Optimizing Procedural Delivery Methods for Novel Male Contraceptive Implant

A Technical Report submitted to the Department of Biomedical Engineering

Presented to the Faculty of the School of Engineering and Applied Science

University of Virginia • Charlottesville, Virginia

In Partial Fulfillment of the Requirements for the Degree

Bachelor of Science, School of Engineering

Veda Raghu

Spring, 2022

Technical Project Team Members

Abby Rieck

Abigail Myers

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Shannon Barker , Department of Biomedical Engineering

Optimizing Procedural Delivery Methods for Novel Male Contraceptive Implant

Abstract

Contraline is a Charlottesville-based startup developing a novel, long-lasting, and reversible contraception option for men. Their injectable hydrogel, ADAM™, is designed to physically occlude the vas deferens, an excretory sperm duct in the male reproductive system. The narrow lumen of the vas deferens inhibits accurate delivery of the hydrogel formulation. However, current models of the male reproductive anatomy fail to accurately simulate *in vivo* conditions and, thus, impede refinement of the delivery procedure. Thus, the aims of this project are two-fold: firstly, to develop an *in vitro* model of the vas deferens that accurately mimics the anatomical properties of the vessel *in vivo*, and secondly, to devise a method for confirming the accurate cannulation of the vas deferens lumen. To model the vas deferens, four distinct formulations of polydimethylsiloxane (PDMS) were shaped into vessel structures using injection molds. Canine vas deferens samples, control tubing, and the resultant PDMS models were subjected to tensile testing to experimentally determine their respective mechanical properties. The canine tissue samples had a representative Young's modulus of 16.76 ± 6.89 MPa, while the highest Young's modulus observed in the PDMS samples was 1.470 ± 0.185 MPa, revealing an order of magnitude discrepancy. The Flexelene ™ tubing samples, which served as an experimental control group, offered the closest match to the mechanical properties of the vas deferens, with a representative Young's modulus of 6.501 ± 0.828 MPa. An assistive cannulation device design was finalized, incorporating a curved handle structure to fit the index finger, a ridged handle face to guide and secure the positioning of the thumb, and puzzle-piece-like notches to secure the exposed vessel across the flat surface of the device. Future refinement of this device will significantly improve the efficacy and efficiency of the contraceptive delivery procedure.

Key words: contraception, vas deferens, modeling, biomimetic, Young's modulus, tensile testing, cannulation

---

Introduction

In a 2022 report, the United Nations (UN) Population Fund revealed that nearly half of all pregnancies worldwide are unplanned (1). To prevent unintended pregnancies, a reported 922 million reproductive-aged women worldwide report the use of contraception (1). While modern innovation has drastically improved the efficacy of contraception, these advancements have also introduced a notable gender bias in the landscape of contraceptive technology. Despite the broad range of female contraceptive options – including the hormonal birth control pill, the intrauterine device, the female condom, and female sterilization – the technological options for men to prevent pregnancy remain threefold: condoms, withdrawal, and male sterilization (10). Contraceptive practices in the United States distinctly reflect these gendered disparities in contraceptive innovation. Female sterilization and the oral contraceptive pill represent the leading contraceptive methods in the United States, comprising 18.6 percent and 12.6 percent of contraceptive use, respectively (1). By contrast, male-dependent methods, such as male sterilization and male condoms, prove notably less prevalent, accounting for 5.9 percent and 8.7 percent of nationwide contraceptive use, respectively (2). Further, male sterilization represents the only long-acting, reversible contraceptive (LARC) method currently available to men, accounting for a mere 2 percent of contraceptive use worldwide (3).

Male sterilization, known more commonly as a vasectomy, is an outpatient procedure performed by a urologist. The vasa deferentia (plural) are long, muscular tubes which connect the epididymis – sperm storage structures located on each testicle – to the ejaculatory ducts in the male reproductive system. These vessels serve as channels for the transportation of sperm during ejaculation. During a vasectomy procedure, the vas deferens is externalized from the scrotal sac after application of a local anesthetic. The exposed vessel is then cut and cauterized to impede sperm flow. While vasectomies are widely recognized as reversible procedures, nearly one third of vasectomy

patients report new fertility-related complications following the reversal procedure (4). Such reports raise significant concerns surrounding the reliable reversibility of a vasectomy procedure.

Contraline, Inc. is a Charlottesville-based start-up aiming to bridge this widening gap in the contraceptive landscape with the introduction of a novel, long-lasting, and reliably reversible contraception option for men. Their proprietary hydrogel formulation, ADAM™, is designed for injection into the lumen – or internal channel – of the vas deferens. Following injection, the hydrogel swells to form a physical barrier to sperm flow. Sperm cells blocked by the hydrogel barrier degrade naturally and, with time, are reabsorbed into the walls of the vessel. Further, at the end of its lifespan, the occlusive hydrogel liquifies, thus removing the barrier to sperm flow. ADAM™ offers a non-hormonal contraceptive solution for men, thereby reducing the likelihood of side effects often associated with hormonal methods. However, accurate injection of the hydrogel into the narrow lumen of the vas deferens remains a significant barrier to the success of Contraline's technology.

The average lumen of the vas deferens is less than two millimeters in diameter. This narrow target has proven a significant challenge during clinical applications of ADAM™ as operating urologists struggle to consistently and accurately cannulate the vas deferens for hydrogel injection. Problems with hydrogel delivery have been further exacerbated by limitations associated with *in vitro* testing conditions. Current models of the male reproductive anatomy offer an unrealistic representation of *in vivo* conditions and, thus, oversimplify testing of the hydrogel delivery procedure. These inaccuracies inhibit company-wide efforts to develop a procedural or technological solution that enables consistent placement of the syringe into the vessel lumen.

