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Tracheal Injury after Endotracheal Intubation and Anesthesia in Rabbits

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This case report describes sublaryngeal tracheal injury and ulceration in 15 rabbits from 3 institutions as sequelae to routine intubation and general anesthesia with isoflurane in oxygen. The rabbits were intubated for general anesthesia and mechanically ventilated for experimentally diverse procedures, with periods of anesthesia lasting 1.5 to 5 h. Of the 15 animals, 6 developed minimal to moderate postanesthesia clinical signs of moist rales or cyanosis or both; 2 of these 6 rabbits later died unexpectedly, their deaths attributed to respiratory obstruction by necrotic tracheal debris. The pathogenesis of this lesion is reviewed. Our findings suggest that rabbits may be predisposed to developing serious tracheal injury and clinically significant sequelae in association with routine intubation.

Abbreviation: LMA, laryngeal mask airway

Endotracheal intubation is regularly conducted on rabbits in research institutions and companion animal practice. Indications for endotracheal intubation include airway protection, maintenance of airway patency, positive pressure ventilation, reducing operating room waste gas, and maintenance of appropriate oxygenation.[10] In veterinary medicine, endotracheal intubation is used most often to provide inhalant anesthesia and typically is thought to increase anesthetic safety. Inhalation anesthetic agents are used frequently for rabbit anesthesia because of their reliability, efficacy, ease of manipulation of anesthetic depth, and decreased recovery time compared with injectable agents.

Rabbits have been used extensively as a model for human tracheal injury, and many reports describe experimental tracheal lesions associated with intubation in this species. Gross and histologic tracheal lesions have been created experimentally in rabbits by manually damaging the tracheal mucosa and by overinflating endotracheal tube cuffs.[19,23,32] Endotracheal tube placement is difficult in rabbits, because the rabbit pharynx is long and narrow, and the tongue is relatively large. The procedure is further complicated by the tendency of the rabbit to develop laryngospasm during intubation attempts.[17,29] Both blind and laryngeal visualization techniques are used in this species.[7,9,31,34] Despite numerous papers describing intubation techniques in rabbits, postintubational complications have not been reported, and these complications are rare in other species. In this report, we describe inadvertent sublaryngeal tracheal injury in 15 rabbits from 3 different institutions after intubation with endotracheal tubes for anesthesia with isoflurane in oxygen.

Case Reports

New Zealand White rabbits from all 3 institutions were purchased from Charles River Canada (St Constant, Quebec, Canada). Vendor surveillance reports indicated that animals were from colonies serologically negative for *Encephalitozoon cuniculi*, cilia-associated respiratory bacillus, *Clostridium piliforme*, reovirus, rotavirus, *Pasteurella multocida*, *Salmonella* spp., *Bordetella bronchiseptica*, *Pseudomonas aeruginosa*, *Clostridium perfringens,* and hepatic and intestinal coccidiosis. A trachea from a female rabbit from the same source, used for antibody production and never previously anesthetized, was collected at euthanasia and sectioned as described, to provide control tissue. For histologic evaluation, tissues were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Four representative cross sections were cut from the following areas of all tracheas: proximal larynx, distal end of larynx, 2 cm distal to the larynx, and tracheobronchial bifurcation. The mucosa and submucosal of each section was evaluated according to the scoring system listed in Table 1 and summed for a final score (maximum score of 8). The highest final score for any section was assigned as the overall tracheal score for each animal.

All facilities and procedures involving animals are in compliance with the Animals for Research Act of Ontario and the *Guidelines of the Canadian Council on Animal Care*.[4] The institutional animal care and use committees approved the study protocols.

Case 1. Ten 17-wk-old (3.2 to 3.5 kg) female rabbits were selected to investigate effects of butorphanol and meloxicam on the minimum alveolar concentration of isoflurane (Table 2). Animals were group-housed in floor pens on hardwood chip substrate, on a 12:12-h light:dark cycle, and at constant temperature (20 ± 4 °C) and relative humidity (30% to 70%). Rabbits were fed (Teklad Global High Fiber Rabbit Diet, Harlan Teklad, Madison, WI) twice daily and provided with timothy hay and fresh water ad libitum. Each rabbit was anesthetized 3 times at biweekly intervals over the course of 5 wk. Isoflurane anesthesia was induced by facemask in animals restrained via a towel wrap, and each rabbit was intubated atraumatically with a 3.0- to 3.5-mm uncuffed, Sheridan endotracheal tube by use of a videoendoscope instead of a stylet. Anesthetic lines were secured to the animal's head by gauze ties and were taped to the table, to minimize movement. Animals were instrumented for monitoring of rectal temperature, arterial blood oxygen saturation, and direct arterial blood pressure. Animals were mechanically ventilated at a tidal volume of 30 to 45 ml, and

