Changes in the Cricoarytenoid Joint Induced by Intubation in Neonates

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Objective: To characterize the histopathologic characteristics of the cricoarytenoid joint (CAJ) as a means to understand the mechanisms of vocal cord fixation in children after prolonged intubation.

Design: Histologic analysis of laryngeal specimens obtained from infants who had died secondary to various causes and who had been intubated from 1 to 30 days.

Main Outcome Measure: Histopathologic characteristics of CAJ.

Results: Laryngeal specimens from infants who had been intubated for prolonged periods of time demonstrated evidence of hemorrhage, infection, inflammation, and fibrosis within the CAJ. Furthermore, a statistical correlation was found between the length of intubation and the presence of these histologic abnormalities.

Conclusions: To our knowledge, this is the first study to demonstrate histologic changes in the CAJ in laryngeal specimens of children who have been intubated for prolonged periods of time. Such histological changes in the CAJ could explain the mechanism of vocal cord immobility in children after intubation.

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Endotracheal intubation in the neonatal period is associated with laryngeal injury in some cases.1 These include submucosal hemorrhage, granuloma formation, subglottic edema, glottic edema, and subglottic stenosis. Fixation of the vocal cord is also one of these complications. In the absence of an interarytenoid adhesion or posterior glottic stenosis, this is caused by either recurrent laryngeal nerve paralysis or cricoarytenoid joint (CAJ) dysfunction.

The human CAJ may be involved in a number of pathologic conditions. Arthritis of both inflammatory and degenerative etiology has been shown to cause CAJ dysfunction.2,4 However, the most common cause of CAJ disease is thought to be intubation injury. The microscopic changes in the posterior glottis following intubation have been well documented, but to our knowledge, histopathologic changes in the CAJ have not been described.1

The study described herein aims to analyze the histopathologic changes in the CAJ in response to prolonged or repeated endotracheal intubation in the neonate. The hypothesis of this study is that vocal cord fixation following intubation is secondary to CAJ dysfunction.

METHODS

We obtained institutional review board approval from Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio. Larynges were obtained from 13 cadavers of infants who had been intubated for varying durations; postmortem examination was being performed on the cadavers. The medical charts of these patients were reviewed for the following information: age, sex, frequency and duration of intubation, and associated medical problems. Four specimens were discarded owing to inadequate sample collection. The remaining 11 patients ranged in age from 1 to 48 weeks with a mean (median) age of 12 (2) weeks. The sex distribution was 5 female and 6 male infants (Table 1 and Table 2).

The laryngeal specimens were fixed in 10% formalin, dehydrated in ethanol, and embedded in paraffin according to standard protocol. Four-micron sagittal sections through the CAJ were cut and stained with hematoxylin-eosin. Tissue sections were examined with a microscope (model Eclipse E400; Nikon Corp, Tokyo, Japan) equipped with a digital camera.

RESULTS

NORMAL CAJ PATHOLOGIC FINDINGS

In 8 cases, the CAJ was considered normal (Figures 1, 2, and 3 and Table 1). In these
cases, the articulating bodies of the CAJ consisted of unremarkable cartilage without evidence of ossification. The cartilage of the cricoid and arytenoid transitioned seamlessly to collagen fibrils that surrounded the joint capsule. The capsule of the CAJ was a narrow structure formed by a network of collagen fibrils and a few scattered elastic fibers and was lined by a single layer of flattened elongated cells. The joint capsule had contributions from the posterior cricoarytenoid ligament. In certain areas, depending on the plane of section, there was no joint space recognized. In these areas, the cricoid and arytenoid cartilage seemed almost fused with only a few collagen fibrils intervening. This loss of joint space was thought to be the result of sectioning artifact.

ABNORMAL CAJ PATHOLOGIC FINDINGS

There were abnormal findings in 4 cases (Table 2). In 1 case, the patient had been intubated on 4 different occasions for a total intubation time of 30 days. The length of the last of the 4 intubations was 21 days. The histologic findings of the CAJ at postmortem examination were consistent with an acute arthritis. The lining of the joint and the surrounding collagen fibrils were necrotic. There were dilated small capillaries surrounding the joint space and extravasated red blood cells in the joint capsule. There was an inflammatory infiltrate within the joint space composed predominantly of mononuclear cells, bacteria, and necrotic cellular debris (Figure 4 and Figure 5).

There was evidence of an acute arthritis in 3 other cases, although the findings were less severe than in the first case. In 1 of these cases, there was clearly hemorrhage into the posterior aspect of the CAJ capsule (Figure 6). In another case, there was a fibrous intracapsular exudate consistent with an organizing hematoma (Figure 7). In the last case, there were minor

*Table 1. Demographic Data, Intubation History, and Relevant Medical History for Patients With Normal Histopathologic Findings of the CAJ*

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Sex</th>
<th>Intubations, No.</th>
<th>Longest Duration of Intubation, d</th>
<th>Total Duration of Intubation, d</th>
<th>Relevant Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>F</td>
<td>4</td>
<td>4</td>
<td>14</td>
<td>Preterm 32-wk infant: necrotizing enterocolitis, small bowel resection, cholestasis, varices Imperforate anus, rectovestibular fistula</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>Meconium aspiration, patent ductus arteriosus</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Preterm 34-wk infant: necrotizing enterocolitis, disseminated intravascular coagulation</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Term infant: low Apgar scores</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>Term infant: trisomy 21, congenital heart disease, cardiac surgery on day 3</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>Congenital pneumonia, patent ductus arteriosus</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>Preterm 36-wk infant: gastroschisis, short bowel syndrome, liver failure</td>
</tr>
</tbody>
</table>

Abbreviation: CAJ, cricoarytenoid joint.