Therefore, the goal of this research is to create and employ an anatomically-accurate model of the vas deferens to aid the development of a cannulation feedback mechanism for accurate delivery of the hydrogel into the lumen of the vas deferens. To ensure successful completion of this project, a list of specific aims was generated.

The first aim requires the development of a three-dimensional *in vitro* model of the vas deferens which accurately mimics the anatomical properties of the vessel *in vivo*. The design of this model was informed by both physical design parameters, such as vessel diameter, lumen diameter, and wall thickness, as well as mechanical parameters, such as tissue elasticity. The refined model will provide a tool to optimize current methods of hydrogel delivery. The biomechanical properties of the vas deferens remain largely undefined by previous research in the field of male reproductive health. A 1979 study by Batra et al. characterized the viscoelastic properties of rat, bull, and rabbit vas deferentia using Fung's Exponential model. However, these outdated and non-universal metrics were not easily applicable as effective design parameters. Therefore, to confirm the mechanical properties of the vas deferens *in vivo*, tensile testing was conducted using canine samples.

The second aim of the project involved the development of a method to confirm accurate cannulation of the vas deferens' lumen. The proposed delivery solution needed to function under the direction of a single user, to be readily incorporated into the existing procedure, to be relatively inexpensive and easily reproducible, and to ensure accurate cannulation within two attempts by the operating urologist. Current methods involve using guide wires during the cannulation process, which is a time-consuming and tedious method that does not always result in success. Successful development of a delivery solution will improve ease of use for practitioners, reduce time associated with hydrogel delivery, and ensure overall accuracy of the procedure. Together, these improvements will aid Contraline in bringing the first long-term, readily-reversible male contraceptive option to market.

Materials and Methods

Material Selection for Model Fabrication

The shortage of research on the biomechanical properties of the human vas deferens *in vivo* presented a significant challenge to precise material selection. Thus, to inform material selection, the mechanics of similar soft-tissue structures were analyzed. The urethra and vas deferens are similar in both function and composition. The vessels unite

at the ejaculatory duct, and, together, form the primary passageway for sperm during ejaculation. Like the vas deferens, the urethra is a multilayered tubular structure composed of smooth muscle cells. Given these similarities in composition and proximity, it was hypothesized that the biomechanical properties of the urethra may be utilized to approximate the biomechanical properties of the vas deferens. Similarly, the tunica albuginea (TA) is a thick fibrous coating that envelops and protects the spongy tissue of the penis as well as promotes penile rigidity during erection. This envelope is a bi-layered structure composed primarily of collagen. While penile TA tissue differs significantly from the vas deferens in both form and function, the biomechanical properties of this tissue were considered in material selection in order to account for biomechanical variation across the male reproductive system. Based on biomechanical analyses of porcine urethral tissue and human penile tunica albuginea, it was estimated that the elastic modulus of the vas deferens would range between 0.5 and 10 Megapascals (MPa). These estimations were used to inform material selection. Similarly, it was estimated that the ultimate tensile strength of the vas deferens would range between 0.3 and 2.5 MPa.

Guided by these design parameters, a material search was conducted. To achieve a reliably replicable model design with feasible application as a soft-tissue vessel, it was determined that the ideal material should be: (1) a synthetic elastomer, (2) easily molded or extruded, (3) relatively inexpensive, (4) widely used in applications as a soft-tissue biomimetic. Based on these parameters, eight candidate materials were identified, including polyurethane (PU), expanded polytetrafluoroethylene (ePTFE), polydimethylsiloxane (PDMS), polyglycerol sebacate (PGS), polycaprolactone (PCL), Poly(lactic-co-glycolic acid) (PLGA), and Dacron.

To narrow these material candidates, Dr. Liheng Cai, an Assistant Professor of Materials Science at the University of Virginia was consulted. Based on collected research and the additional guidance of Dr. Cai, PDMS was ultimately selected, and Sylgard® 184 was purchased for model fabrication. PDMS is a two-part silicone elastomer comprised of a liquid-based curing agent and base.

The high tunability of PDMS represents a distinct advantage of the material, especially given the uncertainties surrounding the mechanics of the vas deferens tissue. By varying the ratio of base to curing agent, PDMS readily yields a wide range of material elasticities. This would allow for the mechanics of the material to be altered based on the results from the tensile

