Published in final edited form as:

J Clin Neurosci. 2019 March ; 61: 153–159. doi:10.1016/j.jocn.2018.10.103.

Reconstructing patient-specific cerebral aneurysm vasculature for in vitro investigations and treatment efficacy assessments

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Abstract

Perianeurysmal hemodynamics play a vital role in the initiation, growth and rupture of intracranial aneurysms. In vitro investigations of aneurysmal hemodynamics are helpful to visualize and measure blood flow, and aiding surgical planning approaches. Improving in vitro model creation can improve the feasibility and accuracy of hemodynamic investigations and surgical planning, improving clinical value. In this study, in vitro models were created from three-dimensional rotational angiography (3DRA) of six patients harboring intracranial aneurysms using a multi-step process involving 3D printing, index of refraction matching and silicone casting that renders the models transparent for flow visualization. Each model was treated with the same commercially-available, patient-specific, endovascular devices (coils and/or stents). All models were scanned by synchrotron X-ray microtomography to obtain high-resolution imaging of the vessel lumen, aneurysmal sac and endovascular devices. Dimensional accuracy was compared by quantifying the differences between the microtomographic reconstructions of the fabricated phantoms and the original 3DRA obtained during patient treatment. True-scale in vitro flow phantoms were successfully created for all six patients. Optical transparency was verified by using an index of refraction matched working fluid that replicated the mechanical behavior of blood. Synchrotron imaging of vessel lumen, aneurysmal sac and endovascular devices was successfully obtained, and dimensional errors were found to be $O(100\ \mu\text{m})$. The creation of dimensionally-accurate,

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CONTRIBUTORS: All authors made significant contributions to the conception, design, implementation, data collection and analysis, and drafting of the manuscript.

COMPETING INTERESTS: No author has competing interests to report.

ETHICS APPROVAL: Ethics approval was received from the institutional review board.

PROVENCANCE AND PEER REVIEW: Not commissioned; externally peer reviewed.

DATA SHARING STATEMENT: No further data available for sharing.

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optically-transparent flow phantoms of patient-specific intracranial aneurysms is feasible using 3D printing technology. Such models may enable in vitro investigations of aneurysmal hemodynamics to aid in treatment planning and outcome prediction to devise optimal patient-specific neurointerventional strategies.

Keywords

Aneurysm; Blood Flow; Computational Fluid Dynamics; Micro-CT; 3D Printing

INTRODUCTION

Initiation, growth and subsequent rupture of intracranial aneurysms are thought to be significantly influenced by vascular anatomy and hemodynamics^{1,2}. Endovascular treatments typically entail either (i) filling the aneurysmal volume with metal coils, or (ii) diverting blood flow away from the aneurysmal sac using flow diverters. In either case, the objective is to encourage thrombosis of blood within the aneurysm, thereby isolating it from vascular blood flow and hopefully, preventing rupture^{3,4}. Understanding hemodynamics in the perianeurysmal region, prior to and following treatment is critical to developing improved treatment protocols and strategies towards improving outcomes.

The precise anatomic configuration of coils or flow diverters after deployment is required to accurately calculate peri- and intra-aneurysmal hemodynamics after treatment⁵. However, endovascular device geometry and deployed configuration is highly complex and traditional imaging modalities lack the resolution to image the coil mass / flow diverter in detail in vivo. Moreover, the location and intricacies of cerebral vasculature limit direct observation and measurement of blood flow as well. Thus, information obtained via imaging modalities such as computerized tomography (CT), 3D rotational angiography (3DRA), ultrasound and magnetic resonance imaging (MRI)^{6,7} provide estimates, but are not definitive to be employed in in vitro and in silico investigations to elucidate aneurysm hemodynamics and for surgical planning purposes.

