Systematic Procedure for Transitioning Intracranial Hemorrhage Treatment from CT to MRI Guidance

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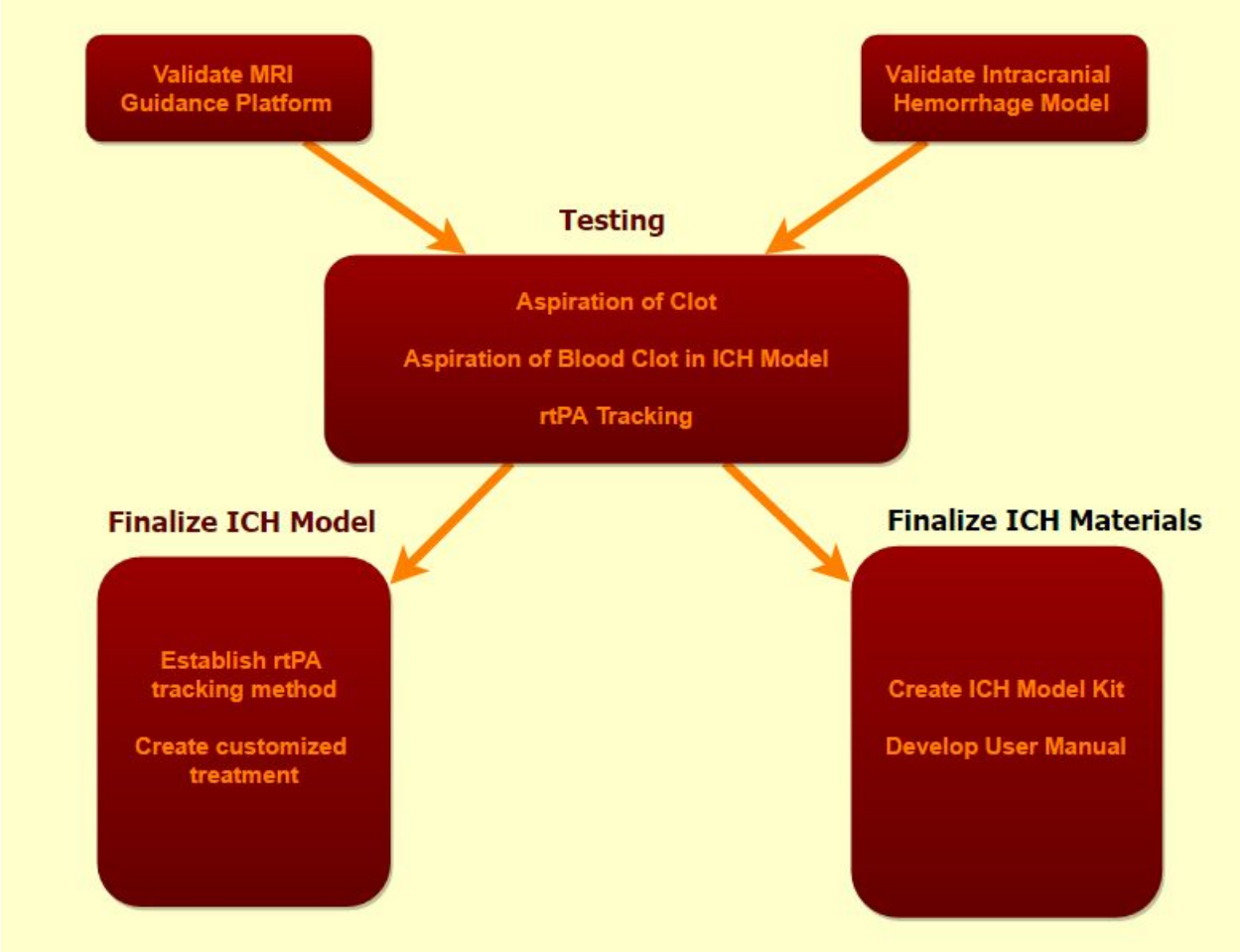
Abstract: Computed Tomography (CT) is currently the main guidance method used to treat Ischemic Intracranial Hemorrhage (ICH). (add source) Advances in Magnetic Resonance Imaging (MRI) and real-time imaging software now allows for MRI to reach outside of its traditional diagnosis-only application into the realm of image-guided interventions. Using MRI for guidance during ICH treatment is advantageous over CT. MRI provides higher resolution images and higher-contrast clot characterization which allows a surgeon to find plasma pockets in the clot and drain these areas before administering clot-busting rtPA during a procedure. MRI feedback also allows for a surgeon to track rtPA distribution in the clot in real time when rtPA is mixed with a MR-visible solution such as gadolinium. CT treatment doses for ICH treatment are standardized and conservative. rtPA tracking with MRI has the possibility of personalizing treatments. This paper provides a first step in transitioning ICH treatment to MRI by outlining a systematic procedure for performing treatment techniques on a nonliving ICH model that mimics an actual ICH procedure. After performing ___ tests on ____ICH models, an imageJ analysis of MR-images and cross sectioning of ICH models confirmed that rtPA was successfully administered and tracked with a ___ % confidence interval. Based off these results, "personalized treatment" with MRI feedback was a (success/failure).