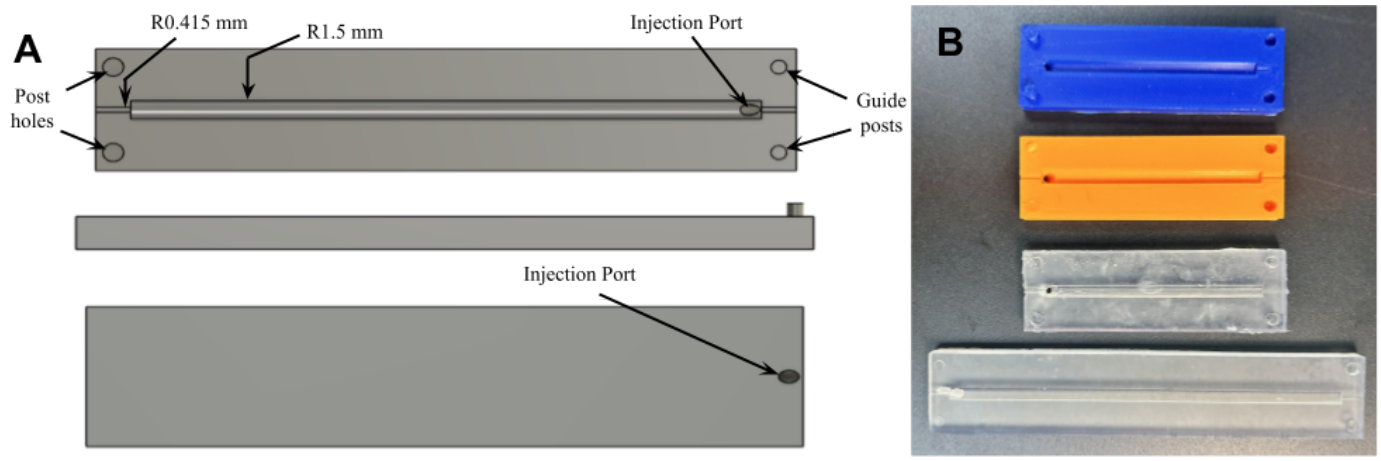

Figure 1. Final Mold Design. (A) The final mold was designed as a mirrored system whereby two copies of the same component comprise one complete molding device. The radii of the narrow wire channel and wider injection channel total 0.415 mm and 1.5 mm, respectively. Thus, when combined with the other mold half, the molding system yields models with an outer diameter of 3 mm and an inner diameter of 0.8 mm, consistent with the physical dimensions of the human vas deferens *in vivo*. (B) An iterative design approach was employed in the fabrication of mold components. While initial prototyping was conducted using extrusion-based printers, final mold components were constructed using stereolithography printers. The mold design was also lengthened midway through the model fabrication process to account for defects that frequently occurred at either end of the model due to injection-induced air bubbles. By lengthening the mold design, sizable models for tensile testing were more consistently achieved.

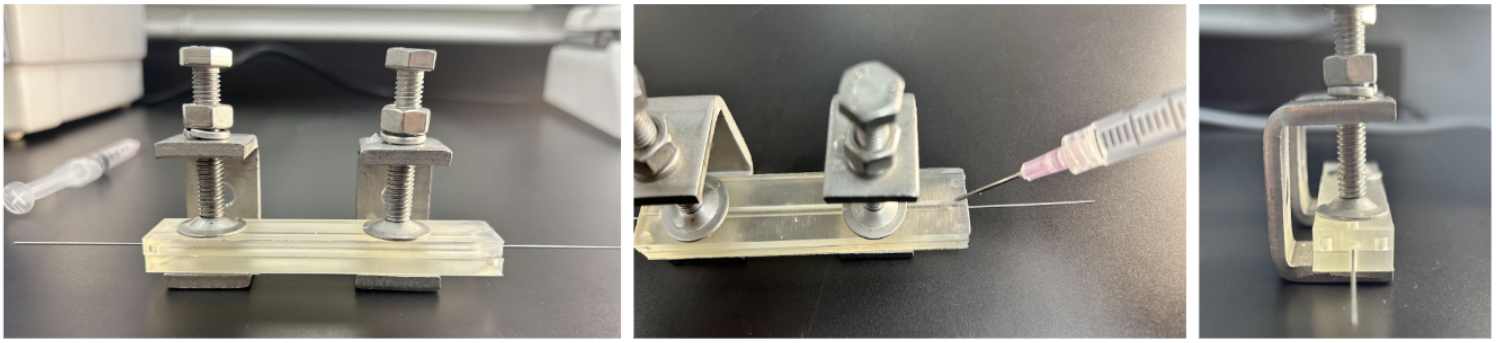

Figure 2. Mold Preparation and Injection Procedure. The injection molding process was optimized to yield uniform models for all PDMS ratios. To form the vessel lumen, a 20 gauge (0.8 mm) metal wire was positioned between the two mold halves and secured in place using two C-clamps. A 22 gauge needle was used to inject PDMS elastomer through the upward-facing injection port. The material flowed through the hollow mold, and excess material was expelled through the opposing injection port, indicating that the mold was adequately filled.

testing of vas deferens tissue samples. Specifically, it was hypothesized that adding increasing amounts of curing agent would yield increasingly stiff elastomeric properties.

Mold Design and Prototyping

In order to mold the liquid-based elastomer into vessel-like structures, injection molds were designed in Autodesk Fusion 360® (Figure 1A). Physical dimensions of the average human vas deferens were used as parameters to inform the mold design. The finalized mold was designed as a mirrored system, with two copies of the same part comprising the total molding device. The opposing sets of guide posts and post holes provided a system to align and stabilize the mold halves. Further, the injection ports positioned on the external faces of the mold halves served as points of entry and exit for the material. Consistent with the predetermined design parameters, the finalized mold yielded vessel models with an outer diameter and inner diameter of 3 millimeters (mm) and 0.8 mm, respectively. and initially printed using fused deposition modeling methods. The length of the mold totaled 100 mm though the lengths of the resultant models varied based on injection efficacy.

Because the mold dimensions required design on small scales, printer resolution presented a significant limitation to the production of injection molds. Initial iterations of the mold design were produced using extrusion-based printers; however, the printed components failed to yield a functional molding system due to the resolution limitations. The finalized design was fabricated using a resin-based stereolithography printer, which offered a significantly higher resolution by contrast (Figure 1B).

