Research of Customized Aortic Stent Graft Manufacture

Lei Zhang[1, 2, 3], Xin Chen[1, 2, 3, *], Muhan Liu[1, 2, 3]

[1] Department of Mechanical Engineering, Biomanufacturing Center, Tsinghua University, Beijing 100084, P.R.China
[2] Biomanufacturing and Rapid Forming Technology Key Laboratory of Beijing, Beijing 100084, P.R.China
[3] Key Laboratory for Advanced Materials Processing Technology, Ministry of Education, Beijing 100084, P.R.China

[*]stoneszhang@mail.tsinghua.edu.cn

Abstract. Thoracic descending aorta diseases include aortic dissection and aortic aneurysm, of which the natural mortality rate is extremely high. At present, endovascular aneurysm repair (EVAR) has been widely used as an effective means for the treatment of descending aortic disease. Most of the existing coating stents are standard design, which are unable to meet the size or structure of different patients. As a result, failure of treatment would be caused by dimensional discrepancy between stent and vessels, which could lead to internal leakage or rupture of blood vessels. Therefore, based on rapid prototyping sacrificial core – coating forming (RPSC-CF), a customized aortic stent graft manufactured technique has been proposed in this study. The aortic stent graft consists of film and metallic stent, so polyether polyurethane (PU) and nickel-titanium (NiTi) shape memory alloy with good biocompatibility were chosen. To minimum film thickness without degrading performance, effect of different dip coating conditions on the thickness of film were studied. To make the NiTi alloy exhibit super-elasticity at body temperature (37℃), influence of different heat treatment conditions on austenite transformation temperature (Af) and mechanical properties were studied. The results show that the customized stent grafts could meet the demand of personalized therapy, and have good performance in blasting pressure and radial support force, laying the foundation for further animal experiment and clinical experiment.

1. Introduction

Aortic dissection is a kind of aortic aneurysm，which occurs when a tear in the endothelial causes blood flowing into the space between the mesothelial and endothelial, forcing the layers apart. Aortic dissection is an extremely sever lesion among vascular diseases. Without treated in time, the natural mortality rate could reach 36 to 72% within 48 hours after diagnosis [1].

The thoracic aorta consists of the thoracic ascending aorta and the descending thoracic aorta. According to whether the ascending aorta is involved, Stanford classification [2] divide aortic dissection into type A and type B. For type B, endovascular aneurysm repair (EVAR) has been widely used as an effective means for the treatment of descending aortic disease.

Aortic stent graft consists of film and metallic stent. Film material contains polyester, polytetrafluoroethylene and other biopolymers. As the implantation method of aortic stent graft mostly is self-expanding, metal part requires the super-elasticity of NiTi alloy shape memory alloy to unfold.

When insert the self-expandable metallic stent(SEMS), compress and fold the SEMS into a protective sheath, and implant the protective sheath into the location of lesion by the delivery system. Then, withdraw the protective sheath and the stent will gradually unfold by itself because of the super-elasticity of NiTi alloy. The stent will hold a structure to support the vessel and prevent further expansion of the aneurysm. As is shown in Figure 1.

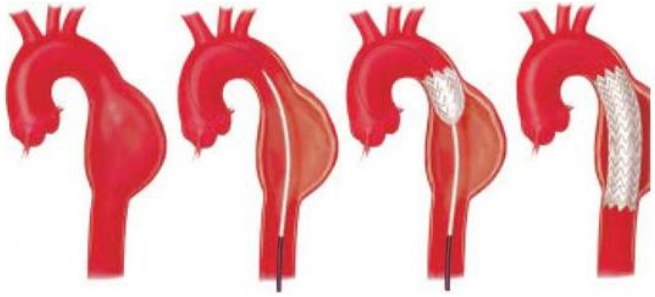

Figure 1. Implantation of aortic stent graft.

At present, size and structure of aorta stent graft are uniform. However, there are differences in the size or shape of each person's blood vessels. Mismatch stents may cause internal leakage or rupture of blood vessels, resulting in failure treatment. Therefore, we proposed a customized aortic stent graft manufactured process based on 3D printing. According to the real structure of patient's descending thoracic aorta, we can manufacture the personalized and suitable stent graft within a short time, which can avoid treatment failures cause by dimensional discrepancy. The stent manufactured by this process has good compliance and mechanical properties. The method will improve the success rate of endovascular aneurysm repair, represents one of the development directions of tissue engineering and medical 3D printing technology, has a good clinical application prospect.

