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Quantification of tissue engineered trachea performance with computational fluid dynamics

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Abstract

OBJECTIVES—Current techniques for airway characterization include endoscopic or radiographic measurements that produce static, two-dimensional descriptions. As pathology can be multilevel, irregularly shaped, and dynamic, “minimal luminal area” (MLA) may not provide the most comprehensive description or diagnostic metric. Our aim was to examine the utilization of computational fluid dynamics (CFD) for the purpose of defining airway stenosis using an ovine model of tissue engineered tracheal implantation (TETGs).

METHODS—TETGs were implanted into sheep and MLA was quantified with imaging and endoscopic measurements. Graft stenosis was managed with endoscopic dilation and stenting when indicated. Geometries of the TETG were reconstructed from 3-D fluoroscopic images. CFD simulations were used to calculate Peak Flow Velocity (PFV) and Peak Wall Shear Stress (PWSS). These metrics were compared to values derived from a quantitative respiratory symptom score.

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Conflict of interest statement: J.J. is a cofounder of Nanofiber Solutions, Inc., the company that provided the grafts for the study. C.K.B. is on the scientific advisory board of Cook Biomedical. C.K.B. and C.B. are co-founders of LYST Therapeutics, LLC. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Level of Evidence: NA

RESULTS—Elevated PFV and PWSS derived from CFD modeling correlated with increased respiratory symptoms. Immediate pre- and post-implantation CFD metrics were similar and implanted sheep were asymptomatic. Respiratory symptoms improved with stenting, which maintained graft architecture similar to dilation procedures. With stenting, baseline PFV (0.33 m/s) and PWSS (0.006 Pa) were sustained for the remainder of the study. MLA measurements collected via bronchoscopy were also correlated with respiratory symptoms. PFV and PWSS found via CFD were correlated ($R^2=0.92$ and 0.99 respectively) with respiratory symptoms compared to MLA ($R^2=0.61$).

CONCLUSIONS—CFD is valid for informed interventions based on multilevel, complex airflow and airway characteristics. Furthermore, CFD may be used to evaluate TETG functionality.

Keywords

Tissue engineered tracheal graft; TETG; tissue engineering; tracheal stenosis; computational fluid dynamics

Introduction

Long-segment tracheal defects are rare, but associated with high rates of morbidity and mortality. Few therapeutic options exist for patients with tracheal defects involving over 50% of the airway in adults and 30% of the airway in children¹. Current options for management range from palliation to complex surgical reconstructions requiring multiple interventions throughout the patient's life¹. Airway replacement with a tissue engineered tracheal graft (TETG) is a potential solution for long segmental tracheal defects, but clinical experience has highlighted complications including graft stenosis and collapse. The ability to monitor the development of this complication is limited by the current options which include 2-dimensional measurements on imaging, or via bronchoscopy. Thus, comprehensive, quantitative, 3-dimensional, geometric assessment of the graft within the airway, and its impact on airflow could provide a powerful tool for longitudinally monitoring the evolution of tracheal neotissue and assessing the viability of potential constructs.

Clinical algorithms to determine timing of airway evaluation are currently influenced by the patient's symptoms, comorbidities, and subjective assessments such as bronchoscopy. However, there is rarely an objective measure used prior to interventions. Previous work has used a variety of animal models to study laryngotracheal stenosis as well as tissue engineered constructs for airway replacement. Some of these models have attempted 2-dimensional measurements with or without correlation to symptomatology. Stenosis, development of granulation tissue, and malacia has all been described in both animals and clinical patients who receive tissue-engineered tracheal grafts. As graft patency is one of the most important outcomes of a successful tissue engineered airway, precise quantification of the dynamics involved within the airway may allow modifications of either the conduit or post-implantation algorithms for management, allowing successful translation into the clinic.

