Neurovascular Modeling: Small-Batch Manufacturing of Silicone Vascular Replicas

BACKGROUND AND PURPOSE: Realistic, population based cerebrovascular replicas are required for the development of neuroendovascular devices. The objective of this work was to develop an efficient methodology for manufacturing realistic cerebrovascular replicas.

MATERIALS AND METHODS: Brain MR angiography data from 20 patients were acquired. The centerline of the vasculature was calculated, and geometric parameters were measured to describe quantitatively the internal carotid artery (ICA) siphon. A representative model was created on the basis of these image datasets, we created a median virtual model, which was transformed into a physical replica by an efficient batch-manufacturing process. The coefficient of friction of the luminal surface of the replica was reduced by up to 55% by using liquid silicone rubber coatings. The modulus ranged from 0.67 to 1.15 MPa compared with 0.42 MPa from human postmortem studies, depending on the material used to make the replica.

RESULTS: The average diameter, length, and curvature of the ICA siphon were 4.15 ± 0.09 mm, 22.60 ± 0.79 mm, and 0.34 ± 0.02 mm⁻¹ (average ± standard error of the mean), respectively. From these image datasets, we created a median virtual model, which was transformed into a physical replica by an efficient batch-manufacturing process. The coefficient of friction of the luminal surface of the replica was reduced by up to 55% by using liquid silicone rubber coatings. The modulus ranged from 0.67 to 1.15 MPa compared with 0.42 MPa from human postmortem studies, depending on the material used to make the replica.

CONCLUSIONS: Population-representative, smooth, and true-to-scale silicone arterial replicas with uniform wall thickness were successfully built for in vitro neurointerventional device-testing by using a batch-manufacturing process.
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The vessel centerline

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ated on the basis of the geometry of the core. The distance between the

vasculature, was encapsulated by the outer shell, which was cre-

cination object was fixed to assure that there were no shells, holes, noise,
or bad edges and was smoothed before skeletonizing. The resulting
centerline was composed of control points equally spaced at a con-

stant 0.4-mm interval.

Vessel Characterization and Model Selection

The path length of the extracted centerline and the diameter of the

best-fit circle to the vessel cross-section at each control point were

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= [x(s), y(s), z(s)] was first parameterized by arc length (s) and then fitted with a 10th-order polynomial for

smoothing. To evaluate the goodness of fit, we applied the degree of

polynomial varying from 2 to 22 to the original dataset, respectively,

and the root mean square error (RMSE) was calculated.25

The smoothed centerline was resampled to give control points at constant 0.05-mm intervals for curvature evaluation. The curvature

(k) at each control point and the AC were given by23,24:






where r'(s) and r''(s) denote the first and second derivatives of the
centerline, and n indicates the total number of points.

The nonparametric Wilcoxon signed rank test was performed (Prism 5; GraphPad Software, La Jolla, Calif) to compare the median of each vessel feature against a hypothetic median, which was every single geometric parameter for the left and right ICA siphons in each

Patient. In this test, a P value > .05 indicated that there was no statistically significant difference between the median of a group of samples and the hypothesized median.

Generation of the Vascular Replica

A mold with a core-shell structure was created for silicone injection

(Magics; Materialise). The inner core, representing the geometry of the vasculature, was encapsulated by the outer shell, which was created

on the basis of the geometry of the core. The distance between the

core and shell was the thickness of the silicone replica, which can be

precisely controlled. In this study, the wall thickness was 1 mm.

The virtual design was transformed into a physical object (Prodigy

Plus; Stratasys, Eden Prairie, Minn) by using fused-deposit manufact-

uring26 to build the model in a layer-by-layer manner, with a layer

thickness of 0.178 mm. The production capacity per batch was deter-

mined by the size of the target vasculature. For instance, 6 ICA-mid-
dle cerebral artery (MCA) core-shell models with a dimension of 47

× 41 × 81 mm³ each can be built in 1 batch and completed in 30 hours.

