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Patterned, tubular scaffolds mimic longitudinal and radial mechanics of the neonatal trachea

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ABSTRACT

Tracheal damage, abnormality or absence can result from the growth of tumors or from Congenital High Airway Obstruction Syndrome. No optimal or routine treatment has been established for tracheal repair, despite numerous attempts with natural and artificial prostheses. The fetal trachea is comprised of cartilaginous rings connected by an elastomeric tissue. In an effort to design an engineered trachea replacement, we have synthesized 2-hydroxyethyl methacrylate hydrogels with moduli of 67 ± 3.1 kPa (soft) and 13.0 ± 1.8 MPa (hard). Given the criteria for longitudinal extensibility and lateral rigidity applied during respiration, we evaluated a series of patterned hydrogels with different sizes of hard and soft segments to mimic fetal tracheas. A 1:2 ratio of soft:hard segments resulted in a construct capable of 11.0 ± 1% extension within the elastic range. Tubular constructs with this ratio required similar load/length for cyclic compression as ovine trachea samples. Achieving biomimetic mechanical properties in a trachea replacement may be essential for achieving normal respiration in recipient patients.

Statement of Significance

Fetal abnormalities or tumors can result in tracheal absence or damage. Despite numerous attempts with natural and artificial replacements, there is still no routine treatment for tracheal repair. The literature recognizes the importance of tracheal lateral rigidity and longitudinal extensibility for normal respiration. Achieving closely matched mechanical properties may provide proper function and help decrease implant fibrosis and subsequent occlusion. In this study, we evaluated the mechanics of a series of patterned, tubular hydrogels with different ratios of hard and soft segments to mimic alternating cartilage and ligament sections in fetal tracheas. We compared our results to that of sheep trachea. This is the first report to assess both radial rigidity and longitudinal extensibility in an engineered trachea construct.

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1. Introduction

The most critical anomalies affecting the neonate at the time of birth are those impeding the ability to breathe. Attempts to manage the effects of large tracheal defects have included various surgical techniques, autografts, allografts, and numerous natural and artificial prostheses, including reconstruction with a decellularized airway, and 3D engineered cartilage constructs grown with autologous amniotic mesenchymal stem cells [1–5]. However, no optimal or routine treatment has been established due to complications, such as stenosis, infection, implant extrusion, implant weakening over time, poor or no growth, and inconsistent functional outcomes, even when complete epithelialization has been observed. As a result, trachea structural congenital abnormalities continue to be associated with high rates of morbidity and mortality.

The native trachea is a multi-component structure, consisting primarily of trachealis muscle, mucosa, submucosa membrane, glands, epithelium and cartilaginous rings, all in a connective tissue framework [6,7]. The adult human trachea is on average 1.8 cm in diameter and 12 cm in length, although it lengthens and widens during inhalation and narrows and shortens during exhalation [7,8]. Neonatal diameters and lengths are significantly smaller, ranging from 3 to 4.5 mm [9] and 20 to 30 mm [10], respectively. The rings, composed of hyaline cartilage, extend up to five-sixths of the way around the trachea, and are responsible for holding the trachea open in spite of the changes in interthoracic pressure which occur during respiration [11].

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It is believed that changes in overall stiffness of the trachea may be a contributing factor to the altered lung function seen in obstructive lung diseases [12]. Adult human trachea rings have been reported to have an elastic modulus between 1 and 20 MPa [13,14]. The trachealis muscle is the more active component of the trachea, capable of responding to external stimuli [6]. The smooth muscle network additionally allows changes in trachea length [7]. While the circumferential tangent modulus is higher, the tangent modulus of smooth muscle in the longitudinal direction only reaches around 50 kPa at 20% strain [6].

In order to serve the same purpose as the native organ, construct mechanics must be sufficient for the engineered trachea to maintain a patent airway in the face of physiological loading conditions. Furthermore, achieving closely matched, anisotropic mechanical properties in a tissue engineered replacement will be important not only for graft patency, but also for full functionality of the graft. If the stiffness is mismatched, granulation at the anastomoses may induce fatal obstruction or bleeding [15]. Abnormal longitudinal properties – observed in the case of vertical tracheal fusion – lead to ongoing respiratory problems [16]. Indeed, as early as 1929, physiologists determined that a completely rigid tube would not allow for normal lung ventilation [17]. During respiration the trachea may extend 20% in the adult and up to 46% in neonates [18]. These observations make a strong case for the development of a trachea replacement that can adequately approximate the longitudinal extensibility and lateral rigidity conferred to native trachea by its cartilage and smooth muscle composition [6,19]. Construct anisotropy can be achieved via biomimetic patterning.