Computational fluid dynamic (CFD) modeling is an intriguing technology that is non-invasive and allows quantitative assessment of airway quality over time. Using fluid flow properties such as wall shear stress and flow velocity, CFD has demonstrated utility in

assessing of the upper respiratory tract and airway reconstructive procedures^{2–5}. However, CFD has not been applied to airway stenosis. Our group has previously described an ovine model of tissue-engineered tracheal graft implantation that was limited by a high incidence of stenosis⁶. A follow-up study demonstrated that the clinical life of the graft could be prolonged using endoscopic interventions, specifically airway stenting⁶. Using 2-dimensional measurements, we were not able to demonstrate a correlation between minimal airway size and time free of symptoms or other outcomes⁶. However, determination of changes in minimal luminal diameter using radiographic and invasive endoscopic methods may not have accurately reflected graft and airway dynamics. Using our previously described ovine model, this study aims to examine the correlation between respiratory symptoms and CFD metrics of peak flow velocity (PFV) and wall shear stress (WSS).

MATERIALS AND METHODS

Animal Care and Ethics Statement

Nationwide Children's Hospital's (Columbus, OH) Institutional Animal Care and Use Committee reviewed and approved the protocol (AR13-00071). Representatives of the Animal Care staff monitored all animals pre-, intra-, and postoperatively. Care was in accordance with humane care standards published by the Public Health Service, National Institutes of Health (Bethesda, MD) in the Care and Use of Laboratory Animals (2011), and U.S. Department of Agriculture regulations outlined in the Animal Welfare Act.

Procedure Details

Scaffold fabrication—Scaffolds manufactured by Nanofiber Solutions, Inc. (Columbus, OH) were manufactured as previously described^{7,8}. A biosynthetic scaffold was electrospun using 20% polyethylene terephthalate and 80% polyurethane mixture. Three-dimensional (3D) polycarbonate rings were arranged between two sheets of scaffold to confer additional support. Sterilization of the scaffold was performed via gamma irradiation.

Graft seeding and implantation—Under general anesthesia, autologous bone marrow was harvested from juvenile sheep (*Ovis aries*, $n=2$). Autologous bone marrow derived mononuclear cells (BM-MNC) were isolated with a disposable filtration system⁹. The tracheal scaffold was then vacuum seeded with isolated BM-MNC and immediately implanted, replacing a 5 CM segment of native trachea as previously described^{6,9}.

Respiratory symptom score—Following implantation, animals were monitored daily for the manifestations of graft stenosis. Based on our prior experience with orthotopic tracheal replacement, the most common signs and symptoms of graft stenosis observed in the lamb model include: stridor, tachypnea, retractions, increased work of breathing, hypoxia with oxygen saturation <85%, cyanosis, wheezing and cough^{6,7}. We quantified these metrics on a daily basis by noting each metric's absence (0 points), presence with exertion/agitation (1 point), and presence at rest (2 points) with a maximum possible score of 14 if all metrics are present at rest (Table 1). The total value was assigned as the daily Respiratory Symptom Score (RSS). The RSS was developed collaboratively between veterinary and clinical staff in order to quantitatively and longitudinally observe symptoms^{6,10}. Standard post-procedure

surveillance in large animals does not include a categorical assessment of respiratory symptoms^{11–16}. Therefore, we use the RSS to supplement veterinary protocols established by our institutional and federal regulatory bodies to ensure the humane management of our animals. While clinical decision making still ultimately depends on the physical exam, the addition of RSS has also permitted more objective characterization of the evolution of the manifestations of graft stenosis.

To validate the newly defined RSS, we evaluated symptoms scores of 7 sheep for 19 measurements during the period of the current study. Based on the CT measurement of total number of 7 sheep, the RSS was found significantly correlated with the area of greatest stenosis ($P < 0.05$, supplemental Figure 1). The decision to perform an emergency intervention was not based on the RSS score; rather RSS scores were documented in order to determine if respiratory symptoms were quantifiable and if they correlate with decisions to perform surgical procedures.

