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4D printed bifurcated stents with kirigami-inspired structures

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TITLE:

4D Printed Bifurcated Stents with Kirigami-Inspired Structures

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KEYWORDS:

3D printing, 4D printing, kirigami, shape memory polymer, bifurcated stents, blood vessels

SUMMARY:

Using a 3D printer, a shape memory polymer filament is extruded to form a branched tubular structure. The structure is patterned and shaped such that it can contract into a compact form once folded and then return to its formed shape when heated.

ABSTRACT:

Branched vessels, typically in the form of the letter "Y," can be narrowed or blocked, resulting in serious health problems. Bifurcated stents, which are hollow in the interior and exteriorly shaped to the branched vessels, surgically inserted inside the branched vessels, act as a supporting structure so that bodily fluids can freely travel through the interior of the stents without being obstructed by the narrowed or blocked vessels. For a bifurcated stent to be deployed at the target site, it needs to be injected inside the vessel and travel within the vessel to reach the target site. The diameter of the vessel is much smaller than the bounding sphere of the bifurcated stent; thus, a technique is required so that the bifurcated stent remains small enough to travel through the vessel and expands at the targeted branched vessel. These two conflicting conditions, that is, small enough to pass through and large enough to structurally support narrowed passages, are extremely difficult to satisfy simultaneously. We use two techniques to fulfill the above requirements. First, on the material side, a shape memory polymer (SMP) is used to self-initiate shape changes from small to large, that is, being small when inserted and becoming large at the target site. Second, on the design side, a kirigami pattern is used to fold the branching tubes into a single tube with a smaller diameter. The presented techniques can be used to engineer structures that can be compacted during transportation and return to their functionally adept shape when activated. Although our work is targeted on medical stents, biocompatibility issues need to be solved before actual clinical use.

INTRODUCTION:

Stents are used to widen narrowed or stenosed passages in humans, such as blood vessels and airways. Stents are tubular structures that resemble the passages and mechanically support the passages from further collapsing. Typically, self-expanding metal stents (SEMS) are widely adopted. These stents are made from alloys composed of cobalt-chromium (stainless-steel) and nickel-titanium (nitinol)[1,2]. The downside of metal stents is that pressure necrosis can exist where the metal wires of the stent come into contact with the live tissues and the stents are impacted. Furthermore, the vessels of the body can be irregularly shaped and are much more complex than simple tubular structures. In particular, there are many specialized clinical procedures to install stents in branched lumens. In a Y-shaped lumen, two cylindrical stents are simultaneously inserted and joined at a branch[3]. For each additional branch, an additional surgical procedure needs to be conducted. The procedure requires specially trained doctors, and the insertion is extremely challenging due to the protruding features of the branched stents.

The complexity of the shape of bifurcated stents makes it a very suitable target for 3D printing. Conventional stents are mass produced in standardized sizes and shapes. Using the 3D printing fabrication methodology, it is possible to customize the shape of the stent for each patient. Because shapes are made by repeatedly adding layer-by-layer of the sectional shapes of the target object, in theory, this method can be used to fabricate parts of any shape and size. Conventional stents are mostly cylindrical in shape. However, human vessels have branches, and the diameters change along the tubes. Using the proposed approach, all these variations in shapes and sizes can be accommodated. Additionally, although not demonstrated, the used materials can also change within a single stent. For example, we can use stiffer materials where support is needed and softer materials where more flexibility is required.

The shape changing requirement of bifurcated stents calls for 4D printing, namely, 3D printing with the additional consideration of time. 3D printed structures formed using specialized materials can be programmed to change their shape by an external stimulation, such as heat. The transformation is self-sustained and requires no external power sources. One special material that is suitable for 4D printing is an SMP[4-9], which exhibits shape memory effects when exposed to a material-specific triggering glass transition temperature. At this temperature, the segments become soft so that the structure returns to its original shape. After the structure is 3D printed, it is heated to a temperature slightly above the glass transition temperature. At this point, the structure becomes soft, and we are able to deform the shape by applying forces. While maintaining the applied forces, the structure is cooled down, becomes hardened and retains its deformed shape, even after the applied forces are removed. Subsequently, at the final stage, when the structure needs to return to its original shape, such as the moment when the structure reaches the target site, heat is supplied so that the structure reaches its glass transition temperature. Finally, the structure returns to its memorized original shape. **Figure 1** illustrates the various stages previously explained. The SMPs can be easily stretched, and there are some SMPs that are biocompatible and biodegradable[9, 10]. There are many uses for SMPs in the field of medicine[9,10], and stents[11, 12] are one of them.

The patterns of the stents and the folding design follow the Japanese paper cutting design called "kirigami." This process resembles the well-known paper folding technique called "origami," but the difference is that in addition to folding, cutting of the paper is also allowed in the design. This technique has been used in arts and has also been applied in engineering applications[2,3,13,14]. In short, kirigami can be used to transform a planar structure to a three-dimensional structure by applying forces at specifically designed spots. In our design requirements, the stent needs to be a simple cylindrical shape when inserted into the pathways, and the cylinder should divide along its length where each half should unfold to a fully cylindrical shape at the targeted branched vessel. The solution lies in the fact that the main vessel and the side branches are folded into a single cylinder such that the side branches will not interfere with the walls of the vessels during the insertion. The unfolding command signal comes from the increase in the ambient temperature above the glass transition temperature of the SMP. Additionally, the folding will be conducted outside the patient body by softening the 3D printed bifurcated stent and folding the side branch into the main vessel.

Conventional methods required the insertion of multiple cylindrical stents whose number equals the number of branches. This method was inevitable because the protrusions of the side branches hampered the walls of the pathways and made it impossible to insert a complete bifurcated stent in its entirety. Using the kirigami structure and 4D printing, the above problems can be resolved. This protocol also shows the visualization of the effectiveness of the proposed method using a silicone vessel model fabricated after the shape of blood vessels. Through this mock-up, the effectiveness of the proposed invention during the insertion process and further possibilities of new applications can be seen.

The purpose of this protocol is to clearly outline the steps involved in printing an SMP using a fused deposition modeling (FDM) printer. Additionally, techniques involved in deforming the printed bifurcated stents to the folded state, the insertion of the folded bifurcated stents to the target site, and the signaling and unfolding of the structure to its original shape are given in detail. The demonstration of the insertion utilizes a silicone mock-up of blood vessels. The protocol also provides the procedures involved in fabricating this mock-up using a 3D printer and molding.

PROTOCOL:

1. Blood vessel mock-up design for the demonstration

1.1) Set the diameter of the proximal main vessel to 25 mm, the diameters of the distal main vessel and the side branch equal to 22 mm. Set the total length of the vessels equal to 140 mm. Set the length of the proximal main vessel, the distal main vessel and the side branch to 65 mm, 75 mm and 65 mm, respectively. The complete blood vessel is shown in **Figure 2** and **Figure 3**.

1.2) Print the computer model of the branched vessel by using an FDM 3D printer. Use a polycarbonate filament.

2. Blood vessel mock-up fabrication by molding

2.1) Create a box-shaped container that will house the 3D printed part. Set the container dimensions to 110 x 105 x 70 mm and use an acrylic plate.

2.2) With the 3D printed branched vessel placed at the center of the box, gently pour the silicone inside the container to minimize bubble formation. Dry the liquid silicone and harden it for 36~48 h.

2.3) Remove solidified silicone from the container and cut it in half to remove the 3D printed part. Rejoin the divided silicone at the cut plane. The resulting joined body is the blood vessel mockup. The final result is shown **Figure 4.**

3. Design of the branched stent based on kirigami

NOTE: The size of the branched stent is made to snuggly fit inside the Y-shaped pathway of the blood vessel mockup. The interior is made hollow, and the surface tubular meshes are designed to functionally fold and return to the full unfolded configuration.

3.1) Design the trunk of the bifurcated stent following wavy patterns similar to conventional stents. Set the diameter of the trunk to 22 mm and the length of the trunk to 38 mm.

3.2) Design the bifurcated branches to be a cylinder, as shown in **Figure 5B**. Set the diameter of the branch to 18 mm and the length of the branch to 34 mm.

3.3) Set the total length of the stent to 72 mm. The final shape is shown in **Figure 6**.

4. 3D printing with SMP filaments

4.1) Print the bifurcated stent in an FDM 3D printer using an SMP filament. The major composition of this filament is polyurethane. The commercial vendor also provides these filaments in the form of pellets so that the end user can also add additional substances to tailor the characteristics of the material **(Figure 7)**.

4.2) Use slicing software for model slicing and to control the settings of the 3D printer. Set the extruder temperature to 230 °C and the temperature of the printer bed to room temperature. Set the layer height to 0.1 mm to minimize the staircase effect.

4.3) Set the printing speed to 3600 mm/min. Set the amount of interior fill percentage to 80%. Include the supporter formation during printing, which is needed because the structure is hollow in the interior. **Figure 8** illustrates the printing process.

5. Smoothing out the surface

NOTE: The following steps are required because rough surfaces can damage the vessels by abrasion.

5.1) Remove the supporters using cutters **(Figure 9A)**. The supporters are attached at the interior of the stent. When removing the stents, exercise extreme caution to avoid tearing the stents.

5.2) Rub the surface against sandpaper **(Figure 9B)** to remove the layer lines, striations, or blemishes on the printed surface. Repeated polishing may be needed where the supporters are removed by the cutters.

5.3) Paint the surface using a spray in a well-ventilated location, and wear a personal mask. Clean, sand, and dry the surface. Protect from overspraying by applying thin layers of repeated paints. Use black paints to enhance the contrast between the silicone vessel mockup and the stent **(Figure 9C).**

6. Deforming the bifurcated stent

6.1) Place the bifurcated stents in warm water such that the temperature is above the glass transition temperature. When the stent becomes softened, push one half of the branch against the other half. Nest one half within the other half, as shown in **Figure 10a**.

6.2) Fold the two branches into a single cylinder so that it can travel through the main vessel. Perform the same nesting process to the other branch. Subsequently, the two halves of the cylinders are closed into one, as shown in **Figure 10b**.