2. Materials

2.1. Film materials

Existing aortic stent graft materials are mainly of polytetrafluoroethylene (PTFE) [3] and polyethylene terephthalate (PET) [4]. Polyurethane (PU) has become the preferred material for the replacement of PTFE and pet because of its good biocompatibility and easy formability. It has reported that [5], there is no difference about complications and patency between PU and PTFE after long term implantation in human body.

Polyurethane is polymerized by polyol (polyether and polyester), isocyanate and chain extender (diol and amine), containing -NHCOO- (carbamate) in backbone. According to the different types of polyol, polyurethane material can be divided into polyether polyurethane and polyester polyurethane. The hydrolysis resistance of polyether type polyurethane is very well, and it has a better biocompatibility than polyester polyurethane [5].

The polyether polyurethane, produced by Zhejiang Huafeng Chemistry Co., Ltd, has been used to the film of aortic stent graft. The material has been certified by the U.S. Food and Drug Administration (FDA), which has good biocompatibility and resistance to hydrolysis.

2.2. Metal materials

NiTi shape memory alloy has special practical value and widely application in medicine for its excellent super-elasticity, shape memory, and good biocompatibility [6, 7].

NiTi alloys exhibit super-elasticity (SE), which occurs at a narrow temperature range just above its transformation temperature; in this case, the material is in the austenitic state, exhibiting enormous elasticity, some 10~30 times that of ordinary metal.

2.3. Sacrificial materials

Sacrificial core material should be consistent with soluble in water and insoluble in organic solvents, non-toxic, good formability and other characteristics. Currently available materials include sugar and polyvinyl alcohol (PVA), etc. Polyvinyl alcohol, with low melting point, good biocompatibility, resistance to organic solvents and molding performance, is the ideal sacrificial core material [8].

3. Method

Additive Manufacturing (AM) [9], also known as 3D printing, is an advanced rapid prototyping method. Complex models can be manufactured by one-time molding. In this paper, AM technique was used as a part of the manufacturing process of stent graft.

A RP sacrificial core – coating forming (RPSC-CF) technique based on 3D printing was proposed by Zhang Lei [10], and multi-branched blood scaffolds with multi-layered wall were manufactured with the technique. Based on RPSC-CF, a customized aortic stent graft molding technique has been proposed in this research.

Step one, customized aortic stent was designed according to patient's computed tomography(CT). Step two, water-soluble and non-toxic sacrificial core was fabricated by fused deposition modeling (FDM), which is one type of 3D printing technique. Step three, bio-polymer materials was coated on the surface of the sacrificial core layer by layer with dip coating process. Step four, NiTi alloy were weaved on the stent, then bio-polymer materials were coated again to make film and metal stent integral. Finally, water-soluble sacrificial core was dissolute in water and customized aortic stent graft was manufactured.

4. Results

4.1. Design of customized aortic stent graft

4.1.1. Compute Tomography of Stanford B Type Patient. The CT image of the 82 years old male patient was provided by the Beijing Huaxin Hospital. According to stratification scan imaging data, the patient's thoracic aorta three-dimensional model was restored by Mimics10.01. After eliminating noise from other tissues and smoothing the surface, the thoracic aorta model is shown as figure 2.

Figure 2. Aorta three-dimensional model restored by Mimics10.01.

4.1.2. Structure Design of customized aortic stent graft. The aortic stent graft in this article is prepared for Stanford B. The diameter of the proximal end of the descending aorta is larger, and the distal end of the descending aorta is smaller. Moreover, due to individual differences, the diameter of the thoracic descending aorta presents irregular changes along the axial direction. Generally, the diameter of descending aorta near the heart is around 20cm, while elders' descending aorta near the heart may increase to 30cm due to loss of blood elasticity.

In order to accurately obtain the size information of the descending aorta, diameter is taken along the axial direction of the aorta by every 5mm, and then the three-dimension model of the stent is established by SolidWorks2012. Meanwhile, to make the stent adaptable and flexible to the structure of blood vessels, "corrugation" is designed to avoid the wrinkle caused by bend of vessels. At the same time, in order to make the stent effectively fixed in the disease area, the diameter of the main part of the stent should be greater than the diameter of the vessel 15%, the port diameter should be greater than 25% of the diameter of the vessel. The stent designed by us is shown as Figure 3.

