IN VITRO VERIFICATION OF SHAPE MEMORY POLYMER VASCULAR OCCLUSION PLUG

An Undergraduate Research Scholars Thesis

by

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ABSTRACT

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The objectives for the current *in vitro* experiments are to perform verification tests that demonstrate the safety and feasibility of a proposed vascular occlusion plugs (VOPs) and the validity of the device design criteria. Tests will be executed to monitor the following qualities: migration, working time, device friction, and particulate generation. Results from device testing provides positive conclusions regarding the feasibility of the VOP design for peripheral embolization. There was limited risk of unintended embolization due to device migration. Expansion rates provide sufficient time for a physician to deliver the device trough a standard catheter. Frictional forces during expansion in catheter do not prevent delivery. Devices do not fracture or generate particulates that may cause thromboembolisms. All of the measured characteristics will aid in the design and optimization of novel SMP-based peripheral embolization devices.

CHAPTER I

INTRODUCTION

Clinical need

Blood is moved from the leg toward the heart predominantly by the propelling action of the leg muscles. As blood moves from the deep to the superficial system via muscular contractions, the superficial venous pressure increases. [1] Pelvic congestion syndrome (PCS) occurs when hypertension and elevated venous pressure cause valve incompetence in the ovarian veins. Venous blood flow then deviates from its normal path and forces flow in a retrograde direction so that fluid accumulates and causes bulging varicose veins. [1-3] Lower extremity venous insufficiency affects approximately 25% of women and 15% of men. [4] PCS manifests itself as chronic pelvic pain in as high as 39.1% of premenopausal women worldwide and accounts for 10 to 15% of outpatient gynecologic visits in the United States. [5] In fact, it is estimated that 6 million people in the US suffer from severe symptoms of chronic venous insufficiency such as pain, varicose veins, edema, and venous stasis ulcers. [6]

Current treatments

Treatments for venous insufficiency aim to block or divert blood flow to a specific region of the body. The most common region for treating lower limb venous insufficiency is within the great saphenous vein (GSV) (**Figure 1**). [8] There are four treatment modalities most often used to treat varicosities: surgical ligation, sclerotherapy, endovenous ablation, and implantation of embolic devices.

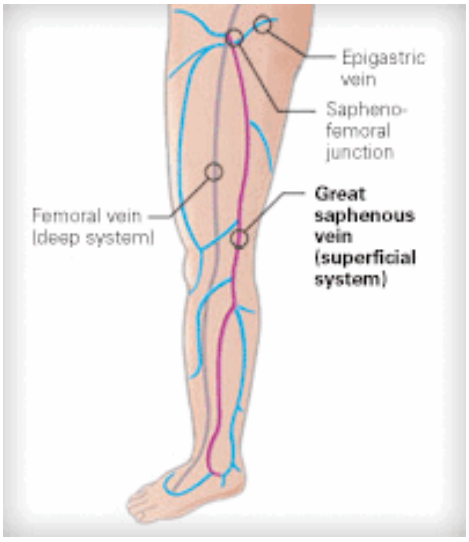

Figure 1. Schematic of lower limb veins. [7]

GSV incompetency is conventionally treated with ligation and stripping at the saphenofemoral junction. The treatment is effective with low recurrence rates. It is also more cost effective than endovenous ablation. [9] However, it is a surgical procedure with multiple negative effects including: requires general anesthesia, increased risk of infection, excessive nerve damage, and scarring or bruising with postoperative pain. [9, 8] Additionally, recurrence of incompetency occurs in up to two-thirds of patients after five years. [10] Sclerotherapy involves injecting a chemical solution directly into the vein. The liquid sclerosant chemically burns the endothelium causing the vessel walls to spasm and stick together. [11] This process ultimately causes blood to clot. Sclerotherapy can be used to treat short tortuous vessels and does not require anesthesia; [9] however, it is difficult to compress the ablated vein in the pelvic region. [11] Because this method uses a chemical solution, there are potential consequences of the chemical flowing downstream in the vessel. Other negative indications include recanalization, recurrence, thrombophlebitis, skin pigmentation, and tissue necrosis. [9] Endovenous laser ablation, or cauterization to close the veins, requires the use of detailed imaging and advanced understanding

