Automated Cuff Pressure Modulation

A Novel Device to Reduce Endotracheal Tube Injury

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**Objective:** To assess whether dynamically modulating endotracheal tube (ETT) cuff pressure, by decreasing it during each ventilatory cycle instead of maintaining a constant level, would reduce the extent of intubation-related laryngotracheal injury.

**Design:** Single-blind, randomized controlled animal study using a previously validated live porcine model of accelerated intubation-related tracheal injury.

**Setting:** Animal research facility.

**Patients:** Ten piglets (weight, 16-20 kg each) were anesthetized and underwent intubation using a cuffed ETT.

**Interventions:** The animals were randomized into the following 2 groups: 5 pigs had a novel device to modulate their cuff pressure from 25 cm H2O during inspiration to 7 cm H2O during expiration, and 5 pigs had a constant cuff pressure of 25 cm H2O. Both groups underwent ventilation under hypoxic conditions for 4 hours.

**Main Outcome Measure:** Laryngotracheal mucosal injury after blinded histopathological assessment.

**Results:** The modulated-pressure group showed significantly less overall laryngotracheal damage than the constant-pressure group (mean grades, 1.2 vs 2.1; \(P < .001\)). Subglottic damage and tracheal damage were significantly less severe in the modulated-pressure group (mean grades, 1.0 vs 2.2; \(P < .001\), and 1.9 vs 3.2; \(P < .001\), respectively). There was no significant difference in glottic or supraglottic damage between the groups (\(P = .06\) and .27, respectively).

**Conclusions:** This novel device reduces the risk of subglottic and tracheal injury by modulating ETT cuff pressure in synchronization with the ventilatory cycle. This finding could have far-reaching implications for reducing the risk of airway injury in patients undergoing long-term intubation. Further clinical study of this device is warranted.

tracheal damage. Recent surveys from the United Kingdom and France demonstrated that most anesthetists and pediatric intensive care unit physicians were not routinely using cuffed ETTs for intubation in children, predominantly because of concerns about cuff-related tracheal injuries. The pathological process of cuff-induced stenosis is thought to begin with pressure on the laryngotracheal mucosa, especially when the cuff is overinflated, resulting in impaired tracheal mucosal blood flow, edema and ischemic necrosis, and eventually formation of fibrotic scar tissue. Unfortunately, no studies have been effectively designed to prospectively compare the incidence of subglottic stenosis between children intubated with cuffed and uncuffed ETTs.

Developing a mechanism to significantly reduce ETT-related tracheal injuries could result in major benefits for the pediatric population and a more widespread use of cuffed ETTs. It would also be beneficial in reducing the risk of intubation-related injury in older children and adults in whom cuffed ETTs are the only available option. Attempts to reduce cuff-related injuries by automated maintenance of a constant cuff pressure have failed to reduce tracheal injury in an animal model.

We have previously developed and reported on a hypoxic animal model for the investigation of intubation-related laryngotracheal injury. The objective of the present study was to use this model to test the hypothesis that dynamically modulating ETT cuff pressure by briefly decreasing it during each ventilatory cycle instead of maintaining a constant level would reduce the extent of intubation-related laryngotracheal injury.

METHODS

The study had the full approval of the local research ethics board and animal care committee. Ten female piglets, each weighing 16 to 20 kg, were anesthetized and underwent intubation using a cuffed ETT. The animals were randomized into the following 2 groups: in 5 pigs a novel device was used to modulate the cuff pressure from a maximum of 25 cm H2O during inspiration to a minimum of 7 cm H2O during expiration. This automated device was therefore dynamically modulating the cuff pressure with a periodicity precisely synchronized with the ventilatory cycle.

Ventilation was maintained using a volume-cycled ventilator (Air Shields Ventimeter; Narco Health Company, Hatboro, Pennsylvania). The right auricular vein was cannulated for intravenous injection of pentobarbital sodium (25 mg/kg). The animals were paralyzed by means of an intravenous injection of pancuronium bromide (a bolus dose of 0.2 mg/kg and a maintenance dosage of 0.2 mg/kg/h) to prevent any ETT movements during the procedure. The left carotid artery was cannulated for invasive blood pressure monitoring and hourly arterial blood gas sampling.

