Virchows Archiv A Pathol Anat (1988) 413:257–264

Virchows Archiv A
Pathological Anatomy and Histopathology

Necrotizing Tracheobronchitis: A complication of high frequency jet ventilation

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Summary. The tracheal and bronchial lesions observed are described in seven patients, presenting with respiratory distress syndrome and receiving both conventional and high frequency jet ventilation for various periods. The histological findings are related to the duration of the exposure as well as the number of pulsations administered to the tracheobronchial tree. Severe damage to the mucosa leading to acute tracheobronchitis, hyperplasia and hypersecretion of the mucosal glands may explain some of the clinical symptoms observed, especially the upper respiratory obstruction. Care should be taken to limit these changes which may lead to various degrees of stenosis in survivors receiving this mode of therapy.

Key words: Respiratory distress syndrome – Necrotizing tracheobronchitis – High frequency ventilation – High frequency jet ventilation – Conventional mechanical ventilation

Introduction

High frequency ventilation (HFV) has recently become a valuable asset in the treatment of critically ill patients in need of mechanical ventilatory support. The technique includes various types of ventilatory support of which high frequency jet ventilation ((HFJV) is one of the three most popular systems employed in the clinical setting (Chang and Harf 1984; Froese and Bryan 1987; Sjöstrand 1980; Wetzel and Giora 1987). This technique of ventilation has found application in intensive care units and operating theatres, especially those dealing with cardiac or thoracic surgery and otolaryngeal problems (Bishop et al. 1987; Carlon et al. 1981, 1985a–b; Gallagher 1985; O'Sullivan and Healy 1985; Schlenkhoff et al. 1986).

Evidence from animal experiments and data accumulated from patients subjected to this technique suggests that it is not without side effects on both the lung parenchyma and the tracheobronchial tree (Nordin et al. 1982; Ophoven et al. 1984).

We have had the opportunity to study the lesions in the tracheobronchial tree of seven patients coming to postmortem who were exposed to HFJV treatment of variable duration. The morphological findings in these cases are reported and compared with those described in the literature.

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Materials and methods

Seven cases presenting with necrotic tracheobronchic lesions associated with HFJV were seen at the Institute of Pathology between 1985 and March 1988. The patients' ages varied between 18 months and 61 years. There were 3 males and 4 females and all presented with the adult (A) or infantile (I), respiratory distress syndrome (RDS) (Table 1).

All seven patients suffered from severe infections with progressive hypoxaemia and they were all exposed for various periods to conventional mechanical ventilation (CMV) and later to HFJV for variable duration of time, 18 h to 24 h. In every case, HFJV was superimposed on CMV as shown in Table 2 which summaries the ventilatory exposures of the patients.

Table 1. Material

Patient	Age (years)	Sex	Clinical diagnostic
1	48	F	ARDS
2	61	F	ARDS
3	15	F	ARDS
4	35	M	ARDS
5	60	M	ARDS
6	58	M	ARDS
7	$1^1/_2$	F	IRDS

Table 2. Ventilator setting during CMV-HFJV

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7	
	CMV	HFJV	CMV	HFJV	CMV	HFJV	CMV	HFJV	CMV	HFJV	CMV	HFJV	CMV	HFJV
FIO_2	0.7	0.7	0.7–1	0.7–1	0.6–1	0.6–1	0.6–0.9	0.6–0.9	0.6–0.8	0.6–0.8	0.6–1	0.6–1	0.7–1	0.7–1
F (min^{-1})	10	300	18	250	26	400	24	400	28	250	20	350	40	600
VT (litres)	0.05	0.074	0.250	0.060	0.200	0.032	0.26	0.042	0.300	0.060	0.28	0.044	0.100	0.018
VE (litres)	0.9	22.1	4.5	15.0	5.2	12.8	6.24	16.96	8.4	15.0	5.6	15.4	4.0	11.0
TI/TE	3/1	1/3	1/1	1/3	2/1	1/3	3/1	1/3	1/1	1/3	2/1	1/3	2/1	1/3
Peak AWP (cmH_2O)	70		60		60		60		55		55		65	
PEEP (cmH_2O)	15		10–15		15		15		10–12		5–12		10	
Duration (hours)	18		72		48		64		153		175		240	