of the anatomy of lower extremity veins. This procedure has low recurrence rates, is minimally invasive, and has rapid recovery. [9] If precision is lacking, laser energy can damage small arterial branches around the vein in patients and cause severe peripheral artery disease. Complications include bruising, soreness, tenderness, and indurations along the treated vein segment. [8] The fourth treatment modality is permanently implanted embolic devices made up of platinum coils. [11] Coils are delivered through a micro catheter to block flow in the desired vein with a cluster of material. Platinum coils have high flexibility and good for visualization under fluoroscopy. [11] There is poor tissue healing and high recurrence from these metallic implants. The proposed shape memory polymer foams provide what many of these treatments lack: rapid occlusion. Foams are porous materials that provide high surface area for high volume occlusion. There exists a clinical need for a vascular plug to achieve faster occlusion than current platinum coils to treat lower extremity venous insufficiency.

Previous research

The focus of this research is to characterize the behavior of thermally actuated, amorphous, covalently crosslinked shape memory polymer (SMP) foams. SMP foams are soft, compliant materials that can be fabricated into essentially any shape. Their initial geometry can then be deformed by raising the temperature of the material above its glass transition temperature and applying a force. While the force is still applied, the foam can be cooled below its transition temperature to program the material into a temporary, secondary shape. The SMP foam will remain in its secondary shape until it is reheated above its transition temperature (**Figure 2**). [12] This shape memory property makes these materials optimal for minimally invasive endovascular interventions, as a compressed foam can be delivered *via* catheter and then expand to fill the

vessel upon heating to body temperature. This work focuses on the application of SMP foams for endovascular intervention in lower extremity venous insufficiency.

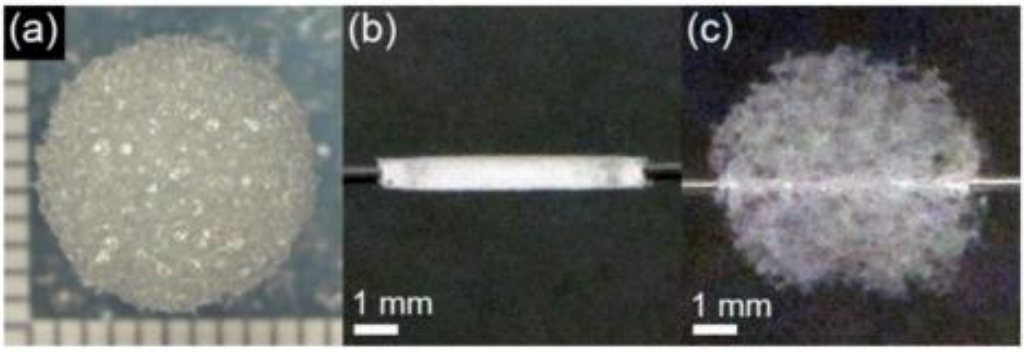

Figure 2. Shape memory polymer, a) Original shape b) temporary shape, and c) thermo-responsive shape recovery.

In a previous porcine study, a SMP foam was implanted in an aneurysm in the right carotid artery for up to 90 days. Scanning electron microscopy (SEM) images of the explanted sample showed that there was complete covering of the exposed foam with endothelial cells aligned parallel to the arterial blood flow, the surface exhibited a lack of mural thrombi, and the aneurysm was completely healed. Histology of the aneurysm revealed an increase in connective tissue and decreased swelling after treatment with the SMP foam. [12] In another *in vivo* vascular occlusion study, foams deployed into porcine hind limbs occluded within 90 to 128 seconds. [13] Thus, benefits of this treatment include rapid thrombus formation, high material compliance to accommodate collagen contraction and lesion shrinkage, and tissue scaffold-like behavior allowing for rapid cellular infiltration and stable long-term healing with minimal inflammation. Desired outcomes such as these may allow for reduced procedural and recovery times for the patient, as well as a reduced likelihood of recurrence.

