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Tissue Compatible Segmented Polyurethane Hollow Fiber as a Scaffold for Hybrid Blood Vessel

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The purpose of the research is preparation of a new-type hybrid artificial blood vessel with small inner diameter less than 4mm. We paid attention to the mechanical property and blood compatibility of the material for preparing such blood vessel. As a core material, segmented polyurethane (SPU) was used. The inner surface needs a good property with excellent antithrombogenicity initially but later adhesiveness of endothelial cells. Thus, the surface should be covered with blood compatible phospholipid polymer. On the outer surface, the smooth muscle cells (SMC) can be adhered and connected well with living organisms. Conditions required for such an artificial blood vessel are that there is pliability, which can control the dynamic characteristic by the cells and strong elasticity without blood disclosure. Since the core material should be avoided to make a mismatch of mechanical compliance, it needs to have the dynamic characteristic of living blood vessels; J-curve. Thus, we considered that porous structure of the core material is good for this purpose. The core material with a sponge structure was prepared from SPU and the phospholipid polymer by hollow fiber processing technique.

Key words: phospholipid polymer, hollow fiber, segmented polyurethane, J-curve, smooth muscle cell

1. INTRODUCTION

1.1 Overview of artificial blood vessels

Currently, cardiovascular disease is the secondary cause of death to malignant tumor and blood vessel disease including cerebrovascular disorder is the biggest killer. The best treatment for such disease is replacement by artificial blood vessels or auto grafts. Large-diameter artificial grafts are used in affected area such as thoracic aorta and aorta abdominals whose inner diameter is more than 10mm. And, medium-diameter artificial grafts are used in affected area such as femoral artery whose inner diameter is more than 5mm and less than 10mm. But, now, auto grafts are almost used and less small-diameter artificial grafts are used in affected area such as coronary artery whose inner diameter is less than 4mm. The serious problem of autogenously graft is that the diameter of grafts decreases and they are occluded by thrombosis because of arteriosclerosis. Accordingly, the development of small-diameter artificial grafts with good patency is urgently needed. If it can be, the reshuffle of blood vessels of diabetic foot ulcer can be and more early recovery is expected by sufficient blood supply to tissue under the skin of serious burn patients. And they have spillover effects on the improvement of safety of large- and medium-diameter artificial blood vessel and on application of an approach for binding site between artificial organ and living tissue.

Present small-diameter artificial graft has mainly the following problems; i) inner surface covered with mural thrombus after transplantation, ii) imperfectly-formed layer of endothelial cells, iii) compliance mismatch with native artery. As complete solution to these problems, we proposed tissue compatible hybrid blood vessel as follow.

For i)
Coating of antithrombogenic phospholipid polymer
For ii) Controlled-release of endothelial growth factor
For iii) Design of materials which have J-curve property

1.2. Design concept of inner surface

The reason why less small-diameter artificial grafts are used is that they are easy to be occluded. Presently, polyester and polytetrafluoroethylene are used as materials of artificial blood vessel in clinical use. After transplantation, blood induces foreign-body reaction against these materials and makes overall mural thrombus on the inner surface of artificial blood vessels. At this moment, small-diameter artificial grafts are occluded. In case of large-and medium-diameter, human vascular endothelial cells (HUVEC) grow groundling on the mural thrombus only 1-2cm from the anastomotic site and no one knows when the mural thrombus uncovered by HUVEC removes. So, in only part with the quick blood flow velocity, the mural thrombus become stabilized and the grafts keep going long term patency. In fact, in affected area with the slow blood flow velocity such as main vein whose inner diameter is more than 10mm, auto grafts are used.

Therefore, our research suggests a new-type inner surface, which promotes growth of HUVEC (Fig.1). First, the inner surface is covered with some gradient concentration by blood compatible water-soluble phospholipid polymer, composed of 2-methacryloyloxyethyl phosphorylcholine (MPC), *n*-butyl methacrylate (BMA), and 2-methacryloyloxyethyl butylurethane (MEBU). The MPC polymer could suppress blood coagulation well even when the polymer contacts with human whole blood without anticoagulant. Also, the MPC polymer with the MEBU moieties was good property to attach the SPU surface through hydrogen bonding between urethane unit in both the SPU and the MPC polymer.

