Controlled Drug Delivery to Tracheal Tissue and the Laryngotracheal Complex from a Novel Coated Endotracheal Tube Augmenting SARS-CoV-2 Care

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FINAL REPORT

Date: 1 November 2023

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DECLARATION OF INTEREST

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Air Force, Department of Defense, nor the U.S. Government. This work was funded by Project Code Number AC12EM01. Authors are military service members, employees, or contractors of the US Government. This work was prepared as part of their official duties. Title 17 USC §105 provides that 'copyright protection under this title is not available for any work of the US Government.' Title 17 USC §101 defines a US Government work as a work prepared by a military service member, employee, or contractor of the US Government as part of that person's official duties.

NOTICE AND SIGNATURE PAGE

CONTROLLED DRUG DELIVERY TO TRACHEAL TISSUE AND THE LARYNGOTRACHEAL COMPLEX FROM A NOVEL COATED ENDOTRACHEAL TUBE AUGMENTING SARS-COV-2 CARE

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
3 February 2023	Final Report	1 Oct 20 – 1 Feb 23

4. TITLE AND SUBTITLE

Study Title: Controlled Drug Delivery to Tracheal Tissue and the Laryngotracheal Complex from a Novel Coated Endotracheal Tube Augmenting SARS-CoV-2 Care

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
United States Air Force, 59th Medical Wing (59MDW/ST).
1255 Wilford Hall Loop, Building 4430
Lackland Air Force Base, 78236-9980

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution A: Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT-

Advanced airway devices to deliver therapeutics directly from endotracheal tubes are lacking in the treatment of patients with acute respiratory distress syndrome (ARDS, from SARS-CoV-2 [COVID-19] or other etiologies), extended periods of intubation, prolonged field care, and multi-domain operations. Prolonged endotracheal intubation poses numerous challenges to clinicians to include long-term breathing, voice, and swallow complications, acute laryngeal injury (ALgI) including tracheal or posterior glottic stenosis, and ventilator associated pneumonia. No current mitigating technologies allow for airway maintenance with reduced mucosal injury and local drug delivery for management and prevention of lung function. This project aims to employ a polymer-mesh coated endotracheal tube platform capable of delivering various antifibrotic, antiviral, anti-inflammatory, and other therapeutics. We hypothesize that continuous delivery of therapeutics will lead to improve local wound healing, resulting in more native biomechanical tissue properties and decreased fibrosis and stenosis. A total of 81 swine underwent transglottic stent placement divided into groups of injured/non-injured and traditional endotracheal tubes or ones with electrospun fibers loaded with dexamethasone, Roxadustat, acyclovir, anti-SMAD3 SiRNA, or empty and left in place for varying durations. Less fibrosis and inflammation was present on histologic evaluation of injured larynges when therapeutic-loaded polymer tubes were employed compared to traditional endotracheal tubes, particularly in the case of dexamethasone. Biomechanical testing also revealed more native tissue properties when employing dexamethasone-loaded polymer endotracheal tubes. Collectively, these data suggest a promising role for employing electrospun, polymer coated endotracheal tubes loaded with dexamethasone or other therapeutics.

15. SUBJECT TERMS- Drug-delivery, electrospinning, airway, laryngeal injury

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT:**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			Dr. Diana del Monaco 59MDW/ST
U	U	U	UU	16	**19b. TELEPHONE NUMBER** *(include area code)* 210-292=5957

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1.0 EXECUTIVE SUMMARY

Therapeutic loaded, electrospun polymer coated endotracheal tubes were developed to fill an unmet need treating complex laryngotracheal injuries and prevent long-term complications from intubation. Current technologies are lacking to deliver therapeutics to the laryngotracheal complex in a continuous fashion or in the intubated patient. This study was designed to leverage a preclinical model to test the effectiveness of electrospun endotracheal tubes loaded with dexamethasone, Roxadustat, acyclovir, and anti-SMAD3 SiRNA. Compared to traditional endotracheal tubes, all therapeutics, though especially dexamethasone, resulted in decreased fibrosis and more native biomechanical properties.