Background on proposed research

A polyurethane SMP foam embolization device has been investigated for vascular occlusion. The vascular occlusion plug (VOP) is fabricated as a cylinder 10 or 20 mm in length and 8 mm in diameter (**Figure 3**). The SMP foam component can be categorized into two main groups based on device stiffness or pore size. Crosslink density, which affects the transition temperature, is controlled by altering the polyol component of the polyurethane and is divided into three different types: H40, H50, and H60, based on increasing the concentration of N,N,N′,N′-tetrakis(2-hydroxypropyl)ethylenediamine (HPED, H)). Thus, H60 has the highest crosslink density of the tested formulations and the longest expansion time.

The pore size is also broken down into three main types: small (500 μm), medium (1000 μm), and large (1500 μm). For this study, only large pore devices were analyzed. Upon contact with circulating blood, the foam diameter undergoes up to 8X expansion to effectively occlude large peripheral vessels with a single device. Based on the efficacy of the SMP foam for aneurysm treatment, it is hypothesized that it will perform in a similar manner for this application in the peripheral vasculature. To utilize these foams as VOPs, verification of safety and feasibility of use is required.

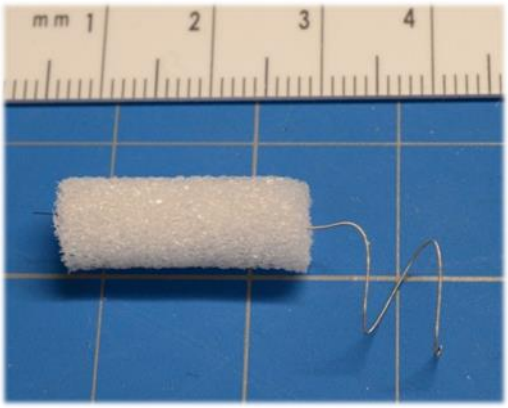

Figure 3. Vascular occlusion plug design. Each device is crimped to approximately 1 mm in diameter for non-invasive delivery through a catheter. The vascular plug design contains a distal platinum coil that anchors inside the vessel while the foam expands. Each device was made with 3 coil revolutions.

Research objectives

The objectives for current *in vitro* experiments are to perform verification tests that demonstrate (i) the safety and feasibility of the proposed VOPs and (ii) the validity of the device design criteria. Tests will be executed to monitor the following qualities: migration, working time, device friction, and particulate generation.

CHAPTER II

METHODS

Device migration

To ensure the SMP foam is retained within the treatment region, the VOPs are tested in a thin-walled silicone model of a human GSV maintained at 37°C under varying flow rates. To fabricate the silicone model, a tapered mold was machined out of Delrin® that is 6 cm in length. The model, made of Sylgard®, has a wall thickness of approximately 600 μm and tapers outward to mimic the physiology of the GSV (**Figure 4**). The lumen of the model tapers from an inner diameter of 5.8 mm up to 6.8 mm over the 6 cm length to cover a majority of the diameters seen in the thigh region of the GSV *in vivo*. The taper of the model is more than three times of that typically seen clinically to provide a rigorous model for testing device stability [14].

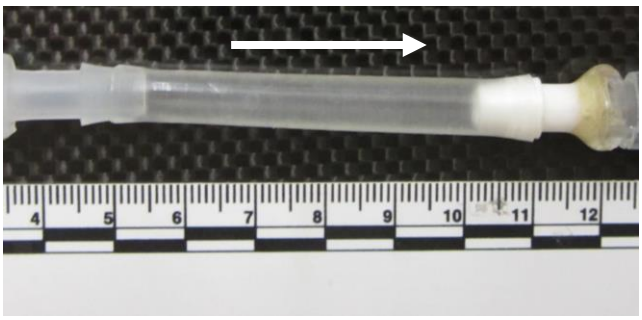

Figure 4. Tapered GSV lumen model. Thin-walled silicone model diameter tapers from 5.8 mm up to 6.8 mm over the length of 6 mm to represent the GSV diameters found in vivo. Direction of flow is indicated by the arrow.