Abbreviations: FIO_2, fractional inspired O_2 concentration; F, breathing rate; VE, VT, minute volume, tidal volume; PEEP, positive end expiratory pressure; Peak AWP, peak airway pressure; CMV, Conventional mechanical ventilation; HFJV, high frequency jet ventilation; TI/TE, inspiration/expiration duration ratio

Bacterial studies were performed on tracheal biopsy material in all cases. Streptococcus pneumoniae was isolated from cases 1 and 6, Staphylococcus aureus and Bacillus fragilis from case 2, Legionella pneumophila and Aspergillus fumigatus from case 4, and Bacillus melanino-genicus from case 7. No organism was grown from cases 3 and 5.

As the clinical histories in all cases were very much alike, a summary of two cases (those with the shortest and the longest duration of ventilation) will be summarized as examples.

Case 1. This forty-eight year old female presented with fever, a dry cough and right sided chest pain which increased on respiration. The following day she was hospitalized in a state of circulatory shock. On admission her temperature was 39° C and chest roentgenography showed bilateral white lung fields. Sputum was positive for pneumococcus. Her condition deteriorated rapidly within the next two days necessitating conventional mechanical ventilation and HFJV. Despite aggressive intensive treatment, her condition deteriorated steadily and she developed necrotising tracheobronchitis. She died 13 days after admission.

Case 7. This 18 month-old female infant was transferred from another hospital to our intensive care unit. Her illness had begun 10 days previously when she was found to be apathic. On admission she was comatose, with neck rigidity and covered by purpuric spots over her entire body. A spinal tap and blood cultures revealed Neisseria meningitis which persisted in spite of specific antibiotherapy. Her symptoms were complicated by circulatory shock and IRDS. She was ventilated mechanically including HFJV. Intensive therapy including extracorpreal CO_2 elimination did not improve the clinical situation and she died after 10 days of HFJV.

In all cases the lung and neck organs were removed "en bloc". The larynx and the tracheae were opened posteriorly. The tracheae and the proximal portion of the main bronchi were oedematous and diffusely haemorrhagic.

In cases 2 and 4, several cartilage rings in the mid portion of the trachea were exposed, especially in case 5 which presented with tracheopathia osteochondroplastica. At the carina, the mucosa was eroded leaving the cartilage uncovered and bulging outward.

Case 6 presented with a thick muco-haemorrhagic material in the lumen of the trachea and main bronchi. In addition, there were ulcerations due to biopsies taken during the course of the ventilation.

In case 7 the entire lumen of the trachea and main bronchi were obstructed by a thick, gelatinous, haemorrhagic material, focally adherent to the mucosa.

The organs were fixed in 10% formalin and sections taken, embedded in paraffin and cut at 5 μ. These were stained with haematoxylin-eosin, van Gieson-elastin and period acid Schiff (PAS) stains, and where necessary, with Gram or Grocott stains.

Results

In case 1 there was erosion of the mucosa with oedema and or necrosis involving the basal lamina and extending into the submucosa. In some areas, superficial ulcers were observed. There were focal haemorrhages. The inflammatory reaction was slight and made up principally of polymorphonuclear leukocytes. There were scattered foci of squamous cell metaplasia. The glands were often dis-