Graft surveillance—Rigid bronchoscopy and 3D fluoroscopic imaging was performed to evaluate graft architecture and patency as previously described⁶. These evaluations were performed pre-operatively and following graft implantation at either planned surveillance points (3, 6, 12, and 20 weeks) or on urgent basis based on symptomatology. Sedation and anesthesia were performed in a similar fashion to that of implantation as described previously⁶. Minimal luminal area was defined by bronchoscopy and confirmed with axial reconstructions of 3D fluoroscopic images. The minimal luminal area was then quantified using endoscopic airway measurements as previously described⁶. In short, optical forceps (round, 10350L) were mounted on a 5.5 mm diameter/50 cm length Hopkins Straight Forward 0 Degree Telescope (10320AA, Storz Tuttlingen, Germany). Images were then calibrated with a set scale, permitting the use of image processing software to digitally measure the airway lumen (ImageJ, v1.49, NIH, Bethesda, MD)¹⁰.

Urgent intervention, including dilation or stenting, was made based on clinical assessment by the primary investigator (otolaryngologist). Baseline bronchoscopic and fluoroscopic imaging of the graft was obtained prior to and immediately after intervention if performed.

CFD modeling

3D fluoroscopic images were obtained at the time of airway surveillance to construct CFD models of TETG geometry (Figure 1) using methods described previously for human upper respiratory airway^{17,18}.

Briefly, images were imported into the commercial software AMIRA (Visualization Sciences Group, Hillsboro, OR, USA), which is capable of extracting the 3D airway geometry from different 2D images. After necessary smoothing and artifact correction, a three-dimensional surface geometry of the trachea airway was generated. A second commercial software package ICEM CFD (Ansys, Inc., Canonsburg, PA, USA) was then applied to generate tetrahedral volume elements inside the trachea geometry. The trachea model mesh used for the simulations ranged from 0.5 million to 1.3 million finite elements.

ANSYS Fluent 16.2 (Ansys, Inc., Canonsburg, PA, USA) was employed to solve the steady incompressible Navier-Stokes equations, which are the governing equations for the airflow. The standard shear stress transport $k-\omega$ turbulence model was used to simulate the flow field with a turbulence intensity of 10% imposed at inlet location¹⁹. Along the tracheal walls, the no-slip boundary conditions were applied, and the walls were assumed to be rigid. A physiologically realistic flow rate of 250 ml/s was applied between the inlet and the outlet. This flow rate was chosen to simulate normal respiration. The numerical solutions of the continuity and momentum equations were determined using the finite-volume method. The continuous pressure and velocity fields were discretized using a second-order upwind scheme for numerical simulations. The SIMPLEC algorithm was used for pressure-velocity coupling. The simulations were performed as steady-state. The converged simulation results were determined once the residual of each variable was less than 10^{-5} . Both PFV and WSS values were obtained from the converged simulation results. The numerical method applied in the current study has been used and validated to model human nasal airflow^{18–21}.

Statistical Analysis

All Pearson correlation calculations were performed using GraphPad PRISM 7.0 (GraphPad Software, Inc. La Jolla, CA). P values less than 0.05 was considered statistically significant.

Results

Baseline Measurements

Bronchoscopic and CT measurements were acquired at scheduled intervals and at each airway intervention. Independent of these assessments, RSS scores were documented daily. Elevated RSS correlated with findings of graft stenosis requiring endoscopic intervention. Minimal luminal bronchoscopic area was weakly ($R^2=0.61$) correlated with RSS for the two subjects (Figure 2). The two-tailed P value obtained via Pearson correlation calculation was 0.0063 (data were normally distributed) (Table 2).