To test the stability of the VOP, the devices (1 cm length) are delivered through a 5F catheter into a flow loop (**Figure 5**) and deployed through the catheter at the small end of the GSV model lumen. Each device is given time to fully expand under an initial flow rate of 40 mL/min, four times the GSV flow rate typically seen *in vivo* (10 mL/min). [15] The pump is then increased by 50 ml/min every minute until the device is seen to move. The device was tested until the peristaltic pump maxed out its capacity at 1000 ml/min. The last flow rate at which the device did not move more than 2 mm over a 1 minute time interval is recorded as the maximum flow rate of the device. A digital camera (Canon Power Shot SX230) is positioned over the lumen to capture an image for each time interval. Taking the average of 5 devices for each foam composition (H40, H50, and H60), the highest flow rate in which the device did not migrate was recorded. Images captured with the digital camera are used to monitor device migration.

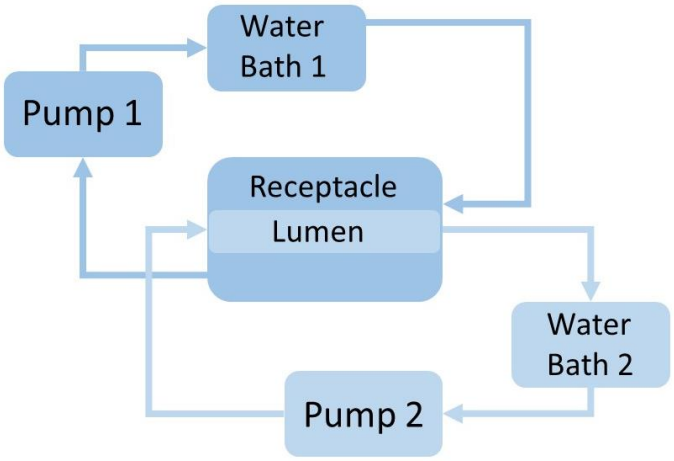

Figure 5. Schematic representation of the flow system components and flow directions.

Working time

Working time is defined as the time from when the device is first introduced into the catheter and the time at which the device can no longer be advanced through the catheter due to excessive foam expansion. Too short of a working time will prevent the device from being delivered through the catheter, and too long of a working time may result in excessive waiting times for the physician to verify total vessel occlusion, resulting in customer dissatisfaction and prolonged procedural times. To perform working time studies, a water bath equilibrated at 37°C is implemented such that the devices under investigation can be monitored without any radial restrictions. A stopwatch is used to monitor the time between device introduction into the water bath and the time at which the device reaches its original shape. Images of the device are taken using the digital camera at 30 second intervals for up to 15 minutes. ImageJ software (NIH, Bethesda, MD) is used to analyze the foam diameter at each time interval. Taking the original diameter, the percentage of original shape recovered over time is calculated. The average results of 5 devices for each foam composition (H40, H50, and H60) were then reported.

Device friction

The frictional force of the device retraction through the catheter is monitored to provide a measure of friction between the device and catheter walls as a function of time. For the device friction studies, a three-foot long piece of 0.010" diameter nitinol wire is glued to the proximal end of the VOPs. The devices are then introduced into the flow system shown in **Figure 5**, and the nitinol wire is attached to a MTS single-column tensile testing machine (Insight 30 Material Tester) to measure frictional force as the devices are retracted. Device retraction occurs at a rate of 50.8 mm/min through the catheter while the flow system flushes 37°C water through the GSV

model lumen at 40 ml/min. [15] A current clinical vascular occlusion device, the Amplatzer Vascular Plug (AVP, St. Jude Medical), is used for comparison of frictional forces. [16]

Particulate generation

Verification of the amount of particulate generation is used to ensure that the foam does not fracture or release particulates that could potentially cause emboli downstream from the device. After the flow system is equilibrated at 37°C, the VOP is crimped and loaded into a 5F catheter that is navigated to the middle of the GSV model lumen. A guidewire holds the VOP into the desired location of the lumen. The foam is instantly exposed to water to induce actuation. Using a peristaltic pump, the flow rate through the model lumen is increased to a maximum flow rate of 40 mL/min [15], providing a rigorous *in vitro* test for the VOP. A baseline particulate measurement is taken with just the catheter and guidewire in the model lumen prior to introducing the foam. Then, a sample is taken while the foam is in the catheter but not yet deployed. The final sample is obtained after the foam is deployed from the catheter. The outlet of the GSV model lumen is drained to capture all particulates and fluid that are flushed through the device.

