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VASCULAR ARTERY SIMULATION MODEL FABRICATION FOR PRE-SURGERY KIT FOR STENT APPLICATION THROUGH 3D PRINTING

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ABSTRACT

Thrombosis occurs of a blood clot in the vein and blocking blood flow. The formation of a clot within the artery is called arterial thrombosis. Due to arterial thrombosis, there are heart attacks and strokes that result in more than 17.9 million deaths worldwide each year. Covid-19, one of today's problems, further increases the mortality rate. The thrombosis mechanism includes factors coming from the blood and the vessel wall. This mechanism is based on local blood flow mechanisms and 3-dimensional (3D) vessel geometry. Microfluidics chip-based vascular models examine the interaction between blood and the vessel wall in vitro studies in thrombosis. Until now, the 3-dimensional geometry of the arteries and blood flow system of healthy or unhealthy individuals have not been fully modeled. In this study, a patient-specific occluded blood vessel model was obtained from computed tomography angiography (CTA) data, and miniature vascular structures were developed with a 3D printer. These structures were printed using Acrylonitrile Butadiene Styrene (ABS). 3D ABS samples were used in Polydimethylsiloxane (PDMS) based soft lithography molds to occur microfluidic systems containing miniaturized replicas of in vivo vessel geometries. A comprehensive simulation of stented vasculature was performed by flow analysis of artificial blood and cell culture by placing a commercial stent on PDMS-based models. This project has aimed to develop and characterize modules by creating microfluidic systems using 3D printers to examine the effects of stents placed in the patient's complex vascular system and to simulate operations before treatment and stent placement.

Keywords: Patient-specific modelling, 3D printing, Microfluidics, Stent.

1. INTRODUCTION

The first reason of heart attacks and strokes is arterial thrombosis, causing more than 17.9 million deaths worldwide each year [1]. According to the American Heart Association, the number is expected to grow to more than 23.6 million by 2030. Due to increasing death, physicians constantly need to learn new skills in clinical treatment, for example; 3D printing helps in the struggle to keep up with an all-changing clinical environment [2]. Thrombosis is a complex process initiated by several genetic and acquired factors. For example, blood-borne factors, dynamic fluid effects, and vascular wall dysfunction. Although, animal models are the most appropriate experimental tool to study the pathophysiology of thrombosis in laboratory applications, even though these models mimic the mechanical multifactorial complexity found in arterial thrombosis but cannot completely explain human disease or human physiology. For instance, rodent platelet biology and clotting dynamics vary between species. Mouse thrombocyte differs from human platelets in size, number, and structure, but they are very similar functionally [3-4]. For this reason, in vitro blood flow chambers were perfused with blood, in vivo models were created and used [5]. In recent years, it has been observed that organs can be produced in chips designed in vitro. Thus, the samples were produced that show the characteristics of human physiology with

unprecedented realism [6]. Furthermore, it has enabled the production of 3D structures that realistically mimic the natural shape of human tissue with its complex structure and can be useful in replicating the structure of human blood vessels [7-8]. Microfluidic vascular systems have been modeled and fabricated to analyze blood flow and reveal defects and problems before the required applications and treatments for cardiovascular diseases [9-10]. Many years ago, surgeons had to depend on their anatomical knowledge of the human body and other things as they progressed through the operation. Computer technology is easier than the other approaches. Medical imaging technologies provide the data on 3D structure and function at the cellular, tissue, organ and organism levels. Computer-aided design (CAD) and computer-aided manufacturing tools are providing collection and digitization with the complex architectural information for tissues and organs. It can also be modified or designed, with the benefits of the usage of computer-aided design tools, on demand The idea of 3D printing surgical models is improved so soft tissues are 3D printed in parts or whole and provided to the surgeons [11-12].

Computerized tomography angiography scans were acquired from Digital imaging and communication in medicine (DICOM). These DICOM files, consisting of two-dimensional texture image segments, can be combined to produce 3D samples. These files were read and segmented with 3D-Slicer. All slices are converted to a 3D sample using the “model making” option in 3D-Slicer [13]. Especially, Fused Deposition Modeling (FDM) 3D could be the convenient technique to fabricate architecturally complex vessel design, also it has high printing resolutions for manufacturing microfluidic chips [14-15]. There were much current imaging and diagnostic technologies, such as magnetic resonance imaging (MRI) and computer tomography (CT), have been explored to acquire information about the targeting tissues and achieve the CAD data of the grafts. The CT imaging is based on the variable absorption of X-rays by different tissues. MRI also can provide high spatial resolution in soft tissue via using nuclear magnetic resonance. The contrast of biological structures can be strongly increased with the use of contrast agents. The area where 3D printing was most commonly used in cardiovascular. Bioprinting technologies and 3D printers help the pre-treatment of heart diseases. For example; modeling vessels for providing pre-operative studies, the development of organ models, and producing artificial organs. [16].