PDMS Composition and Molding Procedure

The finalized injection molds were utilized to produce vas deferens models. To achieve a range of material stiffness, the formulation of the PDMS elastomer was iteratively tuned by modifying the ratio of base to curing agent. Four distinct PDMS formulations were produced for modeling. The experimental groups are denoted as 10:1, 6.67:1, 5.88:1, and 5:1, representing the respective weight ratio of base to curing agent for each formulation. Further reductions to the PDMS formulation ratio were not

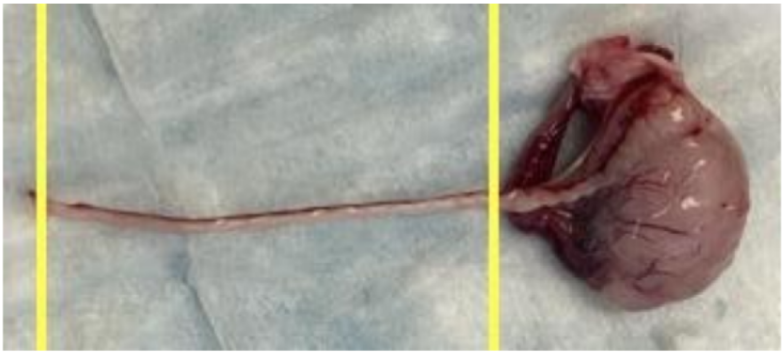

Figure 3. Canine Vas Deferens Dissection. Frozen specimen containers were thawed in warm water baths. Once thawed, testicle samples were immersed in warm water to remove the gelatinous outer coating of OCT compound. Using forceps and hemostats, the vas deferens, a pearly opaque vessel structure, was separated from other tissue structures in the spermatic cord. The exposed length of vas deferens was then cut just below the convoluted structure of the epididymis using surgical scissors. The yellow markings above indicate the typical vas sample extracted from a large canine subject.

considered due to limitations associated with the curing process.

To decrease variability among models, a consistent molding procedure was developed and implemented. Prior to material injection, a 20 gauge (0.8mm) metal wire was inserted into the central narrow channel of the mold and positioned so that it extended from both ends of the mold component in the lengthwise direction. The mold halves were next aligned using the opposing sets of guide posts. Then, with the wire still positioned between the two halves, the mold was clamped using 3" C-clamps (Figure 2). To minimize the leakage of PDMS during the injection process, the upward-facing injection port was wrapped in paraffin wrap. Each PDMS formulation was loaded into a 20 milliliter (mL) syringe with a 22 gauge needle and injected into the molds at an angle of approximately 45 degrees. Finally, the opposing injection port was similarly wrapped in paraffin wax to reduce leakage during curing. The molds were placed in a 120°C oven for 35 minutes to accelerate the curing process. Following this curing period, the metal wire was removed from the mold using vice grips, leaving behind a uniform and narrow lumen within the vessel model. The mold halves were subsequently unclamped and the vessel model released. After removing frayed ends and other irregularities with a razor blade, the final models were stored in labeled containers for future testing. For each respective PDMS formulation, approximately fifteen models were fabricated.

Canine Vas Deferens Dissection

In cooperation with the Animal Hospital of Ivy Square, canine testicle samples were collected from the clinic's routine neutering services. During this procedure, veterinarians remove the testicle and a short segment of the spermatic cord from the canine scrotum. Tissue samples were placed in specimen containers primed with optimal cutting temperature (OCT) compound and then frozen for tissue preservation. On a weekly basis, these samples were retrieved, thawed, and dissected to isolate the vas deferens from the other reproductive structures (Figure 3). The vas deferens was cut just below the convoluted structure of the epididymis. Following dissection, the isolated vas deferens tissue was re-embedded in OCT compound and stored in a –80°C freezer until tensile testing could be conducted.

Histology Analysis of Canine Vas Deferens Cross Section

Given the narrow physical dimensions of the mammalian vas deferens, conventional calipers were not suitable for accurately measuring the dimensions of the collected canine samples. Therefore, to quantify the cross-sectional area (A) of the vessel, histology analysis was conducted using macro imaging techniques. After isolation of the canine vas deferens tissue, a histology analysis was conducted by mounting a tissue slice onto a glass slide. The mounted cross-section was examined under a microscope and the resultant images were analyzed using ImageJ software. Using the software's circular measurement tools, the outer and lumen areas of the vessel cross-section were measured (Figure 4). The average outer and lumen areas were calculated across all images, totaling 4.238 ± 0.846 mm^2 and 0.101 ± 0.022 mm^2 respectively. To estimate the total cross-sectional area (A) of the canine vas deferens, the average lumen area was then subtracted from the average outer area, totaling 4.136 ± 0.843 mm^2. This normalized measurement for cross-sectional area was later employed to calculate the Young's modulus of the canine vas deferens (Equation 1).

Tensile Testing and Analysis of Young's Modulus

To evaluate the mechanical properties of both the canine vas deferens tissue and the fabricated models, tensile testing was performed using an Instron machine. To systematically remove slack from loaded samples, each sample was subjected to a creep test prior to the start of tensile testing. At the completion of each creep test, the sample length (L) was calculated by subtracting 34 mm – a constant specific to the Instron setup – from the measured elongation length. Following the creep test, uniaxial tensile testing was performed. For all samples, a strain rate of 0.9 percent (%) per second was applied until a maximal 25 percent strain was achieved. As the literature lacks

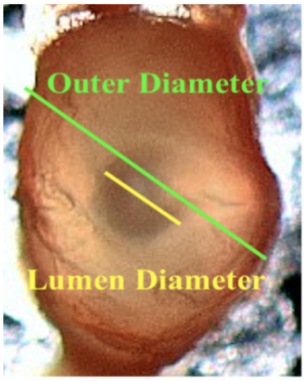

Figure 4. Histology Analysis of Vas Deferens Cross Section. In order to normalize load-extension data by sample geometry, histological analysis of vas deferens cross sections was conducted using ImageJ software. The cross-sectional area of the vessel was averaged across all imaged samples, totaling 4.136 ± 0.843 mm^2. This representative average was employed as a constant A in the calculation of Young's modulus for canine samples.

consensus on the optimal strain rate for tensile testing vas deferens tissue, a strain rate of 0.9% per second was chosen generally as a preliminary rate for testing. Similarly, a maximal strain of 25 percent was selected to reflect a feasible range of physiological force. Double layer vas deferens biomimetic models were purchased from LifeLike BioTissue to serve as an experimental control group. Latex and Flexelene™ tubing were used as control samples and tested alongside the market-available biomimetic models, the canine tissue samples, and the PDMS models (10:1, 6.67:1, 5.88:1, 5:1).