The contents of each collection basin are then placed in a Chemtrac PC5000 (Chemtrac, Norcross, GA) particle counter. The particle counter outputs raw counts of the total number and size of particulates generated during each run. Particle counts from the SMP foams are then compared to the limits for small volume infusions stated in United States Pharmacopeia (USP) standard number 788 (**Table 1**) to characterize the foams on the basis of particulate generation.

Particulate data is collected for two distinct size ranges: > 10 μm and > 25 μm, as recommended by USP 788.

Table 1. USP 788 Acceptable limits for injection of parenteral infusion. [17]

Volume	Particle Size Limit	Acceptable Number of Particulates
>100 ml	>10 μm	25/ml
>100 ml	>25 μm	3/ml

CHAPTER III

RESULTS

Device migration

Each H40, H50, and H60 device was deployed through a 5F catheter with the coil entering the small end of the GSV model lumen first. Taking the average of 5 devices for each foam composition, the highest flow rate in which the device did not migrate was recorded. Results show that the devices remained stable up to 90 times the average GSVflow rate of 10 ml/min [15] (**Figure 6**).

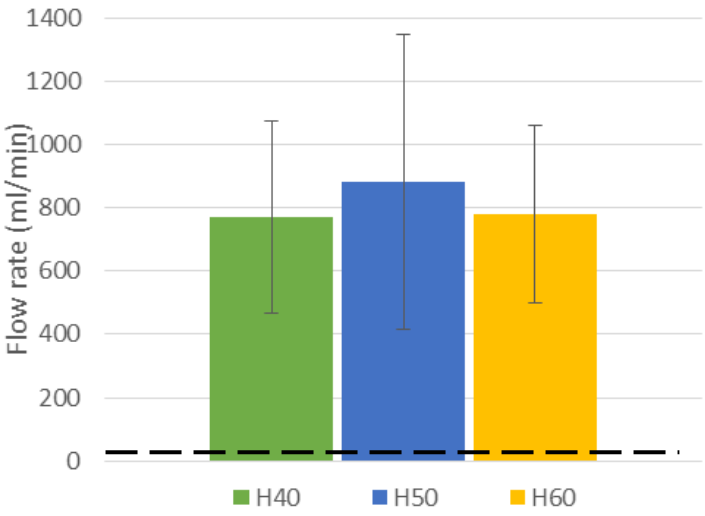

Figure 6. Flow rate at which devices migrated at least 2 mm in 1 minute. Dashed line indicate average flow rate in GSV.

When comparing the three foam compositions, the formulations produced similar results. In the final device design, the distal platinum coil serves as an anchor for the device. The coil

revolutions have a larger radius than the foam and provides a stronger radial force than the foam. Thus, the foam composition did not have as large of an effect on device migration as the size of the coil revolutions. Future studies could be done to observe how the coil diameter and number of revolutions effect migration.

Working time

A study was carried out to analyze the effects of crosslink density (HPED (H) concentration) on working time. **Figure 7** shows the percent shape recovery over time after submersion with H40, H50, and H60 large pore foams.