Highlights

- The aim of this project is to develop a model which successfully mimics ICH clot reduction.
- The model should also have similar imaging capabilities to that of ICH clot under MRI.
- This model can be used to better predict clot characteristics and improve patient care.

Funding

“This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.” **we need to ask wally about this

Introduction

Strokes affect hundreds of thousands of people unexpectedly each year, 10-15% of which are caused by intracranial hemorrhage (ICH). In the United States alone, roughly 10,000 people are victims of ICH each year [1,2]. This devastating form of stroke occurs when a blood vessel in the brain ruptures, and releases a large volume of blood, typically around 60 mL, which then clots. This stroke type is much less common than the subarachnoid hemorrhage, however, it has a much higher rate of mortality. People who do survive have little prospects for rehabilitation and typically require assisted living for the rest of their lives [3].

Currently, there is little that can be done for victims of ICH. One of the largest studies regarding ICH treatment was the "Minimally Invasive Surgery plus rtPA for Intracranial Hemorrhage Evacuation", or the MISTIE trials. MISTIE trials used CT to image the clot and administer rtPA to break down and remove the clot volume from the brain. The MISTIE trials were able to reduce clot volume by one half on average, although the results were incredibly variable as shown in Figure 1a. The variability of results was largely due to the fact that each patient was treated with identical protocols despite a variety of clot characterizations. Every patient had a clot of different size, shape, location, and mechanical qualities. Clot properties of each individual patient must be completely understood in order for personalized and accelerated treatment [6]. The MISTIE trials have sufficiently demonstrated an effective way to treat ICH but also exposed the variability and ineffectiveness of current procedures. This variability can be reduced with the use of MRI to visualize the clot.

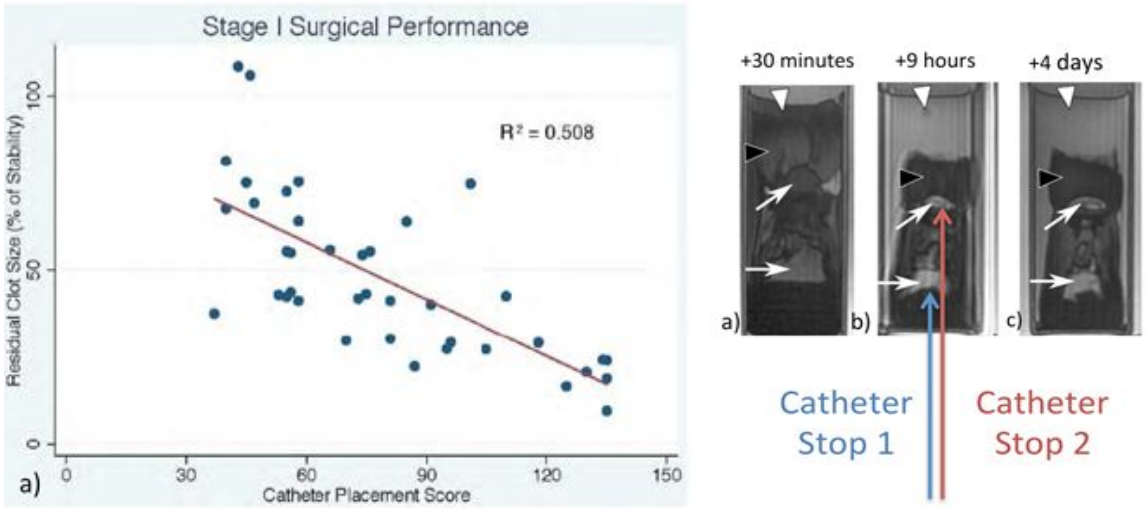


Figure 1: (a-Left) Surgical Performance of MISTIE Trials. (b-Right) Vial of clotted blood imaged in MRI.