Then, the drug delivery system of vascular endothelial growth factor (VEGF) in the core material makes entire field of the inner surface covered with HUVEC. To that end, we need to control the good timing that water-soluble phospholipid polymer begins to slowly dissolve as the speed of the growth of HUVEC. So that means we strive to do the temporal and spatial control of cell response in the material interface.

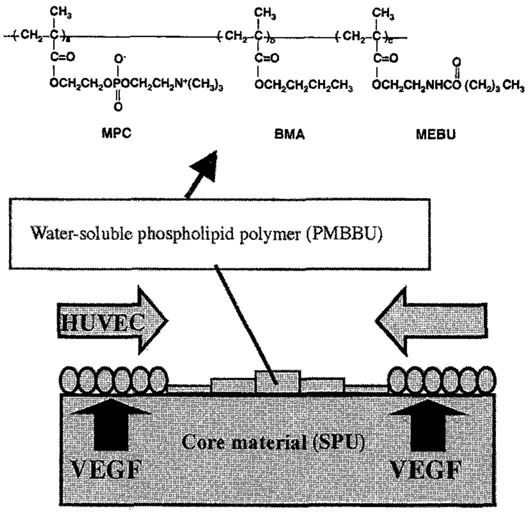

Fig.1 Our new-type inner surface.

1.3. Importance of mechanical compliance of materials

Tissue-engineered blood vessels have problems that the rupture strength of them is very weak – about 0.1 MPa – and the strength decreases as the scaffold degrades. Shortly, they have risk of vascular rupture and blood leakage after transplantation.

Recently, polyester small-diameter artificial grafts covered with polymer alloy of SPU and phospholipid polymer can have antithrombogenic property and maintain good patency over a period up to about eight months. They looked carefully at the situation in occluded grafts and found that all grafts are occluded at the anastomotic site [1-3]. Compliance mismatch between native artery and artificial graft is thought to be aftereffects of this occlusion.

Arterial tissue is continuously exposed to a dynamic mechanical environment induced by pulsatile blood flow that causes shear stress, pressure, and cyclic stretching.

Recent biomechanical studies have strongly implied that all these factors combined contribute to the maintenance or regeneration of vascular tissue structure.

Compliance is the structural property of a pipe that expresses a dimensional change in response to a change in intraluminal pressure. Compliance mismatch between native artery and artificial blood vessel has been long discussed as a cause of graft occlusion during a prolonged period of implantation of an artificial graft with a small diameter. It has been hypothesized that hemodynamical flow disturbance in an artificial graft and stress concentration at an anastomotic site, both of which may be effected by a difference in pressure dependent distensibility between a native artery and an artificial graft, and may effect thrombus formation in artificial grafts and an excessive tissue ingrowths at anastomotic sites, both of which become more detrimental as the diameter of the graft is decreased.

An extensive effort to incorporate compliance mismatch into the development of artificial blood vessels has been made from various aspects including materials, structure, and fabrication. Only a few studies have shown that compliant artificial vessels were experimentally using SPU, which has been proven to be a highly durable, minimally biodegradable synthetic elastomer. However, full bio-mimic compliance matching covering the entire physiological pressure range has not been designed yet.

1.4. Mechanical property of artery

Artery consists of intima, media and adventitia. Intima consists of HUVEC and basal lamina. Media consists of internal elastic lamina, SMC and external elastic lamina and it controls blood flow. Internal elastic lamina consists of erastin fibers whose Young's modulus is 0.2-0.5MPa. External elastic lamina consists of collagen fibers whose Young's modulus is 50-100MPa. Adventitia consists of fibroblast, elastin and collagen and it supports strength of vessels.

At low pressures, an artery can largely expand and contract elastically mainly due to elastin fibers, whereas collagen fibers remain unscratched. As the intraluminal pressure is increased, collagen fibers serve to protect against the pressure load and play an important role in preventing the rupture of the artery at high pressures. These histological and mechanical features of a native artery produce the specific J-curve in the stress-strain relationship. In contrast, commercially available artificial grafts such as polyester and polytetrafluoroethlene grafts, both of which are fabricated with nonelastomeric polymers exhibit little pressure-induced distension.