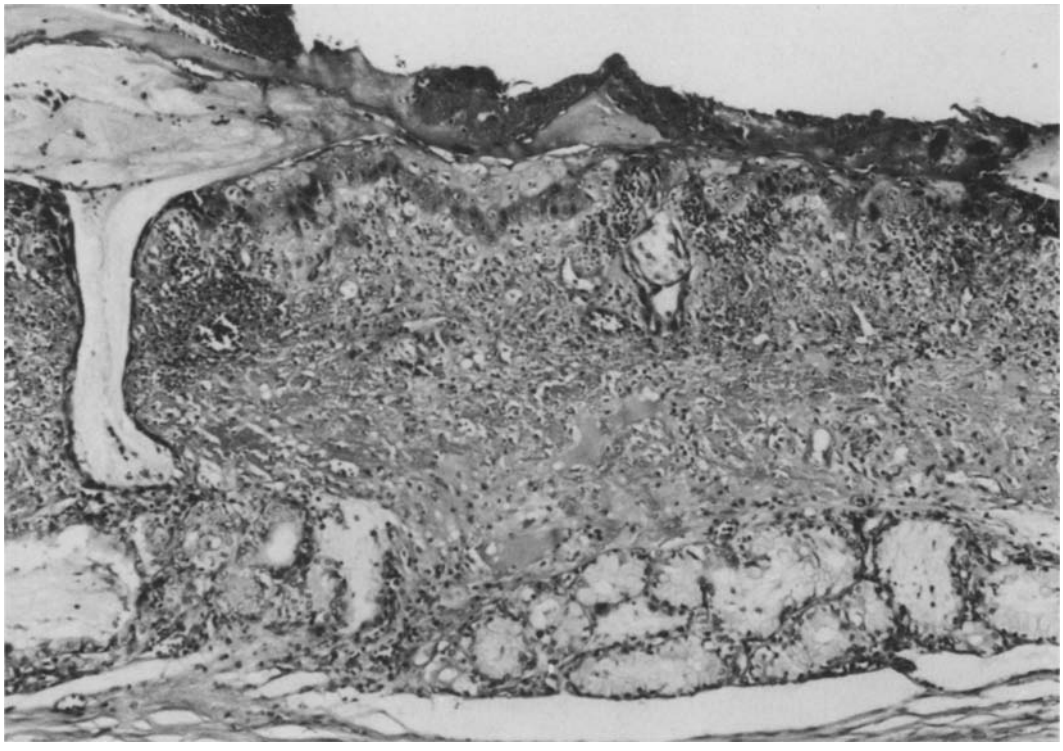


Fig. 1. Case 1. There is extensive necrosis of the broncheal epithelium partly covered by necrotic material mixed with mucus and red cells. Note the metaplastic changes of the epithelium at the opening of the duct with dilatation of the broncheal gland filled with mucus already after 18 h of HFJV (HE ×120)

tended, and contained mucus. The cartilage was not involved in any of the sections examined (Fig. 1).

Similar changes were seen in case 2 where the cartilage was superficially involved in some areas. There was a diffuse infiltration of the necrotic mucosa and the cartilage plates in areas by candida albicans.

In case 3 the epithelial changes were similar to those of case 1, but somewhat more extensive. There were numerous ulcerations of the mucosa. Some of the ulcers reached the cartilage rings which were eroded. There were extensive haemorrhages, occasionally confluent, dissecting the submucosal tissue. Squamous metaplasia was more extensive and also involved the excretory ducts of the glands.

In case 4 the necrotic changes involved both the superficial layers and the deeper layers (Fig. 2a). There was an inflammatory infiltrate composed principally of polymorphonuclear leukocytes, localized in the superficial layers. Squamous metaplasia of the surface epithelium was prominent. The epithelial surface mucosa was separated from the submucosa by an eosinophilic, hyaline membrane of variable width (Fig. 2b). There were patchy zones of necrosis. The glands and excretory ducts were markedly distended with mucus and the ductular cells showed squamous metaplasia. The glandular epithelial cells were hyperplastic.

Case 5 showed calcification and partial ossification of the cartilage rings as well as the intercartilage tissue. Ulcers were prominent over these areas and there was extensive necrosis of the mucosa. In case 6 the histological changes were similar to those present in cases 2, 3, 4 and 5. There was a diffuse acute inflammatory infiltrate (Fig. 3). Although there was poor preservation of some parts of the material, areas of squamous metaplasia were prominent.