4.1.3. Sacrificial Core Manufactured by FDM. In this paper, PVA wire with printing temperature of 180-210℃, produced by Shenzhen Esun Industrial Co., Ltd, has been used to be the material of 3D printing. The sacrificial core manufactured by FDM is shown as figure 4.

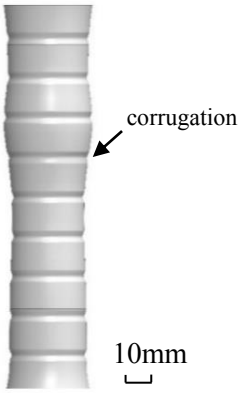

Figure 3. The sacrificial core designed according to the CT images of patient.

Figure 4. Sacrificial water solubility core manufactured by FDM.

4.2. molding process of film

4.2.1. Biocompatibility test of coated materials. Biocompatibility test is a criterion to evaluate whether a material is suitable to be biological materials. In this paper, hemolysis test and platelet adhesion test have been done to compare the biocompatibility of PU and PTFE.

Hemolysis test is to detect the broken red blood cells in the blood. The aim of the experiment is to test the influence of materials on the red blood cells. The national standard requires that hemolysis rate of the biomaterials to be below 5%. Results are shown as table1.

Although the hemolytic performance of PTFE is slightly better than that of PU, 0.46% of hemolysis rate is still far below the national standard. The hemolysis rate of the two materials are both substantially lower than 5%, which indicate that the damage degree of the two materials on the red blood cells is slight. The result shows that both the two materials have good hemolytic performance.

Table 1. Hemolysis rate of PU and PTFE

Materials	PU	PTFE	National Standard
Hemolytic Ratio（%）	0.46	0.03	5

Platelet adhesion test is to evaluate the blood compatibility of biomaterials. This test is especially important for materials to be implanted in the blood, because the adhesion of platelets on the surface of the material is an important step in the process of thrombosis.

By means of SEM, there is almost no adhesion of platelet on the surface of PU, however, a little platelet adhesion appears on the surface of PTFE. No large amount of aggregation on the surface of the two materials appear, presenting well in platelet adhesion test. As is shown in figure 5.

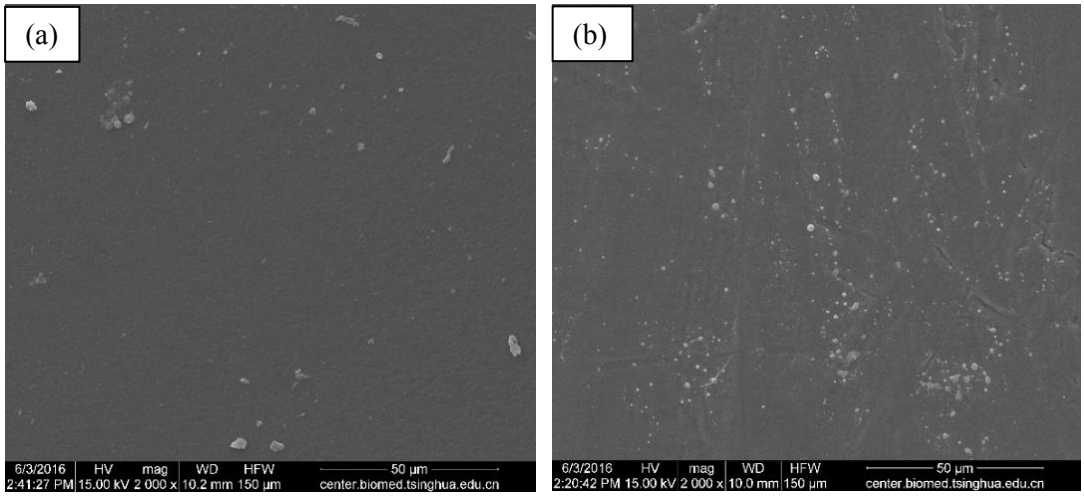

Figure 5. After Platelet adhesion test, surface of PU (a) and PTFE (b) were observed by SEM.

4.2.2. film-making process. The PU film was fabricated by dipping coating technique, which was proposed by Jenaer Glaswerk Schott & Gen in 1939 [11]. For flat substrates, film thickness [12, 13] is affected by the solution concentration, pulling speed, dip coating times etc.