The extrusion tips in the heated build envelop deposited the model

copolymer of acrylonitrile, butadiene, and styrene [ABS]) and support

materials along the designated tool path. Both materials fused together to form a solid model. The soluble support material was

removed in the sodium hydroxide solution at 70°C, which required

approximately 24 hours.

Xylene and 2-propanol were infused into the mold alternately to

smooth the core and the inner wall of the shell. Repeating the alternate rinse procedure 5 times, each time for 1 minute, achieved an adequate

smoothing result. The rinsed mold was dried in the ventilation system

before silicone infusion.

Sylgard 184 silicone kit (Dow Corning, Midland, Mich) and an injection molding-grade silicone, LIM 6030 pail kit (Momentum,

New Milford, Conn), were infused into the core-shell mold. The Syl-
gard 184 replica was found to be optically clear and had a higher Shore A hardness. Compared with Sylgard 184, LIM 6030 had higher elong-
ation at break, tensile strength, and viscosity. The amount of thinner, SF 96–5 (GES Waterford Plant, Waterford, NY), added to the LIM

6030 mixture accounted for 7% of total mixture weight. The silicone solution was mixed and degassed in a vacuum oven at room temper-

ature under 76 cm Hg vacuum. Higher injection pressure, at least

1200 mm Hg, was required for the delivery of the viscous LIM 6030

compared with 55 mm Hg to infuse the Sylgard 184 into the mold.

The silicones were cured at 60°C for 12 hours. The whole mold was

immersed in xylene for mold dissolution overnight.

LSR Topcoat Modification

LSR topcoat (Momentum Performance Materials, Albany, NY), a

2-component translucent matte coating with a Brookfield viscosity of

1600 centipoise, was infused into smooth open-ended straight sil-

cicone tubes (11 cm in length and 4 mm in diameter) by using a per-

staltic pump and then was cured at 110°C in a ventilated oven for 30

minutes. This procedure was repeated from zero to 3 times. The effect of multiple coatings on the coefficient of friction (COF) was evaluated

by using a customized friction rig (TA-265A; Texture Technologies,

Hamilton, Mass), which was designed according to American Stan-

dard Test Method (ASTM) D1894.

During the friction test, the inner lumen of the replica slid 20 mm

over a flat surface at a sliding speed of 5 mm/s 25 times. All tribological

tests were conducted under ambient conditions with a constant tem-

perature of 21°C. Five specimens were tested for each silicone mate-

rial, and the average force was obtained to determine the static and
dynamic COF of silicone material before and after LSR coating. The

static COF was obtained from the averaged maximum force initiating

motion between test material and surface, whereas, the dynamic COF

was from the average force measured for the duration of sliding.

The Student t test was performed to determine the statistical difference in

friction before and after surface modification.

Tensile Test for Silicone Strips

The stress-stretch relationship (S-S relationship) was obtained by using

an Instron machine (model 5542; Norwood, Mass) equipped with

0.3-kN-load cell, having 651-mm vertical test space. The 5-mm-wide

50-mm-long Sylgard 184 and LIM 6030 silicone strips with an average

thickness of 0.54 ± 0.06 and 0.51 ± 0.02 mm were prepared for the
tensile test. All the specimens (3 specimens for each group) were sub-

jected to the test at a cross-speed rate of 30 mm/min, and the S-S

relationship of the silicone strips was compared with that of the hu-

man MCA from postmortem examination, which was performed

quasi-statically at a strain rate of approximately 0.05 seconds⁻¹.27

Results

The anatomy of the 3 cerebral vessels from patients 1, 2, and 3

are shown in Fig 1A–C, having siphons with an AC ranging from

0.23 to 0.64 mm⁻¹. Patients 1, 2, and 3 were selected to illustrate mild, moderate, and severe curvature, respectively, of the ICA siphon in our patient population.