7. Insertion of the bifurcated stent into the vessels

7.1) Fill a tank with warm water. Set the water temperature to 55-60 °C. Immerse the silicone vessel mockup inside the tank. Orient the mockup such that the main vessel is above and the branches are below.

7.2) Insert the folded bifurcated stent into the opening of the silicone vessel mockup from above. Orient the folded bifurcated stent such that its branches are towards the opening. The folded bifurcated stent will start to expand, and the lower branches will divide such that each branch will slide towards its mating pathway from the bifurcation core of the Y-shaped vessels **(Figure 12).**

REPRESENTATIVE RESULTS:

In this protocol, we showed the procedures required to fabricate a bifurcated stent. The stent uses a kirigami structure to allow the bifurcated stent to fold into a compact cylindrical tube, which is very suitable for sliding through the narrow pathways of blood vessels. The SMP allows the folded structure to return to its original shape when the temperature reaches the glass transition temperature. The original shape, 3D printed using the SMP material, closely matches the branched vessels. In other words, the interior surface of the branched vessels, where the bodily fluid is flowing, is offset further inside by the prescribed thickness of the fabricated stent.

A solid form is created between the interior surface and the offset surface. This solid form exactly fits the vessel and can be used as a model for the stent. Due to the ability of the SMP to return to its memorized shape, the folded structure will return to the predeformed shape once heated above its glass transition temperature. The two branched stents can be easily formed into half-cylindrical tubes by taking advantage of the kirigami structure. The two halves of the cylinders are merged into one cylinder, and the united structure has been shown to slide through the main vessel and reach the bifurcation area. To return the folded structure to its original shape, the experiment was performed in a water at a temperature of 60 °C. It has been shown that each side branch will divide, and each branch will go to its pairing vessels in the bifurcation area. The bifurcated stent was inserted into the Y-shaped vessels as a whole requiring only a single operation. This is much simpler than the conventional operation requiring insertions of each branching stent separately. These results show that it is possible to simplify the stent insertion operation to a single operation, whereas previous stent operations required the number of insertions of side branch stents to be the same as the number of side branching blood vessels.

FIGURE AND TABLE LEGENDS

Figure 1: Shape transformation diagram of the SMP. (**A**) The printed shape is the original shape. (**B**) When heated above the glass transition temperature (Tg), the structure becomes soft. When a force is applied, the structure is deformed to the desired shape. (**C**) The structure is fixed to a deformed shape by cooling. (**D**) When heated again above the glass transition temperature, a recovery force that returns the deformed shape to its original shape is generated. (**E**) The recovered shape is the same as the original shape.

Figure 2: The names of the parts of a Y-shaped blood vessel are shown. Y-shaped vessels have a main vessel and a side branch. The main vessel consists of a proximal main vessel and a distal main vessel. The proximal main vessel is divided into the side vessel and the distal main vessel, which lies above the bifurcated core.

Figure 3: Design of the blood vessel. (**A**) Right side view of the modeled blood vessel. This side is designed as a hook shape to express the three-dimensional nature of a real blood vessel in the human body. (**B**) Front view of the modeled blood vessel. Rotated view of the Y-shaped blood vessel according to **Figure 2**.

Figure 4: Silicone blood vessel mock-up. A container made with acrylic plates and 3D printed blood vessel models are used as a mold to create this mock-up. The mock-up was made using liquid silicone, which was hardened after drying. The front view (**A**) and the side view (**B**) are shown.

Figure 5: Design of the bifurcated stent's branches using kirigami. (**A**) Conceptual design of the stent branch. The sheet is cut along the black line. Subsequently, external forces are applied at the specific points in the specified direction, as marked by the red arrows. The resulting geometry of the operations described in A is shown to the right, B. A planar sheet has been transformed into a three-dimensional tubular shape. (**B**) The design of a tubular stent based on the kirigami structure.

Figure 6: The three-dimensional model of the bifurcated stent. The trunk uses wavy patterns quite similar to the conventional stent design. The two upper branches utilize kirigami structures.

Figure 7: SMP filament. It is produced in a filament form that is easy to print using a commercial 3D printer.

Figure 8: Picture of a 3D printed bifurcated stent using an FDM (fused deposition modeling) 3D printer. The 3D printed bifurcated stent is attached to the 3D printer bed using a double-sided gluing tape to prevent the output from slipping.

Figure 9: Postprocessing of the 3D printed result. (**A**) Removal of the supporters. The bifurcated stent is hollow in the interior and thus requires a supporter during 3D printing. The removal of the supporters is required. (**B**) The bifurcated stent with the supporters removed. (**C**) The bifurcated stent is spray-painted to clearly contrast it from the silicone pathways.

Figure 10: Illustration of the deformation and the recovery shape of the bifurcated stent. (**A**) The stent is heated to make it malleable. Subsequently, forces are applied to fold the branches into a half-cylindrical shape. (**B**) Half-cylindrical shapes are combined into a single tubular structure. The folding procedural steps are from the left to the right, and the recovery process is the reverse of the folding, which occurs from the right to the left.

Figure 11: The original and deformed state of the bifurcated stent. Notice the deformed shape is the shape of a cylinder and can be easily inserted into the trunk portion of the blood vessels. When the compactly folded shape is heated above the glass transition temperature, the shape returns to its original bifurcated shape.

Figure 12: The time lapsed shots of the recovering procedures of the folded stent inserted into the branched blood vessels are shown. (**A**) The procedural unfolding steps when the bifurcated stent is inserted into the Y-shaped vessels are shown. Initially, a single cylindrical tube is inserted. The inserted tube starts to divide once reaching the bifurcated core and returns to its unfolded original shape. (**B**) The timed images of the experiment. The upper left shows the insertion of the folded tube into the opening trunk of the vessel. The upper right shows the division of the inserted stent at the bifurcated core. The bottom row shows the recovery of the stent and the exact fit of the final bifurcated stent that perfectly fits the morphology of the targeting blood vessels.

Supplementary Files. Digital model of the vessel model.

DISCUSSION:

Stents are often used to clear the clogged internal pathways such as the blood vessels and airways of patients. Surgical operation of inserting stents requires the careful consideration of the patient's illness and human anatomical characteristics. The shape of the vessel is complex, and diverse branching conditions exist. However, the standard stent operational procedures are based on mass-produced stents with standard sizes. In this protocol, we showed how to personally tailor the fabrication of the stent based on the exact geometry of the blood vessels. In doing so, we designed the stent so that the interior is made hollow and the surface tubular meshes will fold and return to the full unfolded configuration when activated. We have targeted bifurcated stents, which are typically used during operations with multiple numbers of tubular stents. The design of our bifurcated stents is performed as a whole, and a single operation is required regardless of how complex and how many branches exist in the branched vessels. The key enabling technique that we have used to solve the problem is the SMP. The ability of the structure to return to its original shape is anticipated, so forces are exerted to prevent the expanded pathways from the re-contraction.

Another important idea is the use of a kirigami structure. The most difficult part is how one can shrink the Y-shaped branches into a compact cylindrical tube. This problem has been solved using a kirigami structure. Each branch is folded into half cylinders and then merged together.

We found an optimal temperature of 220-230 °C to memorize the bifurcated stent shape. Based on this fact, the extruder temperature was set to 230 °C. When the temperature was set above this temperature, the accuracy of the shape was compromised. When the temperature is set below this temperature, the SMP clogged the 3D printer nozzle. If different materials are used, then the extruder temperature should be adjusted. The temperature of the printer bed was set at room temperature. We experienced unwanted deformation of the structure when the printer bed temperature was set higher. Additionally, it is recommended that the interior fill is set to above 70%. It is recommended to avoid or minimize the generation of supporters, as they will impose additional postprocessing burdens.

The glass transition temperature of the SMP used was 55 °C, and the softening of the printed structure occurred above this temperature. When folding the printed bifurcated stent, we immersed the whole structure into a water heated bath above this temperature. When different SMPs are used, one should first find the glass temperature of the particular material. The recovery characteristics of other temperatures can be found in Kim and Lee[15], where faster responses were shown for higher temperatures.

We used an FDM 3D printer to fabricate the bifurcated stent. The size of the produced stent was too large to be inserted into real human vessels. Researchers should consider using different types of 3D printers or 3D printers with smaller nozzle diameters. The latter is technically difficult because SMPs are often very viscous and will easily clog the nozzle, especially when smaller diameter-sized nozzles are used.

The limitations of our work are as follows. The glass transition temperature was too high to be used inside patients. Furthermore, this particular material was not proven to be biocompatible. It is also preferable that the stent be biodegradable when the vessel no longer needs the stent to support it from collapsing. These problems could be solved with the use of other types of SMPs and further extensive live experiments.

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DISCLOSURES:
The authors have nothing to disclose.