To minimize compliance mismatch between native artery and arterial graft prosthesis over the entire pressure regions, Sonoda and Matsuda proposed a coaxial double tubular artificial graft which consists of an enhanced compliant inner tube and a less compliant outer tube, both of which were fabricated rolling well-controlled multiply microporous SPU films [4]. Inserting the inner tube into the outer tube coaxially assembled double tubular grafts. First, the stress-strain relationship of canine common carotid arteries, which exhibited a J-curve, was determined as a targeted artery. Two determinant variables, the pressure-induced distensibility of each tube and the intertubular space distance, were defined and formulated in several models of coaxial double tubular SPU grafts, which had various intertubular space distances, micropore densities, and wall thicknesses. The distensibility of the inner tube determined the distensibility in the low-pressure regions, which was adjusted using wall thickness and microporosity. Thinner films with higher porosities resulted in a high pressure-induced distensibility in the high-pressure regions was realized using an outer tube with a thicker wall and lower microporosity. The intertubular distance using the theoretical values determined the transition point from low- to high-pressure regions. On the basis of these results, they presented a prototype model of a coaxial double tubular graft, which show an inverse J-curve that is convex upward.

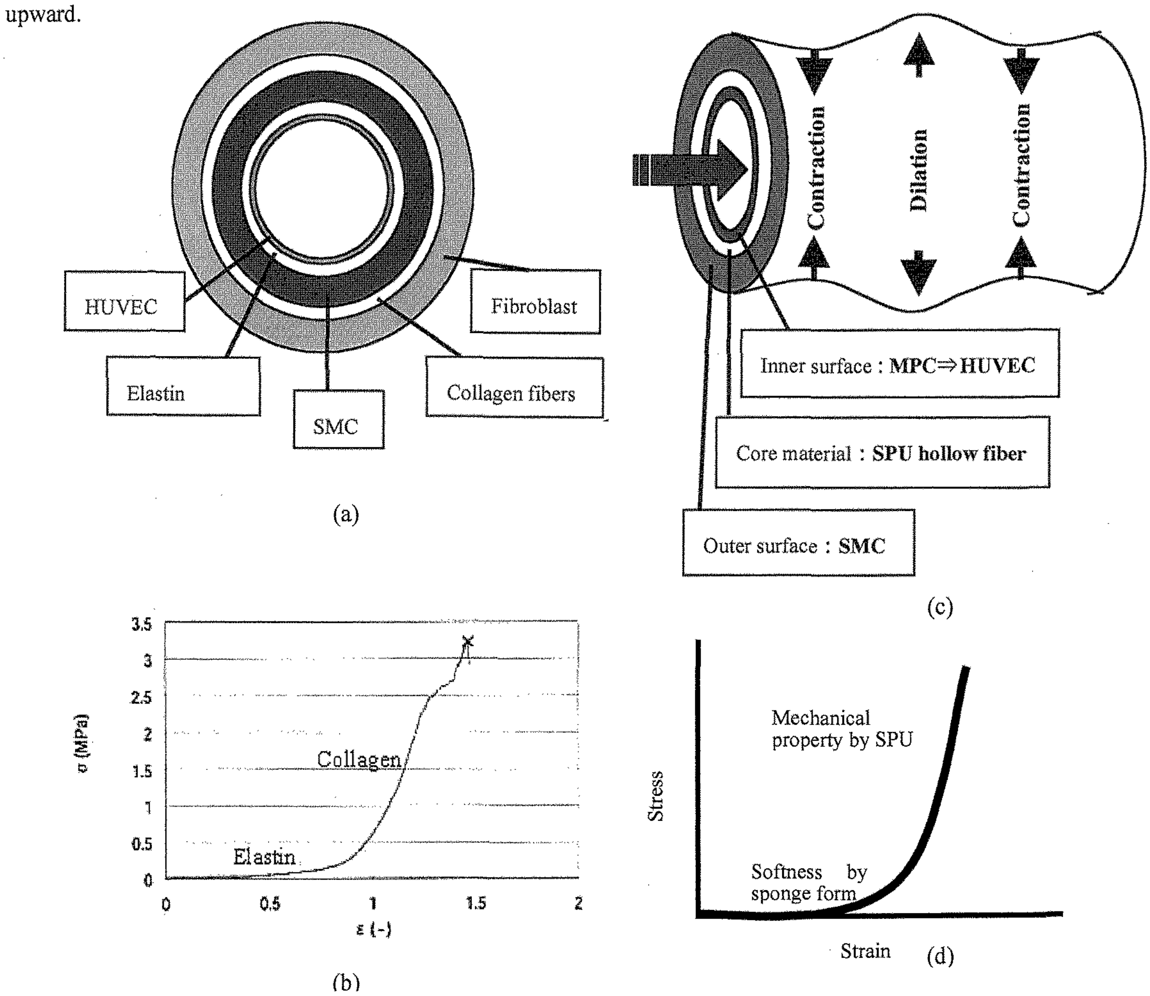