2.0 INTRODUCTION

This proposal addresses developing advanced airway devices for use during respiratory failure and prolonged intubation to deliver therapeutics during intubation for acute respiratory distress syndrome (ARDS from SARS-CoV-2 [COVID-19] or other etiologies), prolonged field care, and multi-domain operations. The objective of this proposal is optimization of a novel, polymer-mesh coated endotracheal tube designed to elute therapeutics in a time and concentration dependent fashion in the setting of respiratory compromise, directly deliver therapeutics to the airway, and prevent long term tissue sequelae. The proposed project employs a polymer-mesh coated endotracheal tube to deliver traditional corticosteroid treatment (dexamethasone), targeted antifibrotic siRNA molecules (anti-SMAD3), valacyclovir, and Roxadustat (FG-4592) and compare wound healing and drug delivery.

Prolonged endotracheal intubation, frequently with large diameter endotracheal (ET) tubes, puts adults at risk of long-term breathing, voice, and swallow complications and acute laryngeal injury (ALgI), including tracheal or posterior glottic stenosis[1-5]. Recent evaluation identified ALgI in more than half of patients intubated greater than 12 hours, with findings persisting for more than two months[6]. With respiratory failure the leading cause of intensive care unit (ICU) admission in the United States and over 55,000 adults treated daily in ICUs, many requiring intubation, recognition of ALgI as a functional impairment to recovery is expanding[7]. Improvement in techniques and technological advancements have reduced but not eliminated the 5% risk of stenosis after prolonged intubation[8-11]. The recent increased number of ventilated patients resulting from the COVID-19 pandemic will increase the number of patients with ALgI. Evidence suggests early intervention may be ideal in treating these patients[12]. Studies demonstrate improvement in ALgI/stenosis with the adjuvant use of intralesional glucocorticoids[12-16]. Others identified improvement with topical or intravenous glucocorticoid administration[17,18]. We also found that SMAD3 regulates vocal fold wound healing[19,20]. Similarly, evidence suggests modulation of wound healing pathways by roxadustat (FD-4592) holds promise in improving wound healing characteristics[21]. Early studies suggest a role for antivirals in COVID-19[22-26]. No studies have assessed these molecules topically in the laryngotracheal complex.

In a broader context, controlled therapeutic delivery from our endotracheal tube platform may serve a larger role in preventing and treating ventilator associated pneumonia (VAP). VAP has long been recognized as a major healthcare burden with worsened clinical outcomes in patients as well as increased resource utilization through prolonged ventilator use and longer intensive care unit stays.[27] Early work on antibacterial coating of endotracheal tubes demonstrates promise in this role of preventing biofilm formation one the ET tube using silver or other molecules.[28-30]

Our novel ET tube coating provides the additional potential of drug delivery locally to tissues, which is hypothesized to break maladaptive fibrotic healing pathways to and encourage healing tissue properties toward native tissues (Figure 1).

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

This study was approved by the U.S. Air Force 59th Medical Wing Institutional Animal Care and Use Committee.

Yorkshire crossbreed swine were used to model prolonged intubation with or without laryngotracheal injury. Animals were premedicated with Atropine (0.05 mg/kg), anesthetized via intramuscular injection of Tiletamine-Zolazepam (4.0- 8.0 mg/kg), and maintained using Isoflurane during injury and endotracheal tube (ETT) placement. For groups with injury, trauma was simulated under endoscopic visualization by mechanically abrading the airway mucosa with a steel brush. A 5 cm ETT with or without dexamethasone was secured within the airway with a 2-0 prolene suture and a surgical button positioned at the midline of the neck for 3, 7, or 14 days (n=3 per each group and time point). Following end of study time points, swine were euthanized using Sodium Pentobarbital (110 mg/kg), larynges were harvested, bisected in the sagittal plane, and frozen at -80°C until further analysis. Figure 2 shows a schematic of the experimental design.

