In Vivo Mechanical Characterization of Blood Clots

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Abstract

The brain is the most complicated and important organ in the body. It is responsible for maintaining proper function, regulatory control and sensory feedback in individuals. The human brain is a highly vascularized tissue and requires a constant supply of nutrition (oxygen) as well as the removal of waste (carbon dioxide) to function properly. Hence, blood is needed as a means of transport for the oxygen and carbon dioxide. When the blood supply is inhibited, primarily due to blood clots, there is loss of brain function distal to the site of obstruction caused by the blood clot. According to the National Center for Health Statistics, in the United States alone blood clots are ranked third in the leading cause of death by diseases. Deep vein thrombosis, pulmonary embolism and strokes are among the leading causes of death due to thrombi. Strokes in particular account for more than 140,000 deaths each year; of these, ischemic strokes account for approximately 87% of deaths. Therefore, means to remove thrombi have been utilized to restore blood flow. However, the composition of blood clots varies depending on the individual. The difference in composition and formation of blood clots affects their mechanical properties. Likewise, the method of treatment for blood clot removal is also affected. There is an unmet need for a protocol that characterizes and categorizes blood clots to facilitate the development of devices specific for removal of certain types of blood clots. The objective of this senior design project is to mechanically characterize blood clots in vivo. The resulting device will provide rapid and reliable readings, be user friendly, affordable, and have good marketability.

Introduction

Worldwide, 15 million people suffer from stroke during a single year\(^1\). Of these cases 6 million will die, which sets stroke as the second leading cause of death over the age of 60. It is the fifth leading cause of death in people between the ages of 15 and 59 years old. From the remaining people who suffer a stroke and do not perish, 5 million are left with a permanent disability such as loss of vision or paralysis. This places stroke as the second leading cause of disability. With stroke at the forefront of both deaths and disabilities worldwide, it is imperative to bring innovation to this area.

There are several types of stroke, one is ischemic stroke which occurs when blood flow to the brain is blocked. A subset of ischemic strokes, thrombotic strokes comprise nearly 50% of all strokes. A thrombotic stroke occurs when a cerebral artery becomes occluded by the formation of the blood clot within the brain. The brain depends on arteries to constantly supply fresh blood.
for nutrients and oxygen as well as removing waste. When an artery is blocked, even if it is for a few minutes, the neurons will not have enough energy to continue working and will begin to die. 1.2 million neurons are lost per minute during a stroke.

Advances in mechanical thrombectomy procedures and stent removal devices provide promising solutions for patients who suffer from stroke. However, the origin and understanding of the mechanical properties of blood clots is not fully understood. Blood clots vary in composition depending on the individual. This difference in composition and formation of blood clots affects the mechanical properties of the blood clot. Some of the possible clots that can form are: highly organized fibrin-rich, fibrin and plasma protein dominate clot, shear-induced fibrin-rich, composite clot with calcification, and others. There is an unmet need for a method that characterizes a variety of blood clots in order to correctly identify the proper device or method for removal of the blood clot. This will allow efficient removal of the clot to increase patient prognosis.

### Functional Requirements of The Device

**Quantitative detection**

The device will give the force needed to penetrate the blood clot. This force will be correlated to the mechanical properties of the blood clot. The force will be found using a potentiometer and pressure chamber. The potentiometer will measure the displacement caused by penetration of the blood clot. The pressure chamber will give the work done on the device. Using the principle that work equals the product of force and distance we will be able to find the force applied to the blood clot. The functionality of the device will be tested using phantoms and synthesized blood clots.

**Delivered by catheter**

The prototype will be inserted via a catheter to ensure that it fits though the specific catheter dimensions. It will also be tested to verify if it will be able to be deployed by the catheter. The device will use the Volcano Spinvision Pullback device where it will deliver the catheter at a constant velocity.

**Electrically stable**

The device will be tested for electrical stability by applying a force to the tip and measuring the voltage on the device. This will allow the determination of whether the applied voltage will be harmful to the patient. The voltage will be tested once the circuit is completed including resistors. This will allow ensure that the proper resistors are used and that there is no circuit shortage.

**Long shelf life**

The shelf life of the device will be tested using extreme conditions such as steam. These conditions will recreate the aging of the device and will determine if the device will indeed have a long shelf life.

**Durability**
The durability of the device will be tested by repeatedly puncturing a synthesized blood clot. This will recreate the \textit{in vivo} function of the device allowing the determination of whether the device is indeed durable.

**Critical temperature**

The device will be tested under body temperature to ensure that the materials that are used will not be altered when immersed in biological fluid.

**Biologically inert**

The device will be composed of metals and polymers that are well known for their biocompatibility, specifically stainless steel.