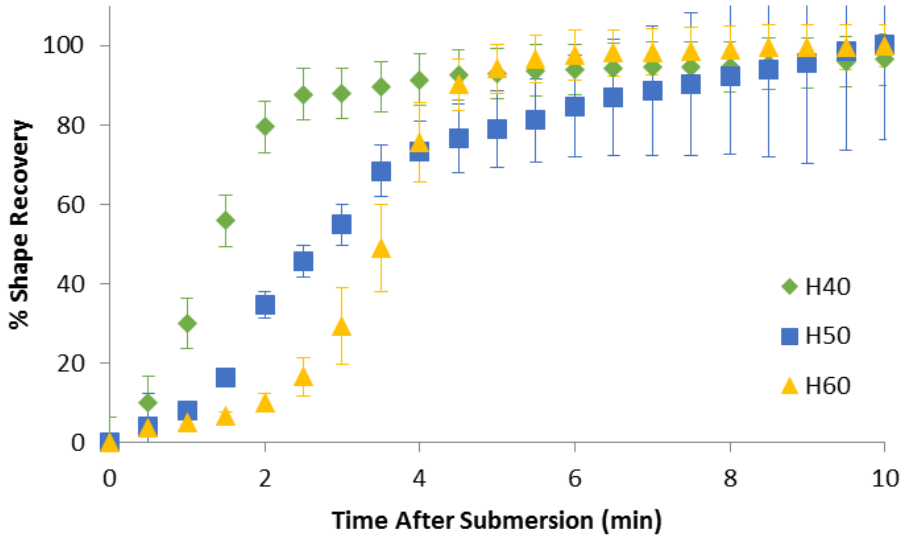

Figure 7. Shape recovery of large pore foams with varied amounts of HPED.

All formulations experience 100% shape recovery after 10 minutes. H60 has the highest crosslink density, resulting in a higher glass transition temperature than that of H50 and H40 foams, which results in slower water plasticization and subsequent expansion. Therefore, H60

experiences the slowest rate of expansion after submersion. In contrast, H40 has the fastest expansion rate due to its reduced crosslink density. This data provides a baseline for understanding how much time a physician has to place the device before complete expansion. Combining these results with device friction measurements, we can quantify the time that a physician has before the radial force from the foam on the catheter is too great to continue the procedure.

Device friction

Device friction can be directly correlated to working time. Hypotheses can be drawn from the trends of large pore foam-based devices and applied to other pore sizes based on the correlation between device friction and working time. As shown in **Figure 8**, the H40 foam formulation experiences a peak force between 2-4 minutes, while the H60 foams have a peak force at 8 minutes. This result is due to the slower expansion rate with increased HPED content and correlates with the working time study results.

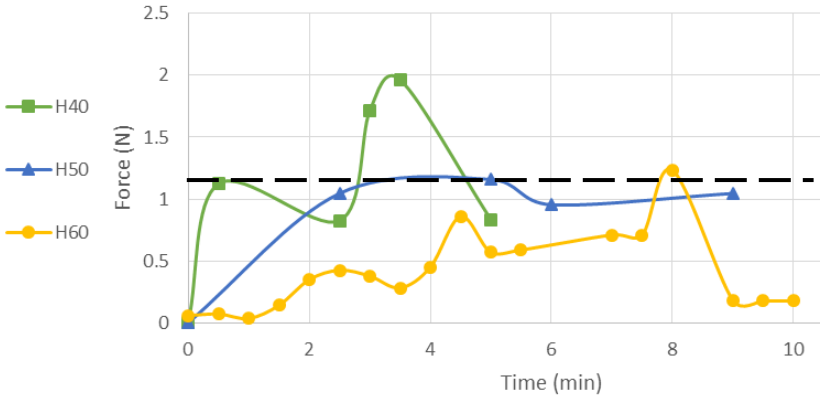

Figure 8. Device friction for H40, H50, and H60 foam compositions, measured using the MTS. Dashed line indicates the friction force of the commercially available AVP device.

After complete expansion, all devices require less than 2.10 N of force to pull through a catheter. This result indicates that a physician only requires 2.10 N to deploy the device regardless of how long the device remains inside the catheter. As a comparison, the AVP, a current device used for a similar application, underwent the same testing procedure. The 14 mm AVP device was used in an 8F catheter, as recommended by the supplier, and pulled for 1 minute. There is not a shape memory element to the AVP device, and radial force is therefore constant throughout. The test results in a force of 1.12 N. (**Figure 8**) Based on this information, the H40 formulation provides almost twice the delivery resistance as its competitors. H50 and H60 formulations reach maximum forces at 4 and 8 minutes, respectively. H50 produces the lowest maximum force at 1.58 N within the desired window. H60 reaches its peak several minutes beyond the maximum desired window of time. This result indicates a delayed expansion which would extend the time to complete the procedure. Based on discussion with clinicians, the target working time for this device is 3-5 minutes. The results from this study indicate that the SMP foam-based VOPs could be successfully delivered in this time frame without getting stuck in the catheter.

