The pathology of neonatal endotracheal intubation and its relationship to subglottic stenosis

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Introduction

The most common serious long-term consequence of neonatal endotracheal intubation is acquired subglottic stenosis (SGS). The incidence in intubated infants is variously reported as between one and eleven per cent but this may be a relatively high range, reflecting the interest of the reporting centres and the various methods of diagnosis. (Fearon *et al.*, 1966; Parkin *et al.*, 1976; Strong and Passy, 1977; Papsidero and Pashley, 1980; Jones *et al.*, 1981; Sherman *et al.*, 1986).

In one study conducted at University College Hospital London (UCH) we reported an incidence of 1.8 per cent of SGS in all intubated neonates in a three year period (1981–83); if only survivors were considered the incidence was 2.6 per cent (Quiney and Gould, 1985). The relatively high incidence during this particular time focussed our attention on SGS and the factors which might precipitate its occurrence.

It is worth stating however, that since this study was performed, and after modifications to clinical management of the newborn were instituted, there has not been one case of subglottic stenosis arising from the neonatal unit at UCH of sufficient severity to necessitate tracheostomy.

Clinical studies have approached the problem of SGS mainly by attempting to identify a factor or factors in the history of the infant which might have precipitated the stenosis such as the gestation of the infant, length of intubation, frequency of intubations, tube size or type, infection of the larynx or the benefits of naso versus orotracheal intubation (Fearon *et al.*, 1966; Abbott, 1968; Choffat *et al.*, 1976; Holinger, 1976; Hawkins 1978; Ratner and Whitfield, 1983; Sherman *et al.*, 1986).

A number of pathological studies have examined the larynges of neonates dying after a period of intubation, and have described the injuries produced by short and long-term intubation (Bozic, 1969; Lindholm 1969; Joshi *et al.*, 1972, Rasche and Kuhns, 1972). Curiously, there are no studies, as far as the author is aware, which describe the detailed pathology of an established case of acquired SGS, probably for two reasons.

First, although there is an increased mortality rate associated with treatment (Fearon and Cotton, 1974; Quiney *et al.*, 1986); SGS, is not, by itself, a fatal lesion and thus very few larynges become available for histopathological study. Second, there appears to be an underlying assumption that we know the pathology of established SGS and that it consists simply of a cicatricial ring of dense fibrous tissue at the level of the cricoid cartilage. Thus, because it is considered that study of the stenotic larynx will not contribute to our understanding of this condition the rare larynx that becomes available is not examined.

The descriptions given below of endotracheal intubation induced injury are primarily based on our own studies at UCH (Gould and Howard, 1985), although many of these changes have been documented previously in other reports (Bozic, 1969; Lindholm, 1969; Joshi *et al.*, 1972; Rasche and Kuhns, 1972).

In addition, a report is included of a larynx from a child who died a number of years after treatment for SGS. This gives some insight into the long-term consequences of endotracheal intubation.

From 1981–83, 43 larynges of infants intubated for periods ranging from less than one hour up to a maximum of 84 days were studied. Seventeen of these had been intubated for a period of greater than three days. From 1984 to the present time, a further 20 larynges from infants intubated for more than three days have been examined. The maximum period of intubation in this group was 144 days.

Attention has focussed on two areas of the larynx. The subglottic region at the level of the cricoid cartilage which is the site of the stenosis; and the posterior part of the glottis, over the arytenoid cartilages.

All larynges are examined in the same way. The supraglottis, glottis and subglottic regions often with the first one or two tracheal rings are cut horizontally into three or four blocks. Following routine processing, each of these blocks is serially sectioned and sections are stained with haematoxylin and eosin at 300μm intervals. Where necessary, intervening levels are stained, sometimes with special stains, to document a particular area in more detail.

Pathology of Endotracheal Intubation

For the purposes of description, the injuries sustained by most larynges following endotracheal intubation have been divided into two periods; a period of acute injury followed by a second phase of healing. A few larynges demonstrate unusual features which might be considered outside the usual pattern of events, but

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which illustrate or highlight a particular aspect of the problem.