In case 7 the tracheal mucosa showed areas of erosion interspersed by thick layers of metaplastic squamous epithelium alternating with layers of necrotic tissue. In other areas, the mucosal surface was covered by a thick eosinophilic material containing cellular debris and other elements giving it a blue-violet hue (Fig. 4a). In places, the cartilage was extensively eroded. The intensity of the inflammatory infiltrates and haemorrhages were variable and there was marked oedema. The posterior wall (acartilaginous) of the lower third of the trachea was most severely altered. The main bronchi also showed ulcerations, but the most striking

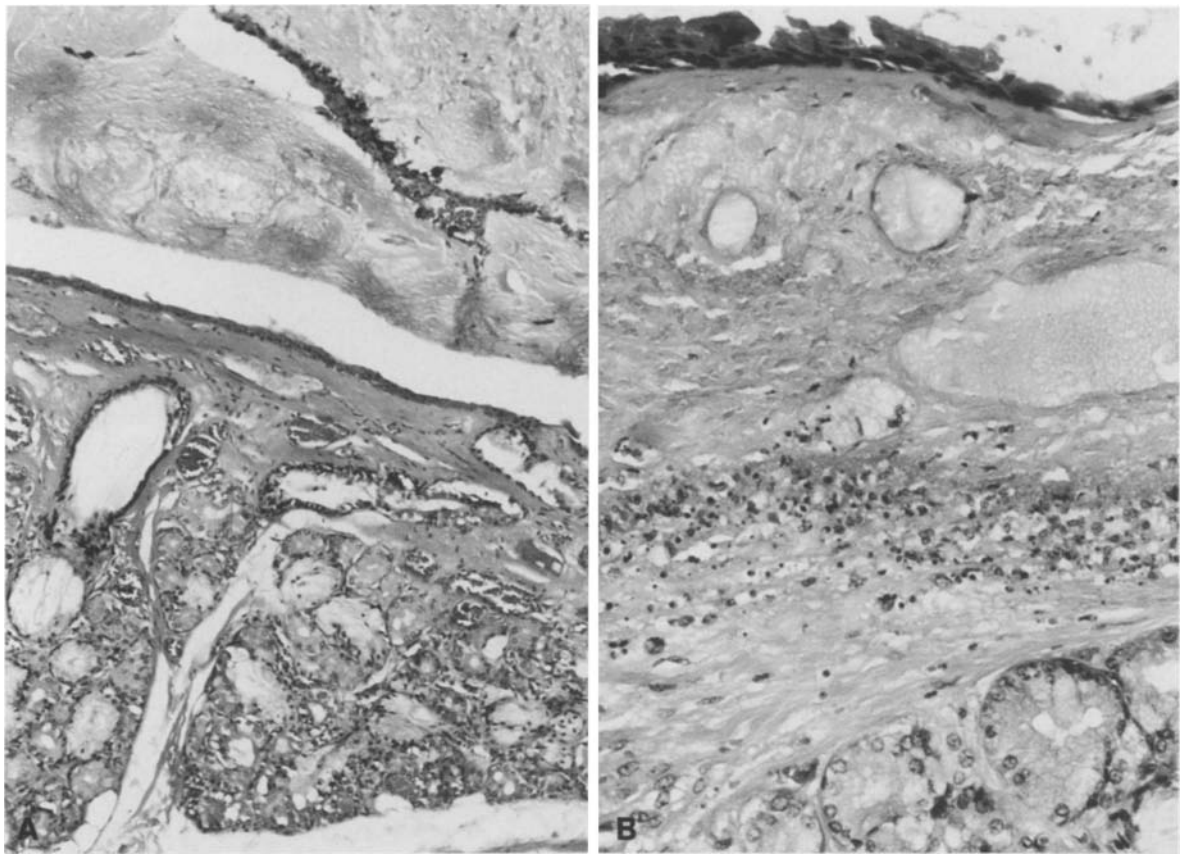


Fig. 2. (**A**) There is epidermoid metaplasia of the epithelium covering a hyalin band. The glands are dilated but the inflammatory reaction is minimal at this level (HE ×120). (**B**) Below the hyalin ban there is marked oedema and a basophilic, necrotic band infiltrated by polymorphonuclears (HE ×225)