Particulate generation

This test is employed to identify worst case scenarios for particulate generation; thus, 2 cm long foams were used to collect particulates. The particulates generated during deployment for each type of foam was recorded. Data collected when the foam was not in the flow loop is used as a baseline to which the data was normalized (**Figure 9**). There are minimal particulates generated while the device is still within the catheter (data not shown). While the device is still tightly crimped, it is unlikely to produce particulates. Most of the particulates were counted after the

device was deployed. The data suggests that the act of pushing the foam out of the catheter generates the majority of the particulates.

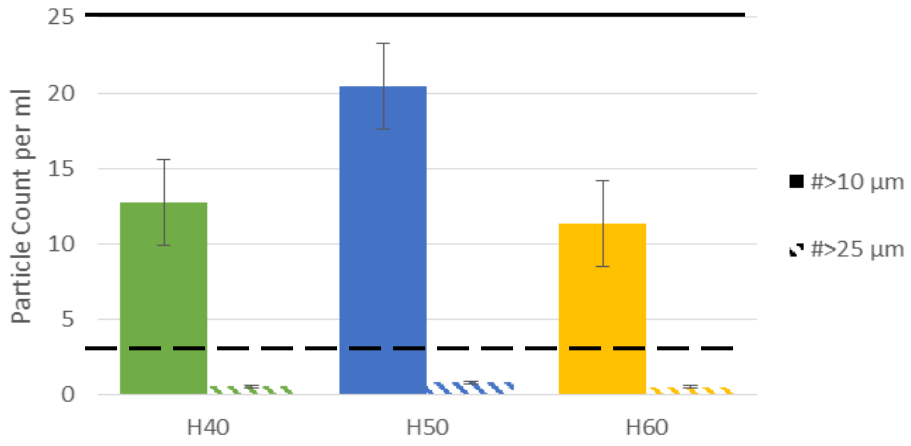

Figure 9. Particulate counts per mL after deployment. Results were normalized with baseline particle counts. Solid line indicates acceptance criterial for particles greater than 10 µm. Dashed line indicates acceptance criteria for particles greater than 25 µm.

The number of particles greater than 10 µm were less than 25 per milliliter, and the number of particles greater than 25 µm were less than 3 per milliliter for all foam formulations. Between the three formulations, H60 produced the lowest amount of particulates. This result could be due to its increased stiffness while in the catheter before the polymer is completely plasticized by the water within the flow loop.

CHAPTER IV

CONCLUSION

This study expanded on the verification of a previously proposed peripheral embolization design by quantifying the stability, working time, device friction, and particulate generation of the large pore device formulation. These devices show promise in peripheral applications requiring increased stability in rapid flowing vessels. The excellent shape memory properties of these materials allows the device to be deployed in minutes. The unconstrained working time results give a baseline for understanding the expansion rate of different foam formulations to enable rational design of a foam formulation to achieve desired working times.

Device friction provides data that is relevant to clinical implementation of the device design and verifies the necessary working time. This information will provide physicians accurate information regarding the time frame in which they have to place the device in the desired location before complete expansion occurs. To conform to health and safety standards of an implantable product, particulate generation must be monitored. Knowing which formulations produce higher particulates is necessary for future product approval and making informed decisions of appropriate foam formulations. All of the measured characteristics will aid in the design and optimization of novel SMP-based peripheral embolization devices.

REFERENCES

[1] A. G. Winer, N. H. Chakiryan, R. P. Mooney, D. Verges, M. Ghanaat, A. Allaei, L. Robinson, H. Zinn and E. K. Lang. 2014. Secondary pelvic congestion syndrome: description and radiographic diagnosis. The Canadian journal of urology 21 (4): 7365-8.