Time-load-extension data was collected from each sample and analyzed to calculate Young's modulus using Equation 1. For each sample, the raw extension data (mm) was plotted against the raw load force (Newtons, N) data to generate a load v. extension curve (Figure 5). To estimate the linear gradient (G), the linear region of the load v. extension curve was isolated, replotted, and modeled with a line of best fit. The linear gradient, G, was represented by the best fit slope. Using this linear gradient (G), the Young's modulus of the sample was calculated using Equation 1 where L is the initial sample length and A is the sample's cross-sectional area.

$$E = G * (\frac{L}{A}) \qquad \text{(Equation 1)}$$

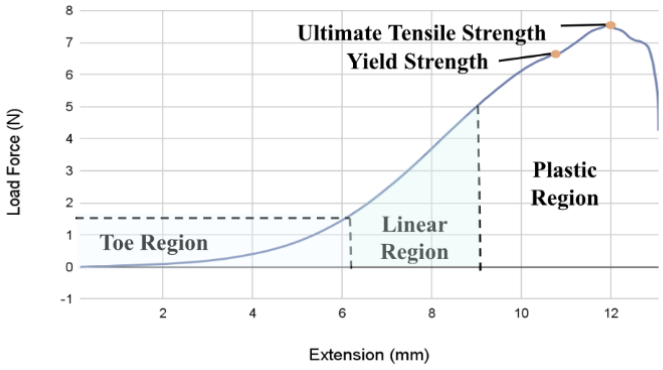

Figure 5. Load v. Extension Curve Generated from Canine Sample. The above plot represents the load versus extension data generated from the tensile testing of a canine sample. For each sample-generated curve, the linear region was modeled with a line of best fit to estimate the linear gradient (G). Bounds of the linear region were systematically adjusted to ensure that the associated R^2 value of the linear model was greater than 0.95, indicating a close fit of the tensile data.

Upon the completion of tensile testing, the Young's modulus values for each sample type were averaged to obtain a representative measurement of elasticity.

Assistive Cannulation Device Design

To generate designs for an assistive cannulation device, a brainstorming workshop was conducted. Following this period of ideation, the Product Development Manager at Contraline, Inc, Tim Barry, was presented with eight initial design concepts. Drawing on his expertise, the design concepts were narrowed, and a puzzle-piece-like feature was selected as a key design element for further development (Figure 6). This puzzle-piece-like feature is intended to stabilize the vas deferens following externalization from the scrotum and to align the lumen along the flat surface, creating a parallel path for cannulation.

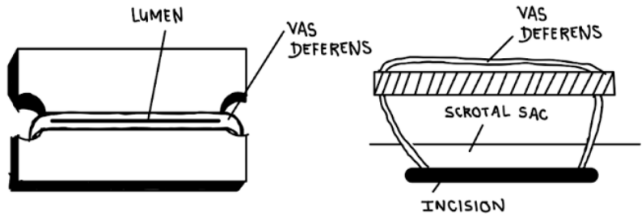

Figure 6. Original Design Sketch for Puzzle-Piece Design Feature. Early design concept sketches were pitched to Tim Barry, who served as the primary subject matter expert for this clinical application challenge. The above illustrations depict both a top and side angle view of the initial puzzle piece design feature.

Results

Biomechanical Analysis

The experimental elastic moduli obtained from all samples within each experimental group were averaged to obtain a representative Young's modulus for each sample type.

The average elastic moduli for the 10:1, 6.67:1, 5.88:1, and 5:1 PDMS models totaled 0.839 ± 0.217 MPa, 1.470 ± 0.185 MPa, 1.30 ± 0.12 MPa, and 1.072 ± 0.055 MPa, respectively. While it was originally hypothesized that increasing the weight ratio of curing agent to base would yield increasingly stiff material properties, the elastic moduli of the PDMS models instead exhibit a bell-curve-like trend which peaks at a fabrication ratio of