Peak Flow Velocity

Due to the cross-sectional area change before and after implant surgeries, the velocity profile of the tracheal flow can be varied accordingly along the airway, especially for the dilation operation. Pre and post implantation PFVs were similar for both sheep. Subject 1 had a pre implantation PFV of 0.25 m/s and a post implantation PFV of 0.47 m/s. Subject 2 had a pre implantation PFV of 0.35 m/s and post implantation PFV of 0.41 m/s. On post operative day 14 for Subject 1 and day 20 for Subject 2, dilation and stenting was performed in response to respiratory distress. At the time of an emergent bronchoscopic procedure, the RSS for Subject 1 and Subject 2 was 7 and 6 respectively. The PFV pre and post dilation for Subject 1 was 4.51 m/s and 0.83 m/s respectively. The PFV pre and post dilation for Subject 2 was 2.31 m/s and 3.17 m/s respectively. At the end of the study for each sheep, RSS scores and PFV were calculated. Subject 1 had a RSS of 0 and PFV of 0.33 m/s. Subject 2 had a RSS of 3 with PFV of 1.97 m/s. PFV was correlated with RSS with an R^2 value of 0.90 (Figure 3). The two-tailed P value obtained via Pearson correlation calculation was <0.001 (data were normally distributed) (Table 2).

Wall shear stress

Wall shear stress (WSS) is an important variable to identify the level of shear force exerted onto a unit area of tracheal tissue. It can be treated as indicator to evaluate the interaction between airflow and tissue. Pre and post implantation WSS values were similar for both sheep. Subject 1 had a pre implantation WSS value of 0.005 Pa and post implantation WSS value of 0.014 Pa. Subject 2 had a pre implantation WSS value of 0.03 Pa and post implantation WSS value of 0.04 Pa. At the time of an emergent bronchoscopic procedure, Subject 2 had a RSS score of 6 and a WSS value of 0.67 Pa, and Subject 1 had a RSS score of 7 and a WSS value of 0.85 Pa. Subject 1's RSS score at the end of the study was 0; CFD determined that Subject 1's WSS value was 0.006 at this time. Subject 2's RSS score at the end of the study was 3; CFD determined that the WSS for Subject 2 at this time was 0.39 Pa. WSS values were found to be correlated with RSS scores with an R^2 value of 0.99 (Figure 4). The two-tailed P value obtained via Pearson correlation calculation was <0.001 (data were normally distributed) (Table 2).

Discussion

Bronchoscopy, and computed tomography, can provide anatomical descriptions of an airway, but do not provide quantitative measures of tracheal flow, or a comprehensive geometric description. CFD bridges this gap by creating a multi-level quantitative and qualitative description of the airway. Historically, CFD has been used to describe airflow in upper airway reconstructive surgery, as well as for modeling fluid flow through blood vessels^{4,22–24}. Previous work has shown that CFD has the potential for use in evaluating treatment planning for airway interventions^{4,25–27}. CFD allows for advanced diagnostic capabilities and is especially useful in cases involving multi-level or complex pathology. For example, if a patient has respiratory tract pathology at the level of the trachea, bronchi, and lungs, CFD allows for description the pathophysiology from each component in isolation or as a combined system. This can lead to improved decision making while devising a treatment plan. The current study demonstrates that CFD modeling more closely correlates with respiratory symptoms than previously described methods.

Clinically, bronchoscopy remains the most important tool for diagnosing and investigating airway characteristics²⁸. The decision to carry out an interventional procedure is currently based solely off of respiratory symptom severity and presence, and not on quantitative measures of airway quality (e.g. bronchoscopic measurements and CFD). Varying degrees of impending respiratory distress have been described in human patients, such as: stridor, a “barking” or brassy cough, and “washing machine” airway sounds²⁹. However, the practicality of objectively quantifying respiratory distress in an acute setting can be challenging²⁹. Diagnoses are frequently delayed because of the rarity of the lesion, or because other more apparent associated malformations draw the attention of the clinician²⁸. Other researchers have therefore developed scales of evaluating respiratory symptom correlation with disease progression in humans^{29,30}. For example, stridor has been noted as a key feature in differentiating between mild and moderate respiratory distress. Additionally, like in this study, retractions, which may vary with activity level, have been noted to indicate the presence of increased respiratory effort²⁹. Human studies mentioned have not linked

respiratory symptoms with quantitative measures of airway quality and this has not yet been done in an ovine model. This study seeks to address the limitations described in these studies to create a more objective and quantitative method of airway characterization for use in a preclinical research setting.

