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In vitro performance of a shape memory polymer foam-coated coil embolization device

Anthony J. Boyle[a,b], Mark A. Wierzbicki[a,b], Scott Herting[a], Andrew C. Weems[a], Adam Nathan[a], Wonjun Hwang[b], Duncan J. Maitland[a,*]

[a] *Department of Biomedical Engineering, Texas A&M University, College Station, TX, USA*
[b] *Shape Memory Medical, Inc., College Station, TX, USA*

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ABSTRACT

Intracranial saccular aneurysm treatment using endovascular embolization devices are limited by aneurysm recurrence that can lead to aneurysm rupture. A shape memory polymer (SMP) foam-coated coil (FCC) embolization device was designed to increase packing density and improve tissue healing compared to current commercial devices. FCC devices were fabricated and tested using *in vitro* models to assess feasibility for clinical treatment of intracranial saccular aneurysms. FCC devices demonstrated smooth delivery through tortuous pathways similar to control devices as well as greater than 10 min working time for clinical repositioning during deployment. Furthermore, the devices passed pilot verification tests for particulates, chemical leachables, and cytocompatibility. Finally, devices were successfully implanted in an *in vitro* saccular aneurysm model with large packing density. Though improvements and future studies evaluating device stiffness were identified as a necessity, the FCC device demonstrates effective delivery and packing performance that provides great promise for clinical application of the device in treatment of intracranial saccular aneurysms.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH), bleeding into the subarachnoid space in the brain due to intracranial aneurysm rupture, is marked by significant morbidity and mortality rates. Incidence of aSAH occurs in 9.7–14.5 out of every 100,000 adults in the United States where at least 25% of patients die and approximately 50% of survivors are left with persistent neurological deficit [1]. Standard endovascular treatment of intracranial saccular aneurysms involves the delivery and implantation of embolization coil devices into the aneurysm to promote thrombus formation, tissue healing, and neointimal growth across the aneurysm neck [2]. However, aneurysm recurrence after endovascular coiling occurs in 20.8% of cases, requiring retreatment in 10.3% of cases [3]. Diminished packing density, which is the ratio of implanted device volume to aneurysm volume, as well as poor or unstable thrombus organization have been associated with increased recurrence, among other mechanisms [4–6]. Polymer-embedded coils, including poly(glycolic acid) and hydrogel-coated coils, were introduced to increase packing density or improve thrombus organization but have not resulted in significantly improved long-term clinical outcomes [7,8]. Therefore, the need still exists for an embolization device capable of increasing packing density and improving thrombus organization.

Shape memory polymer (SMP) foams have been proposed as an advantageous biomaterial for endovascular embolization applications due to their shape recovery capability and interconnected, large surface area porosity [9–11]. Thermo-responsive SMP foams are capable of being programmed to hold a temporary shape until stimulated by heat, at which time they recover their original shape [12,13]. SMP foams have been reported with increased angiographic occlusion, more advanced healing marked by mature connective tissue, and a thicker neointima layer compared to bare metal coils in porcine saccular aneurysm models [9,10]. Though both SMP foams and hydrogels exhibit volume-filling capability, SMP foams exhibit interconnected pores with diameters in the hundreds of microns, compared to hydrogel pore sizes less than 10 μm in diameter [12,14]. This interconnected porosity of the SMP foams acts as a scaffold for blood flow, thrombus formation, and tissue healing throughout the material volume [9,10].

A prototype embolization device was previously designed using radially expanding SMP foam over a nickel–titanium (nitinol) and platinum wire backbone and demonstrated to have

Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; FCC, foam-coated coil; SMP, shape memory polymer.

* Corresponding author.
E-mail address: djmaitland@tamu.edu (D.J. Maitland).

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stable angiographic occlusion and clot formation in a porcine saccular aneurysm model [11]. However, the device exhibited some limitations including restricted working time, which is the time allowed to deliver and reposition the device, and excessive stiffness that increased packing difficulty. To address these limitations, a SMP foam-coated coil (FCC) embolization device was designed utilizing SMP foam over a platinum alloy coil with nitinol core wire. The FCC device is designed to interface with a delivery wire and electrolytic detachment system similar to systems previously used with commercial devices. This study evaluated selected performance and biocompatibility characteristics of the implant device, including ease of delivery and working time through physiologically simulated tortuous flow models and cytocompatibility, to assess feasibility of the device for clinical treatment of intracranial saccular aneurysms.