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Table 1. Tracheal histopathology scoring system

Score	Histologic changes and distribution
Mucosa	
0	normal to minimal; focal cilia loss
1	minimal to mild; locally extensive respiratory epithelial attenuation with loss of cilia
2	moderate; circumferential attenuation of respiratory epithelial cells with loss of cilia and goblet cells
3	focal erosion, marked, diffuse disorganization of respiratory epithelial cells with edema of the lamina propria, mixed leukocytic infiltrate, and focal hemorrhage
4	extensive to diffuse erosion or ulcer with or without surface crusting, mineralization of the lamina propria, mixed leukocytic infiltrate, hemorrhage, cellular debris, and fibrosis
Submucosa	
0	Normal
1	minimal to mild, locally extensive congestion
2	moderate, diffuse congestion and mild perivascular edema
3	moderate, diffuse congestion and edema, with or without focal hemorrhage
4	extensive to diffuse erosion or ulcer with or without surface crusting, mineralization of the lamina propria, mixed leukocytic infiltrate, hemorrhage, cellular debris, and fibrosis

Table 2. Summary of clinical features of the three presented cases

Case	No. of rabbits	Gender, body weight (kg)	No. of intubations	Duration of isoflurane anesthesia (h)
1	10	F, 3.2–3.5	3[a]	4–5
2	4	M, 3.5–4.0	1	1.5–2.5
3	1	F, 3.0–3.5	1	1–1.5

[a]A 2-wk interval occurred between endotracheal intubations.

end-tidal CO_2 concentration was maintained at 30 to 40 mm Hg. Body temperature was maintained at normothermia by means of a circulating water blanket. Lactated Ringer solution was administered intravenously at a rate of 10 ml/kg hourly. Rabbits were maintained in sternal recumbency, and total anesthesia time from induction to recovery ranged from 4 to 5 h.

Two days after the second anesthesia trial, 2 animals developed moist rales, localized over the cranial trachea, and mild cyanosis. Upon physical examination, these animals were bright and inquisitive and were otherwise normal. They were placed in a separate pen, and treatment was initiated with trimethoprim–sulfadiazine (30 mg/kg orally twice daily; Tribrissen, Schering-Plough, Newark, NJ) in light of a primary clinical differential diagnosis at the time of bacterial sinusitis and tracheitis. The 2 rabbits had good appetite, continued to maintain body weight, and demonstrated normal exploratory behaviors and grooming. Despite apparent improvement in condition, 1 animal died suddenly 48 h after initiating therapy, and the second was euthanatized 96 h later because of continuing respiratory stridor. Three other animals developed minimal to mild moist rales over the proximal trachea prior to the third trial. All animals, including those showing clinical signs, maintained good appetite, were normothermic, and maintained or had increased body weights over the course of the study. During 4 trials from the third anesthesia session, cultures for microbiologic evaluation were collected from the tips of the endotracheal tubes prior to intubation and after extubation and from the rabbits' nares; all cultures were negative. Animals were euthanatized by intravenous barbiturate overdose prior to recovery after the conclusion of the third trial.

Gross findings in all animals were limited to the tracheas and included moderate to marked mucosal congestion of the proximal third of the trachea in all animals. Blood-tinged necrotic debris was adherent focally to the tracheas of 3 animals (including the animal that died), just distal to the larynx. In the animal that died, abundant necrotic debris was also present within the nasal cavities, suggesting upper respiratory obstruction as the cause of death. Mild bruising was noted in the laryngeal region of 3 animals.