In this paper, a series of patterned 2-hydroxyethyl methacrylate (HEMA) hydrogels were prepared to mimic neonatal trachea mechanics along the longitudinal and radial axes. HEMA hydrogels have been used in many biomedical applications, including drug delivery and tissue engineering [20]. Their mechanical properties can be varied by changing hydrogel composition (e.g., the monomer, photo initiator, and crosslinker concentrations) and/or the UV exposure time in photopolymerizable systems. The crosslinking density of the gel network is proportional to the gel's elastic modulus and inversely proportional to its swelling [21]. This spatial control over construct mechanical properties makes the development of patterned constructs fairly simple. The main thrust of this work is to demonstrate the effect of the hard:soft (H:S) ratio in banded hydrogel constructs on the longitudinal extensibility and lateral rigidity, both essential mechanics in an engineered trachea prosthetic device.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) was purchased from TCI Chemicals (Montgomeryville, PA). Tetraethylene glycol dimethacrylate (TEGDMA), ethylene glycol (EG), and 2,2′-Azobis (2-methylpropionitrile) (AIBN) were purchased from Sigma Aldrich (St. Louis, MO). Sheep trachea samples from sheep age 8–36 months were purchased commercially from Senat Poultry, Inc. (Paterson, NJ).

2.2. Analysis of ovine trachea

Tracheae were stored at −20 °C for preservation until use, at which time they were thawed and hydrated in water at RT for 2 h. Two tracheae were photographed in relaxed and fully extended positions. Measurements of tracheal cartilage and ligament ring widths were extracted from ImageJ. Average cartilage: annular ligament (C:AL) ratio was calculated for each trachea individually, and the extensibility calculated as (stretched length − relaxed length)/relaxed length) * 100%. Each trachea was cut at the annular ligaments into segments for testing, described below.

2.3. HEMA hydrogel polymerization

Hydrogels were prepared by sequentially combining 5.2% (v/v) diH_2O, 67.3% (v/v) HEMA, 16.2% (v/v) EG, 11.3% TEGDMA, and 2.05% (w/v) AIBN. Materials were used as received. EG was used as a solvent. After AIBN was fully dissolved, approximately 30 min, the mixture was degassed for 20 min. Custom molds were filled with solution and exposed to 368 nm UV light for 6 min to create soft gels. The hard and soft spatial patterns described in Table 1 and shown in Fig. 2B were created by subsequent exposure of 4 min in the presence of a photomask, for a 10 min total exposure time of unmasked areas. The % hard is calculated as the [(size of hard bands * number of hard bands)/gauge length] × 100%.

2.4. Mechanical testing

Testing was performed using an Instron 5543 mechanical testing system with a 10 N load cell. All yield strains were calculated by a 0.02% offset method. Modulus was calculated to 0.5% strain for consistency. Modulus, yield strain, and yield load for tensile and radial compression tests were obtained using MATLAB.

For the evaluation of longitudinal properties, patterned 3 mm thick hydrogel slabs were cut into strips were secured in a mechanical tester with pneumatic grips. Samples were stretched perpendicular to the banding pattern at a strain rate of 1 mm/min. Sample $n = 4$ for each patterned group. Applied stress was calculated using initial cross sectional area of samples, as measured with calipers.

For the evaluation of radial properties, tubular constructs and trachea specimens were laid on their sides between compression plates, as shown in Fig. 3. Complete radial compression of cylindrical constructs was performed at a strain rate of 1 mm/min. Cyclic radial compression was performed at 0.833 Hz to a maximum deformation equaling 15% of the original diameter. This rate is to mimic an average neonatal respiratory rate of 1.2 s/breath. For testing of ovine trachea, compression plates were lined with sandpaper to prevent slipping.

2.5. Mold specifications for producing 3D tubular constructs

A custom mold was constructed using a modified 10 mL syringe and a 10 mL serological pipette. Sylgard elastomer kit was used to create a detachable base in which the syringe and pipette are held in place concentrically. The space between the syringe and pipette was filled with liquid polymer mixture. The mold was then placed

Table 1
Banding pattern specifications.

H:S ratio	% Hard	Hard (H) [mm]	Soft (S) [mm]	Number of bands	Gauge length [mm]
0:1	0	–	–	–	20
1:2	25	4	8	5	32
1:1 (L)	40	4	4	5	20
1:1 (M)	44	2.22	2.22	9	20
1:1 (S)	50	1	1	20	20
2:1	57	4	2	5	14
4:1	73	4	1	5	11
1:0	100	–	–	–	20

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