Dexamethasone loaded polycaprolactone (PCL) fibers were deposited on the surface of the ETTs via electrospinning. Briefly, PCL (Mw=80,000) was dissolved in chloroform (15:85 w/w). Dexamethasone sodium phosphate was added to the homogeneous mixture at a concentration of 10% (w/w) of the total polymer mass along with ethanol used as its solvent. The solution was loaded into a Luer Lock syringe and dispensed from a blunt needle using a pump (Pump11 Elite, Harvard Apparatus, Holliston, MA) at an infusion rate of 1.8 mL/hr. A 5 cm section of ETT (Aircare®) was positioned on a rotating (300 rpm) collector 20 cm below the needle tip where a voltage of 20 kV was applied (Gamma High Voltage Research, Ormond Beach, FL). All chemicals were purchased from Sigma-Aldrich (St. Louis, MO). A representative image of the final ETT segment for implantation is shown in Figure 3B.

The larynges were thawed at 4°C and fixed into a Plaster of Paris sample holder as previously described.[31] A Biomomentum Mach-1 v500css (Laval, Quebec, Canada) mechanical tester with a 1.5N uniaxial load cell was used to perform normal indentation along the vocal fold region of the bisected larynges submerged in phosphate buffered saline (PBS) to maintain moisture (Figure 3A). A 0.3mm amplitude test was performed at a velocity of 1.2 mm/s using a 2 mm spherical indenter tip. The structural stiffness was determined from the normal indentation force vs. displacement graphs.

Mechanical property outcomes will be presented as mean ± standard error. Two-way analysis of variance (ANOVA) testing was performed for ETT type and duration for each group followed by Tukey's multiple comparisons test with GraphPad Prism (v9.4.0 for Windows, San Diego, California).

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

We successfully met the following milestones:

- Created electrospun polymer coated endotracheal tubes with dexamethasone, Roxadustat, acyclovir, and anti-Smad3 si-RNA
- 81 swine endoscopies and surgical procedures completed
- Stents successfully placed in all animals
- Data compiled and analyzed
- Study findings presented at The Fall Voice Conference 2022 (podium)
- Manuscript generation is in progress

5.0 RISK ASSESSMENT

5.1 Risk Analysis:

The largest risk in this project revolved around the safe execution of a preclinical transglottic stent model. Leveraging prior airway burn and swine tracheostomy experience, these risks were minimized through careful observation of the swine post-procedure and frequent assessments.

5.2 Technical Challenges

Creating a consistently dimensional polymer coating was a challenge requiring frequent re-assessment and cleaning of the electrospinning tip. Furthermore, the electrospun pattern allowed for some microbial infiltration that was overcome by readjusting the electrospinning parameters to optimize the polymer coating.

6.0 TRANSITION PLAN

6.1 Military Relevance

Airway compromise is the second most common cause of potentially preventable death on the battlefield [32], with 5-10% of the combat casualty population requiring emergency airway management before reaching a field hospital [33]. The clinically preferred method for airway management in trauma care is endotracheal intubation (ETI) but success rates for ETI are low among far-forward providers and drop to as low as 50% when providers do not maintain continuous practice [34]. Due to the significant skill and training required for ETI, in addition to high acuity provider practices on the battlefield, laryngotracheal injury is often a complication of ETI in deployed settings.

During the most recent conflict, gunshot wounds (GSWs) and explosions were the most common mechanism of injury causing death [35-37]; most potentially survivable deaths due to airway obstruction were caused by GSWs to the upper airway structures [36,38]. In the civilian setting, GSWs to the face require emergency airway management 35% of the time [39-42]. In a 2011 study looking at patients from 2004-2007, the most common type of injuries necessitating airway intervention were penetrating facial and neck traumas [34]; this observation aligns with the study by Mabry et al [43] in which ~2% of total deaths were found to have airway compromise as the likely mechanism of death and all of these patients had traumatic injury to the face or neck. Maxillofacial injuries caused by GSWs, as opposed to other mechanisms of injury, are associated with increased need for tracheostomy, indicating more disruption to airway anatomy [44].