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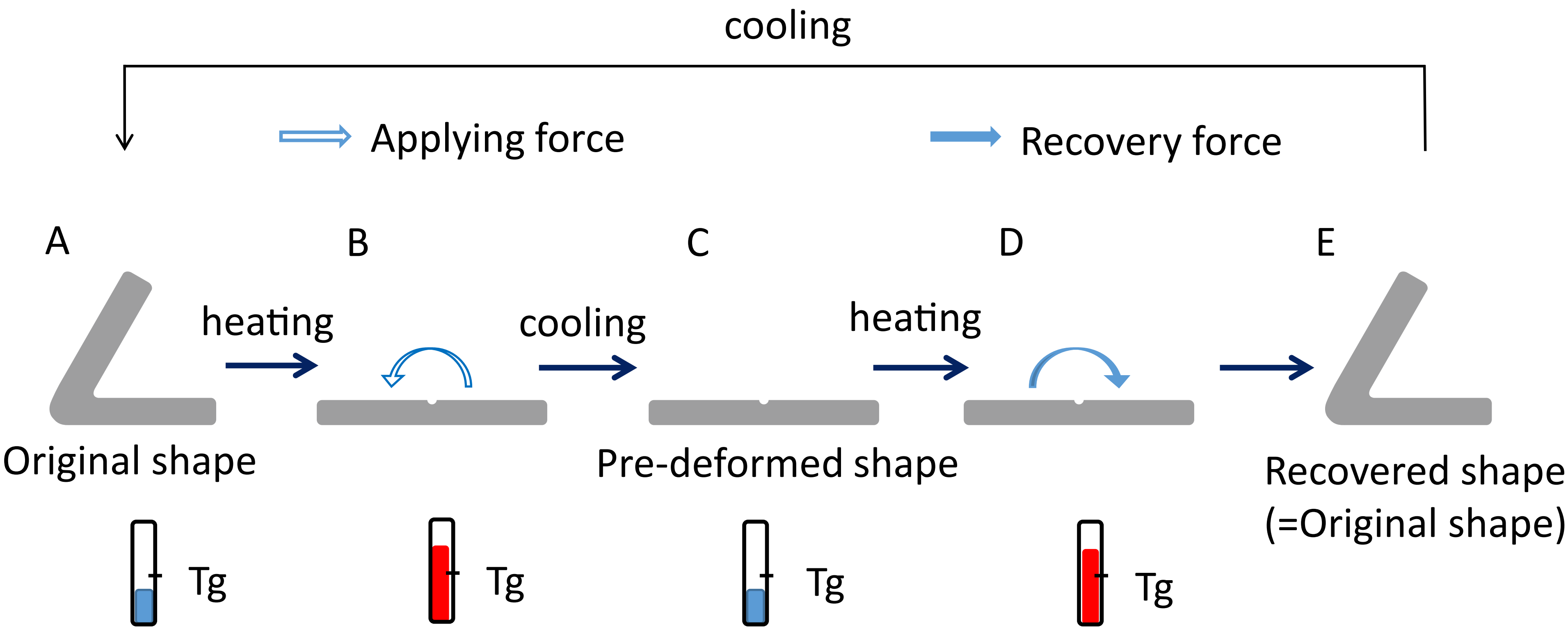
cooling
Applying force
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A
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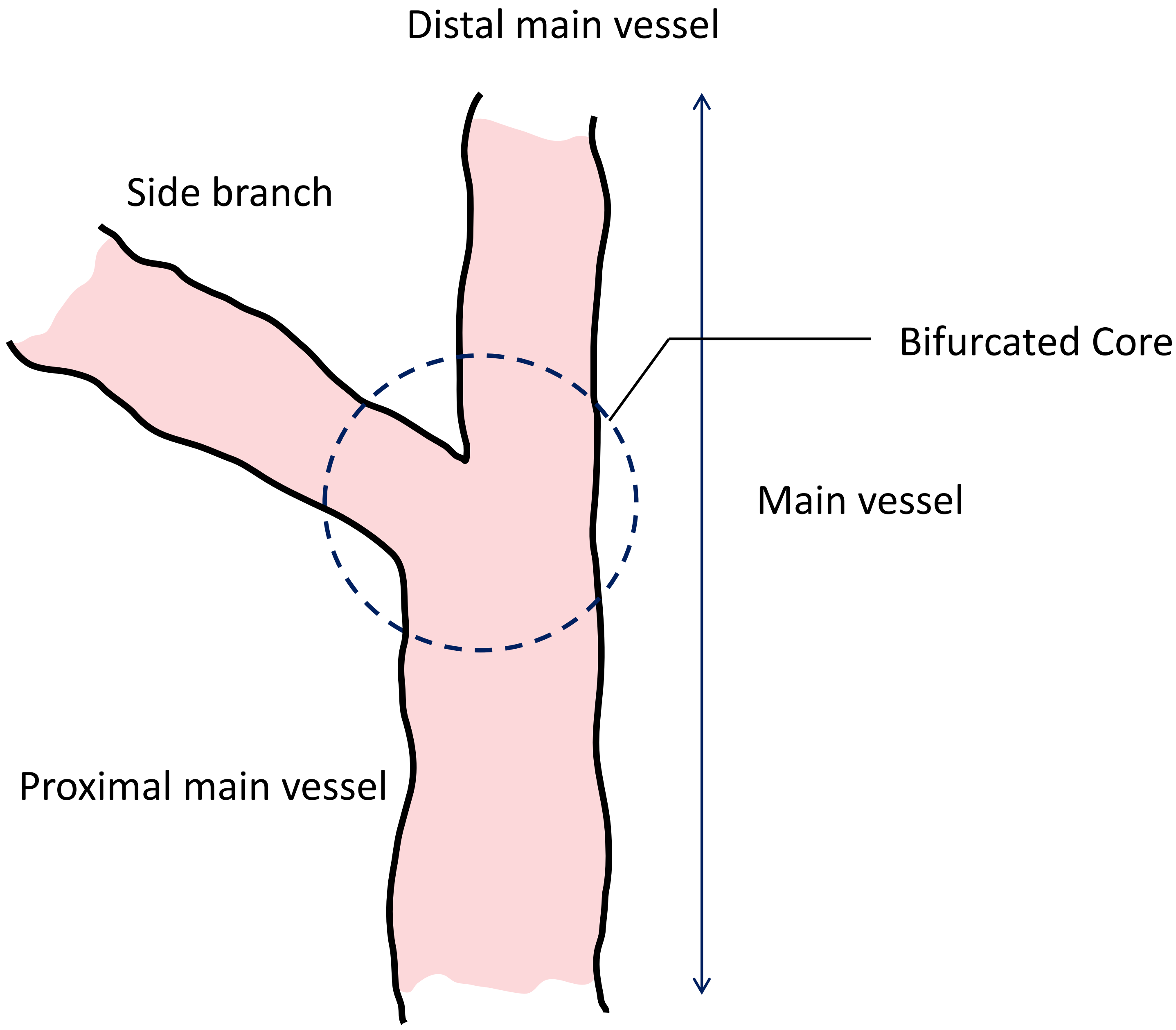
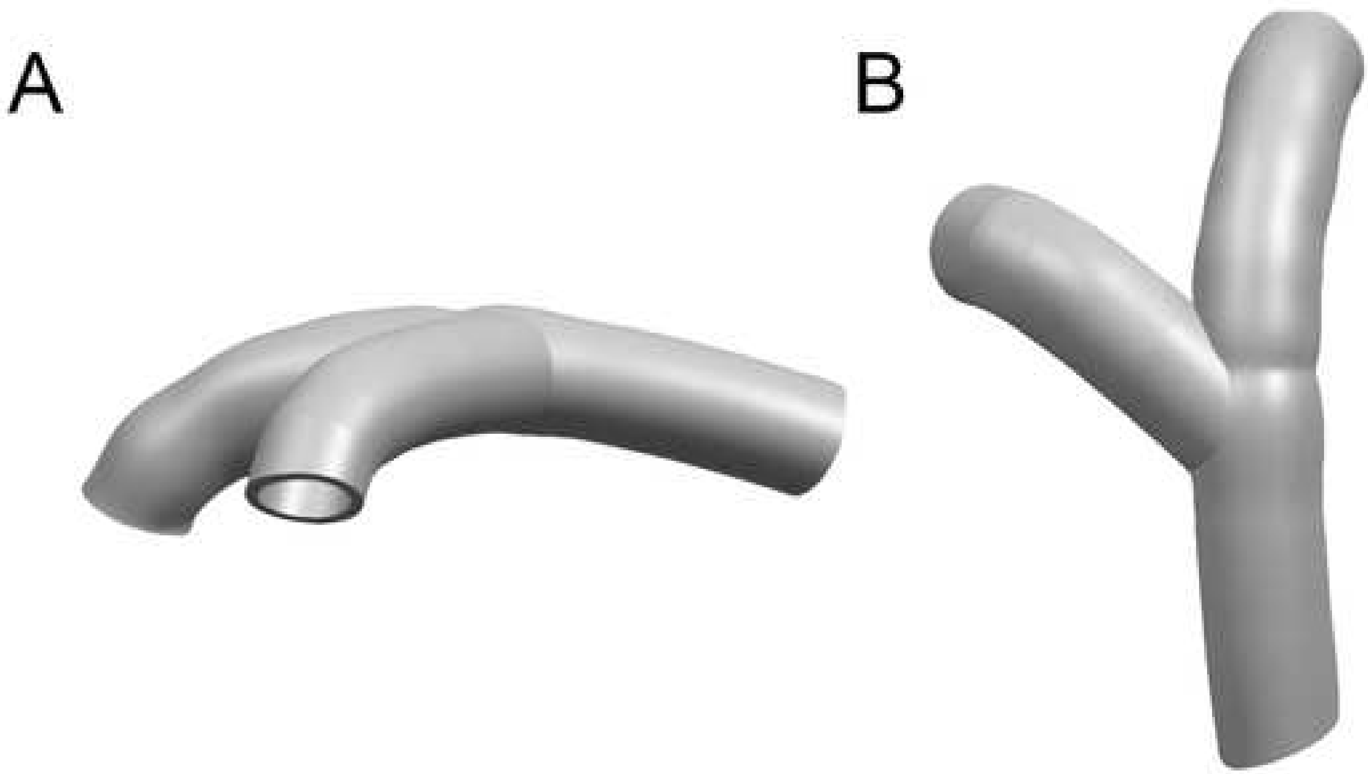
figure2