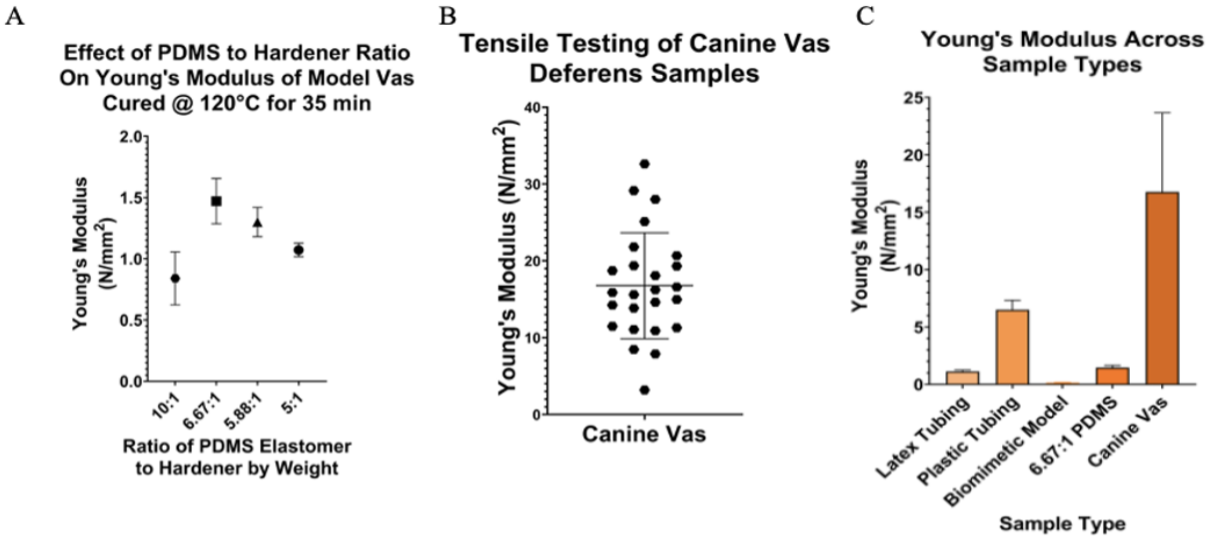

Figure 7. Young's Modulus Analysis. A) The average Young's modulus among the different PDMS ratios were computed and plotted. The ratios utilized were 10:1, 6.67:1. 5.88:1, and 5:1- with the elastic moduli being 0.839 MPa, 1.47 MPa, 1.3 MPa, 1.072 MPa respectively. The elastic modulus peaked at the 6.67:1 ratio. The curing conditions remained constant throughout each of the PDMS sample groups. B) The elastic moduli among each of the canine vas deferens samples were computed and plotted. A wide distribution can be observed, with clustering centered around the average: 16.67 MPa. The conditions of thawing and preparing each of the samples remained constant, however the breed and age of the canine remains unknown. C) The average elastic moduli among the different experimental groups were calculated. The Young's modulus for the canine vas deferens sample was greater than any of the other groups tested. The plastic tubing (control) offered the closest mechanical match at 6.502 MPa. The biomimetic model was not comparable to any of the other experimental groups with a Young's modulus of 0.143 MPa. The latex tubing (control) was most comparable to the PDMS model at 1.137 MPa, however did not offer a viable comparison to the canine vas deferens.

6.67:1 (Figure 6A). This trend can likely be attributed to limitations imposed by the curing conditions. As the curing time and temperature were kept constant across all PDMS model formulations, it can be inferred that the curing capacity of the material is maximized at a PDMS weight ratio of 6.67:1 under these conditions. Earlier studies examining the biomechanics of PDMS at various fabrication ratios have reported comparable trends (6). Models made with a base-to-curing agent weight ratio of 6.67:1 exhibited the highest representative Young's modulus among all PDMS sample groups. As a result, the representative Young's modulus of the 6.67:1 sample group was selected for a comparative analysis with data from both experimental control groups and canine samples (Figure 7C).

The Young's modulus of each canine sample was calculated and plotted (Figure 7B). The moduli values obtained from canine tissue samples demonstrate a wide distribution, which may be attributed to the natural variability in vas deferens geometry among different canine breeds and age ranges. However, the distribution of moduli among the canine samples shows a central cluster around the average Young's modulus, which totaled 16.76 ± 6.89 MPa. This analysis suggests that the representative Young's modulus of the canine vas deferens is approximately ten times greater than that of the 6.67:1 PDMS models.

Among the control sample types, the average elastic moduli of the latex tubing, plastic tubing, and market-available biomimetic models totaled 1.137 ± 0.107 MPa, 6.501 ± 0.828 MPa, and 0.143 ± 0.029 MPa, respectively. Overall, the Flexelene™ plastic tubing offered the closest match to the mechanical properties of the vas deferens with a representative Young's modulus of 6.501 MPa. However, the material stiffness of the plastic

tubing remains 61 percent lower than that of the canine vas deferens.

Device Iterations

To satisfy the second aim of this project, we adopted an iterative design strategy to develop an assistive device for use during procedural cannulation of the vas deferens. After the vas deferens is externalized from the scrotum, the practitioner may encounter difficulties in stabilizing the vessel. If left unclamped, the vessel naturally slides back into the small incision. To prevent the recession of the vessel into the incision, the operating urologist typically uses hemostats to stabilize the vas deferens which requires the use of at least one hand and, in turn, restricts mobility. This can lead to errors when attempting to cannulate the narrow lumen of the vessel with the other free hand. To address these challenges, a flat puzzle-piece-like surface was incorporated into all design concepts as a means to stabilize and level the externalized vessel.

Many of the early design concepts incorporated handling mechanisms that were positioned directly below the table-top surface (Figure 8A). However, following design reviews and urologist consultation, it was determined that these handles would likely impede access to the short segment of the externalized vessel. Taking this feedback into consideration, later iterations were designed with handles which protruded from the side of the table-top surface, thus removing impediments to vessel access and allowing urologists to utilize either hand. Early designs were also relatively large in size, which posed a challenge to feasibility as only a few centimeters of vas deferens are typically externalized during the procedure. Therefore, the design specifications were revised to accommodate smaller lengths of vas deferens. The incorporation of a needle guide to align the barrel of the needle with the lumen of the vessel was also considered.

