techniques would be to reduce the frequency of repeated opening and closing of airway alveolar units from a pressure below the opening pressure to one above[23] by a ventilatory technique such as HFFI. In our model, HFFI significantly decreased the cycles/minute in this smoke injury model (Fig. 2), while maintaining adequate CO_2 clearance. Because peak inspiratory pressures were the same in CON-treated and HFFI-treated animals, the maintenance of alveolar expansion at a lower respiratory rate remains a plausible explanation for our pathology findings.

These subhuman primate data support our clinical findings using HFFI in humans with smoke inhalation injury. The decrease in mortality in patients treated with HFFI compared to nonrandomized, concurrent controls and historical cohorts treated with positive pressure ventilation may be secondary to a decrease in ventilator-dependent barotrauma of an injured airway. These data strongly support the continued use of HFFI with our current strategy for the ventilatory support of patients with smoke injury to minimize additional airway injury.

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Discussion

DR. DAVID N. HERNDON (Galveston, Texas): The authors have elegantly and convincingly demonstrated in this excellent baboon model of smoke inhalation injuries that high frequency flow ventilation, as distinguished from the more frequently studied and clinically used high frequency oscillatory ventilation technique, maintains standard physiologic endpoints as well as conventional ventilatory support with less histologic damage after 7 days of treatment.

One paradox in the data is that the protein levels in the bronchoalveolar lavage of the conventionally treated group return to normal, where they do not in either of the high frequency ventilation treated groups. White blood cell counts in bronchoalveolar lavage were not different among the three groups, leaving us to interpret the elastase data in the bronchoalveolar lavage relatively heavily.

I would like the authors to comment further on the divergence of their biochemical indices, particularly protein in the bronchoalveolar lavage, and the pathologic findings.

I think that I should emphasize the authors' findings that high frequency oscillating ventilation exacerbates morbidity in smoke inhalation injuries. This is probably due to increased air trapping with this technique.

The authors have suggested that optimally managed high frequency flow interruption respirators may improve outcome from smoke injury to the lung, but the number of patients who would have to be studied in prospective analyses to prove this would be quite large.

Finally, I would like to ask if it is possible that operator error in adapting this fairly complex technique might outweigh the potential benefits demonstrated by the study.

DR. JOSEPH M. CIVETTA (Miami, Florida): I wish to commend the authors for their insights that modes of mechanical ventilatory therapy influence the course of acute lung injury.

Their elegant design and careful attention to detail allowed them to show that different components can worsen a given insult in various ways. They demonstrated that high frequency flow interrupt produced the least histologic damage. They suggest that conventional ventilatory support may worsen the initial injury through granulocytic activation and production of elastase.

However, a third mechanism, high inspired oxygen tension, may also affect the course of acute lung injury. We, too, have wondered whether the improved survival we have seen in ARDS, which we had previously attributed to high levels of positive end expiratory pressure (PEEP), might have actually been due to the reflex lowering of FIO-2 whenever arterial oxygen tension rose. There are detrimental effects of high FIO-2 on both ventilation/perfusion abnormalities and the acceleration of mediator-induced lung injury.

The authors' methodology stated in the manuscript was that arterial oxygen tension would be maintained by manipulation of PEEP and FIO-2. Yet the results show that PEEP was not different among groups, but that FIO-2 did increase over time. Thus, it appears that arterial oxygen tension was maintained by increasing FIO-2, raising the possibility that this may have been a factor in the worsening of the pulmonary damage.

There were no actual numbers reported in the manuscript and I would ask the authors what FIO-2 was used, particularly in the groups that showed the most injury.

It may be that insult in combination with mechanical forces and high FIO-2 together determine the ultimate outcome. I would like the authors to comment if additional emphasis should be devoted to possible harmful effects of FIO-2 in both clinical situations and future research directions.

Again, the authors are to be congratulated for extending our understanding of the detrimental effects of therapy upon outcome, a concept not usually recognized in acute lung injury.

DR. RICHARD L. GAMELLI (Maywood, Illinois): I would like to compliment Dr. Cioffi and his associates on a unique and well-done study and thank them for the opportunity to review their manuscript. I address several questions to them.

The first is if they had chosen pressure limited ventilation as one of their treatment arms, what would be their expectation as to how this would have compared to their high frequency flow interrupted technique?

Second, did you determine transmural pressures with an esophageal manometer in any of your studies to give us an indication of total thoracic pressure?

Since the standard indicators of lung injury other than the bronchoalveolar lavage elastase were not consistently different in your treatment arms but there were substantial differences morphometrically, do we need to rethink our understanding of the injury with this entity?

Do you have any information as to tissue specific proinflammatory mediators such as tumor necrosis factor alpha or as to how the mechanical process of the ventilator mode may alter these events?

A couple of practical questions: How did you control the central core temperature in your animals? Our experience in children receiving high frequency jet ventilation with significant thermal injuries has shown that maintaining their core temperature is a major problem.

Finally, if we are to employ this technology subsequently in the clinical arena, should patients be treated with high frequency flow interrupted ventilation synchronous with the diagnosis of inhalation injury? Should we gauge it by the degree of dysfunction or the severity of the insult?

I would like to thank the Society for the privilege of discussing this paper and the honor of membership.

DR. DONALD TRUNKEY (Portland, Oregon): I enjoyed this paper very much, Bill. A couple of questions about the high frequency flow interrupted technique. You stated that you altered the I to E ratio. What was your alteration? What was the optimal I to E ratio? What did this contribute to the overall reduction in air trapping compared to the flow interruption component of this technique?

