Pediatric Pulmonology 3:443–447 (1987)

Clinicopathologic Review

Airway Damage and Mechanical Ventilation: A Review and Commentary

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Key words: Necrotizing tracheobronchitis; high frequency oscillatory ventilation; high frequency jet ventilation; rapid rate conventional mechanical ventilation.

INTRODUCTION

Airway damage during mechanical ventilation is not a new problem. Potential and actual complications have been discussed in the medical literature for many years. Reports of an apparently new form of upper airway damage, called necrotizing tracheobronchitis, and its possible relationship to high-frequency ventilation (HFV), prompted this review.

REVIEW

In 1962, Burton[1] described the effects of premedication, dry anesthetic gases, and cuffed endotracheal tubes on the clearance of tracheal mucus. He also described a fatal complication from inspissated mucus in a child. In 1972, Chalon and coworkers[2] discussed the effects of dry anesthetic gases on tracheobronchial epithelium. They found cytoplasmic and nuclear changes after only 1–3 hours of anesthesia. In addition, they noted losses of surface cilia. These studies were directed at the effects of anesthesia and focused on short-term tracheal intubation.

In 1972, Rasche and Kuhn[3] examined airway sections from the autopsies of 19 intubated infants and 12 infants who had never been intubated. Durations of intubations ranged from 15 minutes to nine weeks. Of the intubated infants, eight showed no damage; three had focal necrosis and/or squamous metaplasia; and eight had extensive necrosis of tracheal epithelium and underlying lamina propria. None of the nonintubated infants showed any evidence of tracheal damage. Focal necrosis was found primarily in the larynx and vocal cords. In the patients with extensive necrosis, there were "whole stretches of epithelium and underlying lamina propria" involved. Six of 11 infants intubated between 2½ and 20 hours had extensive tracheal necrosis. Squamous metaplasia appeared when intubations were prolonged beyond 100 hours. There was no evidence of bacterial infection. There was no correlation between age or weight and tracheal damage. The most important factor associated with tracheal damage appeared to be duration of intubation.

Joshi et al[4] reviewed the autopsies of 172 infants with respiratory distress syndrome (RDS). Forty patients were never intubated. Ten of these patients, who had never been intubated, had mucosal necrosis in the region of the larynx. Of the 132 intubated patients, 126 showed some airway damage. In 24, there were lesions in one or both mainstem bronchi. The majority had limited mucosal and/or submucosal necrosis. Twenty-seven patients had more severe lesions, with necrosis and dense neutrophilic infiltrations. Again, there was a direct relationship between severity of the lesions and the duration of intubation.

Since these studies were published, mechanical ventilation of neonates has changed. Many changes were responses to previously described technical problems. Today, uncuffed endotracheal tubes are used, inspiratory gases are humidified and heated, and endotracheal tube sizes and shapes are now standard. Techniques of neonatal mechanical ventilation have changed as well. Continuous positive airway pressure is now routine. There is a trend toward higher ventilator rates and lower inspiratory pressures. More and more tiny infants survive. Virtually all of these smallest survivors are exposed to some form of mechanical ventilation.

Despite technical advances and dramatic improvements in survival, mechanical ventilators still produce complications. Pulmonary air leaks continue to occur, and the incidence of chronic lung disease is still unacceptably

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Received February 7, 1987; (revision) accepted for publication April 16, 1987.

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high. Ventilator-induced airway injuries are persistent problems in modern newborn intensive care.

In recent years, HFV has been proposed as an alternative, to theoretically reduce the incidence of ventilator-induced airway injuries. The reports of Sjostrand and coworkers[5] in the 1970s and Bland and coworkers[6] in 1980 generated much enthusiasm and high hopes. Since those reports, several investigators have shown that high-frequency ventilators can maintain adequate gas exchange, using lower proximal airway pressures.[7-10] However, two recent studies of high-frequency oscillatory ventilation (HFO) showed that some high-frequency oscillators actually require higher airway pressures than conventional ventilators to produce equivalent gas exchange.[11,12] To date, there has been only one large controlled study of high-frequency ventilation. In this study, conventional mechanical ventilation (CMV) and high-frequency jet ventilation (HFJV) produced equivalent numbers of pulmonary air leaks.[13] Despite these studies, high-frequency ventilation has been repeatedly shown to be clinically useful in the treatment of established pulmonary air leaks and seemingly intractable respiratory failure.[8,10]

The initial investigations into the possible complications of high-frequency ventilation were encouraging. Frank and coworkers [14] studied the lungs of dogs exposed to 2–5 hours of HFO. They found normal alveolar morphology, normal numbers of type I and type II cells, and intact surfactant monolayers. Smith and coworkers[15] studied one dog exposed to transtracheal HFJV for 24 hours. While few details were given, they found no gross or microscopic evidence of airway or parenchymal damage. Frantz and associates[16] studied 52 cats. One group breathed spontaneously; a second received CMV; and a third received high-frequency ventilation using a rotating ball-valve device. After four hours, all had similar pulmonary parenchymal pressure-volume relationships, normal surfactant characteristics, and normal distal lung morphology. Hamilton et al[17] studied 20 rabbits with lung disease caused by saline washout. Ten received CMV; ten received HFO. Hyaline membranes developed only in those animals treated with CMV. None were noted in the animals treated with HFO.

