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Localized Intra-Arterial Drug Delivery Device for Stroke Treatment

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Localized Intra-Arterial Drug Delivery Device for Stroke Treatment

An Honors Thesis submitted in partial fulfillment of the requirements of Honors Studies in

Biomedical Engineering

By

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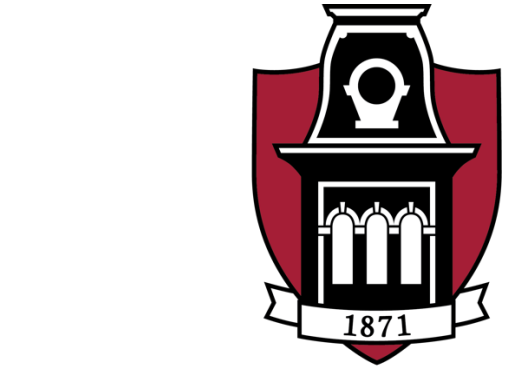

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Abstract

Strokes are one of the leading causes of death and long-term disability in the United States, and according to the Centers for Disease Control and Prevention more than 795,000 people experience a stroke every year. Around 87% of all strokes are ischemic strokes making it the most common form of stroke. While ischemic strokes are treatable, current devices and methods still result in high mortality rates and high risks of hemorrhaging after treatment. The aim of this study is to design and test a prototype of a novel device for the localized delivery of thrombolytics to treat ischemic strokes. The main body of the device was designed in SolidWorks and was printed using a 3D resin printer. Parts of this device were tested with clot analogs. Testing of the fully assembled prototype is still underway.

Introduction

Strokes occur when blood cannot get to the brain either due to a blockage or a ruptured blood vessel. The lack of blood flow prevents the brain from receiving oxygen which in turn causes brain cells to die within minutes. If untreated for too long, a stroke can result in long-term brain damage, long-term disability, and sometimes death. Every year, more than 795,000 people experience a stroke in the United States making it one of the leading causes of long-term disability and mortality in the US.[1] Ischemic strokes make up about 87% of all stroke cases and are mainly caused by fat deposits lining blood vessel walls, also known as atherosclerosis. These fatty deposits can cause cerebral thrombosis, a blockage due to clot formation, or a cerebral embolism which is when a piece of a clot gets caught in a smaller blood vessel.[2]

While prevention is the best way to stop a stroke, thrombolysis and mechanical thrombectomy are the main forms of treatment for ischemic strokes. Thrombolysis is the gold standard of treatment and uses alteplase, or more specifically, recombinant tissue plasminogen activator (r-tPA). The enzyme r-tPA converts plasminogen in the body into plasmin which is used to dissolve the fibrin blood clots.[3] The process of thrombolysis treatment involves r-tPA being administered intravenously to the patient within 3 – 4.5 hours after onset symptoms.[4] Even though IV r-tPA is the gold standard of treatment, it still has its own challenges. Treatment with IV r-tPA can result in complications such as major systemic hemorrhage, symptomatic intracranial hemorrhage, hemorrhagic transformation, and angioedema.[5]

Mechanical thrombectomy involves the physical removal of a clot using a retrieval device. Two main types of mechanical retrieval devices include aspiration devices and stent retrievers. The process for aspiration devices and stent receivers both start by inserting a catheter through an artery in the groin and guiding it to the occluded artery. Aspiration devices use a vacuum to remove the clot and this vacuum is created through either a mechanical pump on the

other end, or a change in pressure gradient caused by pumping saline into the occluded vessel. Stent retrievers are comprised of nitinol and are guided through a clot by a catheter. Once the retriever is in place, the catheter is removed allowing for the stent retriever to expand and entangle the clot before being withdrawn.[6] Similarly to IV r-tPA treatment, mechanical thrombectomy has its own disadvantages. Mechanical thrombectomy is usually only able to treat large artery occlusions which only represents about 10% of patients suffering from ischemic stroke.[7] Also, some studies have shown thrombectomy devices to cause significant damage to the vessels they interact with which increases the chances of hemorrhage and a transient ischemic attack.[8]

Development of an advanced clot removal device requires novel methods to mitigate the risks associated with current treatment methods and devices. The aim of this project was to design a device that will address limitations with current devices and test its individual features within gelatin clot analogs. The testing of individual features is an important design step before attempting to fully assemble the prototype.

Device Overview

The aim of the design was to create a catheter device to treat acute ischemic stroke (AIS) while trying to improve upon current devices. Important factors considered when designing the device included a way to restore blood flow during treatment, a method for thrombolytic drug delivery, a way to prevent clot fragments traveling downstream, and a way to remove the thrombolytic agent. With these goals in mind, the first prototype design of the device, shown in Figure 1, was created using SolidWorks which is a computer-aided engineering and design program.