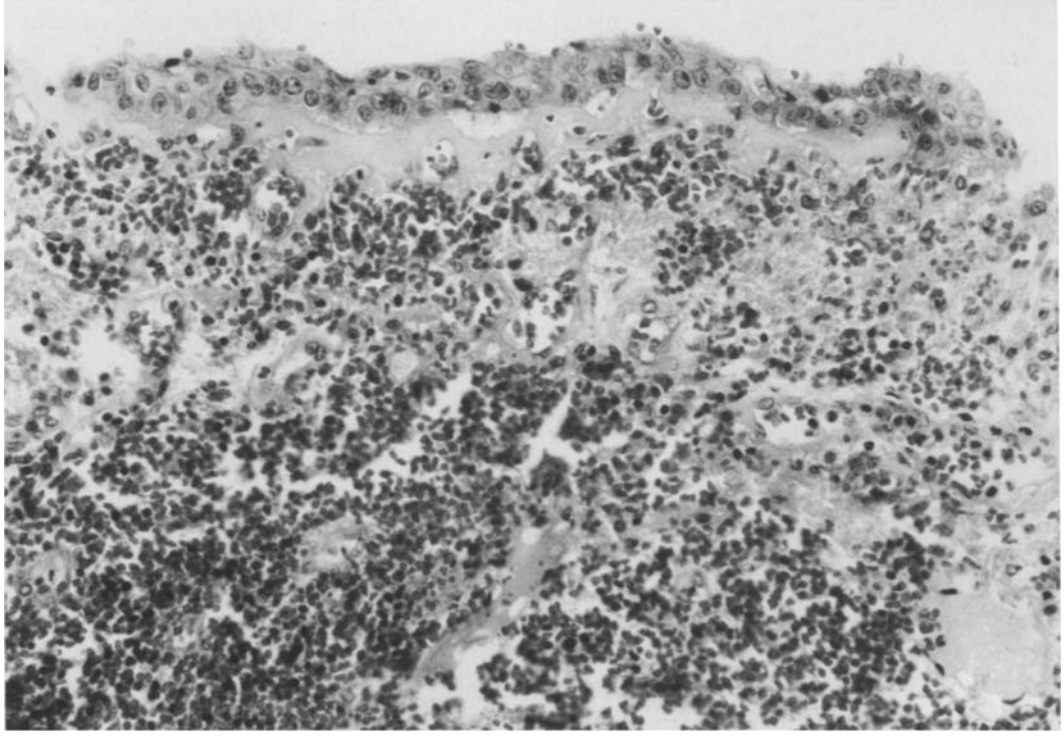


Fig. 3. The mucosa is oedematous, partly necrotic in places and is markedly infiltrated by mononuclear cells and numerous polymorphonuclear cells (case 4) (HE ×225)

