table 7.　死亡原因

TBSB (%)	Age (yeats)	PBD	Cause of Death (死因)
90	32	01	人工蘇生の不成功
85	25	03	人工蘇生の不成功
59	40	07	偶発的な抜管
36	59	40	本研究より除外
47	29	50	抜管後30日
65	60	80	抜管後45日
89	25	12	肺不全
30	88	43	肺炎（黄色ブドウ球菌），肺不全
64	49	01	換気不能
86	29	50	肺炎，アスペルギルス傷感染

TBSB，火傷全サイズ%：　PBD，火傷発生後の日数

考察

皮膚の熱症に吸入傷害が組合わさると，皮膚の熱症のみの場合に帰する死亡率よりも死亡率が大きく増大します．この吸入傷害が死亡の増加に影響することは，予想死亡率が年令に関係するとされる，火傷範囲40～60%の患者に最も明らかに表れています．吸入傷害はまたバクテリア性肺炎の発症を非常に増大しています．以前に述べたように熱症があるが吸入傷害を伴わない患者では肺炎が発症したのは処置でわずか 8.8%でした．過去の記録によれば気管支鏡あるいは^{133} キセノン走査で気道熱傷の吸入傷害をみとめた場合，肺炎の発症は38%で，肺炎と吸入傷害が共にある場合には劇的に成績に影響し，死亡率は60%にも増加します．
理想的には，どんな病気であれ最善の処置とは傷をそれ以上増長させないように病態生理学的に逆コースをとることです．もし，気道熱傷がひどくて，従来のメカニカル人工呼吸の力を借りなければならないときは，このような成績は達成出来ません．気道熱傷に対する病理生理学的な反応は，さらに進展して気管気管支の傷害となり，結果として呼吸系の通路管の粘液によるライニング（内壁がおおわれること）から分離した壊死組織塊を生み，小，中気道の閉塞に至ります．これに加えて粘液性繊毛による移送の機構が悪くなり，その結果分泌物や分離した壊死塊の清浄が出来にくくなります．遠位の気道閉塞は無気肺をもたらし，内皮細胞と肺胞群の上皮結合組織の結合は，バクテリアを更に繁殖させ，ひきつづいて肺炎を発生させる力になります．無気肺と肺炎，それと気道狭窄は換気灌流を大きく攪乱することになるのです．
現行のメカニカル換気補助ではこれらのプロセスの逆行出来ず，分泌物の清浄化の向上を特徴づけることは出来ません．実質的に傷害の存在を増大させるかもしれないのです．吸入傷害患者の現行の従量式換気は，通常１回換気量12～15$m\ell$／kgで行います．このような換気の設定では，ケア中の蘇生期や分泌物の流動化を行っている間に最大吸気圧は往々にして上昇します．
最近 Tsunoは，麻酔で麻痺している健康な羊で，最大吸入圧が水中圧30cmをこえると，従量式メカニカル換気で肺に逆効果を生じると報告しています．FiO_2 40%，1回換気量10$m\ell$／kgとし，最大吸気圧が水中18cmより低くして，換気を受けた動物は，48時間のサポート処置のあと肺機能や組織病理学的に測定で，有害な変化を示しませんでした．１回換気量を増やして動物を換気すると，最大吸気圧は30cmH_2O より大となり，静的な肺コンプライアンス，機能的残気量，動脈血ガスが時間とともに悪化することが実証されました．重篤な無気肺，濡れた状態の肺重量の増加，生理食塩水による肺の注入洗浄液の表面張力の最少値の増加などが，病理解剖で注目されました．これらのデータは，健康な肺でさえ，長期に亘る吸気圧の上昇は，肺傷害を来す可能性を示しています．もし蘇生術のあと肺炎が発症し，酸素正常状態を達成するために吸入酸素濃度増加が必要な場合，そこで感染があれば結果として肺のダメージは増加することになります．Coalson らは，最近過酸素症と感染の相乗効果で肺機能障害とダメージが顕著に生じることを報告しています．霊長類のモデルでは，酸素82%とシュードモナス肺炎の組合せでは11日間で 100%酸素と同じくらい有害であり，一方80%酸素あるいは肺炎が単独に存在するときは肺機能障害は最も小さくなりました．
報告によると，ＨＦＶ（換気頻度は60呼吸／分以上で１回換気量は解剖学的死腔より小である）の有益な効果としては，現行の人工呼吸の場合よりも最大気道圧が低いこと，換気サイクルを通して陽圧気道圧が保たれていること，機能的予備容量が増加すること，肺ガスの分布がさらに効率的なことをあげています．不幸なことに，この特有の高頻度換気にまつわる有益な点は，多くの報告で反駁されています．しかし若しＨＦ

Vの１形体がこれらの有益性を維持し酸素化，炭酸ガス洗浄がより低い吸気圧と吸気酸素分圧で達成すれば，現行の呼吸補助の悪い面を避けた換気補助を提供出来ることになります．