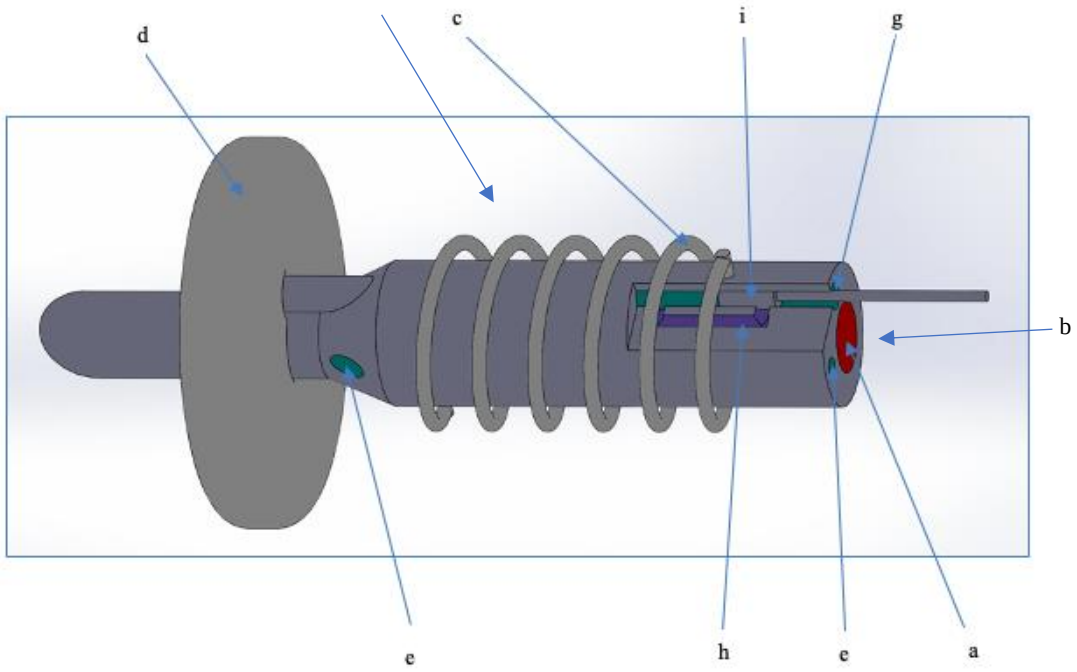

Figure 1. Diagram of first prototype with labels to individual parts. The Bushing and Protective Sheath are not shown to allow for other design features to be seen more clearly. This figure shows the following features: 1a) reperfusion lumen, 1b) location of the bushing (piece not shown), 1c) helical hollow fiber membrane, 1d) balloon, 1e) aspiration lumen, 1f) location of protective sheath (piece not shown), 1g) drug delivery and balloon inflation lumen, 1h) bypass lumen, and 1i) the valve stopper displayed in a cutaway view.

Features and Design Aspects

To restore blood flow, the device has a reperfusion lumen that can be seen in Figure 1a. The reperfusion lumen extends the length of the device and works to restore blood flow as soon as the device is inserted into the clot. This will allow for some degree of blood flow during the treatment process which should minimize further damage to the brain. The bushing, not pictured, is located inside of the reperfusion lumen, and allows the for it to act as a lumen for the guide wire

even though the reperfusion lumen has a larger diameter than the guidewire itself. The bushing will be removed after the device has been inserted into the clot to allow for blood to flow through.

The helical hollow fiber membrane, pictured in Figure 1c, is a permeable, hollow fiber to allow for a thrombolytic drug to be delivered in direct contact with the blood clot. The helical shape allows for the membrane to stay in contact with the clot as it dissolves while also providing a large surface area. The membrane is tightly wound to the device for insertion but will expand outward radially to stay in contact with the dissolving clot. Nitinol wire is to be attached to the membrane to achieve this effect. Another possible use for the helical membrane is to diffuse saline to assist in the aspiration of the thrombolytic drug.

The balloon, pictured in Figure 1d, is used to keep the thrombolytic agent localized as well as any possible clot fragments. Additionally, the balloon allows for higher drug concentration at the occlusion site and may aid in the use of more potent drugs or the off-label use of drugs for treatment as it prevents the drug from traveling systemically throughout the body. The balloon can also be used to ensure the device is centered at the clot rather than towards the outer edges, and this can prevent any damage possible damage to the occluded vessel.

Figure 1e depicts the aspiration lumen which is used to draw out the drug once the clot has been sufficiently dissolved which prevents the drug from flowing downstream. The aspiration lumen works with an external pump to create a vacuum effect and can also be used to aspirate and small clot fragments.