Since the end of the Vietnam War, there have been significant changes in protective equipment, weaponry, and tactics increasing the proportion of injuries to the face and neck. Data from US military casualties treated by US naval personnel between 2004 and 2010 revealed 23% of all injured casualties had combat-related maxillofacial injuries, with 4% of total casualties having severe maxillofacial injuries [44]. Of those with severe injuries, 51% required intubation prior to reaching a Role III Military treatment facility, and 19% underwent eventual tracheostomy reflecting the severity of anatomical disruption [44]. Maxillofacial trauma can cause airway obstruction and loss of airway protection by multiple mechanisms: prolapse of the tongue base or maxillary structures, edema of the pharyngeal tissues, or hematoma formation. Advanced procedures for airway protection are necessary with severe hemorrhage into the airway, hemodynamic instability, or spinal and central nervous system injuries [40,41,43].

6.2 Transition Strategy

This technology has the potential to directly improve the treatment of laryngotracheal injuries throughout all levels of care. To transition this technology from the successful preclinical results to FDA approval and future implementation, there is a plan to leverage the expertise of an interested medical startup company to partner with for the final technical approval process.

7.0 RESULTS

Comparing dexamethasone-eluting ETTs with ETTs coated with polymer alone in uninjured tissue, the structural stiffness at 3 days was significantly greater for laryngeal tissue with dexamethasone ETT placement (26.7 ± 0.781 N/m) than ETT without dexamethasone (20.0 ± 0.524 N/m, $p<.0001$). This trend remained the same at 7 days with structural stiffness values significantly greater in groups with dexamethasone ETT placement (28.6 ± 1.24 N/m) than ETT without dexamethasone (24.4 ± 0.854 N/m, $p=0.0151$). When considering type of ETT placement in the native airway, those without dexamethasone saw a significant increase structural stiffness from 3-7 ($p =0.004$) and 3-14 days ($p<0.0001$). Larynges implanted with ETTs with dexamethasone saw a decrease in stiffness from 7-14 days ($p=0.0104$). These data are summarized in Figure 4A.

In injured tissue comparing uncoated ETTs with dexamethasone-eluting tubes, tissue stiffness at 14 days was significantly greater for tissue after placement of ETT without dexamethasone (23.1 ± 0.725 N/m) than ETT with dexamethasone (17.10 ± 0.930 N/m, $p<0.0001$). For inflamed airways with ETT without dexamethasone, stiffness values increased significantly from 3-7 days and 3-14 days ($p <0.0001$). The structural stiffness of tissue with dexamethasone ETT placement increased significantly from 3 (18.2 ± 1.04 N/m) to 7 days (23.6 ± .528 N/m, $p<0.0001$) and decreased significantly from 7 to 14 days (17.1 ± 0.930 N/m, $p<0.0001$). These data are summarized in Figure 4B.

Vocal fold (VF) stiffness increased with longer intubation for controls and roxadustat from 16.7 (SD±8.02) mN/mm at 72 hours, 25.1 (SD±7.09) mN/mm at 7 days, and 22.8 (SD±7.45) mN/mm at 14 days ($p<0.0001$) for uncoated tubes and 15.0 (SD±7.49) mN/mm at 72 hours to 23.7

(SD±7.42) mN/mm at 7 days and 27.3 (SD±8.42) mN/mm at 14 days (p<.0001) for roxadustat. There was no difference between VF stiffnesses at 72 hours. Valacyclovir-treated tissue had lower stiffness at 7 and 14 days compared to roxadustat (p=0.0002). Roxadustat showed higher stiffness than untreated tissue at 14 days (p=0.016). These data are summarized in Figure 5.