In this study, the complex vascular structure specific to the patient was modeled with the patient's computerized tomography data produced by using 3D printers and microfluidic systems. Afterward, a commercial stent was placed in this model, and a comprehensive simulation of the stent patient vascular structure was performed with artificial blood and cell culture flow analysis. The aim of this project is the development and characterization of modules using 3D printers and microfluidic systems in order to examine the effects of stents being placed in the patient's complex vascular system and to perform pre-trial operations before treatments. First, (Computed Tomography) CT or (Magnetic Resonance Imaging) MRI data of the patient's occluded vessel (.dicom) was obtained. This data then proceeds from the (.dicom) extension to the modeling stage with the 3D Slicer. In the modeling stage, the sample’s design was done using Solidworks. After the desired values were set, the sample was printed with an FDM-type 3D printer using ABS filament. The printed sample was placed in the prepared PDMS mixture [13-17]. The resulting product, after cooling at room temperature, was placed in a seventy-degree oven for four hours and placed in acetone. Necessary tests were performed on the emptied PDMS sample. Finally, the effect of the vessel geometries on platelet aggregation was evaluated by perfusing the vessel models at true arterial shear rates.

2. MATERIALS AND METHOD

2.1. Modelling of the Artery from CT Scan Data

Powder, liquid, or solids are widely used in 3D printing. These materials produce objects through layers. Starting from the bottom and each new layer accumulating was printed to adhere to the previous layer, this creates a gradual structure. The structure of the 3D printed sample was created by the Computer aided design (CAD) model loaded into the 3D printer (Figure 1). CAD models define 3D objects in a series of cross-section layers and allow 3D printers to physically reproduce the models in an additional process. CT scanning

was converted into a model using phantom [13-18]. In order for 3D printers to control, G-code encoding CAD models was used. Print speed, print head temperature, layer height, and pressure can be changed and optimized with the G code.

The sample has five steps in the phantom design process:

1.) Take CT from the patient,
2.) Make a simple model and smooth vasculature,
3.) Make design support for the vasculature,
4.) Support design model

3D printing the phantom (Figure 1).

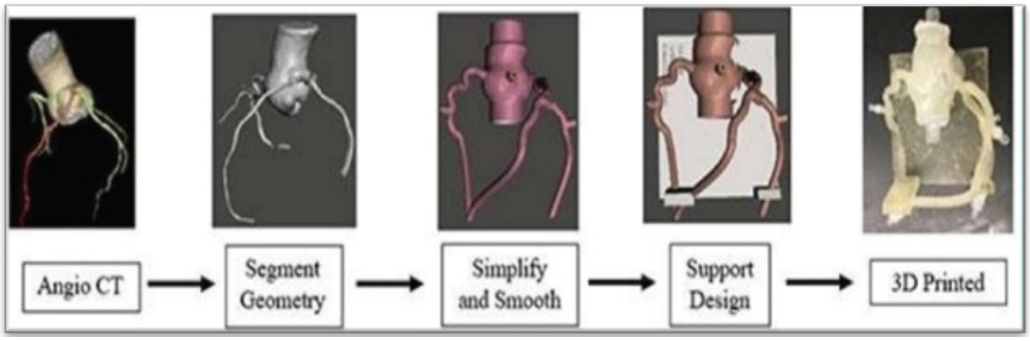

Figure 1. Reference negative sample [19].

ABS is a thermoplastic polymer. The filament has a diameter of 1.75 mm. It was used to print out the artery model by FDM 3D printer. ABS has a low melting point. Due to its use in injection molding and 3D printing easily, it is suitable for modeling negative samples [20]. The ABS was melted just above the glass transition temperature, and then a layer of layer was printed on the side or top of the extrusions to form the object layer. The filament was taken into the nozzle and squeezed at the hot and melted. Then deposited on the layers of the print bed. These layers were combined to accumulate during printing and form a finished negative sample. One of the biggest benefits of FDM 3D printing is its scalability. It can easily scale to any size, and this helps decrease the cost/size ratio. FDM printers are preferred because of their low part costs and simple design. Another advantage is the flexibility of the material. FDM printers can print a wide variety of thermoplastic materials [21-22].