Later studies began to suggest that high-frequency ventilation may have side effects somewhat different from those seen with CMV. Rehder et al[18] studied dogs treated with HFO and CMV. After 24 hours, there was overt bronchopneumonia in the HFO-treated animals and none in those treated with CMV. One HFO-treated dog died suddenly from an acute airway obstruction. Keszler et al[19] studied the lung parenchyma of mechanically ventilated dogs. In each animal, one lung was ventilated with HFJV, the other with CMV. The HFJV-treated lungs showed hyperinfiltration and a trend toward acute inflammation. Bell et al[11] examined the lungs of premature baboons treated with CMV, HFO, and a flow interruptor type of HFJV. Significantly more junctional-saccular hemorrhage occurred after both forms of high-frequency ventilation. Unfortunately, none of these studies examined the upper airways in any detail.

In 1981, Carlon and coworkers[20] reported the first complications of high-frequency ventilation in humans. Two patients treated with HFJV developed hemorrhagic tracheitis and bronchial obstruction. Both died. At autopsy, thick secretions occluded the trachea and both mainstem bronchi. The authors speculated that inadequately humidified gases probably contributed to this tracheal damage. In 1983, we reported clinical tracheal obstructions in three neonates treated with HFJV. One patient died. The airway lesions were unusual, consisting of mucosal necrosis, inflammatory cell infiltration, and luminal obstruction with necrotic debris and mucus. Not long after this report, Metlay and coworkers[22] described similar airway pathology in autopsy studies of 35 infants over a 3-year period. The lesions seemed to appear after 3 or more hours of mechanical ventilation. Pietsch and coworkers[23] described similar airway lesions in 19 infants treated with CMV. Unfortunately, no rates, pressures, or oxygen concentrations were mentioned. Fox et al[24] reported impacted tracheal secretions in five infants treated with rapid-rate CMV, and they described clinical features suggestive of necrotizing tracheobronchitis (NTB). Kirpalani et al[25] reported NTB in eight neonates. Six were treated with HFO; two were treated with manual ventilation and CMV. The authors then reviewed autopsy data from 1981 and 1982. Twelve of 284 neonates had NTB. Two of the 12 had received HFO. Whether others had received rapid-rate CMV was not stated. These investigators meticulously searched for infections, chemical toxins, evidence of physical trauma, and humidification problems. In the end, they concluded that NTB appeared to be a "rediscovered condition related to endotracheal intubation and mechanical ventilation using high mean airway pressures." Harris and coworkers[26] described NTB in 12 neonates following HFJV. The lesions ranged from tracheal ulcerations to total airway obstructions. In 1985, we reported tracheal injuries in 15 of 34 patients treated with HFJV.[10] A later autopsy study[27] examined eight infants treated with HFJV and compared them with eight treated only with CMV. The infants treated with HFJV showed significantly more histologic damage at all levels of the airway.

Today, most clinicians associate NTB with HFJV. However, NTB has been seen following virtually all forms of mechanical ventilation. Reports by Kirpalani et al[25] and Fox et al[24] implicate conventional-rate CMV, rapid-rate CMV, and HFO. Metlay et al[22] and Pietsch et al[23] described NTB in patients treated only with CMV.

Fuksman and coworkers[28] reported NTB in 34 autopsied infants treated only with CMV. Despite current impressions, NTB is not unique to HFJV. Other factors besides type of ventilator are involved in producing this lesion. Important associated problems include severity of underlying illness, shock, infection, total duration of mechanical ventilation, need for high peak and mean airway pressures, early or ongoing asphyxia, and other as yet unknown factors. The contribution each of these makes is unknown, but prolonged exposure to mechanical ventilation of any type plays a major role in the development of NTB.