The drug delivery and balloon inflation lumen, located in Figure 1g, acts as a multipurpose lumen based on the position of the valve stopper as seen in Figure 1i. This lumen allows for the thrombolytic agent to enter the helical hollow fiber membrane, and it can also allow for fluid to inflate the balloon.

The bypass lumen, pictured in Figure 1h, has both ends connected to the drug delivery and balloon inflation lumen. The purpose of this lumen is to allow for fluid to bypass the connection between the helical hollow fiber membrane and the drug delivery and balloon inflation lumen, which allows for balloon inflation without causing any fluid to go to the helical hollow fiber membrane. A detailed schematic can be seen in Figure 2 below.

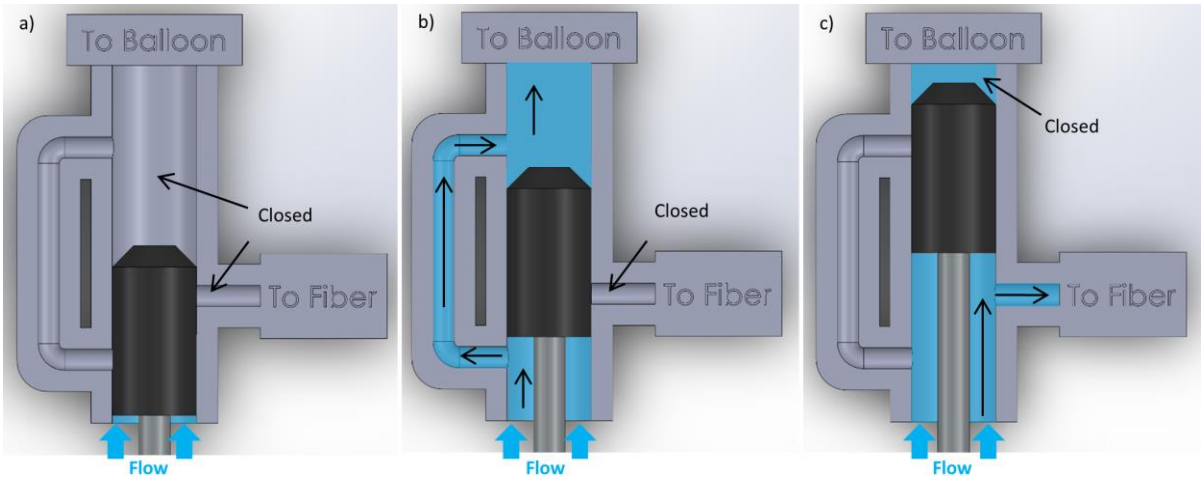

Figure 2. The figures above depict the valve stopper in three of its positions: a) prevents flow to both the fiber and balloon, b) allows flow to the balloon, but prevents flow to the fiber, and c) allows flow to the fiber, but not the balloon.

The valve stopper, pictured in Figure 1i, is used to control where fluids are channeled in the drug delivery and balloon inflation lumen. This allows for a single lumen to provide fluids to both the balloon and the helical hollow fiber membrane and reduces the overall diameter of the device. Reducing the diameter of the device allows for it to potentially operate in smaller vessels. The deployed position blocks fluid from entering the balloon and the helical hollow fiber membrane as seen in Figure 2a. The inflation position blocks the channel to the helical hollow fiber membrane but allows fluid to the balloon for inflation which can be seen in Figure 2b. Finally, the dispensing position blocks fluid from entering the balloon, but allows the thrombolytic agent

to enter the helical hollow fiber membrane where it will be delivered to the clot. This valve is actuated by a stiff wire that extends proximally to the exterior of the device.

Testing Individual Device Features

Individual features were tested before assembling the full device in order to easily detect any concerns. The three individual features tested were the helical hollow fiber membrane, the helical hollow fiber membrane connection to the device, and the valve stopper.

Helical Hollow Fiber Membrane

Initial testing of the helical hollow fiber membrane focused on testing the flexibility of the microporous membrane and its ability to elute a fluid once in a helix shape. Testing of the microporous membrane was necessary due to its fragility. To test flexibility, a copper wire was threaded through the microporous membrane, and the membrane was coiled into a helix shape. This resulted in successful shaping of the microporous membrane without the formation of any kinks, as seen in Figure 3. Formation of kinks in the membrane could cause a restriction of fluid flow, or the kink could develop into a tear. If the microporous membrane tears, most of the thrombolytic agent will be dispensed out of the tear which will result in an uneven dispersal of the drug.