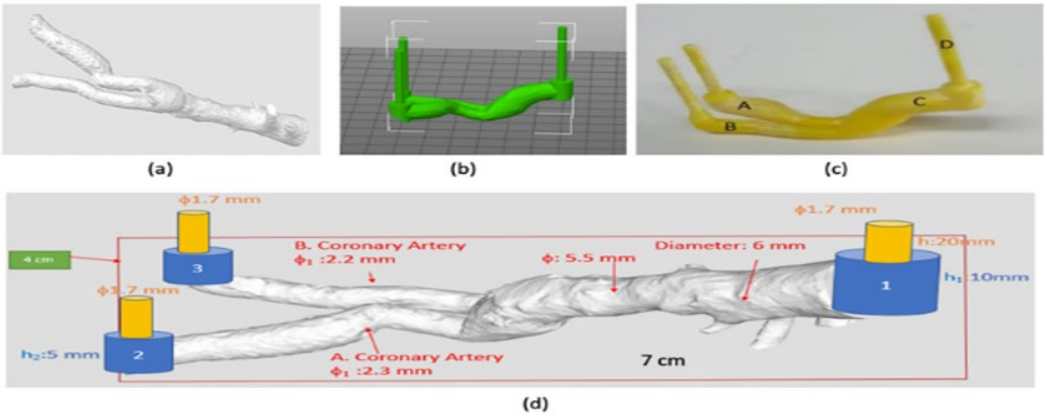

Figure 2. (a) The 3D sample of the artery from the DICOM data of CT scanning, (b) CAD modeling with additional channels for the inlet and outlet of the fluids of the macro fluidic system, (c) The fabricated negative sample, (d) Dimensions of the sample.

The disadvantage of FDM 3D printing is difficult to obtain highly detailed prints and part quality. The material must extrude in layers and must have a predetermined thickness. Another disadvantage of FDM is that each layer is unified. They create weak points in printing and make these prints unsuitable for certain applications [23]. The material formed after printing (Figure 2) and the dimensions of the negative sample (Table 1).

Table 1. Dimension of sample for Figure 2.

Thickness of main vessel [C]	0.475 cm
Diameter of feet [D]	0.9 cm
Thickness of lateral vessel – 1 [A]	0.4 cm
Thickness of lateral vessel – 2 [B]	0.25 cm
Length of feet [D]	1.3 cm
Length of body	3.5 cm
Width of main vessel [C]	0.52 cm
Width of lateral vessel – 1 [A]	0.475 cm
Width of lateral vessel – 2 [B]	0.27 cm

2.2. Fabrication of Negative Artery Model by FDM 3D Printer

The sample was formed from the computed tomography data. The sample was printed with the dimensions and thicknesses by 3D printing. The printing parameters in the FDM 3D printer (Table 2).

Table 2. FDM printing parameters for the artery sample fabrication.

Nozzle temperature(℃)	255
Bed temperature(℃)	100
Process time (min)	25
Sample of printing	Prusa i3s
Slice of program	Prusa slicer
Size of sample (%)	60
Layer of thickness (mm)	0.3
First layer thickness (mm)	0.35
Ambient temperature (℃)	Room temperature

2.3. Surface Treatment of the Printed Samples

In order to obtain transparent PDMS channels of the artery model, the surface of the negative sample has to be a mirror-like smooth surface. The rough printed surface (Figure 3a) was ground to obtain a smooth surface. The grinding paper was 2500. The ground ABS negative sample was held in the acetone vapor to obtain a polished mirror-like surface of the artery model. This process took approximately 15-20 minutes, keeping the temperature between 40-45 degrees (Figure 3b-c). It was left to cool at room temperature for 1-2 hours (Figure 3d).

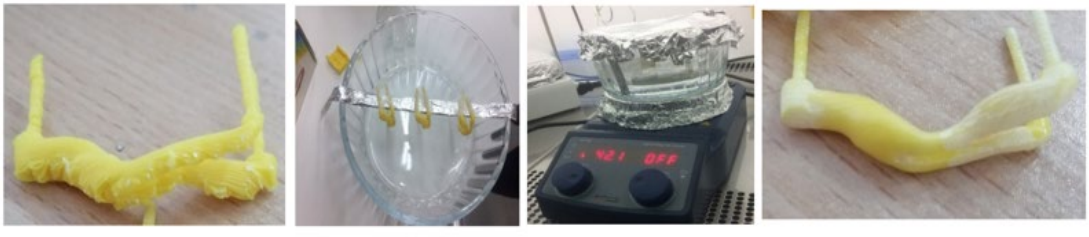

Figure 3. (a)Printed negative sample having rough surface,
(b-c) printed negative samples subjected to the acetone vapor bath at 40C for 15-20,
(d) polished sample.