Several recent animal studies have also addressed the issue of high-frequency ventilation and airway damage. In 1984, we examined the tracheal damage seen following HFJV, using two different humidity systems, and compared it with that seen following conventional rate CMV.[30] Regardless of the humidity system, tracheal damage was always greater during HFJV. Improved humidification lessened the damage, but did not eliminate it. Recently, we compared the airway damage associated with two different high-frequency jet ventilators to that seen following rapid-rate (150 bpm) and conventional rate (20 bpm) CMV.[31] All forms of high-frequency ventilation, including rapid-rate CMV, produced significantly more airway damage than conventional-rate CMV. The damage was inflammatory and occurred predominantly in the region of the endotracheal tube tip. These observations were recently expanded to include HFO (900 bpm) and a high-frequency jet ventilator cycling at rates of 400 bpm and 900 bpm.[32] Again, all forms of high-frequency ventilation produced more airway damage than conventional rate CMV. The damage produced by HFO and rapid-rate CMV was histologically identical to that produced by HFJV. Interestingly, HFJV cycling at 900 bpm produced somewhat less damage than the same ventilator cycling at 400 bpm. HFJV at 900 bpm also produced somewhat less damage than HFO at 900 bpm. A recent preliminary report by Naglie and colleagues[33] examined the tracheas of 13 cats treated with two types of HFJV and conventional-rate CMV. These authors found no differences in any group. However, they caution that there were small numbers of animals in each group.

COMMENTARY

Since 1980, we at St. Paul Children's Hospital have treated 59 patients with HFJV. Details from 34 of these patients were previously reported.[10] Our first 25 patients were treated with the IDC VS600 high-frequency jet ventilator (Instrument Development Corporation). The VS600 was an early, relatively basic device, with no alarms or provisions for airway humidification. Our last 34 patients were treated with the Mallinkrodt/Bunnell Life Pulse jet ventilator. This machine is a computer-assisted, servo-controlled device, with numerous pressure alarms and a sophisticated humidification system. We have used tracheobronchoscopy to diagnose and treat clinical airway obstructions. To date, 13 patients have undergone bronchoscopy; nine (71%) had tracheal inflammations consistent with NTB; six (11%) had significant tracheal obstructions. Forty-one of 59 patients ultimately died. Twenty of the 22 who had autopsies (91%) showed histologic evidence of NTB. Twenty-five patients were treated with the VS600. Nine (36%) had clinical evidence of NTB. Five (25%) had significant airway obstructions. One of these obstructions was fatal. Thirty-four patients were treated with the Life Pulse. Nine (26%) had clinical findings suggestive of NTB, but only one (3%) had a significant airway obstruction. This obstruction was successfully treated by bronchoscopy.

Our clinical and autopsy experiences are perplexing. At autopsy, we found that tracheal inflammation is almost always present following high-frequency ventilation, and that the degree of inflammation is greater than that seen during CMV.[27] Our experience suggests that although tracheal inflammation is present, in most cases it has little clinical significance. To date, none of the 18 patients who were treated with HFJV and survived have shown chronic airway compromise clearly related to NTB.

Can NTB be prevented? As long as mechanical ventilation is used to treat newborn lung disease, some NTB is likely to be inevitable. Strategies to prevent NTB should be similar to those used to prevent bronchopulmonary dysplasia. Prevention of pulmonary barotrauma should prevent the need for HFV. Although short inspiratory times and more rapid rates during CMV have been proposed as useful techniques towards this end,[6,34,35] others have suggested that active expiration during mechanical inspiration, not ventilator rate or pressure, is more important in producing lung rupture.[36,37] Additionally, conventional ventilators may be of limited usefulness at very rapid rates (> 75–100 bpm) due to their design.[38] Since the airway damage we and others have observed is predominantly inflammatory, glucocorticoid therapy may be useful in its prevention. We are currently studying this approach in laboratory animals.

From our six years of clinical and laboratory observations, and our review of the observations of others, we have come to the following *practical conclusions*:

1. Upper airway damage has occurred for as long as endotracheal tubes and mechanical ventilators have been used.

2. Necrotizing tracheobronchitis appears to be a new, more severe airway damage pattern, perhaps an exaggeration of damage previously ascribed to endotracheal tubes and mechanical ventilators.

3. The etiology of this airway damage is probably multifactorial. Humidity, duration of mechanical ventilation, airway pressure, ventilator type, ventilator rate, and other factors seem to be involved.

4. Airway damage appears to be magnified by prolonged mechanical ventilation, decreased humidity, and increased ventilator rate.

5. NTB occurs following all forms of mechanical ventilation, both conventional and unconventional. The popular notion that NTB occurs only following HFJV is simply not true.

6. Clinically significant NTB is unusual. Subclinical (histologic) NTB, that is, erythema of the mucosa seen at bronchoscopy, or nonobstructive clear mucosal and submucosal changes seen at autopsy, is quite common. The long-term effects of subclinical NTB are not yet known.

7. Airway obstructions from NTB are treatable when recognized.

8. Airway damage is more common following high-frequency ventilation. This fact should temper enthusiasm for the general application of this technique. However, it should not prevent the use of HFV in clinical situations (such as severe pulmonary barotrauma) in which it would be beneficial.

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