If the imaging modality of ICH treatment can be transferred from CT to MRI, the MISTIE trials can be improved, simply by providing the ability to visualize the clot with high resolution. Figure 1-b shows vials of clotted blood imaged with MRI. The lighter grey portions of the clot are pockets of plasma, which are drained by the catheter first. The surgeon can administer a dose of rtPA into the newly formed pocket which subsequently allows rtPA to have maximum interaction with the fibrous portion of the clot.

In order to move ICH treatment into MRI, a standard model must first be created to help predict and display the progress of treatment. This model must recreate the conditions of ICH and do so dynamically. The model must be able to change over time as would the brain during actual treatment. Because of this, it is paramount to observe what kind of conditions the brain experiences before and after an ICH.

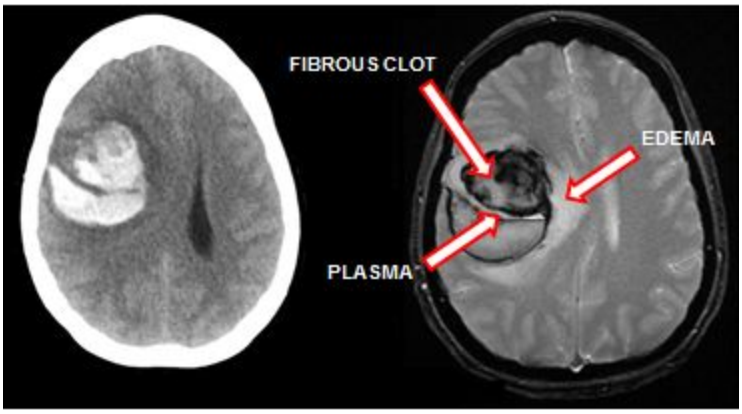


Figure 2: CT (left) and MRI (right) images of a brain clot [8].

One of the first elements of this project that must be understood is the physiology of the brain. The brain is arguably the most important and complex organs in the body, and several key aspects should be replicated. Temperature and pressure were initially of the greatest concern for the model. Ideal temperature of the brain is 37°C and can rise to 42°C during extreme fever; a side effect of intracranial brain hemorrhage. However, after further conversation with our client, it has been concluded that temperature does not need to be regulated.

Another important physiological element that this model must replicate is pressure. While the standard pressure of a human brain is anywhere from 5-15mm, the pressure reached in the model is not important, per our client, as long as the mechanical characteristics of the model are retained [4]. The dynamic movement of the material is the primary mechanical characteristic of interest; the model must be able to successfully collapse upon the clot as it is drained. The collapse could be created by an external force or by the weight of the model itself.

Model Verification:

Materials - Brain Model

- Rubber ellipsoid shell
    - This item acts as the container for the brain material. It is an ellipsoid volume with oval holes at the surface. The ellipsoid shape is anatomically similar to the brain, helps the team create a more reliable model. This was a client request. A balloon was inflated inside the ellipsoid, and coated with a rubber membrane (Plasti Dip--see below). The rubber coated holes serve as ports where catheters and syringes can easily access the clot inside. Because the holes completely cover the model the surgeon has a variety of options for catheter insertion points. One of the holes is left open so the model can be filled with sodium polyacrylate hydrogel.
- Balloons
    - The main purpose of the balloon is to help create the exterior shell of the brain model, as previously mentioned. A balloon slightly larger than the dog toy can be inflated inside of the model to create a surface for Plasti Dip to dry upon.
- Plasti Dip
    - Plasti Dip is a liquid which, when dried, provides a solid yet flexible rubber coating. It can be applied via a paintbrush and was applied onto the dog toy and balloon to form the outer membrane, sealing the dog toy. The hydrogel can reside inside without leaking, and the model still provides multiple entry points for catheter and syringe insertion.
- Sodium Polyacrylate (Brain model interior material)
    - A common hydrogel, Sodium Polyacrylate was utilized, deviating from proposed design ideas of agarose, polyvinyl acetate and gelatin. This alteration was due to the poor preliminary results using agarose gel. Agarose gel was not able to collapse on the void left behind where the drained clot once was. For detailed results on agarose testing and the motive for choosing Sodium Polyacrylate, please refer to Appendix II. It was from this testing, and further consultations with the client, that the team decided void closure should be prioritized over mechanical resemblance of the brain. The water-absorbent Sodium Polyacrylate powder allows for a
    - more viscous hydrogel to form, facilitating void to close. It is important to note that the main reason for this is because the molecular structure of this material is not crystalline. A fluid structure allows for easy collapse in the void after the clot is drained.

Materials - Clot Model

- LDPE bags
    - Low density polyethylene (LDPE) bags were chosen to hold the clot inside the brain model. LDPE is able to adhere to the surface of the catheter or syringe when punctured. This property prevents leakage and allows easy entry of the catheter or syringe.
- Dyed blue water and gadolinium
    - The clot material inside the LDPE membrane is modeled by dyed blue water with a gadolinium solution. The blue water allows the team to visually confirm any leakage into the model, and the gadolinium allows for this confirmation in MRI. The gadolinium is also necessary to provide greater contrast between the clot and the surrounding hydrogel in MR images.

Materials - Extra pieces

- Twine/Rubber Band
    - These components allow for a complete seal to be formed on the LDPE bag replicating the clot. This is a vital part of the procedure as any leakage indicates failure of the model.
- Long Syringe
    - Syringes were used in the testing, as it is able to puncture through the LDPE bags easier than a catheter. It also allows for suction of clot after insertion so that we can test whether brain material collapses on void or not.

Final Prototype:

The final prototype consists of a CAD designed mold consisting of four stabilization screws, two access screws, and one filling screw. The four screws around the perimeter allows for stabilization of the two halves sealing both together. The larger center hole in the top view allows for an access point for insertion of the catheter. The bottom view also has a larger second opening allowing for another access point. The smaller center screw allows for filling of the model with hydrogel. The final model will be fabricated of a hard dense material.

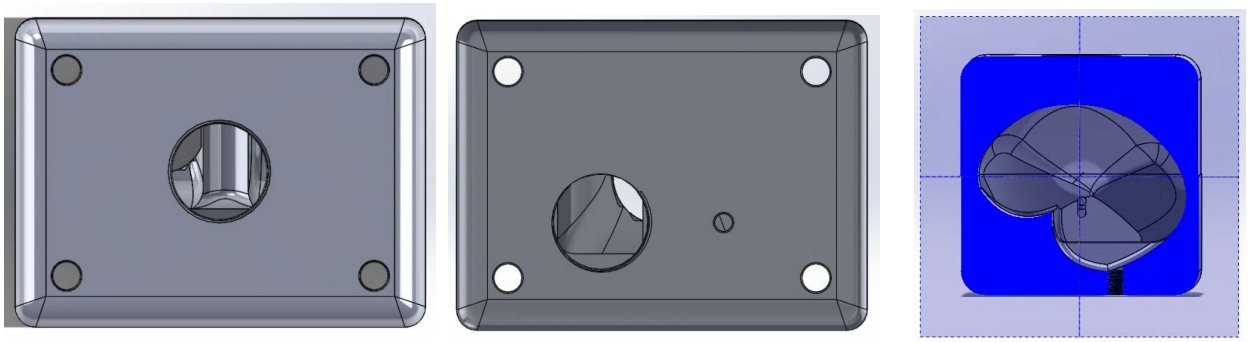


Figure 6: Left (top view), Middle (bottom view), Right (cross section).