Acetone vapor was maintained since the sample's feet were thin. This may result in issues like rupture. As an alternative way, the vaporization time of the sample was shortened, and the sample was immersed in acetone directly at room temperature with the aid of tweezers in acetone for 2-3 seconds. The surfaces of the first printed sample and the sample immersed in acetone are quite different**.** The surface of the sample immersed or waited in acetone vapor was almost smooth.

2.4. Fabrication of the Flexible Artery Samples

PDMS was used to fabricate the artery sample because of its high flexibility, visibility, and

transparency. Also, PDMS has a large molar volume, a low cohesive energy density, is very resistant to ozone and corrosion, stable to atomic oxygen and even oxygen plasma. Other advantages are that the ability to form films, high permeability to various gases, hydrophobic nature, ability to move freely, surface activity, and inertness against chemical and physical effects [24].

The PDMS and the current agent have been mixed at a rate of 10:1 for 5-6 minutes [14]. The mixing process was carried out to ensure that the PDMS and the binding agent were homogeneously combined. After the mixture was prepared, too many air bubbles were observed in it. After the mixture was prepared, a lot of air bubbles were observed in it. A vacuum desiccator was used for approximately 45-60 minutes to remove these air bubbles. The negative sample is made of ABS placed in. molds. As can be seen from Figure 4a, the sample did not touch the left, right and bottom of the container (Figure 4a). After the prepared PDMS was poured on it, it places in the vacuum desiccator to get rid of the air bubbles that formed inside it. It was held for 30-45 minutes. The sample was placed in the oven where the temperature increased to 70 degrees. After 4 hours in the oven, the curing of the PDMS was completed and allowed to cool to room temperature. After the sample reached sufficient temperature, it was removed from the container (Figure. 4b).

The negative vessel sample occurs of the ABS polymer. The sample material is PDMS so, the negative sample inside needs to empty, i.e. to melt the ABS polymer. The ABS polymer had been waited in acetone for three days (Figure 4c), so the ABS polymer was softened. To speed up the dissolving of the ABS polymer completely, acetone send to a vein by syringe. After the ABS dissolved 70-80 percent, the sample had been placed into new acetone. The sample should not hold in the same acetone for a long time. Acetone was changed day by day. When the ABS dissolved in the acetone, the liquid turned yellow. After the ABS dissolved completely, the sample held in the new acetone for one day in order to optained a quite clean and transparent model (Figure 4d).

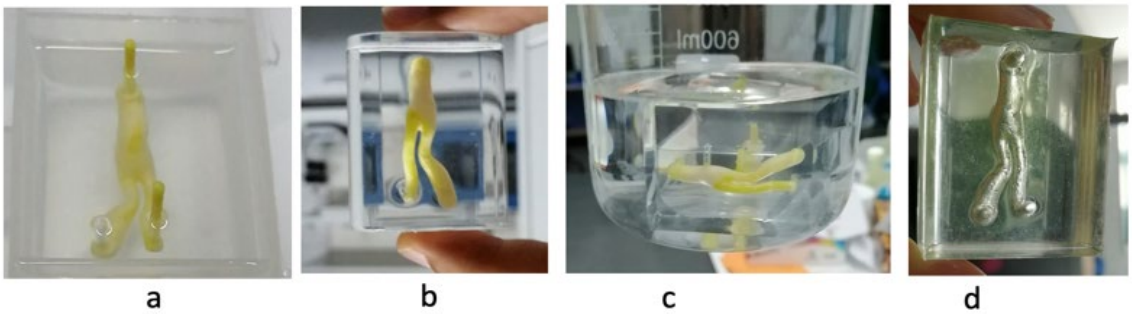

Figure 4. (a) The negative sample was replaced in the PDMS mixture, (b) the sample was cured in the oven (c) The sample was thrown into acetone to dissolve ABS, (d) The ABS solve in the negative sample.

2.5. Stent Placement in Sample

The balloon stents should be pushed into the desired hole (Figure 5a), air was given to the balloon in the stent to inflate, thus opening the stent (Figure 5b). The process of giving air is called the positive direction. Next, the air must be drawn in the negative direction. After the wire and balloon were removed from the stent, they must be removed from the sample. In this way, stent placement is completed.