Table 3. Summary of tracheal histopathology lesion scores from intubated rabbits

Case	Rabbit no.	Mucosa	Score Submucosa	Final
1	1	4	3	7
	2	4	2	6
	3	3	3	6
	4	4	4	8
	5	3	4	7
	6	4	2	6
	7	4	3	7
	8	4	3	7
	9	2	4	6
	10	4	2	6
2	1	4	2	6
	2	4	3	7
	3	4	3	7
	4	4	2	6
3	1	4	3	7

Microscopically, tracheal mucosal lesions were most pronounced in the sections immediately distal to the larynx. Tracheal lesion scores ranged from 6 to 8, with the most severe tracheal lesions observed in the animal that died (Table 3). In 3 animals, there was circumferential ulceration of the mucosa, with an extensive overlying luminal crust composed of necrotic cells admixed with blood and fibrin (Figure 1) and submucosal fibrosis (Figure 2) and mineralization, with a decrease in tracheal lumen diameter (stenosis) compared with that of the nonanesthetized rabbit trachea (Figure 3). In the remaining 7 animals, there was focal to locally extensive, moderate to marked mucosal erosion or ulceration with marked epithelial attenuation (Figure 4) and loss of cilia. Occasional foci of hyperplastic epithelium were present. Associated with mucosal changes

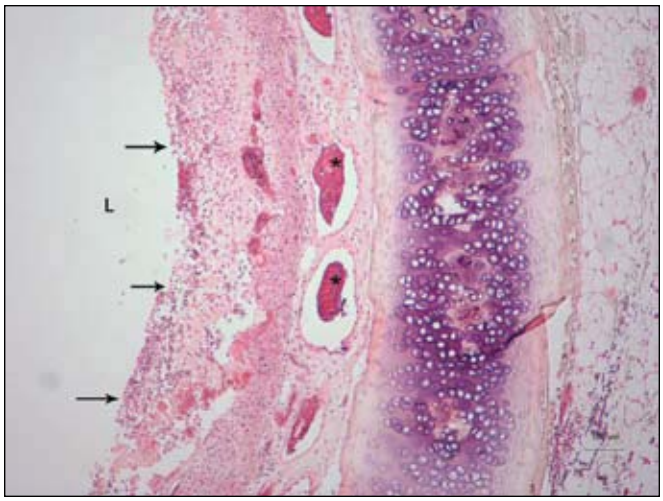

Figure 1. Photomicrograph of tracheal section from a rabbit euthanatized after three 5-h sessions of isoflurane anesthesia with endotracheal intubation. Severe circumferential mucosal ulceration is noted (arrows) with luminal (L) hemorrhage, cell debris, and heterophil accumulation overlying area of ulceration. Submucosal vessels (*) are markedly dilated and congested. Tracheal score of 7. Hematoxylin and eosin stain.

were moderate mixed leukocytic infiltrates consisting of predominantly heterophils with smaller numbers of lymphocytes and plasma cells. In all tracheal sections, there was moderate to marked submucosal venous dilatation and congestion (Figure 1, 4), with moderate to marked edema, and occasional mixed leukocytic infiltrates. Sections distal to the larynx contained fewer microscopic changes of decreased severity, predominantly limited to locally extensive epithelial attenuation and loss of cilia, and submucosal congestion and edema. Mild edema of the laryngeal submucosa and mild hemorrhage within the surrounding musculature was observed in several animals.

Case 2. Four 16-wk-old (3.5 to 4 kg) male rabbits were purchased for a carotid artery graft patency study and individually housed on a 12:12-h light:dark cycle, at constant temperature (20 ± 4 °C) and relative humidity (30% to 70%), were fed ad lib (Lab Rabbit Chow HF5326, Ralston Purina, Strathroy, Ontario, Canada), and had access to water by automatic waterer. Animals were premedicated with ketamine (50 mg/kg intramuscularly) and xylazine (7.5 mg/kg intramuscularly), intubated blindly with a 3.0-mm cuffed Rusch endotracheal tube, positioned in dorsal recumbency on a circulating water blanket, and placed on a pressure regulated ventilator, set at 4 to 8 cm H_2O, for surgery. Anesthetic lines were supported by taping them to the operating table. Heart rate, indirect blood pressure, and temperature were monitored intraoperatively. Prior to recovery, the surgical site was infiltrated with bupivicaine, and animals were treated with buprenorphine (0.05 mg/kg subcutaneously) and again 6 h postoperatively. Surgeries were 1.5 to 2.5 h in duration, and recoveries were unremarkable. Patency of the vascular graft was assessed ultrasonically in conscious animals 24 h after surgery; animals then were euthanized by intravenous barbiturate overdose, and tracheas were collected for microscopic evaluation.