In the vessel characterization, the best-fit polynomial to

smooth the original centerline data was determined by mini-
mizing the error between the polynomial curve and original centerline. The results showed that the total error decreases significantly up to the 10th-order polynomial fit, followed by a more gradual decline. The smoothed centerline was re-sampled before curvature calculation. The AC tends to increase with the decrease of the distance between control points and becomes stable when the distance is < 0.1 mm. This change is significant in the measurement of an ICA siphon with severe tortuosity, whose AC increases from 0.45 to 0.65 mm⁻¹ when the distance decreases from 0.4 to 0.01 mm. In this study, the polynomial curve was re-sampled to have points at constant 0.05-mm intervals for curvature calculation. With the 10th-order polynomial to smooth the original centerline and having control points with constant 0.05-mm intervals, the AC, arc length, and diameter from 20 patients were 0.34 ± 0.12 mm⁻¹, 21.86 ± 4.24 mm, and 4.17 ± 0.64 mm for the left ICA siphon, respectively. For the right siphon, the AC, arc length, and diameter were 0.34 ± 0.13 mm⁻¹, 23.31 ± 5.72 mm, and 4.12 ± 0.44 mm, respectively. In patient 18, the P values resulting from the Wilcoxon signed rank test for comparisons in AC, length, and diameter were all > 0.05, indicating each measured parameter of patient 18 had no significant difference compared with the corresponding median. The P values were .24, .37, and .96 for the comparisons of AC, arc length, and diameter, respectively, of the left ICA siphon, and 0.72, 0.29, and 0.49, respectively, for those of the right ICA siphon. This finding was only observed in patient 18 and led us to select patient 18 as a representative model of the chosen patient population in this study.

A computer mold consisting of a core-shell structure for silicone injection is shown in Fig 2A. Silicone was infused into a mold (Fig 2B), which contained the vasculature of the circle of Willis (CoW) from patient 2 as the core (Fig 2C). Figure 2D, -E shows silicone replicas of the CoW from patient 2 and the representative right ICA from patient 18, respectively. Using this batch-manufacturing process, we made 6 vascular replicas from the virtual model in 92 hours at a material cost of $250. The capital equipment and software used in this study were quite expensive; however, these tools are available at most universities and medical device companies.

The static and dynamic COF of Sylgard 184 and LIM 6030 with various numbers of LSR coatings are given in the Table. The best values were obtained with a single coating for Sylgard 184: COF reduced by 55%, with a minimum static COF of 0.334 ± 0.169 and a dynamic COF of 0.312 ± 0.174. For LIM 6030, a 47% reduction in COF was achieved with 3 layers of LSR topcoat, resulting in a static COF of 0.719 ± 0.121 and a dynamic COF of 0.683 ± 0.120. The S-S relationship of LIM 6030 and Sylgard 184 are shown and compared with that of the human MCA from postmortem examination obtained from the quasi-static test conducted by Monson et al27 in Fig 3. Like human blood vessels, silicone rubber exhibits a nonlinear S-S relationship. Moreover, at low stretch, the slope of the S-S curve of LIM 6030 is 0.67 MPa, similar to that of the MCA from a postmortem examination (0.41 MPa).

Discussion
A great deal of effort has been used to create polymeric vascular models for surgical simulation, interventional practice, and hemodynamic research in vitro. Quantitating anatomic features of the arterial structures for disease or lesion prediction and diagnosis have also been widely investigated. On the basis of our literature search, no studies have yet to apply the vessel characterization results to the replica manufacturing process. In this article, the disclosed manufacturing process of replicas is based on a model extracted from a characterized population of imaging datasets. This could be an even more powerful technique in the future as image data bases grow, allowing an investigator to search for anatomy specific to a precise patient population for whom a given endovascular device is intended.