An alternative approach to understanding endovascular device configuration in conjunction with its effect on blood flow is to use in vitro techniques. In vitro testing relies on constructing flow phantoms for measuring and visualizing endovascular device deployment. Additionally, true-scale (1:1) patient-specific models are critical in surgical planning and determining treatment approaches such as the need for complementary flow diverter support along with coils^{8–10}. Moreover, the success of other research modalities such as in vivo and in silico approaches are dependent upon each other – hemodynamic data from in vivo measurements are applied as patient-specific boundary conditions for in silico simulations, which is turn is validated by in vitro testing^{11,12}. However in vitro techniques can only be exploited when provided with high fidelity, optically transparent patient-specific models at true 1:1 scale. Several previously reported in vitro studies fall short of their utility due to lack of optical properties, non-compatible materials and scaling limitations^{13–16}. Thus, optimizing in vitro approaches will not only enhance bench top hemodynamic

investigations, but also have a ripple effect through other modalities, ultimately improving our understanding of hemodynamics.

In this study, we describe a methodology for creating dimensionally-accurate, patient-specific, and optically-transparent in vitro models of intracranial aneurysms and the measurement technique used to ensure the anatomical accuracy of the final manufactured model to the original patient scan. Further, we demonstrate the implementation of the methodology for creating six patient-specific models with tolerances on the order of 100 μm for conducting in vitro investigations of endovascular interventions.

METHODS

Intracranial vasculature imaging data

Six patients undergoing endovascular aneurysm treatment were enrolled in the study which was approved by the institutional review board. Three-dimensional rotational angiography was obtained just prior to treatment (coils and/or stents) and used to create patient-specific anatomic models.

Segmentation of patient-specific aneurysm geometry

Three-dimensional reconstructions of the lumen were created by segmenting images with the Vascular Modeling Toolkit (<https://www.vmtk.org>) software. Surface smoothing was performed on the raw lumen reconstruction to obtain smooth vessel geometry while still preserving regions of interest such as constrictions. Vasculature immediately surrounding the aneurysm was isolated and converted to stereolithography (STL) format for further processing.

Creating in vitro aneurysm models

To enable 3D printing, segmented STLs were modified to incorporate a base and supports. All models were 3D-printed using Flash Forge Creator Pro (Flashforge, Rowland Heights, California, USA) printers using 1.75 mm PolyLactic Acid filament (MakerBot Industries, LLC, Brooklyn, New York, USA) with a resolution of 100 μm . All models were printed at 1:1 scale with respect to patient vasculature. After printing, support material was removed and the aneurysm models were smoothed by sanding and application of smooth glossy coating (XTC-3D, Smooth-On, Macungie, Pennsylvania, USA); care was taken to restrict the application of the smooth coating to a single, thin layer to avoid modifying the diameter of the models.

Smooth 3D-printed aneurysm replicas were then cast in silicone rubber (OOMOO 25, Smooth-On, Macungie, Pennsylvania, USA). After curing, the silicone rubber was separated into halves (or three parts for more complex geometry) by a plane cut following the centerline of the aneurysm and vascular geometry and the 3D-printed replicas were removed. The two silicone rubber halves were joined back together, creating a “model negative”. Water-soluble optical wax (Freeman Optical Soluble Wax, Freeman Manufacturing and Supply Company, Avon, Ohio, USA) was melted and poured into the silicone rubber negative, thereby forming a wax “positive”.

The water-soluble wax positive was placed in an acrylic casting box. An optically-transparent silicone elastomer (Sylgard 184, Dow Corning Corp., Auburn, Michigan, USA) was chosen for the final model creation due to its optical properties. Sylgard 184, a two-part mix, was degassed under vacuum for several minutes prior to casting in order to eliminate entrapped air bubbles. The degassed silicone mixture was then slowly poured into the casting box and allowed to cure at room temperature for 48 hours. Upon curing, the silicone cast with the wax positive was immersed in water at room temperature to dissolve the water-soluble wax positive, leaving behind the patient-specific, optically-transparent in vitro flow phantom of the vessel lumen and aneurysm sac.

Synchrotron X-ray microtomographic imaging and geometry reconstruction

All silicone models were imaged by a parallel and monochromatic X-ray beam at the European Synchrotron Radiation Facility (<https://www.esrf.eu>) in Grenoble, France, as described previously⁸. The X-ray radiation transmitted through the model was converted into visible light by a YAG 2000 scintillator and subsequently imaged by a digital camera (PCO Edge, PCO, Kelheim, Germany). The model was rotated 360° with respect to an axis perpendicular to the beam and centered on it, so that the attenuation of the beam by the silicone in the model was recorded for every angular position and deconvoluted into a 3D distribution of volumes with different attenuation coefficients (silicone or air) that conform to a model of the flow phantom. The resulting spatial resolution was between 12 µm and 13 µm in all three directions.