Tracheal lesion scores ranged from 6 to 7 for these rabbits (Table 3). Microscopically, there was marked, circumferential attenuation of the respiratory epithelium and complete loss of cilia, with locally extensive, superficial ulceration in the tracheal section just distal to the larynx and moderate to marked submucosal congestion, edema, and hemorrhage in all 4 animals. Changes in the more distal sections of the trachea were limited to mucosal epithelial attenuation with locally extensive cilia loss

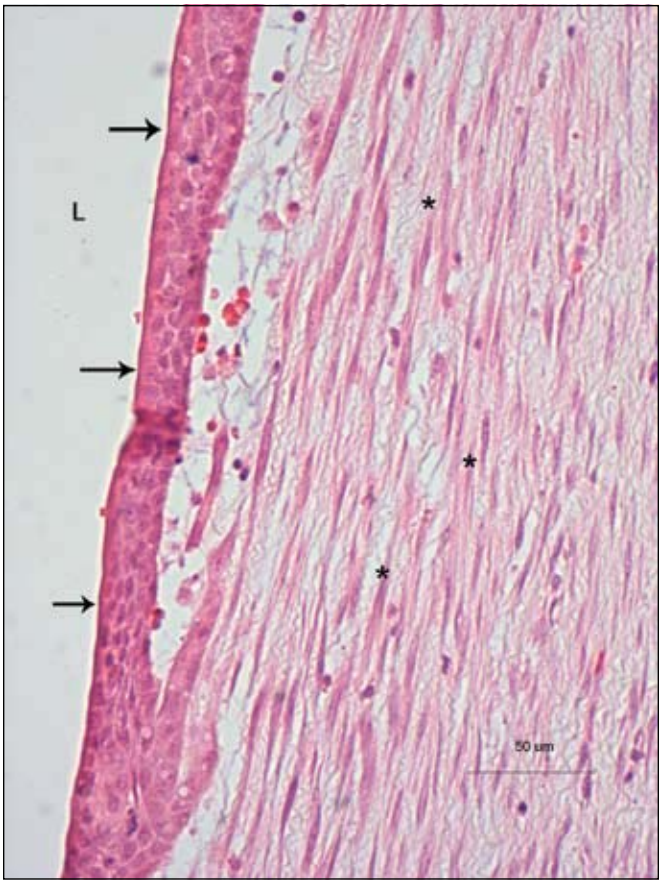

Figure 2. Photomicrograph of tracheal section from a rabbit euthanatized after three 5-h sessions of isoflurane anesthesia with endotracheal intubation, demonstrating squamous metaplasia of mucosal surface (arrows) with loss of cilia, and marked fibroplasia of the lamina propria (*) and submucosa. Lumenal surface of section is indicated (L). Tracheal score of 7. Hematoxylin and eosin stain.

and moderate submucosal congestion and edema.

Case 3. Twelve 15- to 19-wk-old (3.0 to 3.5 kg) female rabbits were selected for shoulder surgical modeling studies and individually housed on a 12:12-h light:dark cycle, at constant temperature (20 ± 4 °C) and relative humidity (30% to 70%), were fed ad lib (Teklad Global High Fiber Rabbit Diet, Harlan Teklad), and had access to water bottles. On the day preceding surgery, a 25-µg fentanyl patch (Duragesic Patch, Janssen, Titusville, NJ) was placed on rabbits and secured by elastic tape. Animals were premedicated with ketamine (50 mg/kg intramuscularly), xylazine (7.5 mg/kg intramuscularly), and glycopyrrolate (0.01 mg/kg subcutaneously); intubated blindly with a 2.5-mm cuffed Rusch endotracheal tube; and positioned in left lateral recumbency for surgery. Body temperature, blood oxygen saturation levels, and heart rate were monitored intraoperatively, and potassium chloride solution (Normosol, Abbott Laboratories, Mississauga, ON, Canada) was administered intravenously at a rate of 10 ml/kg hourly during surgery. Animals were treated with buprenorphine (0.05 mg/kg subcutaneously) prior to recovery and again 6 h postoperatively. Surgeries were 1 to 1.5 h in duration, and recoveries were unremarkable.