Arterial lumen replicas can be obtained from human cadavers.10,14 Postmortem alterations, including the shrinkage of arterial trees, produce dimensional errors of the in vitro model. Using MRA data to acquire the geometry of the target vessels in our proposed manufacturing method avoids this problem and provides flexibility during the postprocessing. Stock et al28 mentioned that the noninvasive non-contrast-enhanced 3D time-of-flight MRA is highly accurate in depicting the arterial segments of the CoW, except the posterior communicating arteries (PcomA), and the same observation also applies to this study. The poor depiction of PcomA could be attributed to the saturation effect of slow flow and the flow parallel to the acquired section plane in addition to the normal anatomic variations in which these vessels are not present.

To smooth the centerline generated from the MRA reconstruction, the RMSE describes how well the fitted curve
matches the original dataset. In this study, the RMSE tends to decrease at a higher than 10th-order polynomial fit. However, a higher polynomial order does not guarantee better fitting results and can lead to oscillations between the data points. The 10th-order polynomial had a RMSE of 0.1 for patients 1 and 2 and 0.16 for patient 3 and was chosen as a smoothed centerline. To take minor changes along the vessel centerline into consideration, we measured and averaged the curvature of every 0.05-mm segment. The median of each vascular feature was used to select a representative model in this study.

Other methods of replica construction have been used, such as that described by Knox et al,11 in which they created a reusable master mold of a lumen replica based on the CT scan data from a live patient to reproduce wax lumen models. The major difficulty of this technique is the fabrication of the master mold, which requires an experienced mold maker and is a time-consuming and expensive process, and the resulting mold is not easily modifiable to change the replica anatomy.

Compared with the method of Knox et al, the construction of our core-shell structure is straightforward and efficient. On average, a virtual core-shell mold can be completed in 20 minutes after receiving the scanning data, enabling reproducible manufacturing of replicas of any selected configuration. Sugiu et al14 used 4–6 thin layers of silicone liquid manually painted onto the wax lumen cast to simulate the vessel wall; however, the thickness and uniformity of the coating were not stated. Seong et al13 fabricated rabbit aneurysm replicas by using the dip-spin method. The lumen cast polished with sandpaper was dipped into the silicone mixture and then mounted on a spinning shaft to obtain a layer of uniform silicone coating. The repeated coating procedure is time-consuming and not reproducible. Our described methodology serves to improve these limitations. The core-shell mold keeps the consistency of the replica dimensions and saves time via the batch manufacturing. Due to the structural constraint, the sandpaper polish is not applicable to our core-shell mold. To

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**Fig 2.** The virtual core-shell structure (A) is designed for the preparation of the physical ABS model (B), which contains the CoW (C) as the core. After the silicone is cured, the ABS model (D) is dissolved in xylene, resulting in a transparent CoW silicone replica (E). With the same manufacturing process, a representative right ICA siphon is built from patient 18.

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**Static and dynamic COFs of Sylgard 184 and LIM 6030 samples for different numbers of coatings after 25 runs***

| Coating No. | Sylgard 184 Static COF | Sylgard 184 Dynamic COF | LIM 6030 Static COF | LIM 6030 Dynamic COF |
|-------------|------------------------|-------------------------|---------------------|----------------------|
| 0           | 0.738 ± 0.093          | 0.707 ± 0.089           | 1.346 ± 0.113       | 1.298 ± 0.113        |
| 1           | 0.334 ± 0.169 (P = .0016) | 0.312 ± 0.174 (P = .0019) | 1.052 ± 0.216 (P = .0273) | 1.026 ± 0.222 (P = .0435) |
| 2           | 0.366 ± 0.114 (P = .0005) | 0.312 ± 0.108 (P = .0002) | 0.815 ± 0.114 (P < .0001) | 0.765 ± 0.098 (P < .0001) |
| 3           | 0.471 ± 0.091 (P = .0018) | 0.416 ± 0.090 (P = .0009) | 0.719 ± 0.121 (P < .0001) | 0.683 ± 0.120 (P < .0001) |

Note: — COF indicates coefficient of friction.