Surfaces were segmented from the 3D stack of the volume obtained from the image deconvolution using ImageJ (<https://imagej.nih.gov>). Lumen geometries reconstructed from the synchrotron scans were compared to the original lumen geometries segmented from the patient-specific 3DRA to determine deviations between the silicone models as manufactured and the original patient vasculature. Comparison of original and in vitro lumen geometries was performed in CloudCompare (www.danielgm.net/cc/) using an iterative closest point (ICP) algorithm.

Treating in vitro models

After initial synchrotron X-ray microtomographic scans of the untreated models, each phantom was treated by experienced neurointerventionalists with the same patient-specific, commercially-available endovascular devices (coils and/or stents) in the same sequence as the actual patient's treatments. A second set of Synchrotron scans were then performed to obtain the geometry and orientation of the endovascular devices. The scanning energy used in this second series of scans (treated models) was varied with respect to the first series of scans (untreated models) in order to capture the endovascular devices accurately and reduce beam-hardening effects.

RESULTS

Aneurysm model fidelity

Comparison of patient anatomical reconstructions from 3DRA and manufactured physical flow phantoms reconstructions from the synchrotron X-ray microtomographic images

revealed excellent agreement (Figure 1). Complex features such as vessel curvature, aneurysmal neck, aneurysmal sac and aneurysmal dome morphologies were successfully replicated for all six patients. Superimposed lumen geometries from multiple virtual patient models and physical flow-phantom images are shown in Figure 2. Median error between patient scans and in vitro models ranged from 70 μm - 280 μm , with an average interquartile range (IQR) of 226 μm (Table 1 and Figure 3).

Endovascular treatment

Each model was successfully treated with coils and/or stents. The treated models were scanned in the synchrotron and the 3D endovascular device microstructure was reconstructed with the same deconvolution method described above. Virtual models with the reconstructed coils were created for multiple investigations (Figure 4) ⁸.

DISCUSSION

Understanding perianeurysmal hemodynamics is paramount for devising efficient patient-specific treatment strategies and progress towards predictive capabilities for outcomes^{1,2,10}. Current imaging modalities provide insufficient resolution to capture the complexities of deployed endovascular device configurations. This information is essential to determining hemodynamic metrics such as wall shear stress, wall shear stress gradient and flow in and out of the aneurysmal sac, which have been strongly linked to predicting treatment outcomes^{17,18}. Despite technological advancements in clinical devices, endovascular treatment carries a high failure rate of 34%, with significant associated morbidity and mortality^{4,19,20}. In vitro investigations can play a vital role in providing a platform to characterize and optimize endovascular interventions.

Creation of adequate in vitro flow phantoms entails adhering to multiple specifications: (i) patient-specific: accurately replicate the complex anatomy of the patient, (ii) dimensional consistency: maintain a uniform scaling across all dimensions in the model so the lumen diameter, length, surface roughness and radius of curvature matches the actual patient vasculature across the entire model at true (1:1) scale, (iii) optical access: allow visible light to transmit through without significant refraction or diffraction, so that the endovascular device inside the model can be completely visualized, (iv) scalability: manufacturable in large enough numbers, both in cost and time required to produce the models required in the study to go beyond the single case proof of concept.

The advent of modern rapid prototyping techniques such as 3D printing has enabled development of state-of-the-art procedures for in vitro model creation. Multiple modalities incorporating rapid prototyping techniques have been used previously for creation of in vitro models. However many of them do not satisfy one or more of the criteria described above^{9,10,21–23}.

In this work, we have successfully created 3D-printed models of six patient geometries at a true (1:1) scale, at a resolution of 100 μm and with excellent agreement and low error compared to the in vivo 3DRA. The mean geometrical error was $O(100 \mu\text{m})$, which is comparable to the resolution of 3D printing. While standard deviation values are provided

for completeness, IQR is a more relevant metric to assess the error, as the error distribution was right-skewed. A mean IQR of 226 μm indicates excellent fidelity in these patient models. While the error distribution was higher for P3 (1st quartile 140 μm , 3rd quartile 450 μm , IQR 310 μm), the geometry of this particular case was extremely fragile and prone to breaking prior to silicone casting, and should be considered the upper limit of error for this method.