Distal main vessel
Side branch
Bifurcated Core
Main vessel
Proximal main vessel



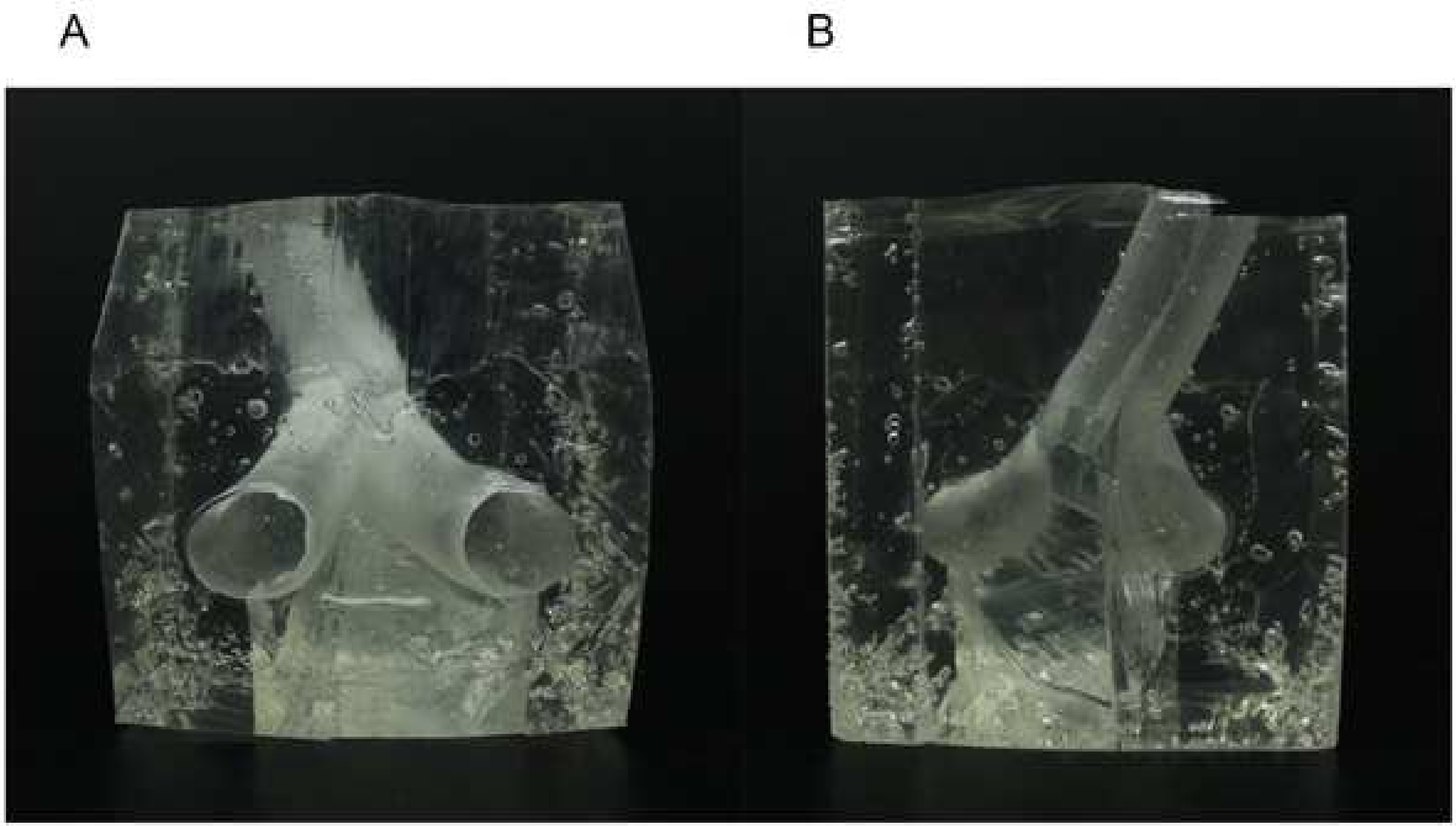


figure5

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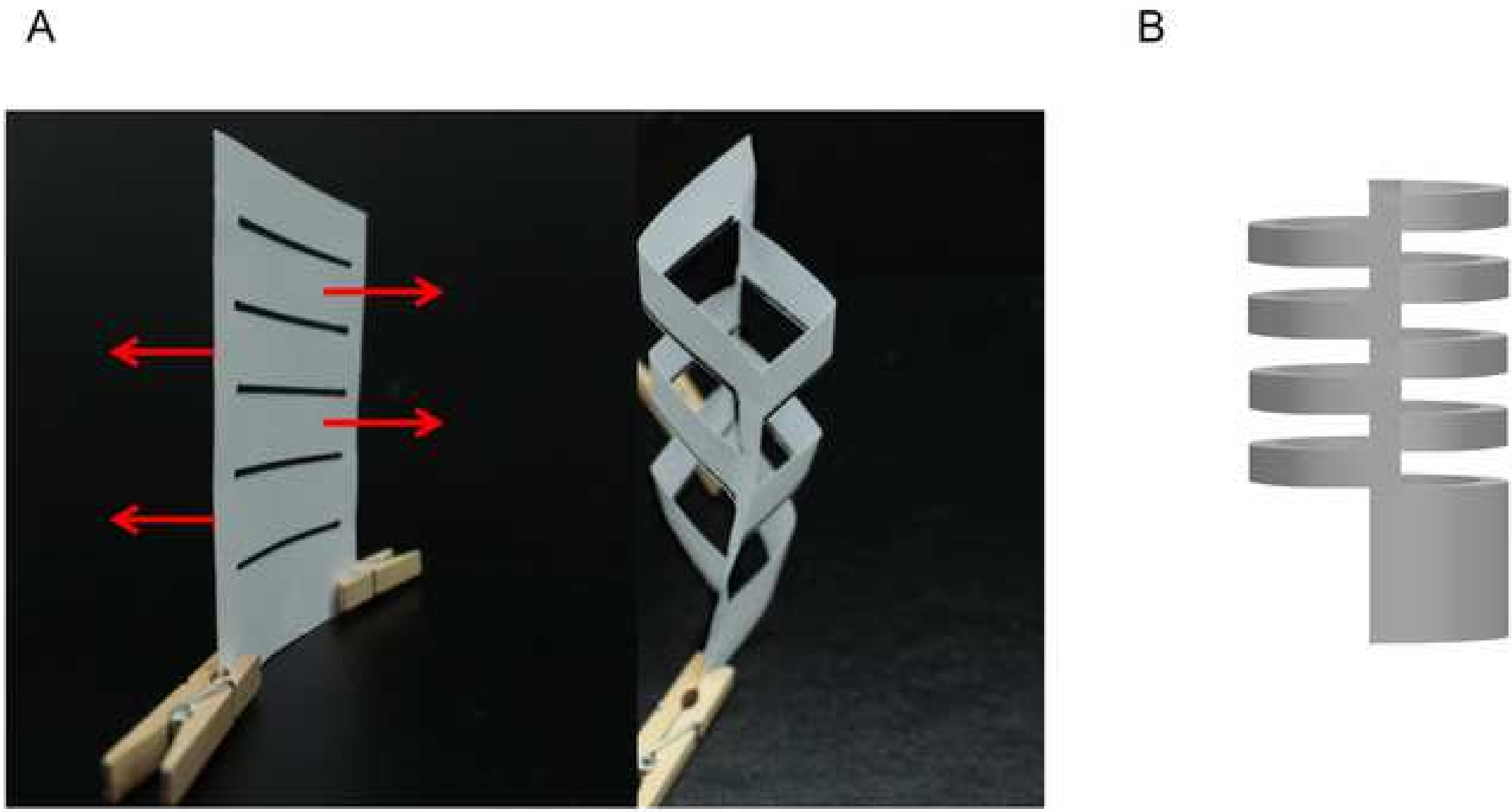

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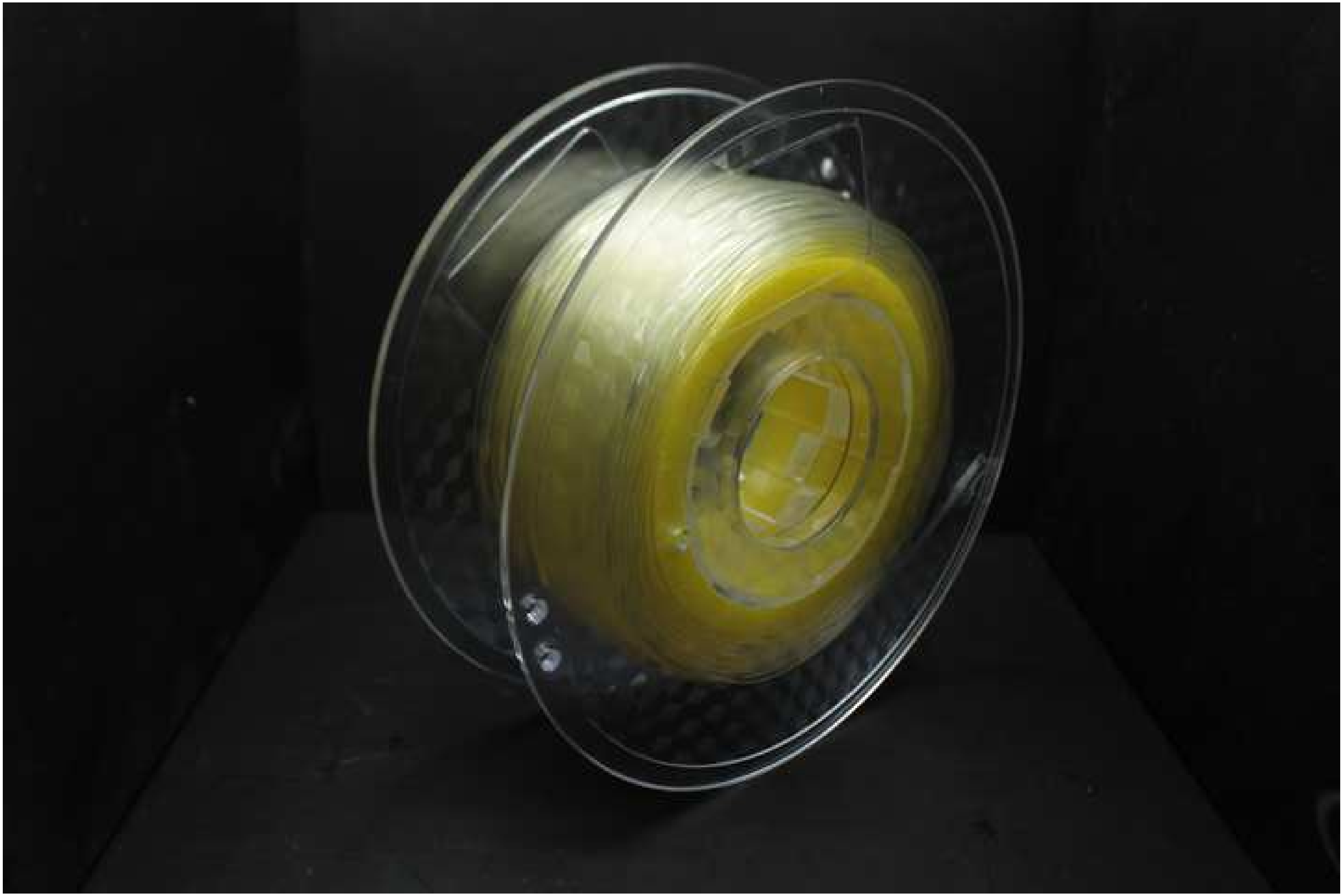