Discussion:

The first clot draining test verifies the model's desired characteristics. This being the ability of the "tissue" surrounding the clot to completely collapse once the the clot has been completely drained. This provides the ability to use the model as a mock simulation of a real ICH event. The plasma removal test ensures that in an MRI environment plasma surrounding the clot can be both located and removed from a hemorrhage site. An ability to verify this characteristic could provide ample benefits to a potential patient. Removal of the plasma removes fluid from the hemorrhage site which decreases the pressure as volume within the "container" decreases. This decrease in pressure allows the patient to become more comfortable. In addition, this removal of plasma decreases treatment time as rtPA is allowed closer to the active site being the fibrous clot. It also prevents the possibility of undesired lysing of healthy blood cells and brain tissue. Tracking of rtPA in an MRI environment is another desired test which could reveal diffusion rates and the locating of rtPA during a procedure.

Limitations:

The scope of this study had several limitations, mainly time, cost and accessibility of materials. Firstly, due to the time scale of the project the team is limited to few months to complete testing and analyze the results. This leaves little time for assessment of results. Also, the nature of this project being reliant on MRI scanners, collaboration with our client and the Wisconsin Institute for Medical Research was key. MRI scanners must be reserved and paid for. Through a grant however, time spent on MR scanners required no out of pocket expenses. However, reserving the scanner often required research to be delayed up to two weeks due to unavailability. Being part of the WIMR, these scanners are tirelessly used by many other researchers. Another limitation is a primary material needed to indicate the overarching success of this project. rtPA is very expensive and is crucial to the results and the integrity of the study. This material, rtPA, can cost upwards of $330 per trial. Because of this fact alone, it was the goal of the team to undergo multiple tests to assure that the model can sufficiently replicate ICH as to avoid any wasting of rtPA fluid. While this cost too was covered by a Grant, money is not to be wasted. Finally, obtaining blood for testing was another hurdle. Blood for testing was obtained from a lab on campus which is difficult to receive in quantities and qualities needed, especially when multiple other labs are requesting blood. Of course obtaining blood alone is not the only consideration, but also handling and disposal as well. Completion of blood safety certifications are necessary to work with blood in the research or medical setting. Proper regulations must be adhered to as well as general safety guidelines. Because many of our experiments are not dependent on the properties of blood to show the viability of our design, often blood was replaced by a surrogate material.

Conclusion:

Intracranial Hemorrhage treatment in CT is outdated and unsuccessful at treating patients when compared to that of the possible MR treatment. The basis of this claim can be found in the results of the MISTIE trials. These trials successfully showed that in large part the success of the surgery is dependent on the surgeon's placement on the catheter. The quality of which they were able to place this catheter into the intracranial clot was dependent on the imaging modality provided to them. It is clear that because clots are non-distinctive in CT, that is it is very hard to distinguish different states of the blood, the information provided to the physician is not adequate enough to optimize the placement of the catheter. MR however, is capable of displaying highly descriptive images of the clot. By using these images instead of the images provided by CT, the physician can make more highly educated decisions and ultimately create a more personalized procedure for the patient. This will directly lead to more clot being capable of drainage in a shorter amount of time. By using our model to prove the concept of ICH treatment in MR, the team can show that the treatment is much more adequate by transferring between imaging modalities. Also, physicians currently treating ICH in CT can use our model to practice and perfect the treatment techniques required in the MR environment. No current models exist which replicate the collapse of brain tissue onto a draining clot, so our model can create a basis for which the medical field can begin to evolve towards MR treatment plans. It is clear after observing the clear benefits of MRI and the success of this model that ultimately the patient's outlook will be improved, and more people will walk away from this possibly life ending occurrence.

References:

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[2] Fan JS, Huang HH, Chen YC, Yen DH, Kao WF, Huang MS, Huang CI, Lee CH as cited in Walter B. “Stroke Summary Aims,” unpublished.
[3] Walter B. “Stroke Summary Aims,” unpublished.
[4] Ziai, Wendy C. et al. “Occurrence and Impact of Intracranial Pressure Elevation during Treatment of Severe Intraventricular Hemorrhage.” Critical care medicine 40.5 (2012): 1601–1608. PMC. Web. 13 Oct. 2016.