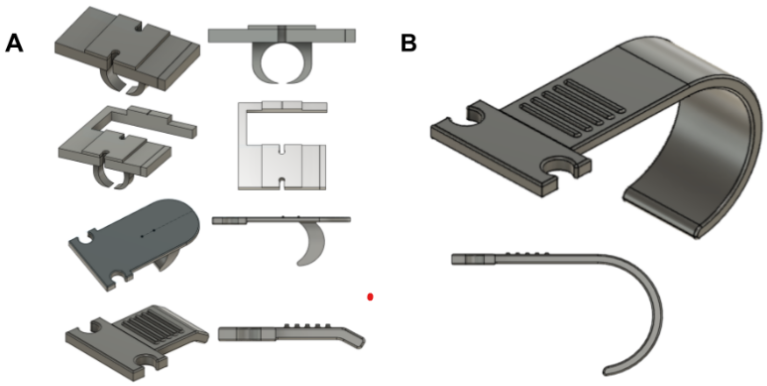

Figure 8. Assistive Cannulation Device Design. A) The iterative design process was adopted during the development of the assistive cannulation device. Four different prototypes were developed and tested through consultations with Urologists. Each iteration incorporated different grips and dimensions. All of the designs developed utilize a tabletop-like space with cutouts to place the vas deferens to provide mobility and control during physicians during the procedure. B) The final design incorporates the tabletop surface along with a curved grip that can be used in either hand. It also incorporates narrow cutouts and a longer plane to allow more control.

After repeated consultation with Tim Barry, the Product Development Manager at Contraline, Inc., and practicing urologists, a design was finalized. The final design incorporates a curved handle structure that is intended to wrap snugly around the index finger. The ridges along the upward face of the handle structure are intended to guide and secure positioning of the thumb. Finally, the notches in the puzzle-piece face are designed to secure the exposed vessel across the flat surface of the device, thus stabilizing the vas and allowing practitioners to access the lumen from multiple angles with ease.

Discussion

Impact

The results of this project research yielded novel insights into the biomechanics of the vas deferens, an area which has remained uninvestigated since studies conducted in 1979. Canine vas deferens samples were chosen as an appropriate analog for the human vas deferens, consistent with Contraline's early development strategies which relied extensively on canines for *in vivo* animal testing. The vas deferens exhibited a remarkably high elastic modulus compared to other mammalian viscoelastic vessels. For instance, the Young's modulus of the human aorta and porcine urethra total approximately 0.546 ± 0.134 MPa and 1.6 ± 0.4 MPa, respectively, whereas the experimental Young's modulus of canine vas deferens tissue was approximately 16.76 ± 6.89 MPa (7,8). The high elastic modulus of the vas deferens may enable the vessel to withstand deformation and collapse under the high pressures and velocities of sperm bolus flow, ensuring a consistent flow rate and preventing blockages or other disruptions in sperm transport. The understanding of the vas deferens' biomechanical properties gained

through this research will inform the development of future model designs. For Contraline, an anatomically-accurate model of the vas deferens will aid the refinement of their vas-occlusive delivery system and, in the long run, serve as a valuable training tool for practitioners who intend to adopt the technology in their clinics.

Limitations

Significant challenges in procuring tissue samples undermined the original experimental design plan of this study. Several months were spent researching and contacting potential sample suppliers including local butcher shops, meat processing plants, local farms, and veterinarian offices. These unforeseen delays in sample procurement hindered the team's ability to use experimental metrics as parameters to directly inform the design of a model. Instead, model fabrication was based on estimations derived from literature. The biomechanical properties of the model were then tested simultaneously with those of the tissue samples, and the results were directly compared. This flawed rearrangement of the experimental design process led to large discrepancies between the mechanical properties of the vessel models and the vas deferens samples.

Similarly, unforeseen circumstances arising from the company's first human trials conducted in late September 2022 led to a reorganization of the project timeline for Aims 1 and 2. Originally, the development of an anatomically-accurate model of the vas deferens, as outlined by Aim 1, was intended to precede the development of a cannulation assistive device, as outlined by Aim 2. In fact, the refined model was intended to serve as a tool to inform and optimize the design of a delivery device. Based on this original timeline, early research efforts were focused on developing a foundational understanding of the vas deferens tissue, from both a structural and mechanical perspective. However, at the conclusion of Contraline's human trial study, new and urgent challenges associated with cannulation of the vas deferens during the insertion procedure were pushed to the forefront of the company's focus. In support of company-wide efforts to solve these crucial pain points, all work related to the accomplishment of Aim 1 goals was temporarily suspended as Aim 2 became the primary area of focus. As such, first semester work primarily involved ideation of assistive device designs and the search for a tissue sample supplier, while the early part of the second semester was focused on securing a tissue source and collecting samples; the remainder of the second semester was then dedicated to the development of a molding system, fabrication of vessel models, and sample testing in accordance with Aim 1. The unexpected changes to the specific aims timeline may have hindered our ability to design a practical delivery solution and further limited our capacity to conduct feasibility studies considering that Aim 1 had yet to be completed.

The wide distribution of experimental elastic moduli values observed among canine samples represents another significant limitation of this research. These large discrepancies may likely be attributed to the use of an averaged value for the cross-sectional area variable (A) in the calculation of Young's moduli. Though Young's modulus is a geometry-dependent metric, an averaged value for cross-sectional area was used after a collection of samples were tensile tested prior to the isolation of a tissue cross-section. Plastic deformation of these samples during tensile testing rendered their cross-sections unusable. As a consequence, the number of samples available for histological analysis was smaller than the number available for tensile testing.

Finally, this research was limited by a small and highly variable sample size, a challenge which may be attributed to factors outside of our control. The team accepted any samples that were available; however, this led to high sample variability due to variation in canine donor age, breed, and size.