Effect of solution concentration on film thickness. The mass concentrations (w/v) of polyurethane and tetrahydrofuran (THF) solution are 7.5%, 10%, 12.5%, 15%. PVA sacrificial cores with 10mm diameter are dip coated at a pulling speed of 8mm/s. After 5 times dip coating, dissolve the core in water and measure the film thickness. The result shows that the film thickness is exponentially related to the solution concentration, as is shown in figure 6.a.

Effect of pulling speed on film thickness. The PVA sacrificial cores are dip coated at the speed of 2mm/s, 5mm/s, 8mm/s and 10mm/s, respectively. Mass concentration of PU and THF is 12.5%. After 5 times dip coating, measure the film thickness. The film thickness exhibits a logarithmic relationship with the pulling speed, as is shown in figure 6.b.

Effect of dip coating times on film thickness. The PVA sacrificial cores are dip coated at the speed of 8mm/s and the mass concentration is 12.5%. After different dip coating times, dissolve the core and measure the film thickness. The relationship between film thickness and dip coating times presents exponential, as is shown in figure 6.b.

4.2.3. Optimum conditions of dip coating . Under the premise of ensuring film performance, thickness should be reduced as far as possible. Meanwhile, considering the stent should be manufacture in a short time, less dipping coating times and higher solution concentration as well as higher pulling speed should be adopted. However, excessive concentration increases the viscosity of the solution, which is not conducive to the volatilization of the solution. Furthermore, high speed pulling decrease the stability of dip coating. So pulling speed of 8mm/s, mass concentration of 12.5% and 4 times dip coating has been chosen to be the optimum dip coating conditions.