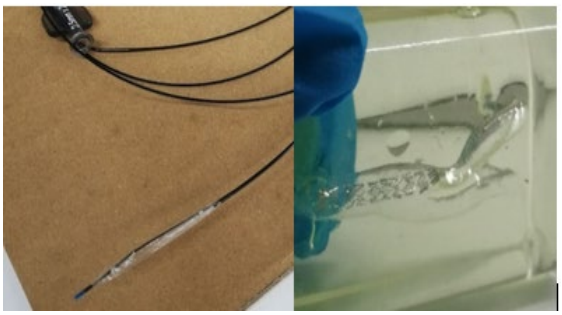

Figure 5. a) After the stent was placed and the balloon was inflated and b) the stent was placed in the sample.

After the stent was placed in the samples, they were cleaned with ethanol or pure water. Ethanol was used as an antibacterial due to its antiseptic properties. Then apply 254 nm UV. UV rays with a wavelength of 254 nm neutralize any microorganism in water without creating any harmful by-products, odors, or tastes and without disturbing the natural properties of water. So, it was used as a disinfectant. After the blood was prepared, a suitable device was set up to pass through the sample. The sample was placed in the apparatus (Figure 6). Followed by nitrogen gas and the oxygen in the sample was swept. The temperature of the blood was set to 37 degrees. The peristaltic pump was set and operated at the desired value.

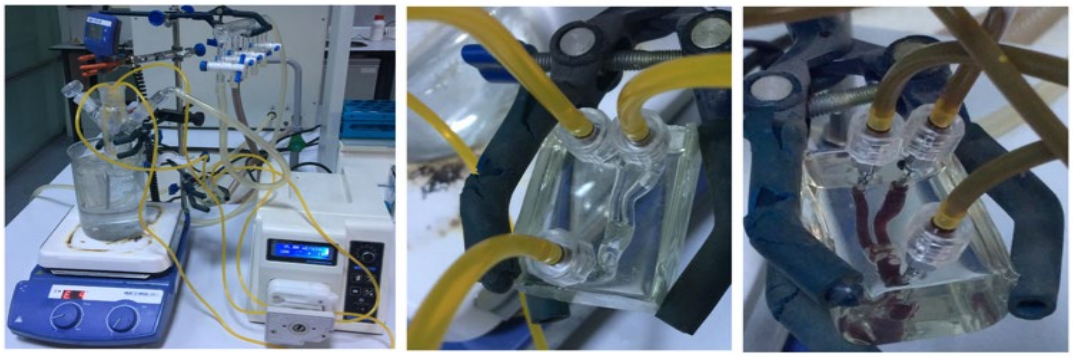

Figure 6. (a) Blood circulation setup, (b) the artery sample having stent without blood, and (c) the artery sample having stent without blood design of the dynamic test bench and close-up view of the sample

Nitrogen gas was introduced inside the blood reservoir before the blood circulated through the sample due to prevent blood clotting. Prepared blood circulated from the reservoir to the artery sample using a peristaltic pump with a flow rate of 35 ml/min through the stented sample. After the blood circulation, the stent-placed channel of the artery sample was cut to examine using a stereo microscope. Thus, the sample was enlarged and ready for observation. After the blood passed through the prepared sample, it was examined under a stereo microscope. The sample was examined from the outside without cutting. The stent placed in the examination is evident. Furthermore, a layer was formed on top of the stent. The inside of the sample was divided into two parts for examination (Figure 7). The accumulation of stent and vessel parts was investigated. In some areas of the stent, blood deposition was observed.

Figure 7. (a) Stent view within the sample, (b)The sample was divided into two

3. RESULTS AND DISCUSSION

3.1. Surface Treatment of the Printed Samples

In order to obtain transparent PDMS channels of the artery sample, the FDM 3D printed negative sample the surface which has to be smooth. That's why acetone vapor have been applied to the samples but the feet of the samples were thin so which caused the problems such as rupture. As an alternative way, they was shortened vapor time, and the sample was immersed in acetone directly at room temperature with the aid of tweezers in acetone for 2-3 seconds. The surfaces of the first printed sample and the sample immersed in acetone have quite different. The surface of the sample immersed or waited in acetone vapor has almost smooth. ABS sample printed with 3D has an extremely rough surface. That's why the sample needs to be grinded and held to acetone vapor or dipping it into acetone at room temperature is necessary. If enough surface roughness is not removed, air bubbles can be formed around the vessel sample when the sample was thrown into the oven (Figure 8a). Therefore, the first thing is that the surface of the sample was ensured to be smooth and then other steps were started. If the necessary steps were taken, the desired sample can be obtained (Figure 8b).