[2] D. Margolisa,b,c, W. Bilkerb,c, J. Santannab,c and M. Baumgartenc,d, 'Venous leg ulcer: Incidence and prevalence in the elderly', *Journal of the American Academy of Dermatology*, vol. 46, no. 3, pp. 381-386, 2002.

[3] J.T. Hobbs, 'The pelvic congestion syndrome', *British Journal of Hospital Medicine*, vol. 43, no. 3, pp. 200-206, 1990.

[4] Callam MJ. Epidemiology of varicose veins. Br J Surg 1994; 81:167–173.

[5] Robinson, J. Courtland. "Chronic Pelvic Pain." *Current Opinion in Obstetrics and Gynecology 5* (1993): 740-43.

[6] Mclafferty, Robert B., Joanne M. Lohr, Joseph A. Caprini, Marc A. Passman, Frank T. Padberg, Thom W. Rooke, Ruth L. Bush, Aamir A. Zakaria, William R. Flinn, Bo G. Eklof, Michael C. Dalsing, Steven J. Markwell, and Thomas W. Wakefield. "Results of the National Pilot Screening Program for Venous Disease by the American Venous Forum." *Journal of Vascular Surgery* 45, no. 1 (2007).

[7] "Venous System Anatomy." Vein Information. Accessed January 14, 2016. http://www.nazveincenter.com/venous.html.

[8] Oguzkurt L. Endovenous laser ablation for the treatment of varicose veins. Diagnostic and interventional radiology. 2012;18(4):417-22. Epub 2011/12/30. doi: 10.4261/1305-3825.DIR.5248-11.0. PubMed PMID: 22205579.

[9] Bhutia, Sherab G., Arun Balakrishnan, and Timothy Lees. "Varicose Veins." *Perioperative Practice* 18, no. 8 (August 2008): 346-52.

[10] Dwerryhouse S, Davies B, H arradine K, Earnshaw JJ. Stripping the long saphen- ous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. J Vasc Surg 1999; 29:589–592.

[11] A. J. Lopez, “Female Pelvic Vein Embolization: Indications, Techniques, and Outcomes,” *CardioVascular and Interventional Radiology Cardiovasc Intervent Radiol*, pp. 806–820, 2015.

[12] J. Rodriguez, Y. Yu, M. Miller, T. Wilson, J. Hartman, F. Clubb, B. Gentry and D. Maitland, 'Opacification of Shape Memory Polymer Foam Designed for Treatment of Intracranial Aneurysms', *Annals of Biomedical Engineering*, vol. 40, no. 4, pp. 883-897, 2011.

[13] J. Rodriguez, M. Miller, A. Boyle, J. Horn, C. Yang, T. Wilson, J. Ortega, W. Small, L. Nash, H. Skoog and D. Maitland, 'Reticulation of low density shape memory polymer foam with an in vivo demonstration of vascular occlusion', *Journal of the Mechanical Behavior of Biomedical Materials*, vol. 40, pp. 102-114, 2014.

[14] Navarro TP, Delis KT, Ribeiro AP. Clinical and hemodynamic significance of the greater saphenous vein diameter in chronic venous insufficiency. Archives of surgery. 2002;137(11):1233-7. Epub 2002/11/07. PubMed PMID: 12413308.

[15] Gusic RJ, Myung R, Petko M, Gaynor JW, Gooch KJ. Shear stress and pressure modulate saphenous vein remodeling ex vivo. Journal of biomechanics. 2005;38(9):1760-9. Epub 2005/07/19. doi: 10.1016/j.jbiomech.2004.10.030. PubMed PMID: 16023463.

[16] "AMPLATZER™ Vascular Plug." AMPLATZER™ Family of Vascular Plugs. 2016. Accessed April 03, 2016. http://sjm.com/professional/products/vas/peripheral-vascular-embolization/embolization-devices/amplatzer-family-of-vascular-plugs#overview.

[17] United States Pharmacopeia (USP) 788: Particulate Matter in Injections. The United States Pharmacopeial Convention 2011.

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