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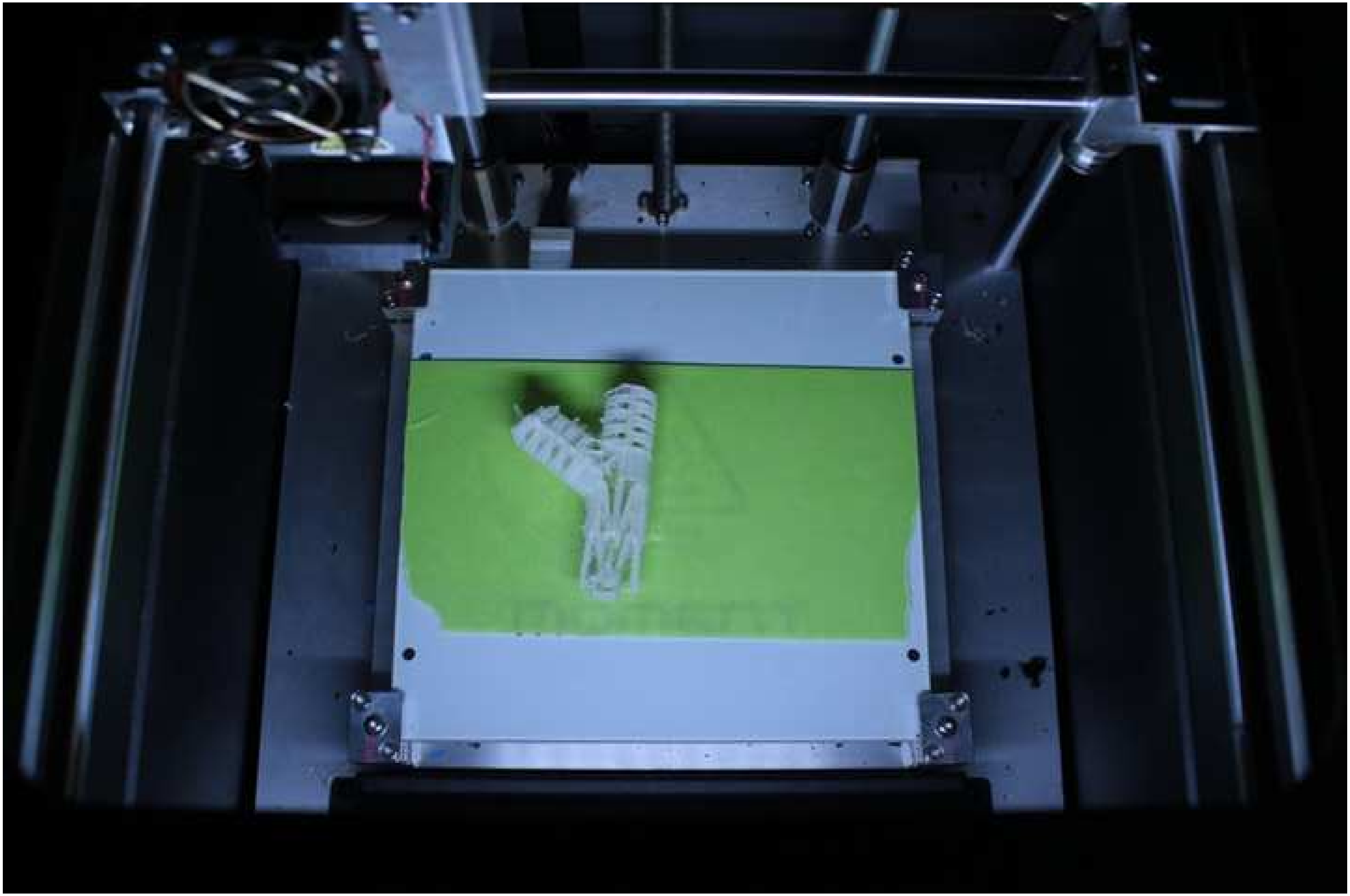

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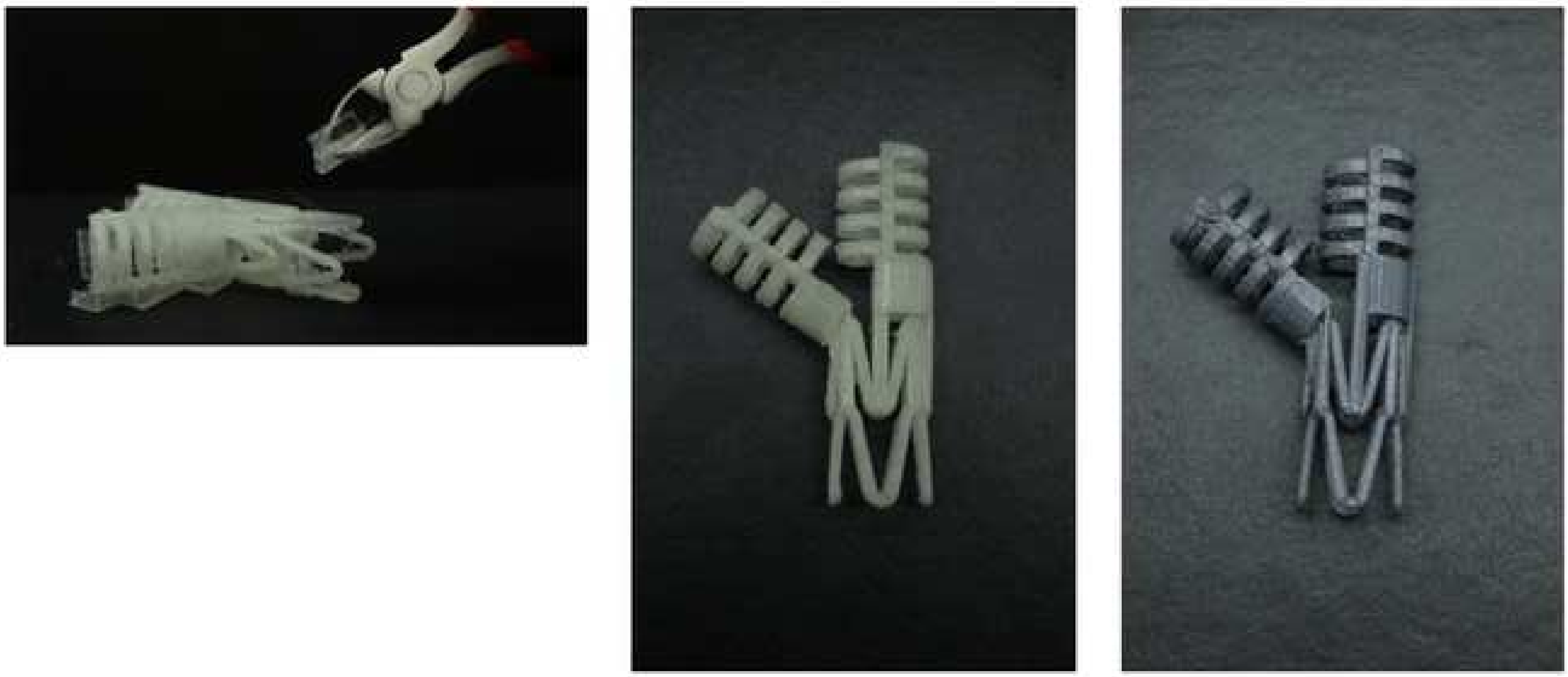

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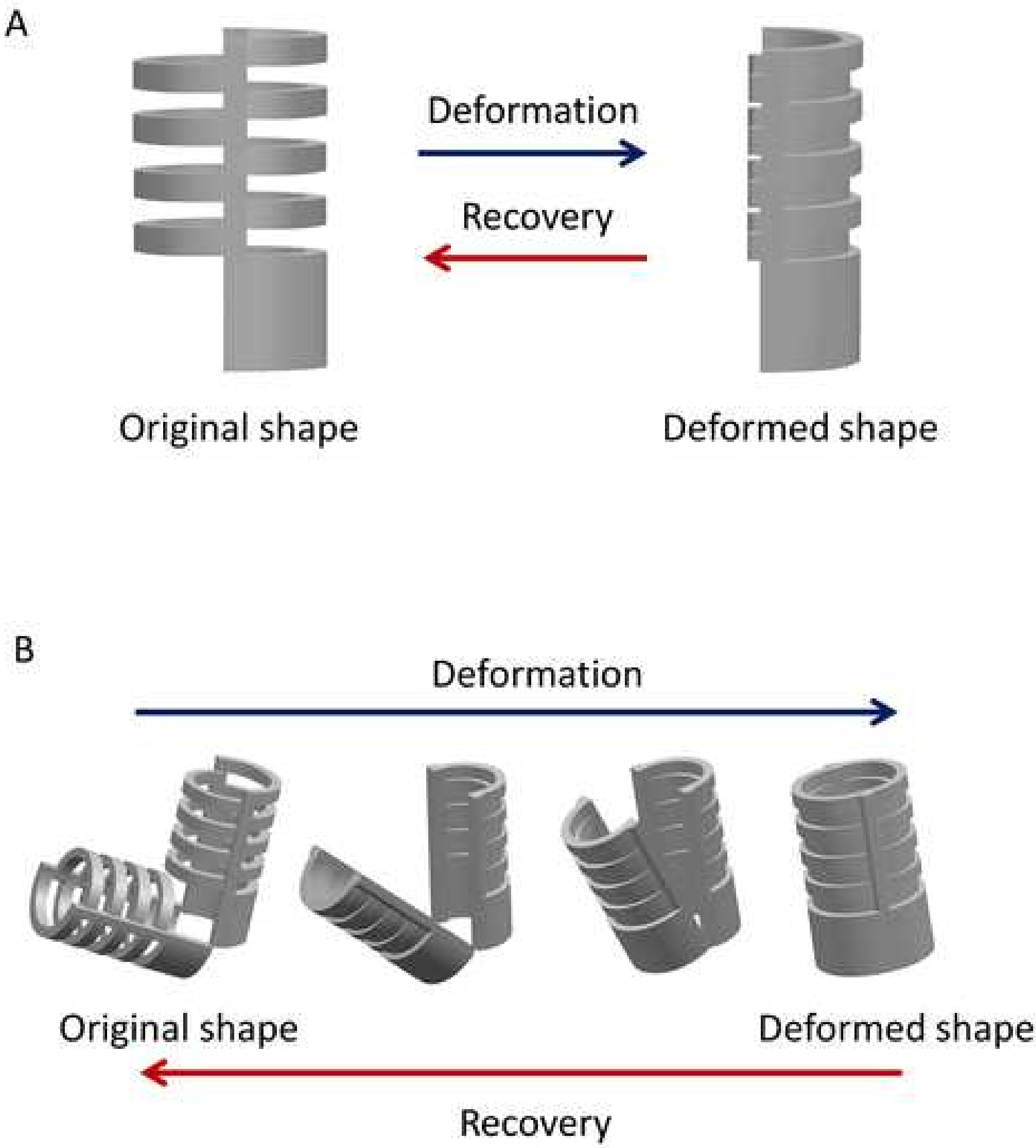