Acute injury

Ulceration of glottic and subglottic mucosa during intubation is almost invariable and the type of injury seen in each site is similar. Due to the shape of the larynx, the endotracheal tube rests posteriorly. In the glottis, this is over the arytenoid cartilages which usually demonstrate the most severe degrees of acute ulceration. Similarly, at the level of the cricoid ring, it is the more posterolateral aspects of the subglottic region which are affected. In the early stages of injury to the subglottis, there may be superficial ulceration but with a deeper layer of oedema in the more loose connective tissue immediately adjacent to the cartilage.

Mucosal necrosis may be full thickness and exposure with partial erosion of the underlying cartilage is not infrequent. When this does occur it is usually very rapid, often within two or three days of intubation. Five of the 37 cases intubated for longer than three days, however, demonstrated acute circumferential necrosis of mucosa. Injury is produced by a combination of mechanical trauma and ischaemic pressure necrosis. Infection may also play a role in some instances and two cases have been seen in which the ulcers were infected. It is possible that the presence of infection causes further injury to the laryngeal mucosa even after extubation.

One puzzling aspect of acute injury is perichondritis. On the outer aspect of the cartilages, usually opposite the worst areas of ulceration and necrosis, an acute inflammatory exudate forms. Although frequently mild and of little significance, it occasionally can be seen to erode the cartilage from the external surface, presumably following fragmentation of neutrophils and the release of their lysosomal enzymes. The cause of the perichondritis is not at all clear. It is possible that the abnormal vertical movements of the laryngeal cartilages, produced by the endotracheal tube, lead to abnormal stresses and therefore damage the perichondrium where it is attached to the surrounding connective tissue.

Healing phase

Evidence of healing of the ulcers may be found at the end of the first week of intubation but usually does not become readily apparent until the end of the second or third week. The ulcers, both over the arytenoid and cricoid cartilages become re-epithelialized with squamous epithelium which is often hyperplastic. Where cartilage erosion has occurred, re-epithelialization may occur almost directly onto cartilage. Metaplastic epithelium can extend into mucosal gland ducts.

Reparative fibrosis is associated with the healing process and may be seen in two main sites. First at the margins or in the base of ulcers. It is of interest that because re-epithelialization of deep ulcers often occurs almost directly onto cartilage with very little intervening connective tissue, the lumen diameter at the deeper ulcers may actually be increased.

The second site of fibrosis is in the deep subglottic mucosa, beneath the mucous glands and adjacent to the cricoid cartilage. Presumably this represents organization of the oedema which may be found at this site in the acute phase of injury. It may lead to slight narrowing of the lumen despite the fact that the injury may be relatively superficial.

Cricoid cartilage necrosis

From the above it might be concluded that cartilage erosion might almost be considered beneficial. However, severe injury may lead to full thickness necrosis of the cricoid cartilage. Of the 37 cases of infants intubated for more than three days, five have shown full thickness cricoid necrosis (Table 1).

Although in one case there was no evidence that this had significantly contributed to narrowing of the laryngeal lumen, in two the reparative fibrosis and partial collapse of the cartilage framework appears to have contributed to alterations in the shape of the lumen. In the remaining two cases, injury was still acute, and the longer term effects could not be assessed.

Case report

We have recently had the opportunity to examine the larynx of an infant who died suddenly, some two years after finishing treatment for SGS. It has provided some information concerning the long-term consequences of SGS and surgery.

Born at 26 weeks gestation (900 gms), this infant required ventilation from birth because of immaturity and hyaline membrane disease. At 12 weeks of age, transfer to UCH was carried out after a diagnosis of SGS had been made following repeated failures of extubation. Subsequent management (under Mr Graham), included tracheotomy, a castellated laryngotracheoplasty at 18 months of age, laser removal of granulations and intralesional steroid. Decannulation was finally achieved at five years of age. Twenty-two months after decannulation he died suddenly due to a respiratory tract infection.