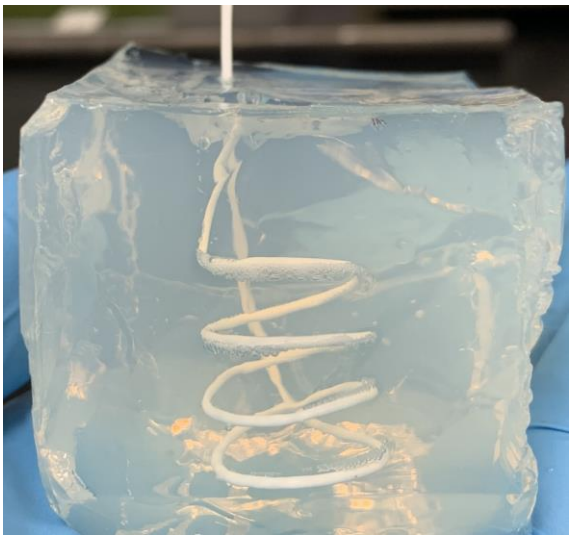

Figure 3. Microporous membrane with copper wire shaped into a helix structure in a gelatin clot analog. No visible kinks or tears in the microporous membrane and small bubbling indicates even delivery of fluid.

Once it was determined that the microporous membrane could be shaped into the desired helical form, testing moved on to attempting to simulate the radial expansion of the helical hollow fiber membrane unit. Initially, a spring with grooves was designed in SolidWorks and printed using an elastic resin as seen below in Figures 4a and 4b. The idea was to stretch the spring out vertically while casting it in the gelatin clot analogs, and then as they dissolved the spring would gradually collapse on itself expanding in diameter during the process. Grooves in the spring served to hold the membrane fiber so that the fiber would retain the same shape as the fiber while still being able to deliver fluid. Unfortunately, the Formlab's Form 2 3D printer was unable to precisely create the desired 1mm groove, so the spring could not hold the microporous membrane.

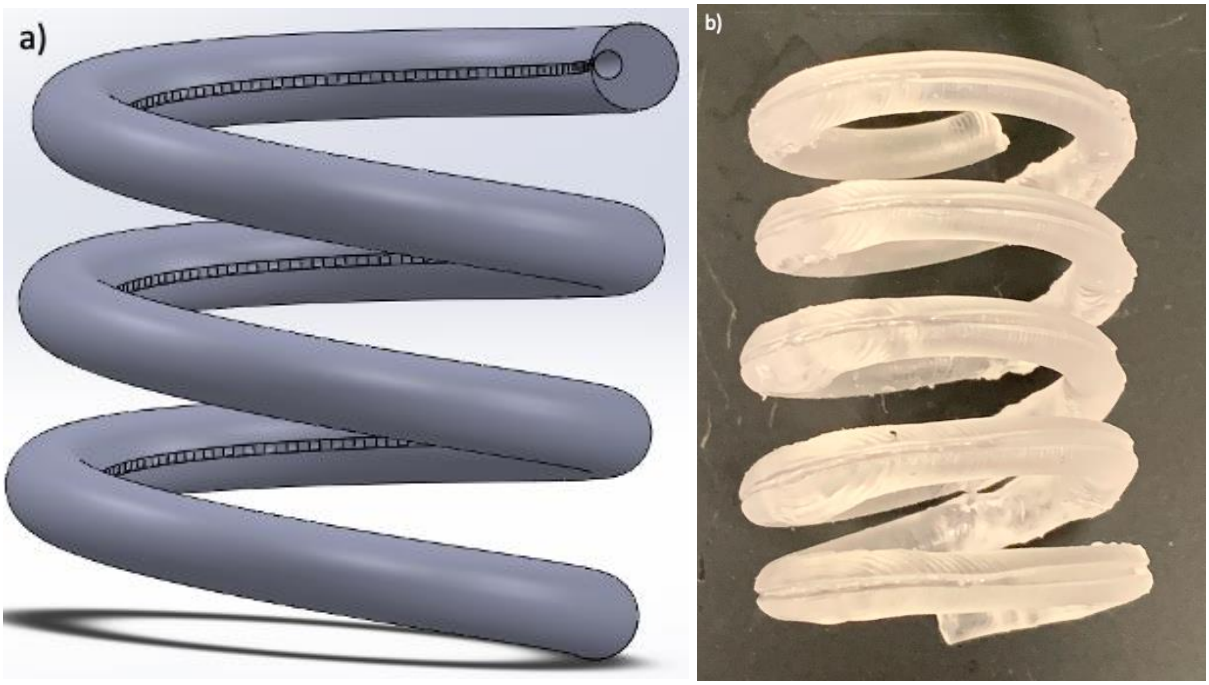

Figure 4. The figures above depict the spring with grooves. 4a is the SolidWorks model and 4b is the physical model printed using elastic resin.