**Sterile**

The device will be sterilized using Ethylene Oxide (EtO). This method uses gas to sterilize the prototype that will be beneficial for both polymer and metal components. This process is known to sterilize in low temperatures useful for devices with electrical components. Bacteriostasis and Fungiostasis tests will be performed to validate the dose used on the device prior to sterility testing.

**Minimally invasive**

Because the device will be delivered via a catheter, it will be tested within small parameters that will prove if it is minimally invasive. Hence, this process will be tested delivered via a catheter.

**Project Specifications**

The project specifications were developed based on the functional requirements of the device. Some project specifications that were considered include the time duration of the procedure, how reliable the device will be, the simplicity of the output, the safety of the device, and the materials used to compose the device, etc.

**Short procedure time**

The device should have a short procedure time of about 30 minutes. The delivery time of the device to its target location in the body should be short because time is a critical factor during emergency procedures.

**Reliable results**

The device should be able to generate reliable results, or obtain results within 20\% of actual value. This will provide the physician with an accurate assessment of the mechanical characterization of the blood clot/thrombus.

**Simple output**
The results obtained should be repeatable for optimal accuracy. A simple output with a force measurement in Newtons should be achieved which allows an easy read for the intended user.

Insulating electrical components

There should be insulating electrical components for the safety of the patents. The electrical components of the device must be electronically stable to avoid any electrical interference and must pass a shock test measured in voltage.

Shelf life

The self life of the device should be around 6 months and have a consistent shelf life to ensure that the product is usable after a certain amount of time.

Durable to last shipment

This device should be durable to last shipment and pass a package integrity test and have high packaging integrity. Therefore, the product should be able to go through various shipping tests such as high altitude and long travel distances to ensure the product works as intended after shipping.

Functions in vivo

The device should be durable and operational when used in vivo with a working temperature range of 37 ± 5 degrees Celsius.

Biocompatible

The device will have to be composed of materials that are compatible for the type of environments needed for surgical intervention. Appropriate materials that are to be used include materials that are biocompatible, materials that do not leave residue or other potential hazardous substances for the patient, and materials that are consistent with current FDA approved catheters and pass all biocompatibility tests.

Sterility

The device is intended to be a one time use product and will need to pass the Sterility Assurance Level of 10⁶ parts per million. This ensures that the product will be sold sterile and will minimize any complications when inserted into the patient.

The size of the microcatheter

The size of the microcatheter will range between 2.4 - 2.9 French⁵. Therefore, the device will be small and will use a microcatheter to access the blood clot, which will allow the device to be minimally invasive.

Inexpensive

A low manufacturing cost of less than $1000 is preferred so the device will be more marketable.

Design Operation and Functionality
For the operation of this device, a guidewire will be previously inserted through the femoral artery to a location anterior to the blood clot that is occluding blood flow in an artery, such as the middle cerebral artery. A catheter will be inserted and the guidewire will be removed. The device will be deployed in the catheter to a location anterior to the blood clot. Once the device is deployed, the surgeon will be able to see the location of the device on the fluoroscopy due to the device being made of radio-opaque material.

The distal end of the device will have an opening for an insulated cable, which will be enclosing various wires of the device to supply power as well as allow data collection. This insulated cable will extend outside of the patient and will be mounted on a motor such as the Volcano Trak Back II catheter motor. The surgeon will turn on the motor, which will advance the device, thus allowing the conical tip to penetrate the clot. The motor will advance the device at a constant velocity and it will advance for a predetermined amount of time. By predetermining these parameters, the maximum displacement will be constrained to minimize the possibility of dislodging the clot but still achieving full penetration. The tip will be composed of stainless steel (Figure 1E). It will be solid, but will have a cylindrical opening on the base to fit the piston. When the tip interacts with the clot, it will be displaced and consequently the glider will slide through the slot it is positioned in.

The glider will be composed of stainless steel, which offers low friction. The body of the device and other components will also be composed of stainless steel, but the outer surface of the device will be coated with polyurethane. The device will be coated with polyurethane to insulate the electrical components. As the glider slides through the assembly, the piston that fits into the tip and through the glider will be displaced also into a chamber that will be enclosing the force transducing technology (Figure 1G). The inner chamber will be filled with a predetermined amount of compressed air that will serve as the force-transducing medium (Figure 1B). When a force is applied on the piston from the displacement of the tip, there will be a change in volume of the chamber in which the air enclosed. This will be calculated by knowing the distance that the piston displaced. This will be measured using a sliding potentiometer (Figure 1H and Figure 3). A microcontroller will be used to receive the signals of the change in voltage associated with the displacement. The reduction in volume of the chamber will consequently increase the pressure. The work for this isothermal process can be calculated, which will allow an estimate of the force that was exerted. These calculations will be done and conditioned to give the user an output that is easy to understand. The output of the force that the clot exerted back will be related to the stiffness of the clot and allow the surgeon to determine which thrombectomy method will be the most efficient to remove the clot. The device will be removed by pulling it from the cable on the distal end. The exploded view of the device with its components can be seen in Figure 1.
Figure 1: Exploded assembly of device