Pathology

In the glottis there was evidence of old arytenoid cartilage ulceration with partial destruction of the vocal process and fibrous replacement. The cricoarytenoid joint showed a fibrous ankylosis and the left posterior cricoarytenoid muscle contained a focus of atrophic muscle fibres typical of a denervation injury. Both the thyroid and cricoid cartilages were disrupted anteriorly due primarily to the surgery. The lumen showed at some

TABLE I

BRIEF CLINICAL DETAILS OF CASES WITH FULL THICKNESS CRICOID NECROSIS.

	Gestation (weeks)	Age (day)	Intubation Period (days)	Nature of Injury Acute	Healed
1	30	10	5	+	−
2	28	84	77	−	+
3	26	28	27	−	+
4	27	144	144	−	+
5	30	44	44	+	+

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levels a striking distortion of its shape immediately beneath the cartilaginous disruption; at other levels, there was a severe stenosis consisting of dense fibrous tissue. At the narrowest point, the lumen was reduced to 3.2 mm.

Intubation Pathology and SGS

It is not possible to extrapolate directly from the pathology of intubation, material from which is abundant, to the pathology of SGS, material from which is lacking. Moreover, the larynges which form the basis of these studies come from a particularly sick group of infants, and it is probable that the frequency of the severe lesions described above is greater than that present in intubated survivors. A further difficulty is that it is impossible to predict which of the infants might have developed clinically apparent SGS had they survived.

Nevertheless, some general conclusions can be drawn from these studies which might contribute to our understanding of the pathogensis of SGS.

Perhaps the major conclusion is that continued intubation does not necessarily give rise to progressive laryngeal injury. The more severe injuries appear to occur relatively early, probably in the first week of intubation. In the first week the infant is likely to be ill, and require more frequent and perhaps more traumatic intubations. Further, as the neonate grows, the replacement tubes may be smaller in relation to the larynx and cause less injury.

In addition, the mucosa during this period is composed of loose connective tissue covered by respiratory epithelium. The subsequent repair processes replace this delicate mucosa with fibrous tissue and squamous epithelium, both of which are more likely to resist further damage, but not, of course, provide immunity to injury.

These observations are in keeping with the various clinical observations which indicate that although SGS is more probable in infants that have had prolonged intubation (Strong and Passey, 1977; Papsidero and Pashley, 1980; Ratner and Whitfield, 1983; Quiney and Gould, 1985; Sherman *et al.*, 1986), it may occur even after a relatively short intubation period of less than one week (Holinger, 1976).

Focal ulceration, even if associated with full thickness mucosal necrosis is unlikely to be of significance in relation to the development of SGS. This lesion is too frequent an occurrence to be a likely explanation of a relatively uncommon complication such as SGS.

A question is raised as to the role of cartilage injury in the development of SGS. Full thickness necrosis of the cricoid ring might cause collapse of the cartilage framework of the larynx, particularly if associated with contracting fibrous scar tissue.

In the case report, posterior cartilage injury was not present and the anterior injuries may have been entirely surgical in origin. Nevertheless, more information is required before collapse of the cartilage framework can be excluded as a potentially significant factor in SGS. Cricoid necrosis of such severity is unlikely to be a lesion unique to UCH. A larynx from an infant dying of bronchopulmonary dysplasia in the neonatal unit of the Whittington Hospital has recently been examined. This demonstrated full thickness necrosis of the cricoid cartilage posteriorly.

A further question concerns the importance of perichondritis. It is probably of relatively little significance in many instances, but the crico-arytenoid joint ankylosis seen in the case report is almost certainly the result of perichondritis affecting the joint space. This would restrict the movement of the vocal cords and contribute in some instances to the hoarseness that some of these children manifest.

A striking finding in our studies is that the epithelium and mucosa, albeit with some fibrosis, may heal with the endotracheal tube *in situ*. Thus, while the presence of an endotracheal tube in the neonatal larynx will always be a potential source of damage, perhaps through overvigorous manipulation, it need not be regarded as an inevitable and persistent cause of acute injury to the larynx. Indeed, it is possible that in some circumstances, the tube may act as a stent around which the damaged tissues of the larynx heal leaving a sizeable lumen, thus avoiding the contractures that might lead to the development of SGS.