The application of CFD to airway characterization was born out of the necessity to quantify performance of a tissue engineered tracheal graft. Graft stenosis is the predominant complication observed, and this occurs in a multilevel fashion^{6,10}. Multilevel pathology is not accurately represented using conventional methods of airway sizing, which provide only single level qualitative imaging or minimal luminal area measurements. CFD allows for evaluation of graft performance as a whole. Previous work has shown that dilation and stenting does not drastically change minimal luminal area, but following the intervention, symptoms improved⁶. CFD proved crucial to the understanding of these results by creating a multi-level geometric and quantitative description of TETGs within the airway.

This was an exploratory study and there are several limitations to this study. The sample size is small, due to the complexity of creating a CFD model and performing work within large animal models. Although the technique was only demonstrated on two animals here, the RSS correlated with emergent intervention times and CFD model descriptions of decreased airway quality (data not shown). Additionally, two study durations (short and long) were presented here and the RSS performed equally well for both; respiratory symptoms in sheep may differ from those of a human. This work needs to be further validated and tested in a larger cohort of sheep or possibly humans.

This is the first study to demonstrate a correlation between TETG-related respiratory distress and an objective method for airflow dynamics. It showed that when radiologic imaging is available, it is possible to obtain flow-related measurements (PVS and WSS) which were found to be correlated with respiratory symptom presence. The Pearson correlation calculation showed that this method compares well to the gold standard ($P < 0.05$). Previous work has shown that percent stenosis derived from CT and bronchoscopic measurements of luminal area is correlated ($P < 0.05$) with RSS in a cohort of 8 sheep (including the two from this study) (supplemental Figure 1)⁶. Furthermore, the validity of correlating symptoms and radiographic measurements has been demonstrated in humans for another condition (tracheomalacia)¹¹. Within TETG models, individual responses to implantation and intervention may vary. Nevertheless, CFD allows for the quantitative and objective assessment of TETG performance. This technique may allow for continued optimization of TETG, as well as algorithms for interventional procedures.

Conclusion

CFD is a valid technique for evaluating multi-level, complex airway geometry, and for quantifying PFV and WSS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Fluoroscopic images were used to create 3D reconstructions of sheep tracheas.

Reconstructions were created using Vitrea and COMSOL softwares. Airflow simulations were created for each geometry using physiologic inspiratory flow rates of 250 ml/s under conditions of laminar flow. PFV and WSS across the graft and adjacent native trachea were thus determined. Changes in the aerodynamics of the implanted graft with and without stenting were also analyzed.

Figure 2.

A representative bronchoscopic view and fluoroscopic image of a sheep subject are shown here. Baseline measurements in the form minimal luminal bronchoscopic area was captured and plotted against respiratory symptom score sum for the two sheep.

Figure 3. CFD measurements of peak flow velocity (m/s) and respiratory symptom scores for a) Subject 1 and b) Subject 2 for the duration of the study. c) Peak flow velocity (m/s) was plotted against respiratory symptoms score and had an R^2 value of 0.90.

Figure 4. CFD measurements of peak wall shear stress and RSS scores for a) Subject 1 and b) Subject 2 for the duration of the study. c) Peak wall shear stress (Pa) was plotted against respiratory symptom score for the two sheep and had an R^2 value of 0.99.

Table 1

Respiratory Symptom Scale

Symptom	Observation	Score	RSS Score
<ul style="list-style-type: none"> Tachypnea Retractions or increased work of breathing Desaturation <85% Cyanosis Stridor Wheezing Cough 	Absent	0	Sum of scores from each symptom assessed (0-14).
	Present during activity	1	
	Present at rest	2	

Table 2

CFD Correlation with RSS

	Minimal Luminal Bronchoscopic Area	PFV	WSS
P value	0.0063	<0.001	<0.001