Future Work

Several of these limitations can be addressed in future work on this project. Importantly, refined material selection should be performed to achieve a more accurate biomechanical model of the vas deferens *in vivo*. Consistent with the experimental moduli obtained from the canine samples, both flexible ethylene-vinyl acetate (EVA) and plasticized polyvinyl chloride (PVC) have reported elastic moduli within the range 15 and 20 MPa and, thus, should be considered as potential materials for future projects. While EVA can be molded using either extrusion

or injection techniques, it is a hard copolymer which may not accurately represent the smooth muscle composition of the vas deferens *in vivo*. PVC can be similarly shaped using injection molding techniques; however, this material requires high temperatures (174 - 190 °C) to achieve proper molding conditions (9). Given the limitations of EVA and PVC, respectively, alternative materials that fall within the appropriate range of elastic moduli should also be considered.

Additionally, the assistive device designed in accordance with Aim 2 should undergo iterative improvement based on continuous feedback from the target end-user. While a urologist was consulted during the device design process, a controlled study to evaluate the ease of use, practical feasibility, and efficacy of the device was not conducted. Conducting qualitative surveys on a regular basis would be beneficial in continuously identifying areas of success and weakness in the design. Further, final prototypes of the design were printed using a plastic resin, a relatively weak and non biocompatible material. Future device development should incorporate a highly durable and biocompatible material that is capable of withstanding sterilization procedures and repeated use.

The design of our existing model could also be enhanced through means other than material modifications. While the final model prototypes accurately emulate the anatomical dimensions of the vas deferens *in vivo*, they are limited by a straight cylindrical design with a concentric shape and a centered, unvarying lumen. In human tissue, the lumen of the vas deferens is not consistently centered and may change in shape or size along the length of the vessel. Further, the vas deferens rarely follows a perfectly straight path but rather curves and coils around the reproductive system. The final model prototypes were also free-standing, unattached to other representative structures of the male reproductive anatomy. In order to provide a more comprehensive representation of the male reproductive system, future models should incorporate additional in vitro structures such as the epididymis, testicle, and prostate. To create a tool for full procedural practice, these structures could be embedded in a model of the scrotum. Lastly, lubricating the model may serve to simulate the bodily fluids which coat the vessel *in vivo*.

Finally, using a refined *in vitro* model to develop a percutaneous delivery system for Contraline's vas-occlusive hydrogel offers a promising, though long-term, future direction. A percutaneous delivery system could revolutionize the field of male contraception by eliminating the need for surgical incisions and sutures. This could expand the pool of potential users who may have been deterred by the invasiveness of the current procedure, making the method more accessible and widely adopted. Such innovations, therefore, have the potential to significantly impact the landscape of contraceptive use, not only in the United States but around the world.

End Matter

Author Contributions and Notes

Myers, A., Raghu V., and Rieck, A. created CAD designs, fabricated model prototypes, generated device designs, conducted tensile testing, and wrote the final report. Barry, T. advised on model and device design as well as provided support in figure creation.

Acknowledgments

The Capstone team would like to thank their continued support of this research project. The Capstone team would like to express our sincerest gratitude to Tim Barry, the technical advisor of this project, for his invaluable assistance and expertise on the technical aspects of this research. The team would also like to thank the Animal Hospital of Ivy Square for their contribution of canine samples. Finally, the team would like to thank Dr. Timothy Allen and Dr. Shannon Barker from the UVA Department of Biomedical Engineering for their advising throughout this project.

References

1. Nearly half of all pregnancies are unintended-a global crisis, says new UNFPA report [Internet]. [cited 2023 May 8]. Available from:https://www.unfpa.org/press/nearly-half-all-pregnancies-are-unintended-global-crisis-says-new-unfpa-report
2. Current Contraceptive Status Among Women Aged 15–49: United States, 2015–2017 [Internet]. Center for Disease Control; [cited 2023 May 8]. Available from:

https://www.cdc.gov/nchs/products/databriefs/db327.htm
3. World population prospects 2022: Summary of results | population division [Internet]. United Nations; [cited 2023 May 8]. Available from: https://www.un.org/development/desa/pd/content/World-Population-Prospects-2022
4. Vasectomy reversal: Purpose, procedure & success rate [Internet]. [cited 2023 May 8]. Available from: https://my.clevelandclinic.org/health/treatments/15459-vasectomy-reversal
5. Mechanical properties of the mammalian vas deferens. i. in the passive state [Internet]. [cited 2023 May 8]. Available from: https://www.tandfonline.com/doi/abs/10.3109/01485017908985057
6. Hocheng H, Chen C-M, Chou Y-C, Lin C-H. Study of novel electrical routing and integrated packaging on bio-compatible flexible substrates - microsystem technologies [Internet]. Springer-Verlag; 2009 [cited 2023 May 8]. Available from: https://link.springer.com/article/10.1007/s00542-009-0930-2
7. Author links open overlay panelConnor V. Cunnane a b, a, b, c, d, e, et al. Cryopreservation of porcine urethral tissue: Storage at −20°C preserves the mechanical, failure and geometrical properties [Internet]. Elsevier; 2021 [cited 2023 May 8]. Available from: https://www.sciencedirect.com/science/article/pii/S1751616121002010#sec3
8. [Internet]. [cited 2023 May 8]. Available from: https://www.researchgate.net/figure/Two-models-of-aorta-wall-The-thickness-and-Youngs-modulus-of-layers-are-shown_fig12_26731015
9. PVC injection molding 101: ICOMOLD [Internet]. 2022 [cited 2023 May 8]. Available from: https://icomold.com/what-is-pvc-injection-molding/
10. Secura, Gina M., Jenifer E. Allsworth, Tessa Madden, Jennifer L. Mullersman, and Jeffrey F. Peipert. “The Contraceptive Choice Project: Reducing Barriers to Long-Acting Reversible Contraception.” American Journal of Obstetrics and Gynecology. Mosby, June 10, 2010. https://www.sciencedirect.com/science/article/abs/pii/S0002937810004308.