*Table 2. Demographic Data, Intubation History, and Relevant Medical History for Patients With Abnormal Histopathologic Findings of the CAJ*

<table>
<thead>
<tr>
<th>Age, wk</th>
<th>Sex</th>
<th>Intubations, No.</th>
<th>Longest Duration of Intubation, d</th>
<th>Total Duration of Intubation, d</th>
<th>Relevant Medical History</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>F</td>
<td>4</td>
<td>21</td>
<td>30</td>
<td>Preterm 32-wk infant: gastroschisis small bowel resection, splenectomy, cirrhosis, sepsis, pneumonia</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>3</td>
<td>32</td>
<td>22</td>
<td>Term infant: complex congenital heart disease, wound infection, chest infection, GI tube</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1</td>
<td>14</td>
<td>14</td>
<td>Term infant: congenital diaphragmatic hernia, ischemic bowel</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>1</td>
<td>15</td>
<td>15</td>
<td>Term infant: malrotation, short gut syndrome, liver failure, DIC</td>
</tr>
</tbody>
</table>

Abbreviations: CAJ, cricoarytenoid joint; DIC, disseminated intravascular coagulation; GI, gastrointestinal.

*Figure 1. Normal cricoarytenoid joint showing the arytenoid cartilage (A) above the cricoid cartilage (C), the cricoarytenoid joint space (JS), the posterior cricoarytenoid musculature (M), and the thyroarytenoid muscle (V) (hematoxylin-eosin; original magnification ×20).*
changes with red blood cells and fibrin within the joint space. In cases with normal CAJs, the infants generally had been intubated for a mean (median) duration of 6 (6) days (range, 1-20 days). In cases in which abnormal CAJ histopathologic findings were noted, the infants had had a mean (median) duration of intubation of 21 (19) days (range, 14-30 days). Using the Mann-Whitney test, we found a significant difference in mean intubation times between the group with normal CAJ histologic findings and the group with abnormal CAJ histologic findings \((P = .02)\).

**COMMENT**

There has been interest in laryngeal trauma following intubation ever since the practice of endotracheal anesthesia began. Although intubation trauma to the CAJ has also been widely reported, none of these studies have looked specifically at the histopathologic findings of the CAJ. For example, Donnelly examined 99 larynges that had been intubated and found 44 specimens with intralaryngeal lesions. However, that study did not examine the CAJ. Other studies have similarly focused exclusively on the macroscopic and functional changes in the larynx after intubation. Several studies have examined the CAJ in the context of systemic connective tissue disorders and to understand the biomechanical properties of the normal CAJ.

Only 1 study has reported the histopathologic status of the CAJ in response to intubation. This study investigated cadaver larynges that were subjected to simulated intubation and extubation trauma and then were assessed using light and scanning electron microscopy. On macroscopic inspection, no fixation or dislocation was observed. Ten of the 30 larynges displayed synovial fold injuries, and 3 of the CAJs had articular impressions. The authors concluded that intubation may result in CAJ trauma, causing synovial injury and hence hemorrhage or synovitis leading to fixation of the joint.

Although limited by a small number of specimens, the study described herein is, to our knowledge, the first to unequivocally demonstrate abnormal CAJ histopatho-
logic findings in infants who had been intubated. Furthermore, this study shows a correlation between the length of intubation and the presence of CAJ disease. Larynges with the longest length of intubation had the most significant findings. Although not proven by this study, blood, necrotic cellular debris, and inflammatory cells present in the CAJ after intubation could potentially lead to fibrosis and fixation of the CAJ. The presence of bacteria within the joint space in 1 of the specimens raises the possibility that intubation can cause septic arthritis of the CAJ and potentially propagate CAJ fibrosis.

Further study is required to determine the significance of histopathologic changes to the CAJ after intubation. In addition, the role of infection, length of intubation, and frequency of intubation should be scrutinized for their role in CAJ disease. Data collected from such studies could potentially change the current thinking on what is considered a safe length of time for intubation and on how to treat infants with vocal cord immobility.

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Author Contributions: Drs Vijayasekaran, Sances, Cotton, and Elluru had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Vijayasekaran, Cotton, and Elluru. Acquisition of data: Vijayasekaran, Sances, and Elluru. Analysis and interpretation of data: Vijayasekaran and Elluru. Drafting of the manuscript: Vijayasekaran, Sances, and Elluru. Critical revision of the manuscript for important intellectual content: Vijayasekaran, Cotton, and Elluru. Statistical analysis: Vijayasekaran. Obtained funding: Vijayasekaran. Administrative, technical, and material support: Sances and Elluru. Study supervision: Cotton and Elluru.

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REFERENCES