The next method to try and simulate the expanding involved the use of the flexible 3D printer filament Thermoplastic Polyurethane (TPU). TPU was chosen based off its unique properties that allow it to be durable like plastic, but also elastic like rubber. Because 3D filament printers use heat to mold the filament, a heat gun was used to help form the TPU into the desired helical shape. Once the TPU was in the desired conformation, a microporous membrane threaded with copper wire was attached to the helical TPU using heat shrink, which is shown in Figure 5. Heat shrink tubing allowed for the microporous membrane to be bound to the TPU without using Loctite glue or wiring. Loctite glue was avoided because it could clog the micropores of the membrane which would prevent fluid from dissolving through and tying the membrane to the TPU with wiring could potentially cause kinking in the membrane which would disrupt fluid flow.

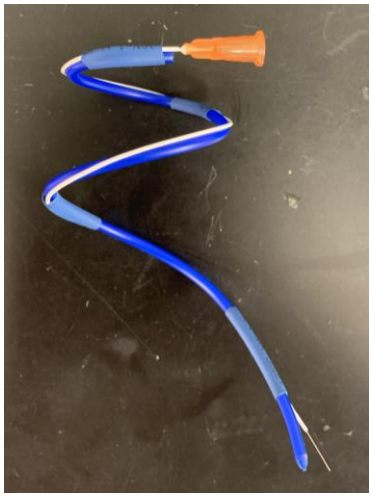

Figure 5. TPU filament (blue) heated and shaped into a helix. Microporous membrane with wiring is attached to the TPU using heat shrink tubing in multiple places.

While the TPU was malleable under the influence of heat, it was difficult to hold in a helical shape while applying heat from a heat gun, so cylinder mold was created in SolidWorks to help hold the TPU during the shaping process. The cylinder mold was designed to allow for clamping on both ends, as seen in Figure 6. The first mold was printed using black PLA filament, but this resulted in the mold melting when exposed to the high heat from the heat gun. The next mold was created using high heat resin to prevent the mold from melting.

Figure 6. Cylinder mold created in SolidWorks to aid in the formation of the TPU helical shape.

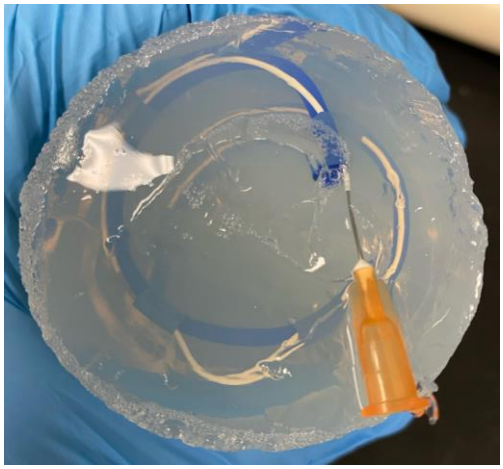

Figure 7. TPU and microporous membrane in gelatin clot analog with no apparent expansion after injecting fluid.

Unfortunately, the TPU helix did not exhibit the desired radial expansion in the gelatin clot analogs, as seen in Figure 7. Nitinol was purchased because both cheaper alternatives were unable to accurately depict the radial expansion of the helical hollow fiber membrane. The first batch of nitinol purchased had a transition temperature of 30°C with diameters of 0.5mm and 0.3mm. A transition temperature of 30°C was chosen because the average normal human body temperature is around 37°C. This means the nitinol would revert to its original shape once it enters the body. However, the device was being tested in gelatin clot analogs which were about 25°C, so the nitinol did not change shape in the gelatin. After subjecting both the 0.5mm and 0.3mm diameter nitinol to heat, there was no noticeable difference in the force generated when reverting to its original shape. As a result, 0.3mm diameter was chosen under the assumption it would allow for more fluid to flow through the microporous membrane. New nitinol was purchased with a transition temperature of 20°C and is currently being tested with the gelatin clot analogs.

Helical Hollow Fiber Membrane Connection

The original design of the device contained a small lumen normal to the outer face of the cylindrical device. This needed to be changed because the fragility of the membrane would cause it to kink when attempting to connect it to the device at a 90° angle. In order to accommodate the microporous membrane, a lofted cut was performed in SolidWorks and tested using a separate connection test piece, as seen in Figure 8.