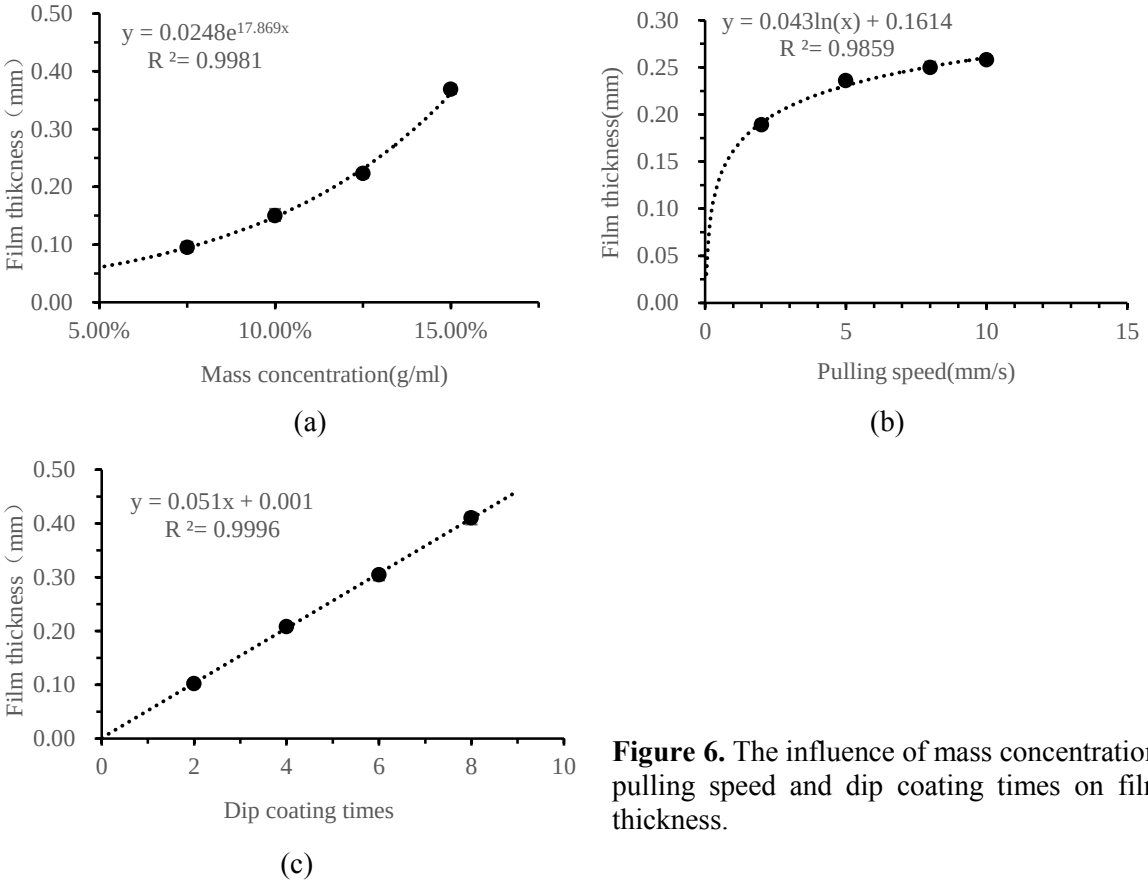

Figure 6. The influence of mass concentration, pulling speed and dip coating times on film thickness.

4.3. Nickel-titanium alloy and shaping process

4.3.1. shaping process of NiTi alloy. Self-expanding NiTi alloy aortic stent grafts rely on the super-elasticity to unfold at the diseased region, to support the blood vessels and prevent further expansion of aortic aneurysm. The super-elasticity appears when NiTi alloy is austenite. So heat treatment of NiTi alloy mainly has two purposes: on the one hand, shaping NiTi alloy; on the other hand, regulating the austenite transition temperature Af to ensure that NiTi has super-elasticity at body temperature (37℃). Obviously, the heat treatment conditions of NiTi alloys are essential to the performance of aortic stent graft.

4.3.2. Heat treatment conditions of NiTi alloy. In this paper, 0.30mm diameter NiTi alloy wire with austenite phase transition temperature (Af) of 12℃ has been used for the study.

Table 2. Element content of NiTi alloy.

Elements	Ni	C	Co	Cu	Cr	Nb	Fe	H	Ti
Wt %	55.65	0.0043	<0.005	<0.005	<0.005	<0.005	<0.005	<0.001	44.3~44.5

The heat treatment temperature of NiTi alloy is generally around 460~500℃. It's difficult to shape the alloy at low temperature. But excessive aging temperature will cause coarse grain, reducing the mechanical performance of NiTi alloy. Meanwhile, long aging treatment time will increase the austenite phase transition temperature Af. According to the TTT curve [14] of Ti-50.8%Ni alloy, aging treatment conditions of 5min, 10min, 15min, 20min, 25min at 460 C, 480 C and 500 C

respectively have been chosen. After that, the stress-strain curve and the phase transition temperature were measured.

4.3.3. Stress-strain cycle curve. Effect of aging time on properties of NiTi alloy. At the same aging temperature, the residual strain increases with the increase of aging time. When the aging time is more than 10mins, the residual strain is more than 3% at all conditions. As is shown in figure7. It shows that NiTi alloy underwent irreversible plastic deformation at a certain extent. As a result, it is not completely recovered the shape before deformation. Therefore, the aging time should not exceed 10min.

4.3.4. Differential Thermal Analysis. Differential scanning calorimetry (DSC) is a thermoanalytical technique which is able to measure phase transition point.

NiTi alloy in the austenitic state has good super-elasticityity, when can provide effective support for blood vessels. So the transition temperature of NiTi should be lower than body temperature 37℃.

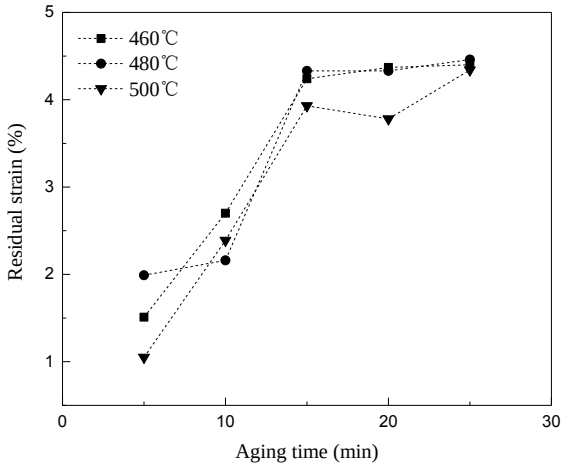

Figure 7. Influence of aging time on Residual Strain.