ＨＦＶの臨床の評価報告で，医師は高頻度ベンチレーターに数種のタイプがあり，それぞれ異なった特徴を持ち，異なった副作用の可能性があるということを認めるべきです．更に本研究で行ったようなベンチレーターを予防的に使った場合と，現行のメカニカル人工呼吸器で治療効果がなかった患者に高頻度装置を治療用あるいは救急に使った場合は区別しなければなりません．ＡＲＤＳの患者の短期の救急処置にＨＦＶを使用して効果を実証した多くの報告があります．我々の以前の報告でも，本研究に用いたベンチレーターで，より低い気道圧と吸気酸素濃度で患者の換気が出来ることが実証されることを示しました．しかし，肺機能が回復したといえすべての患者は死亡しています．他の多くの報告でも，ＨＦＶを使用した換気補助救急モードで，生存への有利性を示すことに失敗しています．本研究において我々は吸入傷害のあとで生じる病態生理学変化を極小化あるいは逆行させ，メカニカル換気補助の逆効果を避ける試みとしてＨＦＶを予防的に使用したのです．

我々のデータは，最近の過去のグループとの比較で，ＨＦＰＶの使用は顕著な肺炎の発症を減少し，死亡率をも減少させたことを示しています．

過去の例をコントロールに用いることには，本質的ないくらかの問題点があります．私達のクリテリアは1976年からずっと同じにしていますが，診断技術が進捗し，より精巧になったために，重症度の低いものが，診断上好結果を示す結果に働いたというようなことがあるかも知れません．

過去30年の間，熱症患者の生存率が向上して来ていることは一般に受け入れられています．そういうものの，吸入傷害と肺炎の成績効果は，本施設で予想に用いた死亡率に示されるように，標準的な処置では依然として惨憺たるものです．更に本研究で予想値を用いていますが，予想のベースになった患者群と比較して本研究の患者群の成績が向とすることに，ある傾向（公正な判断を妨げる）を導きかねません．肺炎と吸入傷害の死亡に関する場合もそうですが，火傷の範囲と年令の両方の効果を説明する予想値は，患者がメカニカルベンチレーターを用いたか否かに関係なく1980～1984年の間に扱ったすべての患者をベースにしたものです．本研究患者群は，極めて重篤で侵害度も最も大である人達です．そしてすべて人工呼吸器のサポートが必要な人達です．このグループの患者で生存した患者と，傷害度の低い患者グループとの比較で実証されたということは，ＨＦＰＶの顕著な有益な効果があるという説明を支持します．端的に言って肺炎の発症が減少した主要因も本研究の患者群の成績の改善も用いた換気方法に依っていると考えることは理に叶っています．

この他に，ベンチレーターのサポートを必要とする患者に対して，ＨＦＶがＡＲＤＳを予防的に使えるかどうかを評価した文献は２つあるにすぎません．

1986年にCarlonが高頻度ジェット換気と従来の換気サポートを無作為に 309名の患者に行った研究を報告しています．ＩＣＵで肺機能不全のおそれのあるすべての患者がこの研究に加わりました．高頻度ジェット換気の使用で，最大気道圧は低くなりましたが，４％の圧損傷の発生を減少させることは出来ませんでした．従来式の補助と比べて全体的成績の向上も見られませんでした．1990年に HurstらはＡＲＤＳの発症のおそれのある 113名の患者に対し，ＡＲＤＳの発症前に，無作為にＨＦＰＶによる換気補助または従来のメカニカルベンチレーションを行った研究を報告しています．両グループの患者が，治療の同じ最終点に至るようにベンチレーターの設定の変更が行われました．どちらのグループもＡＲＤＳを発症する率は変わりませんでした．ＡＲＤＳを発症した患者では，ＨＦＶの場合，従来型のグループと比べて最大気道圧，陽圧終末呼気圧が低く，吸気時間を長くして治療の最終点に到達しました．これらの患者の，バロトロウマの発生や成績は変わりませんでした．これらの研究の双方とも，患患者群が均一でなく，呼吸不全の病因が様々であり，通常全身系の傷害の結果，斑点的実組織の病気や機能不全に到ったものです．この傷害は，人間でも動物モデルでも煙吸引後にはっきり見られ，蘇生術後水腫が急速に解消し，14－21日以内に気道の粘膜が修復されました．ＨＦＰＶが，本研究のような好結果を達成出来た正確なメカニズムはよくわかりません．我々は次のように仮定しました．すなわち，低い最大気道圧でそして低い吸気酸素濃度で呼吸を維持出来る能力が，現行のメカニカル換気補助で生じるイアトロジニック（医師の態度，診断，治療法などによって生じる神経症）な傷害を減少するのかも知れないということです．Tsuno らの報告データを人間にあてはめて推測すると，より低い気道圧での換気は，既傷害のある肺には，特に著るしく有利であることを示しています．更にいくらかの研究は，実験的（in vitro）あるいは生体を用いた試験（in vivo ）においても高頻度ジェット換気や高頻度オシレーションで得られる結果で，不均整の高頻度呼吸は，分泌物の清浄化を向上を示しており，我々の臨床経験もこのことを支持しています．

高頻度パーカッション換気を予防的に用いた重篤な吸入傷害の患者には，気管支鏡の調査で気管チューブの先に大量の分泌物の沈着がみられます．これらの分泌物を除去すると気管支の主茎と遠位の気道が開き，病理的病的な分泌物がなくなります．

最近の過去のグループとの比較で，予防的にＨＦＰＶで処置した患者で肺炎の発症が減少し，生存率が向上したことを実証し得たことは，吸入傷害につづいて発症する余病を減少するのに，小気道の開口の維持が必要であることを示すものです．ここに報告するような有益な効果があり換気による副作用が少ないという事実は，吸入傷害患者のＨＦＶの更なる評価のために引き続いて本方式を使用することの意義を支持するものです．