<table>
<thead>
<tr>
<th>ITEM NO.</th>
<th>PART NUMBER</th>
<th>DESCRIPTION</th>
<th>QTY.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>63571</td>
<td>Front Chamber</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>63572</td>
<td>Pressure Chamber</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>63573</td>
<td>Piston</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>63574</td>
<td>Tip Extension</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>63575</td>
<td>Indentation Tip</td>
<td>1</td>
</tr>
<tr>
<td>F</td>
<td>63576</td>
<td>Displacement Rod</td>
<td>1</td>
</tr>
<tr>
<td>G</td>
<td>63577</td>
<td>Rear Chamber</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>63578</td>
<td>Printed Circuit</td>
<td>1</td>
</tr>
<tr>
<td>I</td>
<td>63579</td>
<td>End Cap</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2: Rendered image of sectioned view of the device
Figure 3: Circuit of device operation components

Testing Plan

Force compression test
The device will be tested multiple times to identify if the device will be able to take multiple reading. Compression testing will be used to ensure that the device will be able to obtain actual readings. Force compression test and accuracy testing will be performed to determine the accuracy of the device. ASTM standards will be used as a standard method for testing. To test if the device is able to take compression readings ASTM D575 Test Method B-Compression Test at a Force for Rubber will be used\(^8\).

Accuracy test
The accuracy of the device will be tested by performing the force compression test, then correlating the force readings to the mechanical properties of the blood clot. The results will be compared to actual mechanical compression testing of a blood clot. This will determine the accuracy of the device. ASTM standards will be used as a standard method for testing. To test the accuracy of the device ASTM E177-14 Standard Practice for Use of the Terms Precision and Bias in ASTM Test Methods will be used\(^9\).

Aging methods
Different types of aging standards/ protocols that are used for medical devices are the ANSI/AAMI/ISO and the ASTM F1980 by using environmental chambers\(^10\). These accelerated aging devices are based on the Arrhenius' equation which states that a 10°C increase in temperature will double the rate of the chemical reaction. Therefore, by changing the temperature of the device, one is able to assimilate the aging of the product. Various variables such as: test temperature, ambient temperature, reaction rate factor, real-time factor (Q10) and real time equivalent days are used in calculating the accelerated aging test duration. The Test Temperature usually ranges between 50°C to 60°C and the Ambient Storage Temperature is between 22°C to 25°C. It was found that the relative humidity of the environment should be kept under 20% so material is not damaged. The expected expiration date of a medical product is
generally based on its manufacture date and an extra month to the aging study is usually added to allow for sterilization and other preparatory means. ASTM standards will be used as a standard method for testing. To aging of the device ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices will be used\textsuperscript{11}.

**Electrical circuitry performance**

The electrical components of the device will be tested to ensure that they are functioning properly by using electrical measurement instruments (multimeter). A voltmeter will be used to determine if the proper voltage is applied to the system. An ammeter will be used to determine the current flowing through the circuit. These two devices will determine if the proper electrical circuitry is functioning properly. ASTM standards will be used as a standard method for testing. To test the electrical performance of the device ASTM D5637-05 Standard Test Method Resistance of Electrical Insulating Varnishes will be used\textsuperscript{12}.

**Device Sensitivity**

The device will be tested for sensitivity to ensure that the device will be able to identify the smallest displacement, which in turn will measure force. The force measuring device will be calibrated to ensure that it provides adequate force readings. ASTM standards will be used as a standard method for testing. To test device sensitivity ASTM E74-13a Standard Practice of Calibration of Force-Measuring Instruments for Verifying the Force Indication of Testing Machines will be used\textsuperscript{13}.

**Deployment/Retrieval testing**

The device will be tested multiple times to verify that the catheter and the device will be able to work effectively. The device must be deployed from the catheter and must be retrieved from it various times in biological fluid to ensure that it functions as needed. ASTM standards will be used as a standard method for testing. To test the deployment and retrieval of the device ASTM F561-05 Standard Practice for Recital and Analysis of Medical Device, and Associated Tissues and Fluids will be used\textsuperscript{14}.

**Environmental testing**

**Size:**

The size of the device will be tested by placing the device in the proper catheter size. If the device fits and can easily glide through the catheter, the device will be able to fit in the body. ASTM standards will be used as a standard method for testing. To test the size of the device ASTM E177-14 Standard Practice for Use of the Terms Precision and Bias in ASTM Test Methods will be used\textsuperscript{15}.