8.0 CONCLUSION/DISCUSSION

Prolonged simulated intubation increased VF stiffness, and the electrospun polymer-mesh dexamethasone local release decreased VF stiffness compared to native ETTs, with this effect appearing to increase with increased simulated intubation time. Similarly, local roxadustat delivery increased VF stiffness compared to uncoated ETTs, while antivirals had little effect on VF stiffness. These data suggest dexamethasone delivery via electrospun polymer ETTs may help reduce laryngotracheal scarring with prolonged intubation and with laryngotracheal injury, and that continuous local VEGF-promotion may also alter scarring pathways after laryngotracheal injury.

For future studies we are looking to complete necessary FDA safety – related studies to meet regulatory requirements for 510K approval. We plan to leverage our preclinical data for new product application with the FDA.

9.0 DELIVERABLES

9.1 Publications:

Manuscript: In Progress

9.2 Presentations:

Presentation Title: Effect of Electrospun Dexamethasone Loaded Polymer Local Delivery on Tissue Biomechanics and Histology in Laryngotracheal Injury in a Preclinical Model.

Conference: The Fall Voice Conference; San Francisco, CA; 7-8 October 2022.

Presentation Title: Effect of Electrospun Valacyclovir- and Roxadustat-Loaded Polymer Local Delivery on Tissue Biomechanics and Histology in Laryngotracheal Injury in a Preclinical Model

Conference: Submission In Progress to The Fall Voice Conference 2023; Washington, DC

10.0 COST

The proposal was funded by the Joint Task Force and Defense Health Agency J-9 (Research) from the Coronavirus Aid, Relief, and Economic Security (CARES) Act in the amount of $2,098,000. All funds were expended.

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FIGURES AND TABLES:

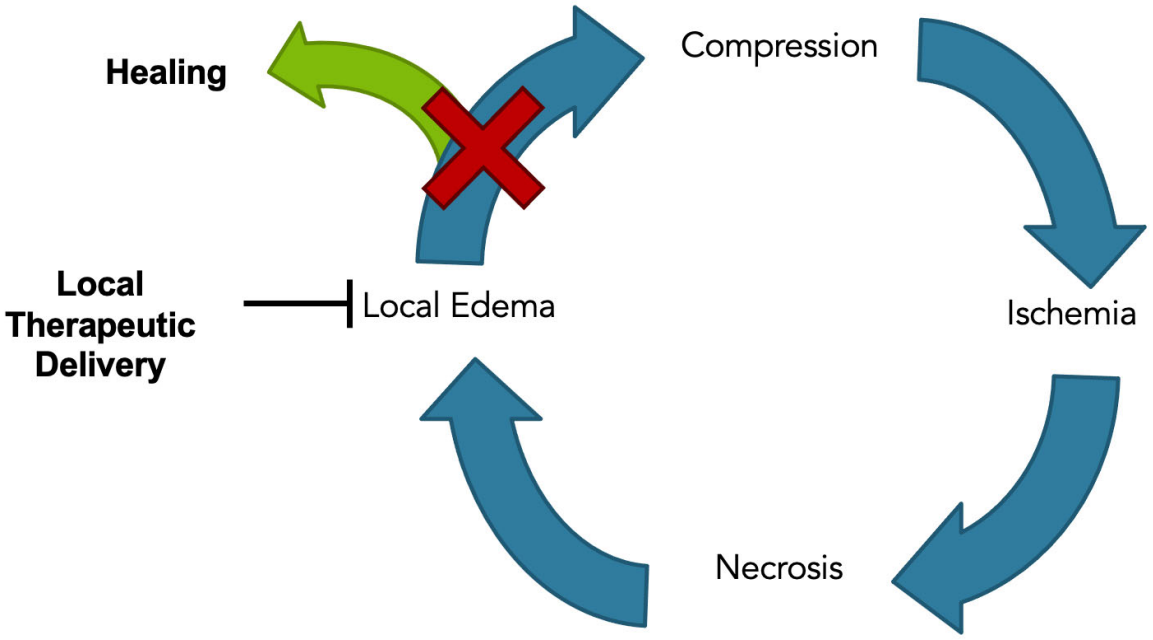

Figure 1: Hypothesized mechanism of improved wound healing with local therapeutic delivery in acute laryngeal injury (ALgI). Reduction in local edema, as well as improved healing due to altered biomechanical signaling, is hypothesized to direct laryngotracheal healing toward native tissue characteristics and reduce scarring.