Appendix A

1. Obtain the following materials:
    a. Low-density polyethylene bags (Clot Holder Material)
    b. 316 mL rubber ellipsoid
    c. Plasti dip
    d. Small paintbrush
    e. Balloon
    f. 0.80 g of sodium polyacrylate hydrogel
    g. One syringe
    h. One catheter
    i. String with slip knot
    j. 50 mL graduated cylinder
    k. 14.5 mL of water per test
    l. Rubber band
    m. Blue dye
    n. Gadolinium solution
2. Inflate an empty balloon into the rubber shell and expand the balloon so that it is snug within the outer shell and tie off the balloon. Figure 10 below illustrates what this step should look like when completed.

Figure 3: Balloon inflated inside the rubber ellipsoid shell.

3. Apply a single layer of Plasti Dip onto the volume with balloon and set it rest until it dries completely.
4. Repeat step 2 three times to form three layers to prevent leakage.
5. When the rubber ellipsoid is sufficiently covered (see Figure 11), puncture and remove the balloon. It is possible the balloon adhered to the inside of the rubber ellipsoid. In this case, the balloon may remain.

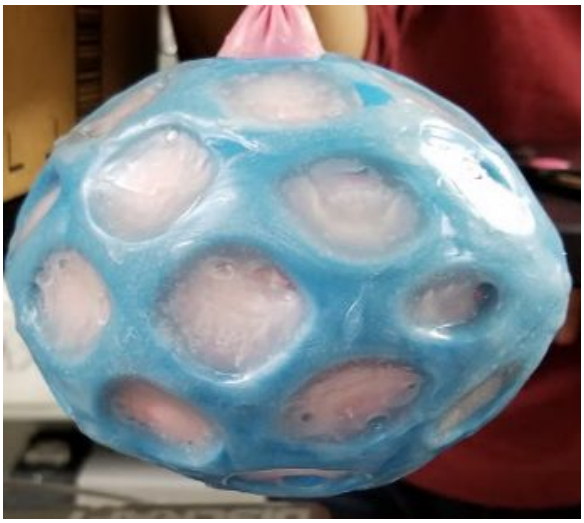


Figure 4: Rubber ellipsoid shell and balloon coated in several layers of Plasti Dip.

6. Pour 0.40 g of sodium polyacrylate into ICH model
    a. Add 50 mL of water at a time - stirring each time to mix the hydrogel - until 100 mL is added to the model
7. Pour 15 mL of water into the LDPE bag, add 5 drops of blue dye and gadolinium solution
8. Press close ¾ of the seal closed along the top of the LDPE bag

9. Squeeze out any remaining air in bag and then seal completely
10. Tilt bag so that water accumulates in the lower corner away from the seal
11. Place the LDPE bag inside the ICH model (corner first), with the opening of the bag remaining outside the model.
12. Twist bag 6 times and secure with slip knot - ensure all of the liquid is captured
13. Use scissors to cut off excess LDPE above slipknot
14. Suspend the clot inside the model using slip knot
15. Secure sting stemming from slipknot to the outside of the model using rubber band. Figure 12 below shows how the model should appear after this step is complete.

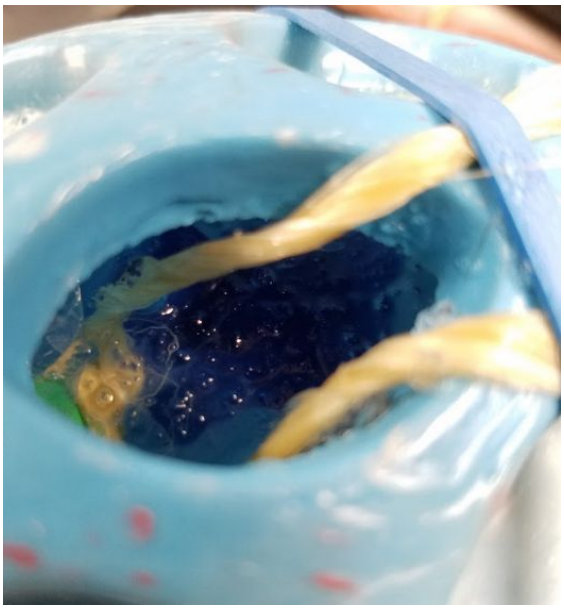


Figure 5: Clot model suspended by twine and rubber band within the brain model to create the final ICH model.