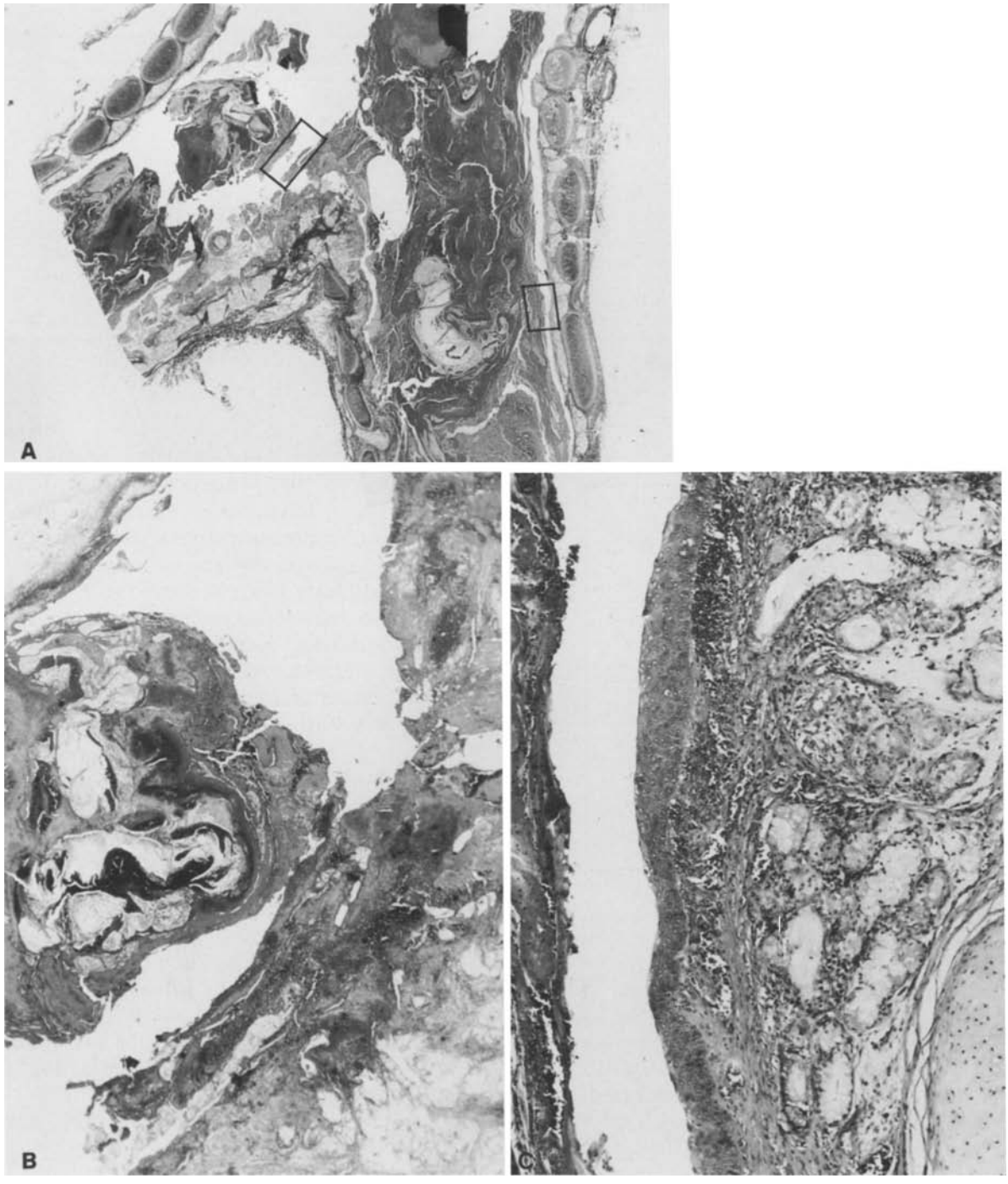


Fig. 4. (**A**) Case 5. Showing the division of the trachea and main stem bronchi. The lumen is obliterated by a mucofibrinous material containing cellular debris but few inflammatory cells. The carinea is completely necrosed (HE ×60). (**B**) Detail of the rectangle on the left showing the extensive necrotic changes of the carinea covered by necrotic, haemorrhagic tissue (HE ×225). (**C**) Left main stem bronchi (rectangle on the right) showing the marked epidermoid metaplastic changes of the broncheal epithelium. Note the underlying band of inflammatory cells and the dilated glands (HE ×225)

feature was the marked squamous metaplasia of the epithelium. This extended into the branches up to about the 4th or 6th generations of the bronchial tree on both sides (Fig. 4b, c). There was also extensive consolidation of both lung fields.

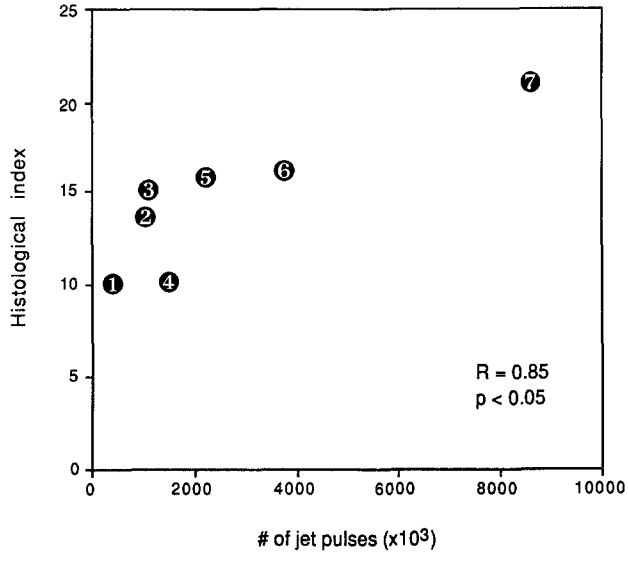
Using an index assaying the severity of the tracheal, injury based on the histological findings by simply adding, for a given patient, all the numbers attributed to the different lesions observed in the tracheal wall and considering patient 1 as having