A unique feature of our study is the endovascular treatment of the in vitro flow phantoms with the same patient-specific endovascular devices (coil and/or stents) from which the phantom was created, seeking to replicate operative coil deployment and aneurysm packing density and high-resolution synchrotron scanning (spatial resolution 12 μm) of these endovascular devices deployed in the aneurysmal region, which has several advantages over in vivo imaging (Figure 5). Firstly, since the synchrotron microtomographic beam is monochromatic with a very low wavelength, the typical beam hardening artifacts observed when imaging aneurysmal coils with conventional microtomography or CT are substantially reduced. Additionally, since the digital camera is placed as close as possible to the in vitro aneurysm model in absorption mode (a few mm away), the coil or flow diverter microstructure and configuration is captured in great detail (Figure 6) due to the difference in X-ray absorption between coils and the surrounding silicone model. This level of detail permits confirmation of anatomical accuracy of the model as well as visualization of the endovascular devices.

Obtaining dimensionally-accurate reproductions of patient-specific geometries can open new avenues of research and clinical translation. The extremely small size and complex nature of the intracranial vasculature previously inhibited accurate reproduction, leading to creation of models multiple times the actual size^{14,15,23}. While dimensional similarity for flow measurements may be argued in favor of such large-scale models, it is impossible to test and implement endovascular procedures in vitro using real, commercially-available coils and stents at that scale. Moreover, conducting ex vivo and in vitro experiments with actual blood²⁴ would not be possible due to the lack of dynamic similarity (Reynolds number and Womersley numbers cannot be realistically matched at scaling factor larger than approximately 1.5) and the non-Newtonian hemodynamics in very low speed (recirculation) regions that leads to thrombus formation in scale up models where velocity scales down (to maintain Reynolds similarity). Thus, in vitro models that reproduce the intracranial vasculature anatomy at 1:1 scale have significant advantages for fundamental and translational studies of aneurysmal hemodynamics and endovascular treatment, as well as providing information (geometry, coil configuration) for CFD simulations^{2,25,26}.

Experimental approaches to flow visualization in vitro, such as particle image velocimetry, particle tracking velocimetry and planar laser induced fluorescence, require that the refractive indices of the working fluid and the in vitro model match in order to reduce refractive distortion. Models using epoxy resin^{13,14} and photopolymers¹⁰, present limited optical access, especially with the refractive indices of common blood-mimicking fluids. All the models reported in this study are distortion-free when imaged with circulating blood-analog fluid, enabling the use of proven flow visualization techniques such as those mentioned above. An added advantage of our models is that any conventional medical

measurement modality such as MRI and endovascular Doppler flow measurement can be easily employed as well for measuring hemodynamics in vitro²⁷ or for fluoroscopic investigations¹⁶.

The above approach provides invaluable information that can aid in surgical planning of endovascular interventions, especially when a specific packing density is desired or to determine if coils alone would be sufficient treatment^{5,10,28}. Treated models scanned using synchrotron X-ray microtomography provide detailed information about endovascular device geometry (such as coil mass morphology) for incorporation into CFD models of treated aneurysms⁸. Detailed hemodynamics for treated in vitro flow phantoms can be investigated in vitro, and computational simulations for quantifying and comparing the efficacy of different treatment approaches can be conducted⁸. This procedure could be repeated using different treatment strategies in the same anatomic models, with measurement of peri-aneurysmal pressure and flow, in order to determine an efficient intervention strategy. The unique characteristics of the model creation described here opens several avenues for furthering our understanding of endovascular treatment and develop patient-specific optimization strategies and predictive capabilities. Materials used in our method are relatively inexpensive (~\$500/model) and each model requires approximately 10-15 person-hours to produce, providing scalability.

There are some limitations to our work. First, the small number of models created do not encompass the breadth and complexity of all possible intracranial aneurysms. However, they do reflect real-world experience at a high-volume cerebrovascular center, rather than idealized or spherical models used in many in vitro experiments. Also, the elastomer material lacks the elasticity of actual human blood vessels, which may be distorted by increased blood flow or by the placement of endovascular devices. However, wall compliance has been shown to have a very low influence on the overall results of aneurysm hemodynamic calculations²⁹.