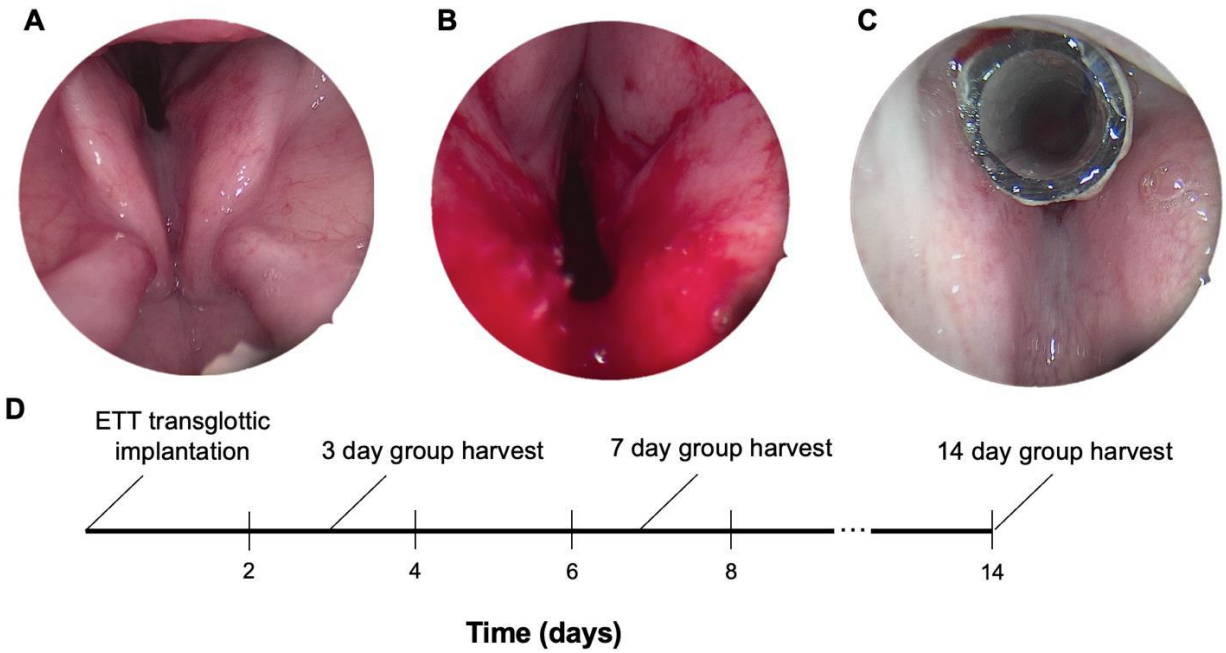

Figure 2: Intraoperative appearance of endolarynx pre-injury (A), after mechanical injury (B), and after transglottic placement of electrospun endotracheal tube placement (C), and timepoints of procedural intervention with animal laryngeal harvest (D)