The rabbits appeared to be making favorable postoperative recovery, but 2 d after surgery, 1 animal developed moist rales, localized to the proximal trachea. The animal was otherwise clinically normal, with good appetite, and was placed under close surveillance. This animal died unexpectedly 2 d later,

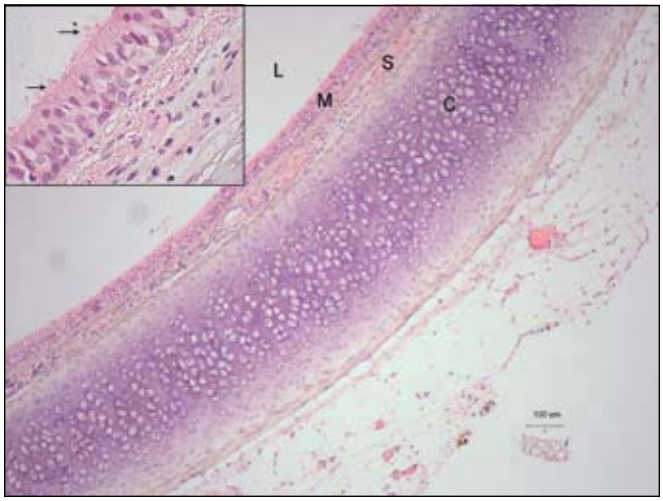

Figure 3. Photomicrograph of trachea from a nonanesthetized adult female New Zealand White rabbit, demonstrating expected histology of mucosa (M), which is supported by a loose, highly vascular submucosa (S) and hyaline cartilage rings (C). Inset: normal tall columnar, pseudostratified, ciliated (arrows) epithelium of rabbit tracheal mucosa interspersed with occasional goblet cells (compare with Figure 4), ×10. Lumenal surface of section is indicated (L). Tracheal score of 0. Hematoxylin and eosin stain.

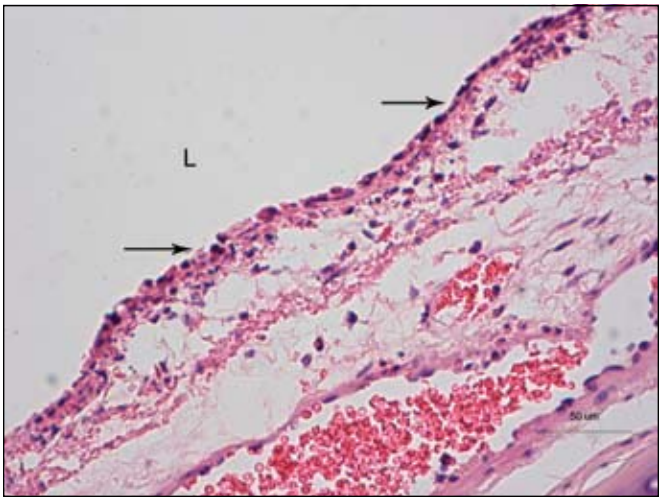

Figure 4. Photomicrograph of tracheal section from a rabbit euthanatized after three 5-h sessions of isoflurane anesthesia with endotracheal intubation, demonstrating marked epithelial attenuation (arrows), lamina propria edema, and vascular congestion. Lumenal surface of section is indicated (L). Tracheal score of 7. Hematoxylin and eosin stain.

despite apparent positive clinical progress. At necropsy, there was patchy redness of the lungs, and tissues were submitted for microscopic evaluation. Microscopically, there was generalized, marked congestion and dilation of submucosal blood vessels and multifocal to locally extensive ulceration and with lamina propria infiltrates of heterophils, eosinophils and mixed mononuclear cells. Overlying the ulcerated areas was fibrinous exudate admixed with frank hemorrhage and cellular debris. Remaining mucosal epithelial cells were attenuated and sparsely ciliated, for a final tracheal lesion score of 7 (Table 3). There was generalized congestion of the lungs, and several small airways contained edema fluid mixed with erythrocytes and cellular debris.

Discussion

Severe tracheal injury after intubation and routine use of inhalant anesthesia has not been reported previously in rabbits. Postintubation tracheal damage is not an isolated event as the injuries occurred in animals from 3 different institutions. The paucity of tracheal lesion reports may be because most surgical procedures involving rabbits in private veterinary practice are of short duration, occur once (such as for neuters), or are sporadic in nature (for example, dental prophylaxis). These findings are clinically relevant because intubations occur frequently in research settings, sometimes multiply within the same study, and rabbits may often be intubated for long periods of time.