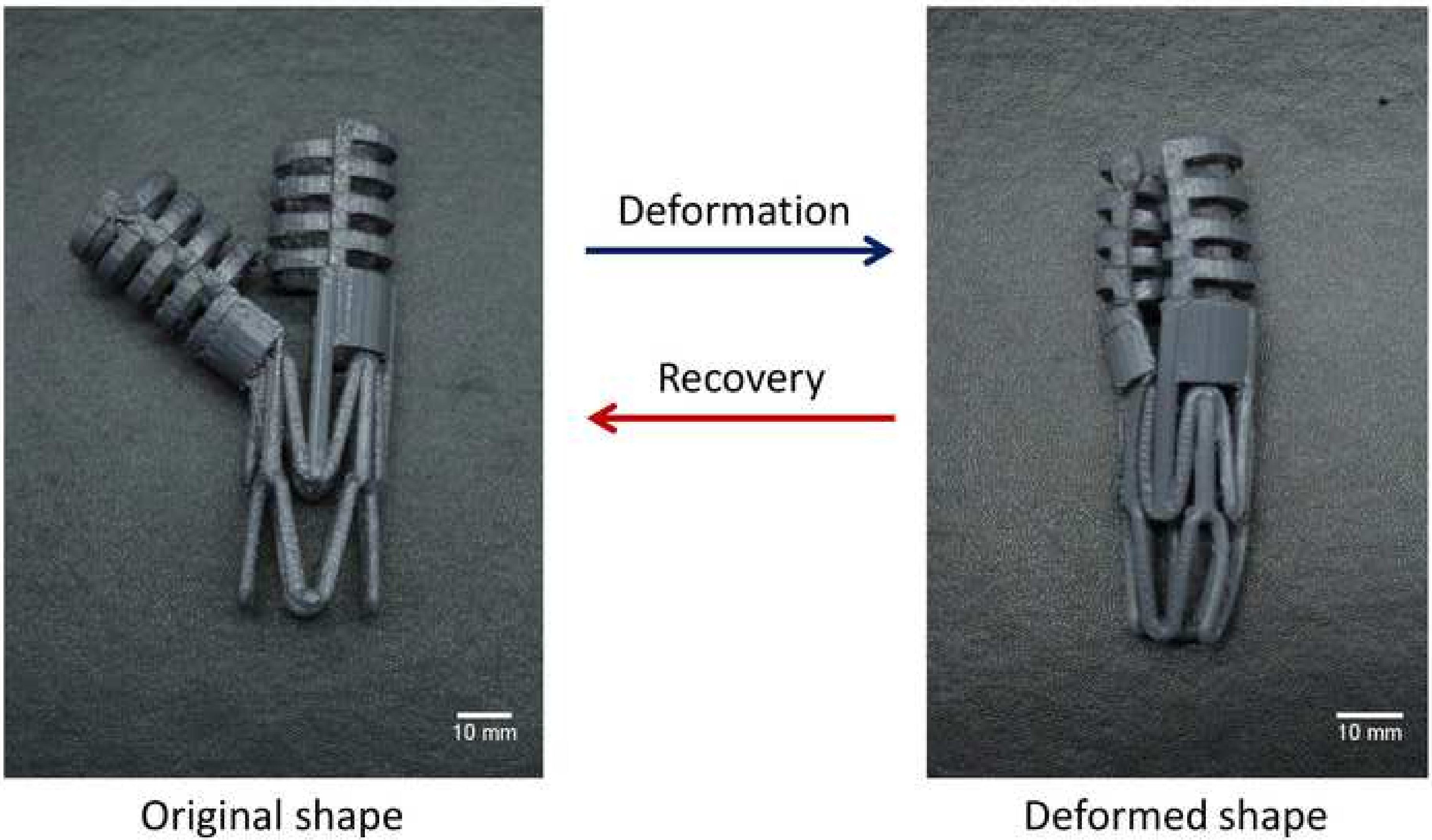
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Recovery
10 mm
10 mm
Original shape
Deformed shape

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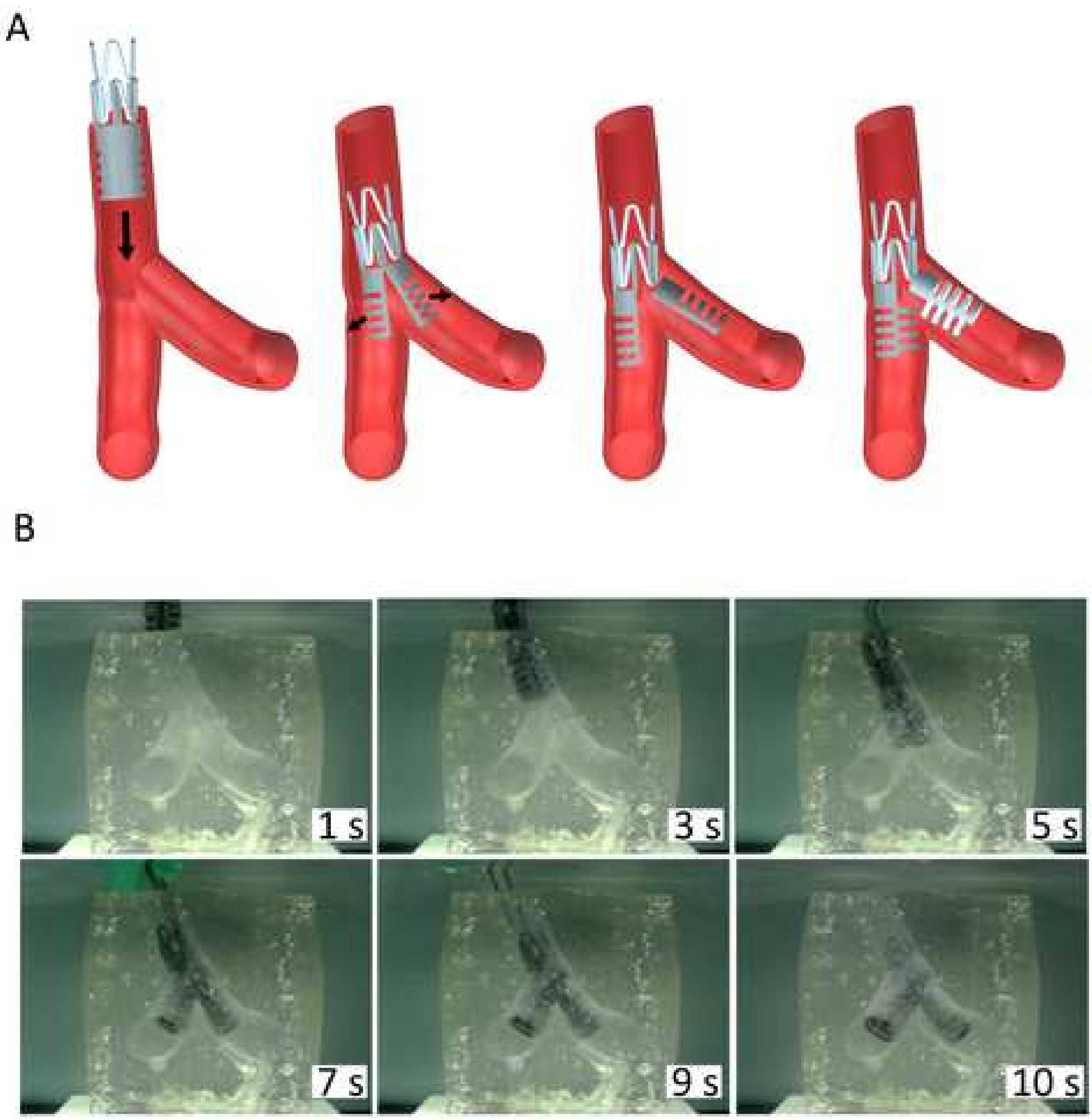

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Name of Reagent/ Equipment	Company	Catalog Number
Fortus380mc	Stratasys	Fortus 380mc
Moment1 3D printer	Moment	Moment 1
PC(white) Filament Canister	Stratasys	PC(white) Filament Canister
PLM software NX 10.0	Siemens	NX 10.0
Sandpaper	DAESUNG	CC-600CW
Shape Memory Polymer filament	SMP Technologies Inc	MM-5520
silicon	Shinetus	KE-1606
Simplify3D	Simplify3D	Simplify3D 4.0.1

Comments/Description
FDM 3D printer for printing blood vessel mock-up
FDM 3D printer for printing bifurcated stent
PC filament for printing blood vessel mock-up
3D CAD modeling software
Smooting out the surface of the bifurcated stent
Shape memory polymer filament
silicon for blood vessel mock-up
Slicing software for model slicing

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Dear Editor

Thank you for the comments on the manuscript. We also appreciate the time and effort you and each of the reviewers have dedicated to provide insightful feedbacks on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

Editorial comments:

General:

1) *Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.*

⇨ We have carefully gone through the manuscript so that there are no spelling or grammatical issues.