Table 3a. Results

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Erosion	++	++	++	+	++	++	++
Ulceration	+	++	++	+	++	++	++
Necrosis	++	+	++	++	++	++	++
Intraluminal mucus	++	++	++	++	+	++	+++
Haemorrhage	+	+	++	−	+	+	++
Oedema	−	+	+	+	+	+	+
Squamous metaplasia	+	++	++	+	+++	++	+++
Cartilagenous lesions	−	++	+	−	++	+	++
Inflammatory infiltrate	+	+	+	+	++	+++	+++
Histologic index	10	14	15	10	16	16	21
Nr of jet pulsations	324×10^3	1080×10^3	1152×10^3	1536×10^3	2295×10^3	3675×10^3	8640×10^3

Jet pulsations = (Nr hours) × 60 × frequency jet/min

Table 3b



a severity index of 10, then the other patients had indices of 14, 15, 10, 16, 16 and 21 (Table 3a). By calculating the number of tracheal jet pulses delivered to the tracheal wall per patient (jet frequency per min × 60 × number of h of jet ventilation) another index can be determined with values for the seven cases respectively of: 324, 1080, 1152, 1536, 2295, 3675, and 8640×10^3 jet pulses per patient which show a significant correlation of number of pulses with severity of effect ($R = 0.894$; $P < 0.05$; Pearson's correlation coefficient). Both indices correlate as observed in Table 3b.

Discussion

Since its introduction, HFJV has been used in the neonatal intensive care unit in various clinical conditions including the idiopathic respiratory distress syndrome (IRDS) and congenital diaphragmatic hernia (Boros et al. 1985; Harris et al. 1984; Kirpalani et al. 1985). It is also employed in adults with ARDS and in postoperative respiratory failure and during laryngoscopy and/or bronchoscopy (O'Sullivan and Healy 1985; Sanders 1967). It was quickly realized that some pulmonary complications (pneumothorax, pneumomediastinum and subcutaneous emphysema) were associated with this type of ventilation and were probably due to barotrauma (Gaylord et al. 1987; Hamilton et al. 1983).

Neonates and infants who had received HFJV and died showed lesions of their tracheobronchial tree in addition and the extension of these depended largely on the duration of the ventilation (Boros et al. 1985). Experiments in various animal models helped to confirm these observations (Hamilton et al. 1983; Ophoven et al. 1984; Smith et al. 1981). Injuries to the tracheo-bronchial tree were observed even though the periods of ventilation with one or several mechanical techniques were of relatively short duration (not exceeding hours or 1 or 2 days at most Boros et al. 1985; Neu et al. 1984).

The low humidity of the driving gas was thought to be the cause of the lesions, with drying of the mucous secretion and the surface epithelium leading to poor or decrease ciliary activity (Carlon et al. 1981, 1985a–b; Forbes 1973; Marfatia et al. 1975; McTutyre et al. 1983; Poulton and Downs 1981). Nordin et al. (1982) have shown early ultrastructural changes in the trachea of experimental animals receiving too little humidification or hyperhumidification during HFJV; the former resulting in more severe changes. They concluded that there is an optimal level of humidification when the changes are minimal.

In man the tracheobronchial lesions are not very different from those observed in experimental animals. Macroscopically, the principal lesions are situated distal to the tip of the tube generally the lower half of the trachea and main bronchi. The mucosa at the level of the tip of the tube and distal to it is general darkish-red, haemorrhagic, oedematous, and within a few days may be covered by a thick, adherent dark-red jelly-like material, or the tracheal lumen may be completely moulded or plugged by it as was observed in two of our cases (cases 6 and 7). This has been observed by several authors after a few days of HFJV and has required removal either by aspiration or by bronchoscopy (Harris et al. 1984; Tolkin et al. 1984). Some authors have used tracheal biopsies in patients receiving HFJV in order to arrive at a precocious diagnosis before the clinical signs of upper airway obstruction (poor chest movements, air trapping and severe CO_2 retention) make their appearance (Kirpalani et al. 1985; Metlay et al. 1983; Tolkin et al. 1984). In addition, we observed in our seven patients that the mucosa of the upper portion of the tracheae was congested, oedematous and was eroded in places. This may be due partly to the endotracheal tube.