Mild injury to the trachea after routine intubation has occurred in a range of species including humans, pigs, horses, and nonhuman primates, but clinical signs are rarely observed.[2,13-15,33] In pigs intubated for 10 min, mild microscopic lesions were seen frequently and consisted of focal loss of cilia with erosion or ulceration of the mucosa without associated clinical signs.[2] After mild mucosal injury in humans, ciliated cells were noted to reappear after the fourth day, and by 7 to 10 d, the epithelium was restored to normal. The absence of complications after short periods of intubation is likely due to rapid respiratory epithelial migration to cover minor defects.[14] More severe injuries to the trachea require 2 to 6 wk to achieve a normal histologic appearance.[14] In human pediatric patients, airway injuries after intubation are not uncommon but are usually limited to mild, focal edema, erosions, and ulcerations of the glottis.[6] Subglottic stenosis is associated with prolonged intubation in humans, and we suggest that it may also occur as potential sequelae in rabbits that have been intubated routinely.[19,21]

A frequent cause of tracheal injury is the endotracheal tube. Cuff-induced injury to the distal trachea caused by pressure necrosis is the most significant complication after intubation in humans;[8,23,26] however, both uncuffed and cuffed tubes were used in the rabbits we report, and lesions occurred well proximal to the cuff position. Uncuffed endotracheal tubes often are preferred for use in small species or juvenile animals in veterinary medicine and traditionally have been recommended for human pediatric intensive care units, routine pediatric anesthesia, and emergency medicine.[11,22] Serious laryngeal damage has been reported to occur in human neonates with uncuffed tubes in situations requiring intubation for longer than 12 to 24 h.[18] Regardless of the type of tube used, we suspect that in some cases of endotracheal intubation in rabbits, the endotracheal tube compresses the tracheal wall distal to the larynx, causing local mucosal ischemia. Once attached to the rest of the anesthesia circuit, the total weight may contribute to the pressure of the endotracheal tube on the tracheal mucosa, even with support of the circuit by gauze.

Size of the endotracheal tube is an important factor that may contribute to tracheal mucosal injury. In human pediatric patients, uncuffed tubes must fit securely to limit air leak and permit satisfactory ventilation, but oversized tube may cause mild laryngeal damage.[16,28] Ulceration of the tracheal mucosa overlying the cricoid cartilage occurred consistently in anesthetized cynomolgus monkeys after use of an oversized endotracheal tube.[33] The average dimensions of the trachea at the level of the cricoid in rabbits ranging from 2.3 to 5.1 kg are 5.81 mm (ventrodorsally) by 5.41 mm (laterally).[20] The rabbits in the current studies weighed between 2.8 and 4.0 kg and were intubated with size 2.5 to 3.5 tubes; therefore the size of the tube likely did not contribute to the injuries noted.

Pronounced movement of the endotracheal tube can cause the tip of the tube to irritate the mucosa and has been implicated in tracheal injury.[5] Movement seemed an unlikely event in the

current study because in all animals, the tracheal lesions were most prominent proximal to the tip of the tube. In humans, marked endotracheal tube movement can occur with flexion and extension of the neck.[5] Once they were placed in position, further movement of the rabbits in these cases was minimal, and flexion and extension of the rabbits' necks did not occur. Although gross movement of the head was not noted, subtle movement of the tube caused by mechanical ventilation may have contributed to the injuries. In a study investigating subglottic stenosis in children, lesions were noted to be worse in those patients requiring mechanical ventilation.[1] Mechanical ventilation may have contributed to the lesions seen in some of the animals that we report but likely was not a primary factor.

Another potential inciting factor for tracheal injury in the first group of rabbits may have been multiple intubations. Reintubation has been associated with moderate to severe tracheal injuries in children.[6] In the first case described, rabbits were intubated a maximum of 3 times over a 5-wk period, and evidence of repeat mucosal injury associated with healing was observed in several animals. Mild tracheal stenosis was present in the most severely affected rabbit that died unexpectedly. Reintubation may have interrupted mucosal healing in this animal, leading to renewed injury and the clinical signs observed. It is clear that rabbits also are susceptible to mucosal injuries associated with a single endotracheal intubation. Tracheal lesions occurred in 5 rabbits that were intubated once each, suggesting that multiple intubations may exacerbate existing damage but that damage may occur after a single intubation episode.