2. Materials and methods

2.1. Device fabrication

The foam-coated coil (FCC) device is composed of shape memory polymer (SMP) foam placed over a platinum–tungsten coil with nickel–titanium (nitinol) core wire. Trimethyl-1,6-hexamethylene diisocyanate, 2,2,4- and 2,4,4- mixture (TMHDI, TCI America Co., Portland, OR), *N*,*N*,*N*′,*N*′-Tetrakis(2-hydroxypropyl)ethylenediamine (HPED, 99%, Sigma-Aldrich Co., St. Louis, MO), triethanolamine (TEA, 98%, Sigma-Aldrich Co., St. Louis, MO), and deionized (DI) water (> 17 MΩ cm purity) were used as received to synthesize SMP foam as previously reported by Hasan et al. [15]. Helical shaped coil assemblies composed of nickel–titanium wire inserted through the lumen of a platinum–tungsten coil were used as received (Heraeus, Hanau, Germany). For each device, SMP foam was cut into cylinders using a 1 mm diameter biopsy punch, and the coil assembly was threaded through the foam cylinder axis. A single leading coil loop was left uncoated by SMP foam at the distal end. The SMP foam cylinder was saturated with a 4 vol% solution of TMHDI, HPED, and TEA in tetrahydrofuran (THF, anhydrous, EMD Millipore Co., Darmstadt, Germany) and then cured by temperature ramp up to 120 °C at 20 °/h and held at 120 °C for 2 hr. The resulting SMP coating adheres the foam to the coil. Under sonication, the devices were cleaned using reverse osmosis (RO) water and isopropyl alcohol (IPA) and then dried at 100 °C for 12 h under vacuum. SMP foam was heated to approximately 100 °C and radially compressed around the coil using a SC250 stent crimper (Machine Solutions Inc., Flagstaff, AZ) to 0.016 ± 0.001 in. (0.41 ± 0.03 mm) in diameter. FCC devices were fabricated with a helical diameter of 6 mm and straight length of 10 cm (6 × 10), a helical diameter of 4 mm and straight length of 6 cm (4 × 6), or a straight length of 20 cm (0 × 20). The devices were placed into a 0.022 in. (0.56 mm) inner diameter (ID) polytetrafluoroethylene (PTFE) tubing for storage and use as an introducer sheath.

For tests using microcatheters, devices were attached to delivery wires. Delivery wires were removed from various sized GDC® embolization coils (Stryker Co., Kalamazoo, MI) and attached to the proximal (clinician side) end of the FCC using 203A-CTH-F UV-cure epoxy (Dymax Co., Torrington, CT). Fig. 1 shows a foam-coated coil device before and after radial compression.

2.2. Shape recovery

SMP foam expansion rate was characterized in an aqueous environment. FCC devices, 6 × 10 size, were straightened and submerged in 37 ± 0.2 °C RO water. Images were taken at 1 min intervals to 10 min total time submerged and at 5 min intervals to 30 min total time submerged. Foam diameter was measured at five different locations along each sample length for each time point using ImageJ software, version 1.50 (NIH, Bethesda, MD).

2.3. Microcatheter tip deflection

Change in microcatheter tip angle during device deployment was measured to assess device stiffness. A 0.022 in. (0.56 mm) ID microcatheter (Stryker Co., Kalamazoo, MI) was steam shaped into a 110° angle with a 1 mm radius of curvature and secured in place. The starting tip angle was measured prior to each sample test from the image using ImageJ software.

Tip deflection was measured for FCC devices, 6 × 10 size, with delivery wire and GDC-18 2D devices (Stryker Co., Kalamazoo, MI) as controls. Samples were introduced into the microcatheter hub and advanced until the device distal tip was 2 cm proximal to the microcatheter tip. The delivery wire was clamped in an Insight 30 material tester system (MTS) (MTS Systems Co., Eden Prairie, MN) proximal to the microcatheter hub. The MTS advanced the device 0.5 cm through the microcatheter, and an image was taken. This was repeated until 5 cm was deployed out of the microcatheter. The tip angle was measured in each test image using ImageJ software and subtracted from the starting tip angle in order to calculate the tip deflection angle.

2.4. Ease of delivery and working time

Ease of delivery and working time were evaluated on FCC devices through a tortuous path with physiologically simulating flow. Tubing with 2.38 mm ID was secured into a tortuous path with radii of curvature and curve angles based on a model reported by Sugiu et al. [16] and as shown in Fig. 2. Deionized (DI) water was heated and pumped through the tubing at average flow rate of 44 ± 2 mL/min. Flow rate was calculated by matching the *in vitro* system Reynold's number to *in vivo* measurements of the middle cerebral artery reported by Reymond et al. [17]. Inlet and outlet temperatures were maintained at 37 ± 1 °C. A 0.022 in. (0.56 mm) ID microcatheter was passed through the tortuous path until the microcatheter tip was past the tortuous path and held in 6.35 mm ID tubing. DI water was flushed through the microcatheter at 0.4 mL/min using a syringe pump.

Ease of delivery was assessed for FCC devices, 6 × 10 size, attached to delivery wires with GDC-18 2D devices as controls. Devices were introduced into the microcatheter, and a timer was started. Devices were then advanced until the distal tip of the device was flush with the start of the tortuous path. The delivery wire was secured vertically and clamped 30 cm proximal to the microcatheter hub using a MTS with 50 N load cell. Delivery force, the force experienced by the clinician during a procedure, was measured as the device was advanced 29 cm at 14.5 cm/min until the device tip was flush with the microcatheter tip.

Working time was then assessed for FCC devices following ease of delivery testing. The delivery wire was re-clamped in the MTS 6 cm proximal to the microcatheter hub. The delivery force was then measured as the device was deployed 5 cm out and retracted 5 cm at 10 cm/min to simulate repeated device repositioning. The deploy/retract cycle was repeated until an end point was observed: a successful retraction after the total submersion time exceeded 10 min, or mechanical damage was observed during a retraction cycle. A submersion time threshold of 10 min was chosen based on SMP foam shape recovery testing. Once an end point was reached, the total submersion time was recorded as the working time.

2.5. Particle counts during delivery

Particle counts and sizes were characterized from fluid collected during simulated repositioning cycles. DI water was passed

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