Fig.2 Fundamental design of new artificial blood vessels. (a) cross-section of integrated cell layer in natural vessel, (b) J-curve property of natural vessel, (c) materials design for new artificial vessel, (d) ideal J-curve property using SPU hollow fiber.

1.5. Concept of material design

We focused on hollow fibers as the core material, which has above mechanical property, J-curve.
As the material of hollow fibers, we used SPU which is good elastomer and has sponge structure that excels in self-sealing. Inner surface of the core material is covered with water-soluble phospholipid polymer all of which replace HUVEC. And besides, SMC are seeded and cultured on the outer surface of the core material. We try to make our new-type hybrid blood vessels distend and contract entraining native artery. Briefly, we try to prepare the artificial blood vessels which can control blood flow keeping time with cardiac cycle and whose inner surface replace HUVEC completely. In some future, we try to prepare the non-cell graft, which replaces cells that grow from native artery on both inner and outer surface.

2. EXPERIMENT

The solution of 15wt% SPU was prepared from *N,N*-dimethylformamide (DMF). We also studied other

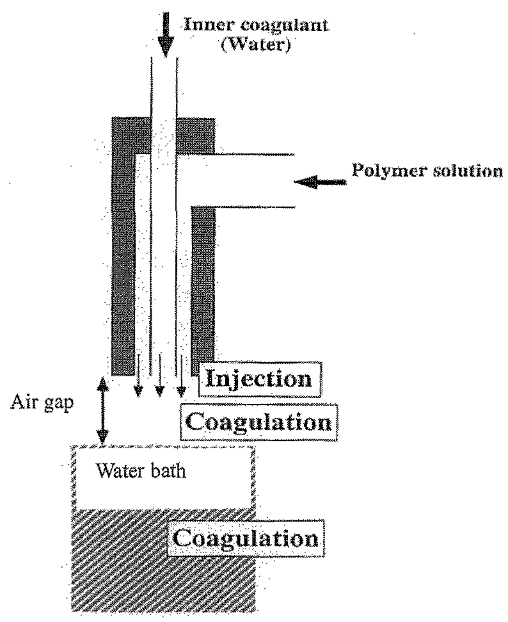

Fig.3 Preparation of hollow fiber

case that it was added 2wt% ethanol (EtOH). SPU hollow fibers were fabricated using a double injection nozzle with an annular spinneret by the dry-jet wet spinning process (Fig.3). The spinneret diameters of inner and outer tube were 15 mm and 20 mm. The polymer solution was pumped at constant speed (10 mL/min) by a metering pump. After leaving the spinneret, the SPU solution dropped freely by gravity into an outer coagulant (distilled water) bath [5-6].