16. Continue adding 50 mL of water at a time - mixing each time - until the clot is fully submerged (250 mL water)
17. Add remaining 0.40 g of sodium polyacrylate and mix gently

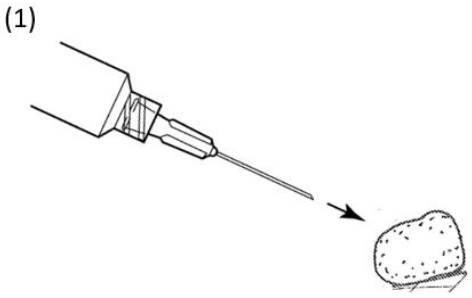
Appendix B

Plasma Extraction:

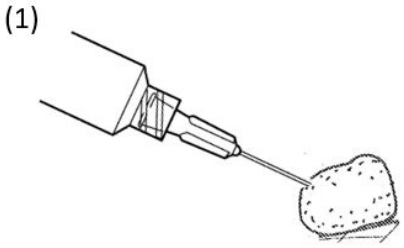
Testing Procedure:

1. *Obtain the following materials:*
    a. 2 Low-density polyethylene bags (Clot Holder Material)
    b. 0.80 g of sodium polyacrylate hydrogel
    c. 1 empty syringe (syringe 1)
    d. 1 syringe filled with __mL rtPA solution and ___mmol gadolinium (syringe 2)
    e. 8 inches of twine
    f. 50 mL graduated cylinder
    g. 1 Rubber band
    h. 2 g agarose
    i. 250mL Erlenmeyer Flask
    j. Microwave
    k. Weigh boat
    l. Hot rubber hand protection (for handling hot flask)
    m. 1 Scoopula
    n. 1 Plastic bag
    o. 1 Plastic Tupperware container 400mL
2. *Prepare agarose gel*
    a. Add 0.2g agarose to erlenmeyer flask
    b. Add 200mL water to erlenmeyer flask
    c. Swirl solution for 30 seconds
    d. Place in microwave on high for 1 minute
    e. Once solution begins to boil, stop heating, remove from microwave, and swirl for 30 seconds
    f. Place back in microwave and repeat step (e) until agarose powder is completely dissolved.
3. Pour agarose gel into 300mL Tupperware
4. Pour 60 mL of water into ldpe bag, use 6 inches of string to tie off bag (tie evenly so that 3 inches of string remain on each side
5. Dip bag into agarose liquid and secure each 3in length of string to the sides of the tupperware container for support
6. Allow agarose to cool for 30 minutes until gel becomes hard
7. Carefully remove plastic bag from agarose using string
8. *Prepare Blood Clot*
    a. Obtain animal blood clot (~60mL) and add to the corner of a plastic ldpe bag
    b. Squeeze out any remaining air in bag and then seal completely
    c. Twist bag 6 times and secure with slip knot - ensure all of the liquid is captured
    d. Place bag in void in agarose gel
9. Pour 0.40 g of sodium polyacrylate into Tupperware container

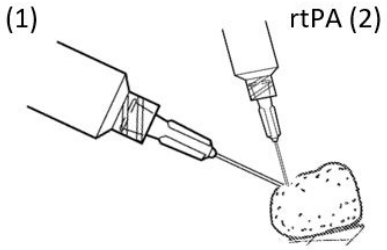
    a. Add 50 mL of water at a time - stirring each time to mix the hydrogel - until 100 mL is added to the model
10. Ensure no air bubbles appear in the gel and move model into the MRI bore
11. Begin acquiring MR images
12. Acquire syringe 1 (empty syringe)
13. Insert syringe 1 needle tip into the blood clot plasma pocket (pictures below show clot and syringe. It is assumed that the clot is surrounded by agarose and hydrogel)



14. Drain plasma pocket using syringe 1



    a. Confirm that pocket has been drained with MR images, leave syringe 1 in place
15. Obtain syringe 2 (filled with rtPA)
    a. Push plunger until rtPA drop is visible at syringe 2 tip (to ensure no air is in syringe 2)
16. Guide rtPA syringe 2 tip into emptied plasma pocket
17. Expel rtPA solution into pocket



18. Monitor clot lysing with MR images and use syringe 1 to drain lysed clot solution