In conclusion, it is clear that this type of pathological study can adequately illustrate the processes of acute injury and healing which normally take place in intubated larynges. However, these observations raise as many questions as they answer, and emphasize that we are unlikely to understand fully the pathogenesis of SGS until we possess firm data concerning the precise pathology of established SGS.

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Gould—Discussion

Cinnamond

What is the definition of subglottic stenosis and what criteria are applied to actually make the diagnosis? Fearon states that subglottic stenosis is present if the diameter of the lumen is less than 3.5 mm, but we see cases in children of neonatal age who may survive well with a lumen of less than 3.5 mm and we see older children in whom there is obvious airway obstruction where the diameter is greater than 3.5 mm, so what do we regard as subglottic stenosis?

Gould

A recent paper from one unit in the States where all infants intubated for more than seven days were examined laryngoscopically, defined subglottic stenosis as any narrowing of the lumen. They found an overall rate of 25 per cent. In our unit we would not confidently make the diagnosis of significant SGS until the infant required tracheostomy.

Graham

One cannot properly define SGS pathologically, because you cannot obtain histology on every child ventilated on a neonatal intensive care unit. There is no strict pathological criterion; one uses clinical criteria, which are children with severe enough obstruction to need a tracheotomy and children with any abnormal signs suggesting narrowing.

Facer

Surely it must cover children who actually have symptoms of obstruction rather than only children who need tracheostomy?

Shaw

If on bronchoscopy you saw a completely normal sized larynx you could exclude subglottic stenosis and consider another cause for the obstruction.

Graham

Yes, but that does not exclude the possibility that there may be very minor histological changes which you just cannot see clinically.

Facer

Surely the word stenosis implies there is a narrowing, whether or not there is actually minor pathological change.

Graham

That leaves us with a clinical definition of narrowing rather than a histological one.

Pearse

At what age?

Graham

At any age.

Pearse

For a working definition you need to limit yourself to the first year or two.

Bull

I saw somebody last week who had been ventilated five years ago and has developed stridor with an infection. Presumably there is a minor degree of subglottic narrowing. The whole problem is a matter of degree, and I do not think you have to postulate that the child has a tracheostomy before you can make a diagnosis of subglottic stenosis.

Pearse

We need a working definition to enable a unit doing one type of intubation to compare results with a different unit using another type of intubation.

Bull

You can define two groups, the ones who have stridor only with upper respiratory tract infections and the group that needs a tracheostomy.

Cinnamond

What is needed is a database showing the size of the normal lumen of the larynx throughout childhood development which we can compare with the findings at surgery or on endoscopy. Hopefully we will be able to show that within certain limits, a lumen of certain diameter constitutes subglottic stenosis.

Graham
Do we have this information?

Cinnamond
Pracy published normal values many years ago but I do not know on how large a selection that was based.

Dinwiddie
Surely it depends on whether you measure the lumen pathologically or endoscopically?

Cinnamond
He measured it endoscopically using standardised endotracheal tubes, in normal children.

You can obtain a large database by using children coming in for other reasons and measuring the size of the subglottis.

Facer
Part of the problem is that you are dealing with very premature babies for whom you do not necessarily have normal sizes. We know the sizes of older children fairly reliably, but with some of these tiny babies that are growing up we do not know whether they would have a normal sized larynx or what their subglottis size is.

Shaw
A premature baby is not even chemically the same as a full term baby. His body composition is different and his larynx unquestionably would be different even if he was never intubated.

Graham
So you may need a different database for premature babies than for normals.

Shaw
The only way to obtain all cases likely to have subglottic stenosis is to take those babies who show any sign of laryngeal stridor on extubation.

Facer
Surely there is a large group that is not going to have symptoms on extubation that you will miss?

Graham
There are two other well-defined groups—those with bilateral recurrent nerve palsy, mostly Caesareans, and those with a pseudovocal cord paralysis from interarytenoid scarring which is not clinically visible.

Shaw
It is very difficult to assess vocal cord movements in small infants on recovery from anaesthesia, even those who have subsequently been demonstrated to have a vocal cord paralysis.

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