The monitoring used during the experiment included heart rate, systolic and diastolic blood pressures, electrocardiography, fraction of inspired oxygen concentration, oxygen saturation, end-tidal carbon dioxide concentration, and body temperature (rectal). Hypoxia was achieved by ventilating with a mixture of air and nitrous oxide. The relative concentrations of air and nitrous oxide were adjusted to maintain oxygen saturation between 60% and 80%, with the lowest accepted level defined as adequate ventilation without compromising the hemodynamic stability of the animal. The animals underwent mechanical ventilation for a total of 4 hours.

The animals were then humanely killed by means of a lethal intravenous injection of pentobarbital sodium (25 mg/kg). The larynx and the trachea were immediately harvested post mortem using a midline incision. The specimen was prepared for pathological assessment by an experienced pathology technician blinded to the intervention group and study hypothesis.

Figure 1. Schematic of automated dynamic cuff pressure modulating device. ETT indicates endotracheal tube.

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DETAILED EXPERIMENTAL PROCEDURE

The animals received a 0.15-mL/kg intramuscular injection of a sedative mixture (each 1 mL contained 38.82 mg of ketamine hydrochloride, 1.18 mg of acepromazine, and 0.009 mg of atropine sulfate). Inhalational induction of anesthesia before intubation was achieved with halothane, and anesthesia thereafter was maintained with isoflurane in nitrous oxide and air/oxygen. The animals underwent intubation with high-volume, low-pressure cuffed ETTs (Kendall-Sheridan Catheter Corporation, Argyle, New York). The ETT size was chosen after visual inspection of the larynx, in consideration of the ability to pass the tube without resistance and the presence of a moderate air leak before cuff inflation to 25 cm H2O. In all cases, the ETT size required was an internal diameter of 6.0 or 6.5 mm. The individual performing the intubation was blinded to the study hypothesis and the intervention group. The ETT cuff pressure was measured using a cuff manometer (Posey Cufflator; JT Posey Company, Arcadia, California). Correct ETT position was confirmed by direct visualization, auscultation, and the presence of end-tidal carbon dioxide. All intubations were successful and nontraumatic. The animals were then placed in a supine position, and the ETT was secured to the snout.

The constant-pressure group had their ETT cuff pressure maintained at a constant cuff pressure of 25 cm H2O throughout the experiment. The modulated-pressure group had their cuff connected to a customized device that consisted of a built-in calibrated manometer, ventilatory pressure monitor, and pump (Figure 1). This device constantly inflated and deflated the ETT cuff with each ventilatory cycle, from a maximum of 25 cm H2O during inspiration to a minimum of 7 cm H2O during expiration. This automated device was therefore dynamically modulating the cuff pressure with a periodicity precisely synchronized with the ventilatory cycle.

Ventilation was maintained using a volume-cycled ventilator (Air Shields Ventimeter; Narco Health Company, Hatboro, Pennsylvania). The right auricular vein was cannulated for intravenous fluid and drug administration. The animals were paralyzed by means of an intravenous injection of pancuronium bromide (a bolus dose of 0.2 mg/kg and a maintenance dosage of 0.2 mg/kg/h) to prevent any ETT movements during the procedure. The left carotid artery was cannulated for invasive blood pressure monitoring and hourly arterial blood gas sampling.

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The animals were then humanely killed by means of a lethal intravenous injection of pentobarbital sodium (25 mg/kg). The larynx and the trachea were immediately harvested post mortem using a midline incision. The specimen was prepared for pathological assessment by an experienced pathology technician blinded to the intervention and study hypothesis. Serial axial sections (cut perpendicular to the trachea in the axial plane) were prepared to allow analysis of the supraglottic larynx (from the level of the epi-
glottis to the upper edge of the arytenoids) and the upper trachea. Serial longitudinal sections (cut in the coronal plane and parallel to the trachea) were prepared to allow analysis of the glottis and the subglottis (immediately below the glottis to the first tracheal ring). The tissues were fixed in 10% buffered formalin and embedded in paraffin. The sections for microscopy were cut to 4 µm thick, mounted on microscope glass slides, and stained with hematoxylin-eosin.