3. RESULTS AND DISCUSSION

We showed a SEM cross-section (Fig.4) of SPU hollow fibers and their stress-strain curve (Fig.5) of them. The graph told us that whereas SPU hollow fibers have J-curve like native artery, their Young's modulus is bigger than it's one and is still stiff materials. Comparing with the rupture strength of the bovine artery – about 3.2MPa, one of SPU hollow fibers was about 1.8 MPa. But, outer surface of them covered with SMC will make its J-curve be close to the J-curve of the native artery. And, to be able to distend and contract by the contraction and relaxation of SMC, SPU hollow fibers must draw gentler J-curve than the native artery. Even if outer surface of the SPU hollow fibers will be covered with SMC, reinforcement of SPU hollow fibers with biodegradable materials is necessary just after transplantation. For the optimization of the core material, we need to know the changes of the structure and J-curve of it by the parameters; composition of polymer solution, air gap, temperature and evaporation time which control the degree of the porosity of SPU hollow fibers or by percents of hard-segment of SPU. First, we showed the change of the structure by a composition of polymer solution (Fig.6). The increase of the porosity will make the structure of the material be softer.

Ye et al. prepared polymer hollow fibers coated with the water-soluble MPC polymer using the same dry-jet wet spinning process. In this case, they used cellulose acetate as a core material, but other preparation condition is as the same as that in this study. Thus the inner surface of the SPU hollow fibers will be modified with the water-soluble MPC polymer.

We also evaluated the safety of the water-soluble MPC polymers using direct injection technique with animal. There was no side effect observed even when the amount of injection was up to 500 mg/kg-body weight. Thus, in the near future, we will synthesize the water-soluble MPC polymer, PMBBU (Fig. 1), and it will be coated on the inner surface of SPU hollow fibers whose sponge layer will have a drug delivery system of VEGF. And SMC will be cultured on the outer surface of SPU hollow fibers.

4. CONCLUSIONS

The SPU hollow fibers with porous structure could be prepared by the dry-jet wet spinning process. They had good J-curve property like one of the native artery. This method will be applied to make hollow fibers coated with the biocompatible phospholipids polymers, which contains inner coagulant solution.

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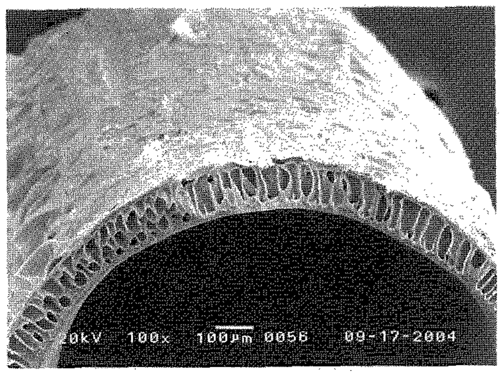


Fig.4 Cross-section of SPU hollow fiber

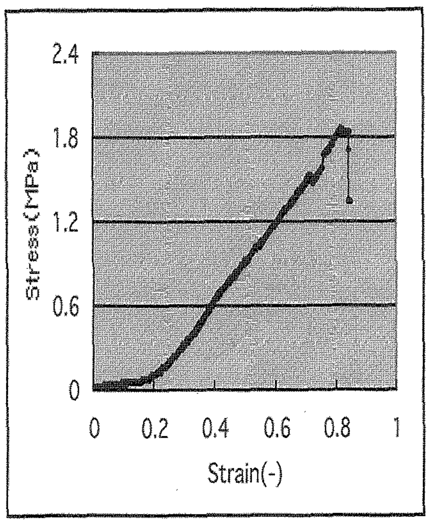
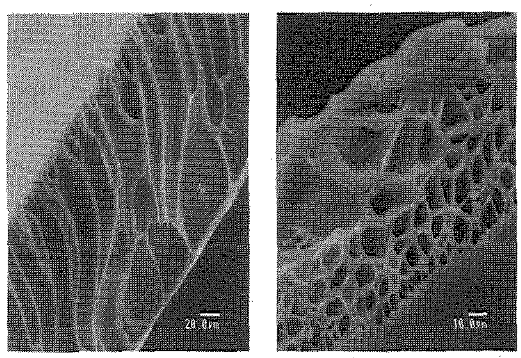


Fig.5 Stress-strain curve of SPU hollow fiber



(a) (b)

Fig.6 Cross-section of SPU hollow fiber
(a)EtOH 0wt%, (b)EtOH 2wt%

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