**Temperature:**

The temperature of the fluid within the chamber will be tested by placing the device in blood that is heated to 37°C (body temperature). The device will be left in this condition for about 30 min [16]. Then the temperature of the inner fluid will be tested to see if the temperature is changing. ASTM standards will be used as a standard method for testing. To test the if the material can withstand body temperature ASTM G142-98 Standard Test Method for
Determination of Susceptibility of Metals to Embrittlement in Hydrogen Containing Environments at High Pressure, High Temperature, or Both will be used\textsuperscript{17}.

Compatibility:
The compatibility of the device will be tested by placing the device in blood. This will determine if the device is causing the blood to aggregate. If this is the case another material will need to be used to ensure that the device does not cause further complications. ASTM standards will be used as a standard method for testing. To test the compatibility of the materials ASTM F748 – 06 Standard Generic Biological Test Methods for Materials and Devices will be used\textsuperscript{18}.

**Discussion of risks resolution**

A risk resolution was determined by specifying the function of each component of the device. Initially, the risks of each device component were established. Thereafter, a resolution was identified for each risk. Determination of how the resolution will affect the performance of the device is important and must be identified. Hence, these risk resolutions were quantified from 1 (low risk) to 10 (high risk). A description of how each resolution affects the function of the device is provided in Table 1.

<table>
<thead>
<tr>
<th>Function</th>
<th>Risk Resolution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guide Wire</td>
<td>1</td>
<td>After tip markers are incorporated, the risk occurrence will decrease.</td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td>No potential risks may be incorporated with adding a tip marker.</td>
</tr>
<tr>
<td>Catheter</td>
<td>1</td>
<td>After tip markers are incorporated, the risk occurrence will decrease.</td>
</tr>
<tr>
<td>Function</td>
<td></td>
<td>No potential risks may be incorporated with adding a tip marker.</td>
</tr>
<tr>
<td>Device</td>
<td>1</td>
<td>After tip markers are incorporated, the risk occurrence will decrease.</td>
</tr>
<tr>
<td>Function</td>
<td>10</td>
<td>By applying more force to the clot, the device could dislodge or compact the clot, increasing the risk.</td>
</tr>
<tr>
<td>Tip</td>
<td>8</td>
<td>By increasing the insertion velocity, the Volcano Spinvicion Pullback device could potentially have a malfunction.</td>
</tr>
</tbody>
</table>
After tip markers are incorporated, the risk occurrence will decrease. No potential risks may be incorporated with adding a tip marker.

<table>
<thead>
<tr>
<th>Component</th>
<th>Risk Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentiometer</td>
<td>9</td>
<td>By increasing the voltage, there is an increased risk of shocking the patient, which could potentially lead to death</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Decreasing the voltage significantly could lead to no results being obtained</td>
</tr>
<tr>
<td>Pressure Gauge</td>
<td>2</td>
<td>By obtaining a lesser friction between the pressure gauge and the chamber, the device could potentially give false readings due to loose movement.</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>If the chamber is tightly sealed, there is greater friction between the piston and the chamber, which could potentially cause inaccurate readings.</td>
</tr>
<tr>
<td>Force</td>
<td>10</td>
<td>Increasing the force could cause the blood to dislodge from the artery, making it more difficult for removal.</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>By decreasing the force, the device may not penetrate the blood clot therefore causing inaccurate readings.</td>
</tr>
</tbody>
</table>

**Table 1: Risk Resolutions**

**Preliminary Results and Discussion**

Preliminary results have been done to determine how the voltage output will be affected by displacement and the maximum amount of force needed to dislodge a blood clot. Results of the latter were simulated using computer programs and were used to determine thresholds and boundaries for our device, in order to minimize the risk of dislodging a blood clot during device operation.

Using Excel we simulated the voltage output when the device undergoes a certain displacement due to a loading force. Using device parameters we determined the ideal voltage output curve as seen in Figure 3. However, due to loading effects that may be present in the resistive sensor, the curve in reality takes on a nonlinear shape. These preliminary results demonstrate that assuming a linear relationship between voltage and displacement introduces error that will need to be calculated during testing.
Additionally, we determined the stresses a blood clot undergoes when it is dislodged. This was found using a finite element analysis performed using COMSOL (Figure 5). Using literature values for the material and geometric properties of blood clots, the blood clot was modeled as a 2D axisymmetric cylindrical element. A boundary condition of a fixed constraint along the outside of the clot to simulate the friction from the walls was applied. The second boundary condition was a 0.01 N force applied to the distal end of the clot. This value was retrieved from literature as the force required to dislodge a blood. The simulation was done with 3032 elements and it was found that the maximum stress on the clot was 9.815 kPa, primarily concentrated at the distal end where the force was applied (Figure 4). The minimum stress experience by the blood clot during dislodgement was 1.09 Pa. During testing we will verify that 9.815 kPa is the fracture stress of blood clots in order to ensure that our device does not apply a stress that exceeds this value.
Figure 4: Stresses acting on blood clot when undergoing dislodgement force

Figure 5: Demonstration of solution convergence for finite element model

References