CONCLUSIONS

Creation of patient-specific, dimensionally-accurate and optically-transparent silicone flow phantoms of cerebral aneurysms is feasible. High-fidelity synchrotron X-ray microtomography quantified the anatomical accuracy of these models. Creation of such models can aid in surgical planning of interventions and permit in vitro investigations of hemodynamics and treatment efficacy, leading to optimized, patient-specific treatment strategies.

Acknowledgments

FUNDING STATEMENT: This work was supported by the National Institutes of Health National Institute of Neurological Disorders and Stroke (NIH-NINDS) grants 5R03NS078539 and 1R01NS088072, National Science Foundation (NSF) grant CBET-0748133, and an unrestricted grant to our academic institution from Volcano Corp., which had no role in the experimental design, data analysis or scholarship of this work.

ABBREVIATIONS:

3D three-dimensional

3DRA	three-dimensional rotational angiography
CFD	computational fluid dynamics
CT	computerized tomography
MRI	magnetic resonance imaging
PIV	particle image velocimetry
PTV	particle tracking velocimetry
STL	stereolithography

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- Aneurysmal hemodynamics are helpful in treatment planning and prediction.
- In vitro models can validate patient-specific computational simulations of aneurysms.
- Dimensionally-accurate, optically-transparent phantoms can be done by 3D printing.
- Such models may inform optimal patient-specific neurointerventional strategies.

Figure 1:

Approach used for creating patient-specific, true scale cerebral aneurysm reconstructions. Beginning with patient angiographic data, the aneurysm and surrounding vasculature is segmented. A 3D printed model of the segmentation is used to create a hollow silicone flow phantom which is treated with patient-specific endovascular devices. High resolution synchrotron scanning is used to delineate the endovascular device configuration. The high resolution scan of the endovascular device can be used for computational studies, while the silicone flow phantom is used for in vitro hemodynamic investigations.

Figure 2:

In vitro cerebral aneurysm flow phantoms and treatment device configuration. (A) Patient angiographic data of aneurysm and surrounding vasculature (B) 3D printed replicas of cerebral aneurysm vasculature obtained from segmentation of angiographic data (C) Optically transparent true scale silicone flow phantoms (D) Synchrotron X-ray microtomographic imaging comparisons of patient 3DRA scans (gray) overlaid on vitro models (red) (E) patient-specific endovascular device configuration of either pipeline or coil obtained from high resolution (12 μ) synchrotron scans. Scale bars represent 5 mm unless otherwise stated.

Figure 3:

Median error between 3DRA patient scans and in vitro models for all six patients. Error bars indicate inter-quartile range (IQR (1st quartile, 3rd quartile)).

Figure 4: Reconstruction of interventional device (coils) obtained from synchrotron X-ray microtomographic imaging of in vitro phantoms that were treated by a neurointerventionalist for multiple patients in the same patient-specific manner (number and order of deployment of coils).

Figure 5.

(Left) Endovascular treatment of the in vitro flow phantoms with the same patient-specific endovascular devices (coil and/or stents) from which the phantom was created. (Right) High-resolution synchrotron scanning (spatial resolution 12 μ m) of these endovascular devices.

Figure 6.

The flow diverter microstructure and configuration is captured in great detail due to the difference in X-ray absorption between the flow diverter and surrounding silicon model. This level of detail permits confirmation of anatomical accuracy of the model as well as visualization of the endovascular devices.

Table 1.

Median error between segmented scans of patient vasculature and synchrotron scans of in vitro phantoms (S.D.: standard deviation, 1st Q: 1st quartile, 3rd Q: 3rd quartile). All dimensions are in mm.

Patient #	Error Median $\pm$ S.D, (1 st Q, 3 rd Q) (mm)
P1	0.28 $\pm$ 0.25 (0.17,0.38)
P2	0.22 $\pm$ 0.24 (0.12,0.37)
P3	0.27 $\pm$ 0.31 (0.14,0.45)
P4	0.19 $\pm$ 0.23 (0.09,0.35)
P5	0.07 $\pm$ 0.06 (0.03,0.1)
P6	0.23 $\pm$ 0.19 (0.11,0.37)