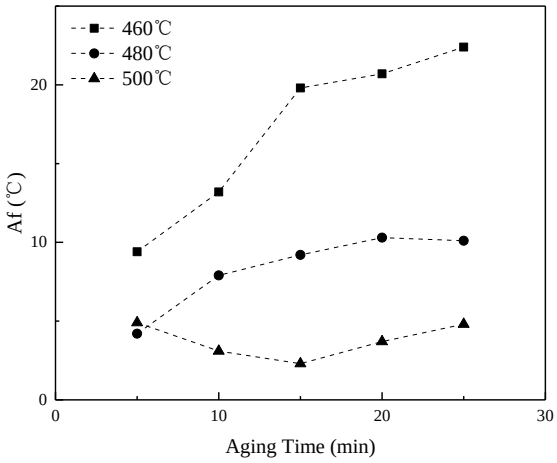

Figure 8. Influence of aging time on Af.

At 460℃ of aging temperature, the transition temperature Af increases rapidly with the increase of aging time. After 25min, the Af is increased from 12℃ to 22.4℃. So aging treatment should be avoided at 460℃. At 480℃ of aging temperature, the Af is also increased with the increase of aging time, but the increase is limited, and Af is controllable. The Af at the aging temperature of 500℃ first decreases then increases, also is controllable. As is shown in figure 8.

The support force of NiTi alloy increases with the decrease of transition temperature Af. NiTi alloys with very low transition temperature have a strong extrapolation, which could injure the blood vessels. Therefore, the transition temperature should be controlled at a reasonable range. So 480℃ is the optimum aging temperature.

4.3.5. Optimum aging treatment conditions of NiTi alloy. Aging treatment temperature should away from 460℃ to avoid rapid increase of transition temperature, and the aging time should not exceed 10min to avoid large residual strain. So aging time should stay within 5~10min at 480℃ or 500℃. But low transition temperature brings strong extrapolation to NiTi alloy. Therefore, 480℃,10min is the optimum aging treatment conditions.

The shaping mold of nickel-titanium alloy is shown as figure 9. Taking into account the thermal inertia of stainless steel mold, the appropriate heat treatment time is increased by 15min. So the optimum aging treatment conditions is 480℃, 25min. After aging treatment, the shape of NiTi alloy is shown in figure 10.

4.4. Aortic stent gragt

The NiTi alloy stent after the shaping treatment was wound on the sacrificible core coated with polyurethane. After twice dipping coating, the sacrificible core was dissolved in water and the customized aortic stent graft remained, as is shown in figure 11.

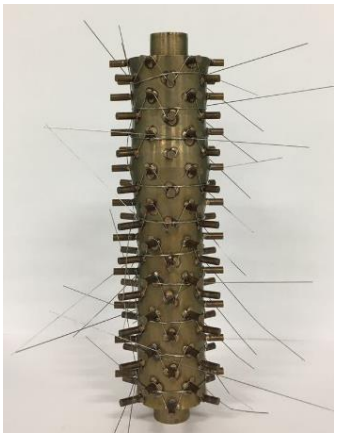

Figure 9. Shaping mold

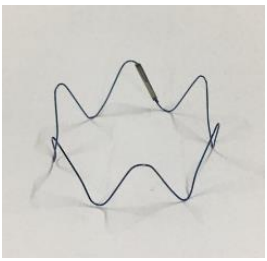

Figure 10. NiTi alloy after aging treatment.

Figure 11. Customized Aortic Stent Graft

4.5. performance test

4.5.1. radial support force. There is no uniform standard to measure the radial support force of the aortic stent. In this paper, bracing force at the moment when the stent is compressed 1/2 diameter, is defined as radial support, as is shown in figure 12. The radial support force of whole stent is 2.1N, and the single ring of the stent is 0.3N. So the stent graft can support an appropriate radical support force.