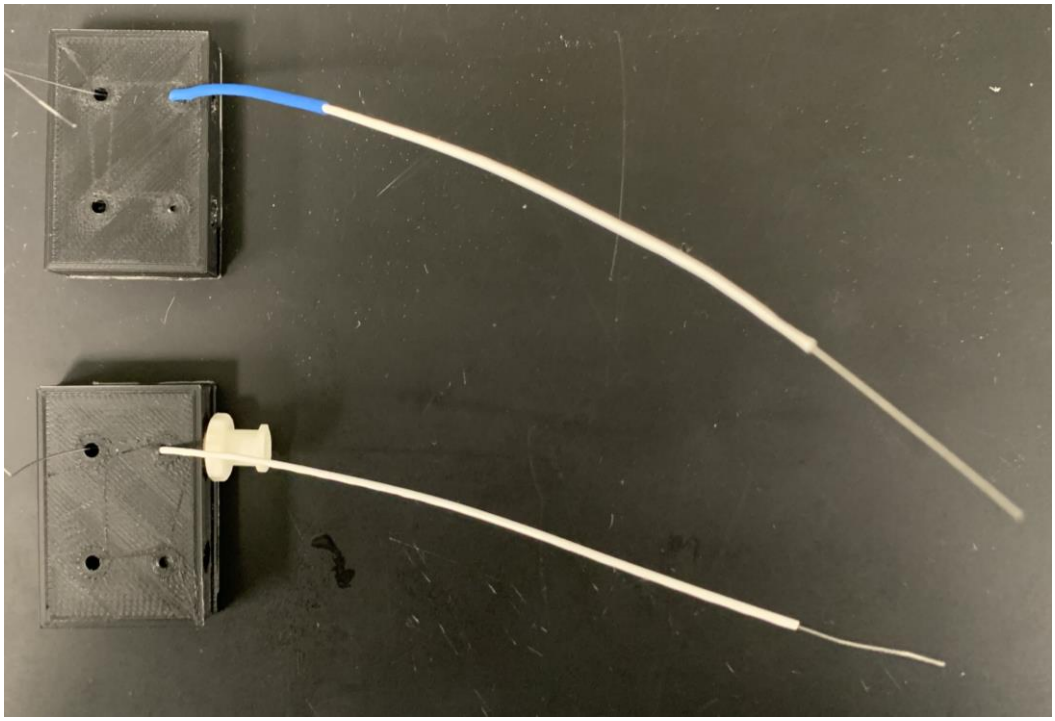

Figure 8. Top view of connection test pieces that were created to check the angle and diameter of the connection lumen that would be implemented on the device.

The connection test pieces were created so that a Luer lock could be attached to either end of a channel. A lofted cut was made to create and angled lumen from the main channel to the connection site on top of the test piece. Another cut was made to help move the extra wiring from the membrane out of the main channel. To test the connection, Loctite glue was used to seal

up the extra openings, and a syringe was attached to the Luer lock. Water was pushed through the channel and would be forced out the connection lumen with the membrane. Even distribution of beading along the membrane indicated that there was no damage to the microporous membrane during the connection. This lofted cut was then added to the main design. SolidWorks designs of the connection test piece can be seen in Figures 9a and 9b.