**HISTOLOGICAL EVALUATION**

All histological evaluations were conducted by a single senior pathologist (G.T.) who was blinded to intervention and study hypothesis. The fixed specimens were evaluated for the severity of tissue damage. We used a previously described laryngeal injury grading system that provided a severity grade from 0 (normal) to 4 (perichondrium involvement) as described in the following tabulation:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No damage</td>
</tr>
<tr>
<td>1</td>
<td>Compression of the epithelial layer</td>
</tr>
<tr>
<td>2</td>
<td>Epithelial loss</td>
</tr>
<tr>
<td>3</td>
<td>Subepithelial and glandular inflammation or necrosis</td>
</tr>
<tr>
<td>4</td>
<td>Perichondrium inflammation or loss</td>
</tr>
</tbody>
</table>

For any given section, the severity was determined as the most severe grade of damage seen in that section.

**STATISTICAL ANALYSIS**

The statistical methods applied for data analysis were determined a priori, using α = .05 for exploring the statistical significance. The overall severity and overall extent of histological damage (using the described grading system) were compared between the modulated-pressure and constant-pressure groups using the Mann-Whitney test. Subgroup analysis was performed to compare severity between the 2 groups at each histological section level (supraglottic, glottic, subglottic, and trachea) using the Mann-Whitney test. After subgroup analysis by section level, subglottic damage and tracheal damage were found to be significantly less severe in the modulated-pressure group than the constant-pressure group (mean grades, 1.0 vs 2.2; P < .001, and 1.9 vs 3.2; P < .001, respectively) (Figure 3). There was no statistically significant difference in glottic or supraglottic damage between the modulated- and constant-pressure groups (mean grades, 0.8 vs 1.4; P = .06, and 1.1 vs 1.5; P = .27, respectively).

**RESULTS**

All 10 animals completed the 4-hour intubation protocol and were included in the data analysis. The baseline characteristics of the animals and the physiological and biochemical variables measured during the experiment are summarized in the Table. There was no significant difference in the baseline variables between the modulated-pressure and constant-pressure groups.

The median severity scores for each group are compared in Figure 2. Overall, the modulated-pressure group had significantly less laryngotracheal histological damage than the constant-pressure group (mean grade, 1.2 vs 2.1; P < .001). The damage in the modulated-pressure group was predominantly epithelial, varying from simple compression to focal loss, with mild superficial acute inflammation. The constant-pressure group had more extensive epithelial damage, including necrosis or erosion, and there was more severe damage and inflammation in the subepithelium, sometimes extending into the glandular layer. The area of most severe damage was typically seen diffusely in the specimens, although the proportion of mucosa affected varied between specimens and with the degree of injury (the more severe the injury, the more focal its distribution appeared to be).

After subgroup analysis by section level, subglottic damage and tracheal damage were found to be significantly less severe in the modulated-pressure group than the constant-pressure group (mean grades, 1.0 vs 2.2; P < .001, and 1.9 vs 3.2; P < .001, respectively) (Figure 3). There was no statistically significant difference in glottic or supraglottic damage between the modulated- and constant-pressure groups (mean grades, 0.8 vs 1.4; P = .06, and 1.1 vs 1.5; P = .27, respectively).

**COMMENT**

This study successfully demonstrated that cuff pressure modulation resulted in decreased severity of injury to the subglottis and upper trachea. The novel device used was capable of modulating the pressure in the cuff of a regular ETT by coordinating the pressure level to be maximal during the in-
spiratory phase and minimal during the expiratory phase. This allowed for regular positive airway pressure ventilation because, during inspiration, the seal was maintained between the ETT and the tracheal mucosa by the inflated cuff but, during expiration, cuff deflation allowed the cuff pressure to drop in the subglottic and tracheal areas.

We hypothesize that these recurring periods of reduced cuff pressure counteracted cuff-related impairment of tracheal mucosal blood flow. In effect, by applying intermittent pressure on the mucosa as opposed to constant pressure, mucosal blood perfusion was less compromised, and this appeared to result in reduced ischemic injury to the subglottic and tracheal mucosa. The use of this novel device can be considered somewhat analogous to the use of alternating-pressure mattresses as opposed to constant-low-pressure mattresses, with the aim of reducing pressure ulcers in immobile patients.19 As would be anticipated, there was no significant difference in the severity of injury at the level of the supraglottis and glottis because these areas were not in contact with the ETT cuff and would not benefit from modulated cuff pressure.