2) *Please reduce the length of the summary-it should be between 10 and 50 words.*

⇨ We have reduced the summary to 10-50 words.

⇨ Original(1st submission) lines 23-26 with deleted sentences marked by a centerline:

Using ~~an FDM (Fused Deposition Methods)~~ 3D printer, ~~a highly viscous SMP (~~Shape Memory Polymer~~)~~ filament is extruded ~~through a nozzle and cooled~~ to form a branched tubular structure. The structure is patterned and shaped such that it can be contracted to a compact form once folded and would return to its formed shape when heated.

⇨ Revised lines 23-25:

Using a 3D printer, Shape Memory Polymer filament is extruded to form a branched tubular structure. The structure is patterned and shaped such that it can be contracted to a compact form once folded and would return to its formed shape when heated.

3) *Please number references in the order they are cited in the manuscript-currently, the first reference cited is number 10.*

⇨ We have renumbered the references in the order they are cited in the manuscript.

4) *JoVE cannot publish manuscripts containing commercial language. This includes trademark symbols (™), registered symbols (®), and company names before an instrument or reagent. Please limit the use of commercial language from your manuscript and use generic terms instead. All commercial products should be sufficiently referenced in the Table of Materials and Reagents.*

For example: Siemens NX, Simplify3D

⇨ We have removed all commercial products in the paper. Instead, we put them in *the Table of Materials and Reagents.*

Protocol:

1) *Please ensure that all text in the protocol section is written in the imperative tense as if telling someone how to do the technique (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "Note." However, notes should be concise and used sparingly.*

⇨ All texts in the protocol sense has been changed to an imperative tense. We have removed all usages of phrases such as "could be," "should be," and "would be" in the *Protocol*.

2) *Please split up Protocol steps so that individual steps contain only 2–3 actions and a maximum of 4 sentences.*

⇨ The Protocol steps are now divided into 7 steps and individual steps contain only 2-3 actions and a maximum of 4 sentences.

3) *The Protocol should contain only action items that direct the reader to do something. Please move the discussion about the protocol to the Introduction, Results, or Discussion, as appropriate.*

⇨ Discussions in the Protocol have been moved to the *Discussion* and *Results*.

4) *There is a 10 page limit for the Protocol, but there is a 2.75 page limit for filmable content. If revisions cause the highlighted portion to be more than 2.75 pages, please highlight 2.75 pages or less of the Protocol (including headers and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol.*

⇨ The highlighted portion is now less than 2.75 pages.

5) *Please add more details to your protocol steps. Please ensure you answer the "how" question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. If revisions cause a step to have more than 2-3 actions and 4 sentences per step, please split into separate steps or substeps.*

⇨ We have added more details to our protocol steps.

Specific Protocol steps:

1) *1.1: Please provide more detail on making the vessel model and/or a sample file (as supplemental materials). Also, what material is used for 3D-printing?*

⇨ The digital model file for the vessel model has been provided as supplemental materials in STL format, the most commonly used file format in 3D printing.

2) *2: This section is confusing-it doesn't seem to have anything to do with the main purpose of the procedure (to make the stent) and is probably better in the introduction.*

⇨ We have removed lines that are unrelated to the processing procedures. The original and the revised sections are as follows:

⇨ Original(1st submission) lines 151-168 with deleted sentences marked by a centerline:

2. Fabrication of the branched stent based on kirigami

Note : The size of the branched stent is made to snuggly fit inside the 'Y' shaped pathway of the blood vessel mockup.

~~2.1) The branched stent is modeled to replicate the branched vessels.~~ The interior is made hollow and the surface tubular meshes are designed to functionally fold and return to the full unfolded configuration. The trunk of the bifurcated stent follows wavy patterns similar to conventional stents. ~~The bifurcated branches are designed following the kirigami structural pattern as shown. **Figure 5A.** shows how the kirigami can be used to transform a flat sheet into a tube. Firstly, multiple horizontal incisions are made horizontally as shown in the left figure of **Figure 5A.** Subsequently, stripes between the incisions are pushed by alternating the pushing directions as shown in the right figure of **Figure 5A**. The resulting shape forms a tube. Notice we have purposely put creases at the center of the stripes to permanently fix the transformed shape for illustration purposes. In practice,~~ we designed the shape to be cylinder as shown in **Figure 5B**. The diameter of the ~~trunk and the~~ branch is ~~22mm and~~ 18mm~~, respectively~~. The total length of the stent is 72mm. ~~Each~~ length of the ~~truck and the~~ branch~~es are 38mm and is~~ 34mm. The final shape is shown in **Figure 6**.

⇨ Revised (line 143-153):

3. Design of the branched stent based on kirigami

Note : The size of the branched stent is made to snuggly fit inside the 'Y' shaped pathway of the blood vessel mockup. The interior is made hollow and the surface tubular meshes are designed to functionally fold and return to the full unfolded configuration.

3.1) The trunk of the bifurcated stent follows wavy patterns similar to conventional stents. The diameter of the trunk is 22mm and the length of the trunk is 38mm.
3.2) Design the bifurcated branches to be a cylinder as shown in **Figure 5B**. The diameter of the branch is 18mm and the length of the branch is 34mm.
3.3) The total length of the stent is 72mm. The final shape is shown in **Figure 6**.

4. *3.1: Please include a file containing the stent model used for printing as supplemental material.*

⇨ The digital model file for the vessel model has been provided as supplemental materials in STL format, the most commonly used file format in 3D printing.

5. *3.3: Please include the sandpaper used in the Table of Materials, and please include a little more information about the sandpapering process.*

⇨ We have added detailed production information of the sandpaper in the Table of Materials and the Protocol. Sandpapering process is written in more detail as follows:

⇨ Original(1st submission) line 196-202 with deleted sentences marked by a centerline:

~~3.3: Due to the complex shape of the bifurcated stent, the surface quality of the printed result was rough. Several steps are needed to smooth out the surface quality. This is~~ required because rough surfaces can damage the vessels by abrasion. ~~Three steps involved in the post-processing are shown in **Figure 9**. We first~~ remove the supporters using cutters. ~~Subsequently, the surface is~~ rubb~~ed~~ against a sandpaper. ~~Lastly,~~ the surface ~~can be~~ spray painted. ~~In the demonstration, we used~~ black paints to enhance the contrast between the silicon vessel mockup and the stent.

⇨ Revised (line 168-182) paragraphs with red font on the added details:
5. Smoothing out the surface

Note : Following steps are required because rough surfaces can damage the vessels by abrasion.

5.1) Remove the supporters using cutters **(Figure 9A)**. The supporters are attached at the interior of the stent. When removing the stents, extreme cautions need to be exercised not to tear the stents.
5.2) Rub the surface against a sandpaper **(Figure 9B)** to remove layer lines, striations, or blemishes on the printed surface. Repeated polishing may be needed where the supporters are removed by cutters.

5.3) Paint the surface using a spray. A well-ventilated location is desired and a personal mask must be worn. The surface must be cleaned, sanded, and dried. Protect from overspray by applying thin layers of repeated paints. Black paints were used to enhance the contrast between the silicon vessel mockup and the stent **(Figure 9C)**.

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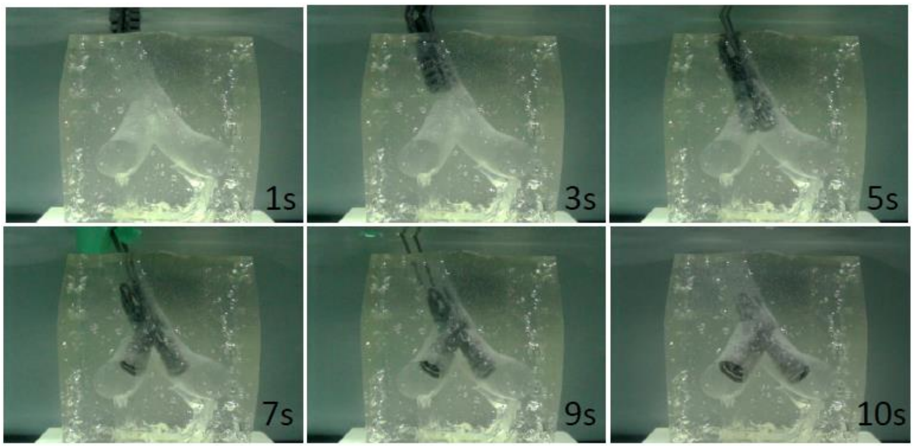
⇨ All figures in the manuscript are entirely different from the ones in the *previous paper (Scientific reports, 8(1), 13911. doi:10.1038/s41598-018-32129-3).*

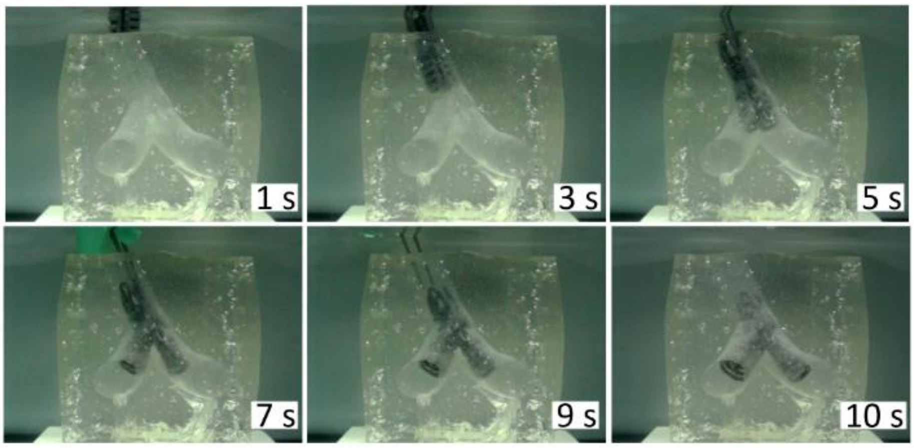
2) *Figure 12B: Please include a space between numbers and their corresponding units (e.g., '1 s' instead of '1s').*

⇨ We added a space between numbers and units. White backgrounds are also added for better readability.