Figure 8. (a) uncomplete removing of the surface roughness and air bubbles (b) sufficient surface smoothness

The prepared PDMS mixture has a lot of air while mixing and if these bubbles would not remove, the PDMS could fill with bubbles around the sample when it was thrown into the oven. With the help of a desiccator, the air bubbles must be removed very well. PDMS was left in the desiccator for 30-45 minutes and then thrown into the heated oven. PDMS mixture was made in a clean container. It was covered when it was removed from the desiccator because PDMS absorbs the dust in the environment very easily. When the temperature of the sample coming out of the furnace reaches room temperature, it was removed from the molds and discarded into pure acetone. However, if the sample always remains in the same acetone, it takes the color of the dissolved ABS. The acetone of the two upper samples was changed once and the acetone of the side-by-side samples was changed twice (Figure 9).

Figure 9. The color depending on the frequency of changing acetone

Therefore, it should change acetone every day for four days and the samples looked much more transparent and non-yellowing than other samples. The acetone of the samples was changed daily and the sample with the desired properties was obtained. There were some difficulties in placing the stent. For example, the balloon may be damaged when inserting an unopened stent, or there may be problems with the stent coming back with the balloon when inflating the balloon and withdrawing the balloon after inserting the stent. In this study, the stent was collected in the mouth while the inflatable balloon was removed. When the stent remains in the body for a long time, it was covered with a layer over time due to the accumulation of blood tissue. The formation of this layer prevents the stent from performing its function and leads to the re-occlusion of the vessel. Therefore, the stent does not constitute a permanent solution for a long time.

4. CONCLUSIONS

In this study, a new approach was studied to develop patient-specific microfludic blood vessel model. Following conclusions were optained;

1. To remove surface roughness; After grinding, it was kept in acetone vapor at 40-45 degrees for 15-20 minutes, or negative samples can be dipped into acetone at room temperature for 2-3 seconds with the help of tweezers. This time can also be increased according to the surface roughness of the sample. In order for the samples not to turn yellow; Acetone was changed daily.

2. For stent placement; Feet was in the same direction as the veins.

3. To acquire images when connected to a peristaltic pump; The depth of the negative sample was less, and the gap was closer to the surface. Dynamically degradable testing was performed before animal blood was drawn to develop biodegradable stents. Pre-made samples can detect diseases or other conditions and can be used to help heal, treat, or prevent disease. Permanent implantation of the stent can alter the hemodynamics of blood flow and again cause vascular occlusion.

5. FUTURE RECOMMENDATIONS

Considering all the studies carried out, the vessel sample was designed in the most appropriate way and the vessel sample was obtained. For the homogeneous passage of blood; All veins should be the same height. The drawing of new sample was drawn with Solidworks (Figure 10).

Computational Fluid Dynamics is widely used to analyze the hemodynamic behavior and wall shear stress distribution in-stent arteries. It makes sense to simulate a steady blood flow, which can be useful in more complex simulations and significantly reduces computation time. These findings provide good insight into future stent placement designs to reduce re-occlusion [25].

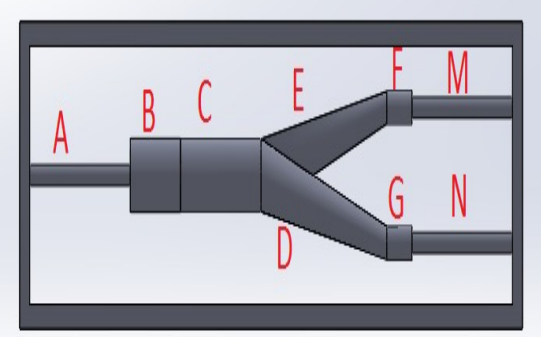

Figure 10. A illustration of new patient-specific microfludic blood vessel model.

The dimensions of the negative sample for printing a new sample (Table 3). It is important to choose the right frame for adequate use of PDMS and position the sample in the right place. The dimensions of the frame for choosing (Table 4).

Table 3. Dimensions of the negative sample.

Parts of sample	Length (mm)	Diameter (mm)
A	20	1.7
B	10	6
C	20	5.9
D	25	2.6
E	25	2.6
F	5	2.7
G	5	2.7
M	20	1.7
N	20	1.7

Table 4. Dimensions of the frame.

Length	100 mm
Thickness	2 mm
Height	6 mm
Width	25 mm

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