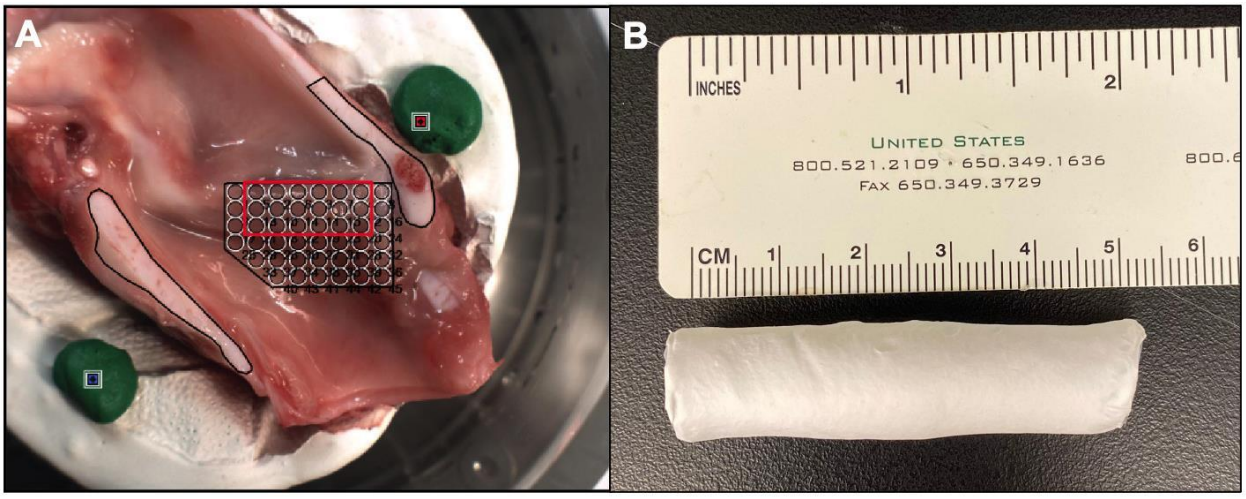

Figure 3: (A) Bisected larynx with overlaid indentation points and region selected for analysis along the midsection of the vocal fold. (B) Polycaprolactone-electrospun endotracheal tube segment ready for implantation.