*The COF is presented as mean ± SD. The Student t test compares the mean COF of the coated and uncoated groups. The 2-tailed P value < .05 indicates a statistically significant difference.
smoothen the lumen surface, the mold is rinsed with xylene and 2-propanol alternately. This procedure allows xylene to gradually dissolve model material and effectively prevents the core-shell structure from collapsing.

Besides the soft replica described above, the rigid-block model provides another option for in vitro use. Wetzel et al.15 used the 3D printer with a resolution of the build layer of 0.076 mm to form the wax copies of the vascular trees based on rotational angiography data. The wax model is embedded in clear silicone, which is then cured to form a solid block. The holes drilled in the silicone block drain the melted wax. After evacuation of the wax, a transparent rigid model containing the vascular lumen inside is prepared. The major concern of this lost-wax technique is the fragility of the wax, which results in the breakage of the vessel branches <1 mm. With the method reported in our study, silicone vascular replicas with branches <0.5 mm were made.

A common concern for selecting silicone as a material for vascular replica fabrication is its high friction. Surprisingly few attempts have been made to minimize the resistance between silicone replicas and medical devices. So far, an alternative material used to prepare a vascular replica in the application of neurovascular modeling is polyvinyl alcohol (PVA).16 The high water content of PVA hydrogel gives the vascular replica a naturally lubricated surface; however, the life of PVA replicas is limited, depending on the rate of water evaporation. Aside from using PVA as a substitute for silicone, Parylene coating successfully reduces the COF of elastomers by forming a thin layer of Parylene film, which closely conforms to the substrate. The restriction of this coating method is the requirement of the coating system for vapor deposition during the process, which may increase the cost and restrain the popularity of this technique. Compared with the aforesaid methods, LSR top-coat offers an easy and efficient option for smoothing the inner wall of the silicone vascular model. The low viscosity allows the LSR topcoat to flow easily through the long and tortuous model; furthermore, it only takes 10–30 minutes to cure 1 layer of coating.

Rubber, like silicone, is generally amorphous, with few strong interactions between molecules. When the tensile force is applied, the tangled molecules are pulled to become stretched. Additional force is needed on the stretched oriented molecules to maintain the constant strain rate. When a vessel is subjected to a tensile force, the elastin and collagen fibers significantly contribute to the low and high stiffness in the S-S curve.29 The results from the tensile test in this study show that the S-S relationship of LIM 6030 is similar to that of human MCA from postmortem examination at low stretch. To make this conclusion, one must clarify and discuss the potential differences between in vivo and in vitro test conditions. The blood vessel wall is an anisotropic composite material in general and receives multidirectional stress in the physiologic environment. All specimens described herein are subjected to uniaxial tensile strength and stretched longitudinally until breakage. Therefore, the results may not represent the mechanical response in vivo. Furthermore, the contribution from the surrounding tissue to the mechanical response of the vessels to the load is not taken into consideration in the in vitro and ex vivo studies. Last, factors such as age, sex, and disease history of donor; type of vessel; and strain rate may cause large variations in the S-S behavior for biologic materials. The cerebral arteries are significantly stiffer and less stretchable before failure compared with systemic arteries.30

The described technique provides an efficient method for representative replica construction. However, there are technical difficulties that might be encountered while preparing the silicone models. Bubble formation during silicone injection may cause defects of the silicone replicas. The high pressure required to infuse silicone liquid with high viscosity into the mold may cause core structure motion, resulting in variation in wall thickness. Finally, more imaging data should be reviewed to create a more realistic environment for medical device testing, endovascular training, and in vitro hemodynamic studies.

Conclusions

Population-representative, smooth, and true-to-scale silicone arterial replicas with uniform wall thickness were successfully built for in vitro neurointerventional device testing by using a batch-manufacturing process.

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