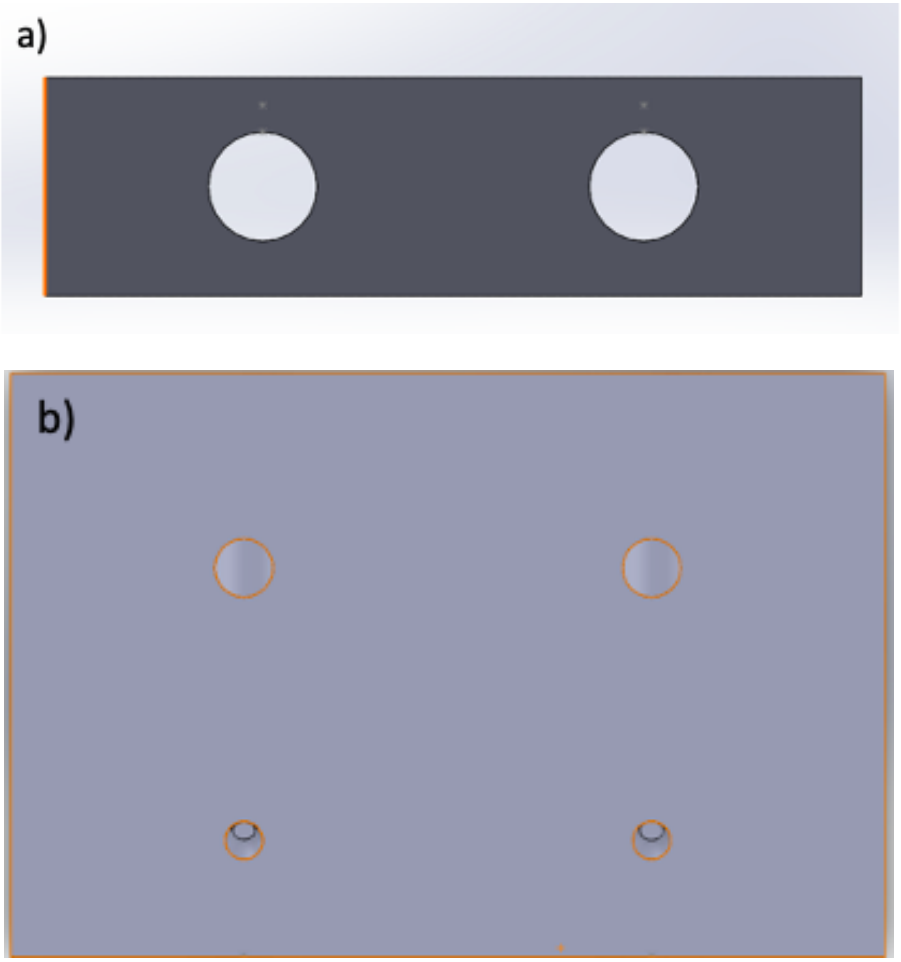

Figure 9. Figure 9a depicts the side view of the connection test piece where the Luer locks would be attached. Figure 9b shows the top view of the piece where the membrane would be attached. The large hole was used thread excess wiring out of the top, so it was not in the main channel.

Valve Stopper

The valve stopper was initially created by layering heat shrink over a stiff wire, but this was unsuccessful due to unevenness created from the layering as well as low ease of mobility inside of the drug delivery and balloon inflation lumen. The next version of the valve stopper was created using the elastic resin and the 3D resin printer. Small cylindrical stopper pieces were created in SolidWorks with a diameter of 0.09 inches and printed using elastic resin. The cylindrical valve stopper was attached to the end of a stiff guidewire and could move well within the drug delivery and balloon inflation lumen. To prevent the piece from sticking or breaking off inside of the lumen, WD-40 water resistant silicone lubricant was applied to the stopper piece. The application of the lubricant greatly increased the ease of mobility within the lumen. The device and stopper can be seen in Figure 10a and 10b.

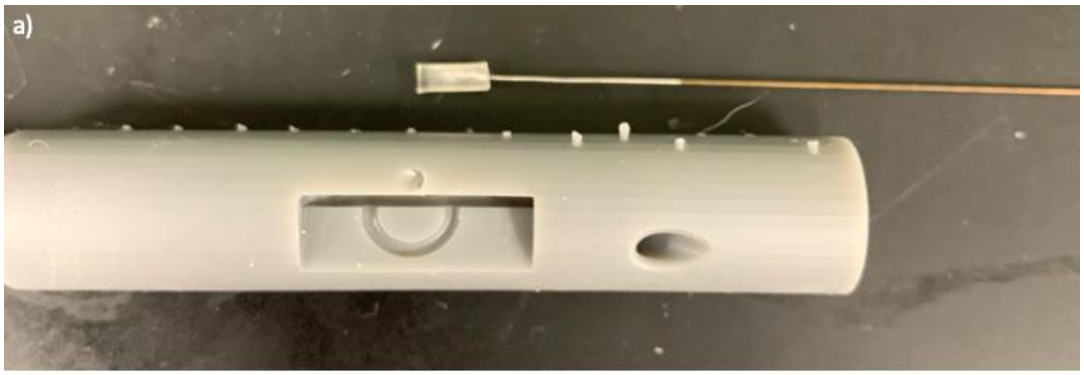

Figure 10. Figure 10a shows the updated prototype with the valve stopper piece and guidewire outside. Figure 10b demonstrates the valve stopper piece in action in the drug delivery and balloon inflation lumen.

Updated Design

The updated design of the device includes more aspiration lumens on the distal end, as seen in Figure 11, and more reperfusion lumens closer to the proximal end, shown in Figure 11c. These extra lumens feed into the main lumens, displayed in Figure 11b, and are included in case a clot fragment causes a blockage in one of the other lumens. The bypass lumen was changed to a half circle shape to promote better fluid flow, illustrated in Figure 11d, and a cover piece was created to go over the cutaway section of the design. The cover piece is created separately to prevent the bypass lumen being filled in during the 3D printing process. Loctite glue will be used to attach the cover piece to the cutaway section.