Rabbits may be more susceptible to tracheal injury because of anatomic differences in tracheal blood circulation and anatomy. Anatomically, the rabbit tracheal layers are the same as those of the human trachea; however, the rabbit has a rich vascular sinus in the submucosa and mucosa, with fewer glands. The main vessels supplying the rabbit trachea originate from the right subclavian artery and supply bilateral longitudinal tracheoesophageal arteries. In the trachea, these pass submucosally between the tracheal cartilages, feeding a rich capillary network within the mucosa. The mucosa contains many sinusoidal ectasias, forming an almost cavernous arrangement within the tracheal wall.[24] Perfusion of the rabbit tracheal mucosa in the resting state is high (0.3 ml/min/g) and when a tracheal tube is inserted, the mucosal perfusion increases at least 10-fold due to reactive hyperemia. This response suggests that any type of mucosal irritation may result in a considerable increase in blood flow and congestion.[24] If there is locally extensive ischemia during anesthesia because of endotracheal tube pressure, reperfusion injury may well result after extubation because of the increased tissue perfusion.

It is unlikely that the anesthetic agents or pharmaceuticals administered in the study exacerbated the tracheal injuries. Although specific volatile anesthetic agents, such as halothane, decrease mucociliary clearance by effects on ciliary function, direct damage to the respiratory epithelium has not been reported.[12] Similarly, the use of nonsteroidal anti-inflammatory drugs, opiates, and opioids has not been associated with tracheal injury and may have muted the inflammatory response noted in the current report.

Numerous studies have discussed the difficulties associated with endotracheal intubation of rabbits, and for this reason alternatives to endotracheal tubes have been explored. The use of pediatric laryngeal mask airways (LMAs) in rabbits was investigated to determine ease of placement and waste gas emission.[27] Placement of a LMA was found to be simpler than either a cuffed or uncuffed endotracheal tube, although the LMA emitted the most isoflurane waste. A more stable physiologic state and a smoother recovery period was noted and attributed to decreased trauma to the upper airway after use of a LMA in rabbits.[27] LMAs and endotracheal intubation also were evaluated in a ferret model for prevention of subglottic stenosis in pediatric patients. Although the LMA did not induce subglottic injury, increasing duration of anesthesia and use of the LMA resulted in pharyngeal injury to ferrets. Ferrets with LMAs developed marked tongue edema and cyanosis during the first 24 h after use, and 3 of 5 ferrets in which LMAs were used died after airway obstruction.[3] Further research on devices such as the LMA is needed to ensure anesthetic safety.

The findings of our investigation are highly relevant because rabbit endotracheal intubation is a common procedure. Complications with endotracheal intubation in rabbits may have occurred in other studies but were not identified, recognized as such, or reported. Hemorrhagic tracheal necrosis in a group of rabbits after endotracheal intubation and anesthesia was reported, but the authors of that study attributed the findings to a complication associated with instilling elastase into an arterial branch of the common carotid artery. It is noteworthy that the location and nature of the lesions, and the time course prior to death[30] were identical to those seen in the present report. Histologically significant tracheal injuries may not always result in clinical signs, particularly as rabbits are stoic animals. In a study examining treatment response to tracheal injury, rabbits with marked histologic tracheal injury did not have any clinically significant signs, although the animals were observed for only 6 h after extubation and were euthanatized after 24 h.[19] Coughing in animals that have been intubated recently is frequently encountered in practice but is often disregarded because it seldom leads to more serious clinical signs. It is also possible that in research institutions, many rabbits are euthanatized shortly after anesthetic procedures, before clinical signs develop. Finally, pronounced lesions may go undetected because gross and histologic examination of the lungs and tracheas of animals that have been intubated recently are not routine practices. Complications associated with endotracheal intubation in rabbits are important from an animal welfare perspective, because they may lead to distress and discomfort.

In conclusion, we report 15 cases of sublaryngeal tracheal injury and ulceration in rabbits intubated for isoflurane anesthesia at 3 different institutions. For all species, the most important risk factors for tracheal injury associated with endotracheal intubation are thought to be endotracheal tube cuff pressure and prolonged intubation times. Neither of these factors played a role in the current report, and we suggest that species-specific tracheal vascular anatomy, subtle tube movement during mechanical ventilation, animal positioning for anesthesia, and repeated intubation may be associated with tracheal mucosal injury in rabbits. Further investigations are required to determine the time course and pathogenesis of these tracheal lesions for optimal airway management of rabbits undergoing anesthesia.

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