⇨ Original(Figure 12B).



⇨ Revised(Figure 12B).



References:

1) *Please do not abbreviate journal titles.*

⇨ There are no abbreviated journal titles in the references.

Table of Materials:

1) *Please ensure the Table of Materials has information on all materials and equipment used, especially those mentioned in the Protocol*

⇨ We have added the production information of the Sandpaper and the material used for the vessel model printing in the Table of Materials.

Reviewer 1 :

Manuscript Summary:
In this manuscript the authors describe the obtaining, through a novel and versatile technique (3D printing), a Y-shaped stent, in order to be used for widening or unlocking the branched vessels. The protocol is well described and presents interest for scientists dealing with medical devices or implants. I recommend the manuscript for publication.

1) *Major Concerns:*

I have concerns regarding the material (thermal, morphological and mechanical properties and biocompatibility), but is not the purpose of the journal to study this.
This protocol is designed for a specific SMP and most probably would not work with other materials (with lower viscosity or Tg).

⇨ We agree that the user who wishes to use different SMP materials should find the 3D printing parameters suitable for their materials. However, finding such parameter should not be the main obstacle in reproducing the experiment as the differences in the 3D printing parameters are not significant for different SMP materials.

Reviewer 2:

4D printed bifurcated stent has been published by your group, which has the same kirigami structure with this manuscript. And the sections listed in this manuscript are also included in the previous paper (Scientific reports, 8(1), 13911. doi:10.1038/s41598-018-32129-3). I recommend that more is to be done to differentiate this work from your previous work, else, there is no novelty in this

work.
In the manuscript, the authors detail how to make a bifurcated stent.

1) *there are no characterizations for the printing filaments and performance tests for the bifurcated stent.*

⇨ The SMP material used in this study is provided commercially by SMP Technologies Inc. It is basically a polyurethane with some additives to increase the mechanical properties. The commercially available product is available in a filament form and has following properties **(Table 1).**

Density	1.21g/cm^3
Glass transition temperature	55℃
Poisson ratio	Below T_g : 0.40 Above T_g : 0.45
Tensile yield strength	48MPa

Table 1 The properties of shape memory polymer filament

2) *How did authors evaluate the stent's properties, such as biocompatibility, degradability, mechanical properties and so on?* These properties are crucial for the stent to ensure its effectiveness.

⇨ The purpose of this protocol is to clarify the processes in producing the branched stent based on kirigami patterns. The protocol explains in detail how a customized stent can be produced using an FDM printer. We do agree that the used materials need to be improved in respect to biocompatibility and degradability for the actual clinical usages. We have measured the elastic modulus of the material as a function of the ambient temperature. The results are shown in **(Table2)**.

Temperature(℃)	Elastic modulus(MPa)
22	444.4
25	403.74
27	257.6
35	141.2
45	33.38
55	5.98
65	2.84
75	0.67

Table 2. The measured elastic modulus of shape memory polymer filament using thermomechanical analysis(TA Instrument® TMA Q400EM™)

Reviewer 3:

The study by Yong-Gu Lee at al. describes a design approach to fabricate SMP stents where a tube-like stent is transformed/deployed into a Y shape configuration after activation at high temperature. The Y shape stent was printed using an FDM printer and subsequently folded/compacted into a tubular shape at high temperature. The folded form of the stent can recover its initial Y shape after activation using high temperature. The concept might be suitable for designing stents and, therefore, can be published in JoVE. In general, I recommend publication in JoVE after revising the manuscript.

General comments :

1) *The title emphasizes on 4D printing of stents which is not true. The SMP stent is programmed mechanically after printing. In addition, the proposed structure is not a kirigami design. Using*

'kirigami-inspired design' in the title seems to be more appropriate. It seems that many other kinds of cellular designs can be replaced by the kirigami design when the stent is made of SMP.

⇨ We have revised the title from "4D printed bifurcated stents with kirigami structures." to '4D printed bifurcated stents with kirigami-inspired structures."

2) *The summary must focus on description of the design and fabrication methodology rather than describing the concept of FDM 3D printing. In addition, it is expected, in this case, to highlight the benefit and application of the proposed approach.*

⇨ We have revised the text to explain the benefits of the fabrication methodology.

⇨ Original(1st submission) line 64-68 with deleted sentences marked by a centerline:

The complexity of the shape of bifurcated stents makes it a very suitable target for 3D printing. ~~3D printing is an additive manufacturing process quite different from the material removing manufacturing processes such as milling and cutting~~. Because shapes are made by repeatedly adding layer by layers of the sectional shapes of the target object, in theory, it can be used to fabricate parts of any shapes and sizes.

⇨ Revised (line 62-71) paragraphs with red fonts highlighting the benefit and application of the proposed approach:

The complexity of the shape of bifurcated stents makes it a very suitable target for 3D printing. Conventional stents are mass produced in standardized sizes and shapes. Using the 3D printing fabrication methodology, it is possible to customize the shape of the stent for each patient. Because shapes are made by repeatedly adding layer by layers of the sectional shapes of the target object, in theory, it can be used to fabricate parts of any shapes and sizes. Conventional stents are mostly cylindrical in shape. However, human vessels have branches and the diameters change along the tubes. Using the proposed approach, all these variations in shapes and sizes can be accommodated. And although we have not demonstrated, the used materials can also change within a single stent. For example, we can used stiffer materials where support is needed and softer materials where more flexibility is required.

3) *Authors should explain what are the alternative solutions to activate SMP, rather than using high temperature in human body which is harmful.*

⇨ The glass transition temperature (55℃) of the SMP used in the manuscript is certainly not possible to be used in humans. Furthermore, no biocompatibility test has been performed for this material making the clinical applicability more unlikely. However, there are materials that exhibit much lower glass transition temperature and at the same time also being biocompatible [9]. Thus, we believe by incorporating such materials, the approach will be viable.

[9] Lendlein, A. Biodegradable, Elastic Shape-Memory Polymers for Potential Biomedical Applications. Science (80-.). 296, 1673–1676 (2002).

4) *Despite the experiment shows branching of the stent after activation, deployment of stent seems to be impractical for real application since the load amplitude at high temperature is very low. Using inflatable balloons to accurately control the level of deployment is inevitable and should be discussed.*

- ⇨ As the reviewer has mentioned the load amplitude is low at high temperature. However, the temperature does not need to remain high after the unfolding. If the temperature is dropped after the unfolding, the load amplitude will be sufficient to support the collapsing vessel. In the real clinical usage, the used material has to be tailored to exhibit prescribed mechanical properties at certain temperature. Specifically, the triggering temperature should be slightly higher than the human body temperature such that the temperature is bearable to the human. Furthermore, the glass temperature should be higher than the body temperature so that the unfolded stent would retain its stiffness.
- ⇨ The inflatable balloons are commonly used in the conventional stent operations. These balloons are used in cylindrical stents. When they are to be used for branched stents, the number of balloons needs to match the number of cylindrical stents. The purpose of using the kirigami inspired stents was to avoid these complications.

And:

1) *In line 45, 'the limitations of our …' is very negative and should be replaced with a positive statement.*

- ⇨ We agree. We have changed the paragraph to a more positive statement as follows.
- ⇨ Original(1st submission) line 45-48 with deleted sentences marked by a centerline:
- ⇨ ~~The limitations of our method are that~~ although we ~~point to~~ the medical stent, ~~the material that we have used has not be proven to be safe on humans and also the material is not biodegradable and will remain at the target site indefinitely.~~
- ⇨ Revised (line 44-46) paragraphs with red fonts highlighting the added sentences:
- ⇨ Although we target our work on the medical stent, biocompatibility issues need to be solved before the actual clinical use.

2) *As mentioned above, this is not a kirigami design and the approach does not represent 4D printing of SMP stents.*

- ⇨ We have changed the title to “4D printed bifurcated stents with kirigami-inspired structure”.

3) *In line 74, 'material triggering ambient temperature' is confusing. In line 75, contraction of polymeric chains is not correct.*

- ⇨ We have changed the “ambient temperature” to the “glass transition temperature”. The “polymeric chains contract” has been changed to “segments become soft”.

4) *In line 85, authors explain: 'SMPs also enjoy additional benefits which are opposite to the problems of metallic stents mentioned above'. What are these additional benefits?*

- ⇨ The additional benefits include the ability to change the size and shapes, and the exclusion of necrosis. Rather than adding the additional benefits we have removed this sentence.

5) *The connection between the literature part and the design approach is poor.*

- ⇨ Due to the limitations in conveying the ideas through drawings we have included the whole model data in the Supplementary.

6) *In line 97, 'ingenuity' should be replaced by 'solution'. *

- ⇨ Correction has been made as suggested.

7) *Silicon, used in this manuscript, is a metal. The correct term is 'silicone'.*

⇨ Correction has been made as suggested.

8) *In line 139, 'modeling' should be replaced by 'CAD modelling'.*

⇨ Correction has been made as suggested.

9) *In line 156, it is not clear what do the author mean by 'the branched stent is modeled to replicate the branched vessels'.*

⇨ A paragraph has been added to explain this in more detail in line 210-213(Revised).

In other words, the interior surface of the branched vessels, where the bodily fluid is flowing, is offset further inside by the prescribed thickness of the fabricated stent. A solid form is created between the interior surface and the offset surface. This solid form exactly fits the vessel and can be used as the model for the stent.

10) *In line 191, the printing speed '3600mm/sec' is extremely high. Is it correct?*

⇨ We are sorry for writing a wrong printing speed. It should have been ‘3600mm/min’. We have corrected the error.

11) *In line 235, 'permanently memorizing its shape' is not true and needs to be removed. The SMP stent at its initial configuration is not programmed.*

⇨ We have removed this sentence.

⇨ The line 235 in the original submission

The original shape closely matches the branched vessels and has been 3D printed using the SMP material~~, permanently memorizing its shape~~

⇨ The lines 209-210 in the revised submission

The original shape closely matches the branched vessels and has been 3D printed using the SMP material.

12) *The manuscript contains several typos and grammatical errors and must be corrected carefully.*

⇨ We have carefully gone through the manuscript to correct the typos and grammatical errors.