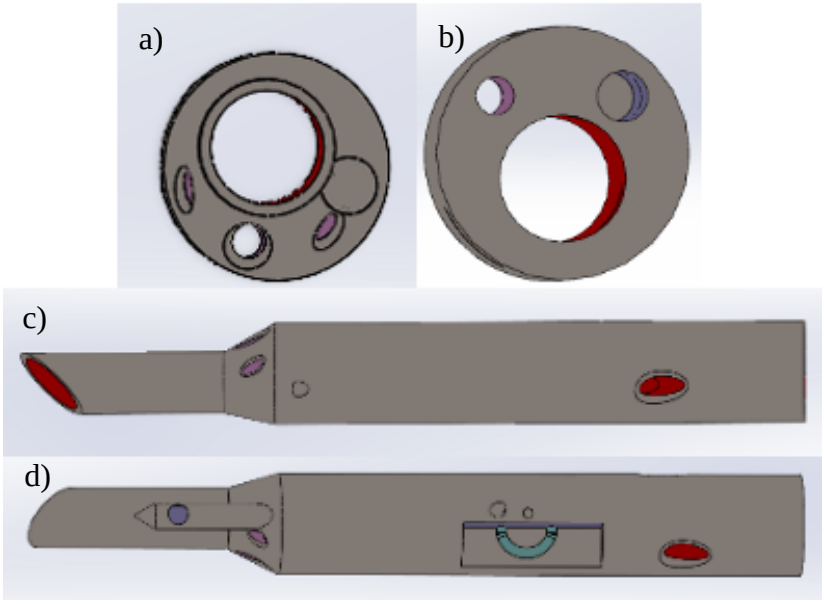

Figure 11. Figure 11a depicts the the distal end of the device with three aspiration lumens below the main reperfusion lumen. Figure 11b is the proximal end of the device and shows the three

main lumens. The purple, blue, and red lumens correspond to the main aspiration, drug delivery and balloon inflation, and reperfusion lumen respectivley. Figure 11c shows a brach of the main reperfusion lumen. Figure 11d shows the half circle bypass lumen in the cutaway section of the device.

Future Work

While most of the individual components have been tested, the nitinol with a transition temperature of 20°C must be examined further to determine if it can radially expand within the gelatin clot analogs. The body of the updated design is ready to be printed once the Formlab's Form 2 3D resin printer is available, but the full device has not been assembled yet by the publication of this paper. Once the device is completed, it should be tested in the gelatin clot analogs to check for leaks around different connections. Connections that are especially vulnerable to leaking include the helical hollow fiber membrane connection and the cover piece connection. An adequate amount of Loctite glue must be applied so that these connections are properly sealed, but excessive amounts could cause the membrane fiber or the bypass channel to be sealed shut. The next part of the device that needs to be attached and tested with the device is the balloon. Future testing should examine the fluid movement into the balloon so that it properly inflates.

Conclusion

SolidWorks is an effective tool for device design and 3D printing shows promise for creating a scaled-up prototype of the Localized Intra-Arterial Drug Delivery Device for Stroke Treatment. Even though individual components of the device have been proven to be functional,

further testing is required before a fully operational prototype can be used to demonstrate a proof of concept. Future work towards this project should continue to adapt as advancements are made in technology and research for treatment of ischemic strokes.

Acknowledgements

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References

1. Stroke facts [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2022 [cited 2022Apr26]. Available from: https://www.cdc.gov/stroke/facts.htm

2. Ischemic strokes (clots) [Internet]. www.stroke.org. [cited 2022Apr26]. Available from: https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots

3. Baig MU, Bodle J. Thrombolytic Therapy. [Updated 2021 Jun 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557411/

4. Jilani TN, Siddiqui AH. Tissue Plasminogen Activator. [Updated 2021 Mar 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507917/

5. Miller, D. J., Simpson, J. R., & Silver, B. (2011). Safety of thrombolysis in acute ischemic stroke: a review of complications, risk factors, and newer technologies. *The Neurohospitalist*, *1*(3), 138–147. https://doi.org/10.1177/1941875211408731

6. Raychev, R., & Saver, J. L. (2012). Mechanical thrombectomy devices for treatment of stroke. *Neurology. Clinical practice*, *2*(3), 231–235. https://doi.org/10.1212/CPJ.0b013e31826af206

7. Oliveira-Filho J, Samuels OB. Mechanical thrombectomy for acute ischemic stroke [Internet]. UpToDate. [cited 2022Apr20]. Available from: https://www.uptodate.com/contents/mechanical-thrombectomy-for-acute-ischemic-stroke

8. Arai D, Ishii A, Chihara H, Ikeda H, Miyamoto S. Histological examination of vascular damage caused by stent retriever thrombectomy devices. J Neurointerv Surg. 2016 Oct;8(10):992-5. doi: 10.1136/neurintsurg-2015-011968. Epub 2015 Oct 27. PMID: 26508129.