In our series the patient (case 1) who was least exposed to HFJV showed various histological features of which the most striking was the swelling of the epithelial cells with a pale cytoplasm. This may be a prenecrotic or early necrotic phase of the epithelial layer before shedding takes place and could explain the marked decrease in ciliary activity noticed by several authors (Fox et al. 1984; Gau et al. 1987; Rock et al. 1976). This was accompanied by marked oedema and congestion of the mucosa. These changes were often localized and gave way to areas of denuded basal membranes and/or eventually to superficial ulceration. The inflammatory reaction was moderate, but multifocal and diffuse. There were focal areas of squamous metaplasia.

Another striking feature was the marked distention of the underlying mucous glands which were filled with a pale PAS-positive mucus. The lining cells were large, hyperplastic, whereas the cells of the glandular ducts were flattened or cubic. Moreover, the ducts were often obstructed by mucus plugs which extended into the tracheal lumen. These changes were more prominent with the increase in duration of exposure; the squamous metaplastic changes extending into the ducts of the glands. This change was already observed in the patient (case 3) who had had only 48 h exposures of HFJV.

The early and extensive breakdown of the epithelial lining and the mucosa, the rupture of blood vessels with haemorrhages and the hypersecretion of the mucous glands could explain the formation and accumulation of the so called mucous plug often mentioned in the literature (Carlon et al. 1981; Harris et al. 1984; Kirpalani et al. 1985). The organism thus has very little resource left for eliminating this material, which can lead to complete tracheobronchial obstruction as observed in cases 6 and 7.

The formation, composition and elimination of this material during HFV has been the subject of much debate. It has been observed both with HFJV and high frequency oscillation (HFO) and is often described as necrotizing tracheobronchitis. Both experimental and clinical studies indicate that the tracheobronchial mucosa distal to the tip of the tube undergo similar changes (Boros et al. 1985).

The squamous metaplasia seen at 18 h becomes more extensive with time and extends well into the broncheal tree for several generations, as has been observed by other authors (Harris et al. 1984; Kirpalani et al. 1985) indicating that damage is not only limited to the area within the immediate vicinity of the tip of the endotracheal tube. This change can also be seen in patients treated over long periods with conventional ventilation (Gau et al. 1987; Keszler et al. 1982; Köhn 1969; Takemura and Akamatsu 1987).

The carina was severely involved in three of our cases. The cartilage rings were denuded in some areas and the mucosa was extensively ulcerated, elsewhere there was thick metaplastic squamous epithelium. In both the lower trachea and the main stem bronchi there were signs of repeated attempts at repair of the epithelium in the form of successive layers of metaplastic squamous epithelial layers separated by a wedge shaped fibrinohyalin band. This may be due to the variation in the direction of the jet flow during various periods. Whether these changes are reversible or not is not known as there is no long term follow-up of survivors.

The lesions observed in cases of conventional mechanical ventilation are well documented (Bishop et al. 1987; Köhn 1969; Rattenborg and Via-Regue 1981; Suguihara et al. 1987) and do not resemble those seen in these cases. The histological findings are comparable to those observed in experimental animals and in patients, especially infants, receiving high frequency jet ventilation for the infantile respiratory distress syndrome. There is the possibility that the severe damage in the seven cases presented is due to the additive effect

of the two modes of ventilation and that the gravity of the lesions depends on the summation of the pulsations administered to the tracheobronchial lower tree. Thus, in order to limit these lesions which may lead to tracheobronchial obstruction or tracheal stenosis in survivors, proper control of the frequency and duration of the pulsations in patients receiving HFJV is manditory.

Acknowledgements. The authors wish to thank Miss J. Stalder and Mr T. Ming for technical assistance, Messers J.-C. Rumbeli and E. Denkinger for the photographs and Miss A. Polichouk for typing the manuscript.

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Accepted April 20, 1988