DR. STANLEY M. LEVENSON (Bronx, New York): I enjoyed the paper. Dr. Cioffi, you've detailed how the photographs were looked at independently by three people who were blinded to the identifying code. Perhaps in the paper you've described, but not in the talk, how the photographs, that is the specific sections, were obtained. In other words, you have an animal that's euthanized, now you have a pair of lungs, who decided where in the lungs the 16 sections were obtained and who looked at them under the microscope to decide what areas would be photographed?

DR. KATHRYN D. ANDERSON (Los Angeles, California): Did you have any of these baboons receiving conventional ventilation followed by high frequency ventilation and was there an intermediate level of damage? And the clinical corollary of that is, can we use conventional ventilation and high frequency as a rescue therapy?

DR. W. G. CIOFFI (Fort Sam Houston, Texas): I will cover all questions in the order that they were asked.

Dr. Herndon and Dr. Gamelli both asked about the normal indexes of lung injury, i.e., alveolar lavage protein levels and white blood cell counts. We interpreted our data to indicate that the protein levels are either only an index of the original injury, or that alveolar protein levels are not as good an index of lung injury as once suspected. Most of the studies that have used protein levels to index lung injury have not used as rigid a pathologic scoring system as ours. The presence of white blood cells within the lung or in the BAL doe not necessarily indicate

that those cells are activated and thus releasing either oxidents or elastase. Thus, the fact that white cells are present but do not release elastase or oxidants, indicates that the BAL white cell count is not in and of itself a good index of pulmonary injury.

Dr. Herndon asked about a prospective study. In order to do a prospective study in patients with the same decrement in mortality that we reported in our concurrent but nonrandomized study would require approximately 400 patients per arm. That is a study that could not be done in any single burn center even over a decade.

The ventilator that we used is somewhat operator dependent. However, it is not that difficult to use and our respiratory therapists are quite good at using the ventilator and training each other. I do not think there would be an enormous lag time in other units wishing to use this ventilatory mode.

Dr. Civetta asked about the inspired oxygen concentration levels and whether they were different between groups. First, they were not different between groups. Second, they did not exceed 50% in any of the three groups. The design of the experiment was that all animals would receive 100% oxygen until their carboxyhemoglobin levels returned to normal and they were then to receive room air. Oxygen concentrations were changed in order to maintain appropriate hemoglobin saturation; however, the FIO2 was never raised above 50%, with the exception of the two animals in the HFO group that died. The increase in the FIO2 in these animals was a perimorbid event..

Dr. Gamelli asked about pressure limited ventilation and why we didn't use that as another potential arm in this study. The first reason is that we wanted to use the ventilatory mode that is most commonly used in intensive care units, and that is volume limited ventilation. Second, we have already completed an ovine study comparing conventional ventilation and pressure limited inverse ratio ventilation and could not demonstrate a significant advantage in the early physiologic changes that occur after smoke injury. Thus, we were not interested in pursuing this idea in a much more expensive primate model. We did not place esophageal probes for measurement of interplural pressure; however, that is a good idea and should be done in the future.

We have saved BAL and plasma samples for IL-8, tumor necrosis factor, and other assays. Before performing these expensive measurements, we wanted to see what our pathology results were.

The question of whether ventilatory mode induced pulmonary damage is granulocyte mediated is complex. There is data in the literature ~~that~~ suggests that high tidal volume ventilation results in a granulocyte mediated pulmonary injury because when those animals are granulocyte depleted before the insult, the severity of the insult is less. That, in conjunction with our elastase data, led us to suspect that granulocytes are at least partially responsible for our observed pathology changes.

Dr. Gamelli, the temperature regulation of our animals without thermal injury was not difficult. However, we used a cascade humidifier placed in line with the ventilator to warm the inspired air.

Finally, several discussants asked if this ventilator should be used prophylactically or as a salvage ventilatory mode. We reported in the *Journal of Trauma* several years ago our experience using this ventilator as salvage therapy. We were always able to reverse the physiologic pulmonary failure over a short period of time in patients who were near death and not responding to conventional ventilation. However, we did not achieve long-term salvage in any of these patients. These results led us to the prophylactic use of high frequency flow interruption in patients with inhalation injury. HFFI is instituted when the diagnosis of inhalation injury is made as long as the patients meet conventional requirements for ventilatory support. Patients were not intubated just so this ventilator could be used.

Dr. Trunkey asked about I:E ratios. When using high frequency flow interruption there are actually two I:E ratios that one must be concerned with. First is the small I:E ratio of the sub-dead space tidal volume breaths, and that is usually set as 1:1. Then there is the larger I:E ratio, if you will, of how long flow continues and how long the flow interruption period is in relation to the inspiratory flow time. We typically set that at 2:1, and do not manipulate that very much unless CO_2 clearance is a problem. In this animal model, CO_2 clearance was not difficult and thus the large I:E ratio was maintained at a 2:1 ratio.

Dr. Levenson asked who performed the lung sections and who decided what to photograph and what to study. This was all performed by one blinded pathologist who took very long longitudinal sections starting at the trachea that continued to the alveoli in the same lobe of all the animals. An average of 16 sections were taken per animal, and the entire section was then enlarged into a photomicrograph. Thus, these were not small, individual areas of the lung that were compared, but large representative lung sections. It was these photomicrographs that were then compared to the panel of standards. The three blinded observers were all pathologists at the University of Texas in San Antonio who had no previous knowledge of the animals and their ventilatory support technique. Thus, we feel we had a relatively unbiased set of observers.

Finally, Dr. Anderson asked if we had used conventional therapy first and transitioned any animal to high frequency flow interruption. We did not do that because we were not interested in pursuing this ventilatory mode as salvage therapy, but rather wanted to see if ventilatory mode after the onset of the injury could alter long-term pathology. Because that was our intent, we did not transition animals.

I think we have shown that if we initiate high frequency flow interruption immediately after smoke injury, we can significantly alter the progression of what appears to be ventilator-induced injury.