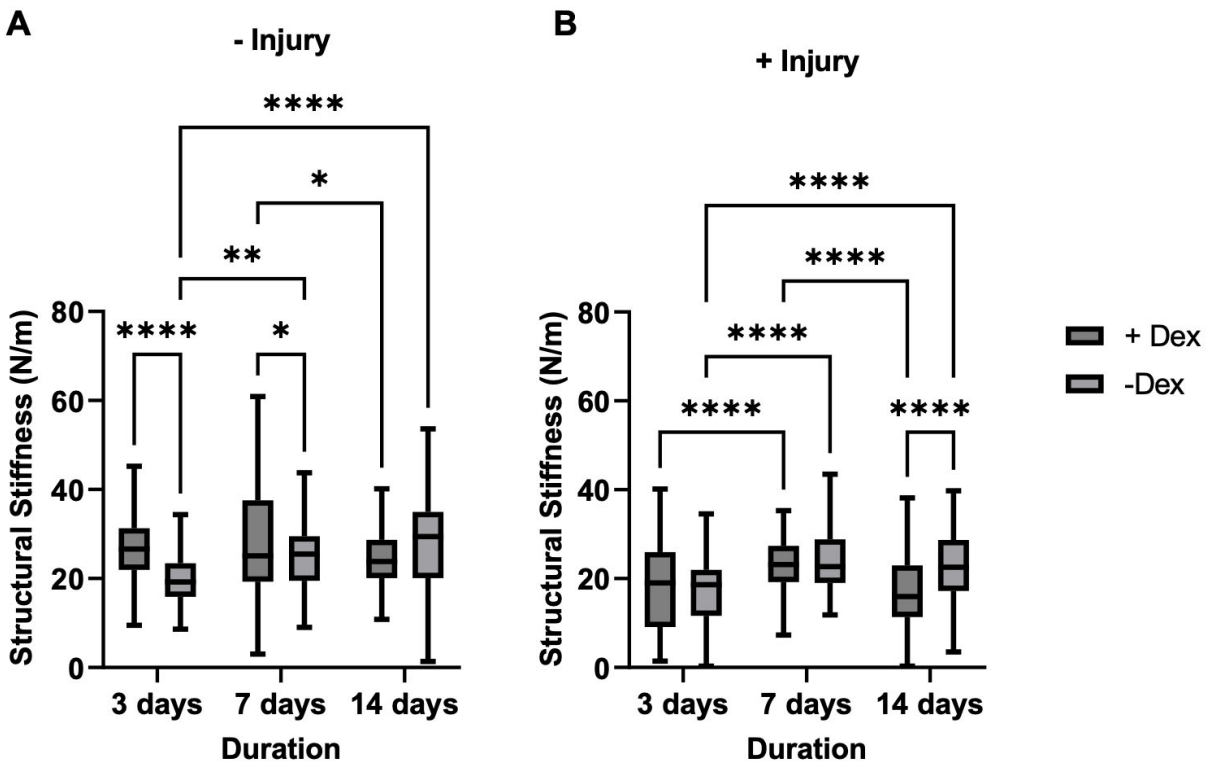

Figure 4: Structural stiffness of (A) native (uninjured) airway with dexamethasone and polymer only coated endotracheal tube (ETT), and (B) inflamed airway with dexamethasone-coated and regular ETTs after 3, 7, and 14 days. Statistically significant differences are indicated by * ($p < .05$), ** ($p < 0.01$), *** ($p < 0.001$), and **** ($p < 0.0001$).

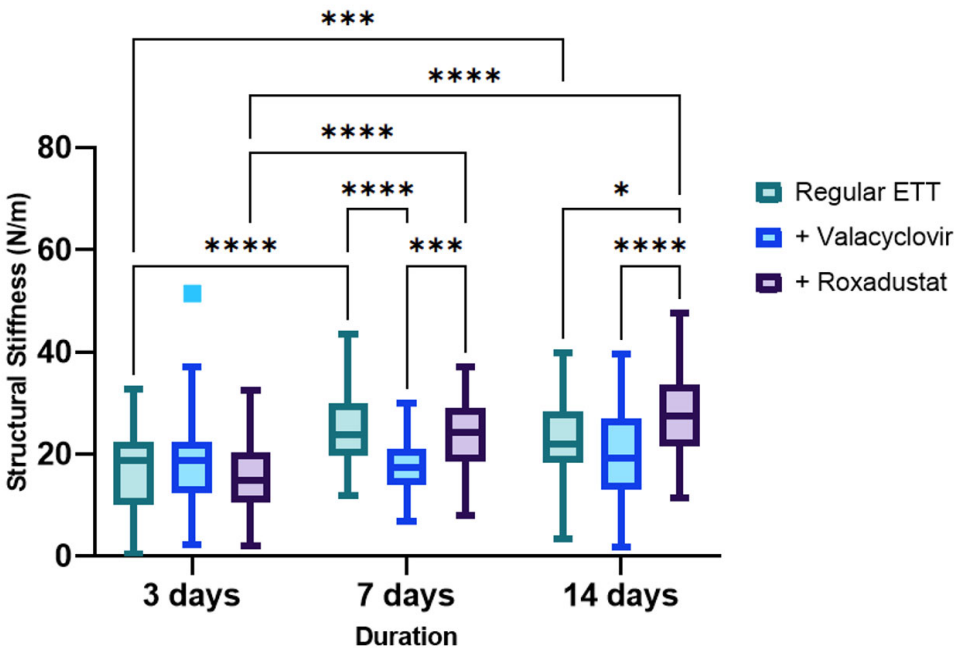

Figure 5: Structural stiffness of inflamed airway implanted with regular endotracheal tube (ETT) compared to valacyclovir-eluting and roxadustat-eluting ETTs after 3, 7, and 14 days. Statistically significant differences are indicated by * ($p < .05$), ** ($p < 0.01$), *** ($p < 0.001$), and **** ($p < 0.0001$).

12.0 LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ALgI – Acute Laryngeal Injury

ARDS – Acute Resipiratory Distress Syndrome

COVID-19 – Coronavirus 2019

ET – Endotracheal

ETI – Endotracheal intubation

ETT – Endotracheal tube

FDA – Food and Drug Adminstration

ICU – Intensive care unit

PCL – Polycaprolactone

SARS CoV-2 – Sudden Acute Resipiratory Syndrome Coronavirus 2

VAP – Ventilator-associated pneumonia

VEGF – Vascular endothelial growth factor

VF – Vocal fold