The present study is not the first attempt to reduce cuff-related injuries, but it is, to our knowledge, the first to use cuff pressure modulation. Other groups have considered this problem by attempting modifications of the ETT design. Lederman et al20 designed an ETT in which the regular cuff was replaced by polyurethane foam coated in latex, and found that this alteration significantly reduced tracheal injury. In a modification of an earlier design by Miller and Sethi,21 Reali-Forster et al22 replaced the ETT cuff with circumferential “gills” and demonstrated a reduction in tracheal injury in a sheep model. Unfortunately, none of these designs have gained popularity. Recently, our own group described a novel ETT design in which the inflatable cuff was replaced with circumferential, self-expanding polyvinyl acetate foam, resulting in reduced laryngotracheal injury in an animal model.18

Another previous approach to reduce cuff-related injury has been through attempts to reduce the risk of over-inflation and subsequent damage due to high cuff pressure. Recent work has confirmed that, in the intensive care unit setting, periods of ETT cuff hyperinflation are common.23 Valencia et al24 described a device that would maintain a constant cuff pressure to avoid damage related to unrecognized increases in cuff pressure. Although a clinical trial of this device demonstrated more consistent control of cuff pressure, tracheal injury was not investigated and no reduction was seen in ventilator-associated pneumonia. Nseir et al16 recently tested a similar device for continuous control of cuff pressure in an animal model. Although they found that their device provided effective continuous control of cuff pressure, no differences in mucosal injury between animals with or without the device could be demonstrated.

Bench testing of the device described in the present report demonstrated that, during the deflation phase of cuff pressure modulation cycles, the cuff maintained some of its volume even at the low inflation pressure (N.K.C. and V.F., unpublished data, November 2008). In addition, the use of an uncuffed ETT in the pediatric population is frequently associated with a persistent air leak throughout the inspiratory and expiratory ventilatory phases, and this air leak may be considered desirable to reduce the risk of tube-related injury.25 Finally, continuous aspiration of subglottic secretions has previously been demonstrated to reduce the risk of ventilator-associated pneumonia and could be used in individuals considered to be at high risk.26,27 We believe that these factors reduce concern about the risk of aspiration during the deflation stage of the cuff modulation cycle and subse-
quent ventilator-associated pneumonia, although this hypothesis requires further experimental investigation.

Animal studies play an essential role in attempts to reduce ETT-related injury through novel strategies, and the animal model used in this study has previously been found to be reliable and effective. Numerous previous animal studies of the effects of intubation have relied on canine models, but these have been severely limited because the animals were awake and ambulant. By ventilating the animals under hypoxic conditions, we were able to demonstrate significant ischemic injury in our control group after only 4 hours compared with previous work from our group showing injury after intubation for 24 hours. Hypoxia is presumed to accelerate and exaggerate the degree of cuff pressure–related ischemic injury on tracheal mucosa. However, it is currently not known whether the same degree of laryngotracheal injury reduction would occur if the modulating cuff pressure strategy were used in human subjects intubated under nonhypoxic conditions.

Nonetheless, this study has provided an exciting new approach to reducing ETT-related mucosal injury. The findings may be applicable to patients in the setting of prolonged intubation in both the intensive care unit and the operating room. In addition, it is unclear from the present study whether the demonstrated reduction in histopathological injury would translate into a reduction in the sequelae of intubation, such as postintubation stridor and development of subglottic stenosis. This will be investigated in future work on this animal model that will include recovery after the period of ventilation to allow assessment of the early and late manifestations of intubation injury. Future work will also focus on refinement of the device design with a view to eventually cautiously extending application to intubated patients.

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Author Contributions: Drs Chadha, Gordin, and Forte 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: Chadha, Gordin, Luginbuehl, Patterson, and Forte. Acquisition of data: Chadha, Gordin, Luginbuehl, Taylor, and Forte. Analysis and interpretation of data: Chadha, Campisi, and Forte. Drafting of the manuscript: Chadha and Patterson. Critical revision of the manuscript for important intellectual content: Chadha, Gordin, Luginbuehl, Campisi, Taylor, and Forte. Statistical analysis: Chadha. Administrative, technical, and material support: Chadha, Luginbuehl, Patterson, and Taylor. Study supervision: Gordin, Campisi, and Forte.

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Additional Contributions: Marvin Estrada of Animal Laboratory Services at the Hospital for Sick Children helped conduct the animal experiments.

REFERENCES