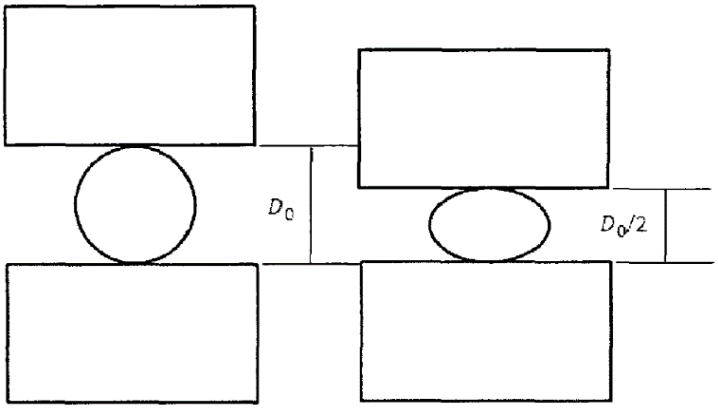

Figure 12. Test method of radial support force

4.5.2. Burst pressure. The endovascular pressure sustained by stent graft is essential to EVAR. Generally, the human normal systolic blood pressure rang is 12.0~18.7kPa, and the diastolic blood pressure range is 8.0~12.0kPa. The burst pressure of customized aortic stent graft is over 100kPa, which is safe enough for implantation into the descending thoracic aorta.

5. Conclusion

In this article, customized aortic stent graft was successfully manufactured by RP sacrificial core – coating forming technique. The stent graft has appropriate radical support force to support the vessels, and enough burst pressure to endure the blood press. Results show that, manufacturing technique of

customized aortic stent graft could meet the demand of personalized therapy, and improve the success rate of EVAR. Moreover, this study lying the foundation for further animal experiment and clinical experiment.

6. References

[1] Anagnostopoulos, C. E.Prabhakar, M. J. & Kittle, C. F. 1972. Aortic dissections and dissecting aneurysms. *The American journal of cardiology*, **30**, 263-273.
[2] Daily, P. O., Trueblood, H. W., Stinson, E. B., Wuerflein, R. D. & Shumway, N. E. 1970. Management of acute aortic dissections. *The Annals of thoracic surgery*, **10**, 237-247.
[3] Xue, L., & Greisler, H. P. 2003. Biomaterials in the development and future of vascular grafts. *Journal of vascular surgery*, **37(2)**, 472-480.
[4] Nerem, R. M., & Seliktar, D. 2001. Vascular tissue engineering. *Annual review of biomedical engineering*, **3(1)**, 225-243.
[5] BAO Junjie, LIU Dubao, LI Bing and XU Gewen. 2007. *Research progress of medical polyurethane materials [J]*, **64**, 72-79.
[6] Cutright, D. E., Bhaskar, S. N., Perez, B., Johnson, R. M. & Cowan, G. S. 1973. Tissue reaction to nitinol wire alloy. *Oral Surgery, Oral Medicine, Oral Pathology*, **35**, 578-584.
[7] Castleman, L. S., Motzkin, S. M., Alicandri, F. P., Bonawit, V. L. & Johnson, A. A. 1976. Biocompatibility of nitinol alloy as an implant material. *Journal of Biomedical Materials Research*, **10**, 695-731.
[8] Holloway, J. L., Spiller, K. L., Lowman, A. M. & Palmese, G. R. 2011. Analysis of the in vitro swelling behavior of poly (vinyl alcohol) hydrogels in osmotic pressure solution for soft tissue replacement. *Acta biomaterialia*, **7**, 2477-2482.
[9] Mellor, S., Hao, L., & Zhang, D. 2014. Additive manufacturing: A framework for implementation. *International Journal of Production Economics*, **149**, 194-201.
[10] ZHANG Lei, 2006, Fabrication and fundamental research of multi-branched blood vessel scaffolds with multi-layered wall[D]. Beijing: Tsinghua University.
[11] Geffcken, W., and Berger, E. 1939. Verfahren zur änderung des reflexionsvermögens optischer gläser. *Deutsches Reichspatent, assigned to Jenaer Glaswerk Schott & Gen., Jena*, **736**, 411.
[12] Landau, L. 2012. Dragging of; 2 Liquid by a Moving Plato. *Dynamics of Curved Fronts*, 141.
[13] GAO Feng and WU Junsen, 2000. Model deduction and verification of coating thickness in pumping process. *Metalware*. **26**, 6-10.
[14] YU Feng and LIAN Cheng, 2004. M, Biomedical nickel titanium alloy, *Science Press.4*

Acknowledgments
The study is supported by Beijing municipal health and Family Planning Commission (2016-2-4121). In this paper, I would like to express my gratitude to Li Lei, Tang Feng and Liu Sibo of Beijing Huaxin hospital. They gave me the guidance about thoracic descending aorta diseases, and provided the blood for the experiments. Meanwhile, thanks Professor Gong Qianming for providing the heat treatment equipment.