A self-renewing, tissue-engineered vascular graft for arterial reconstruction

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Supplemental material is available online.

Objective: Various tissue-engineered vascular grafts have been studied to overcome the clinical disadvantages of conventional prostheses. Previous tissue-engineered vascular grafts have generally required preoperative cellular manipulation or use of bioreactors to improve performance, and their mechanical properties have been insufficient. We focused on the concept of in situ cellularization and developed a tissue-engineered vascular graft for arterial reconstruction that would facilitate renewal of autologous tissue without any pretreatment.

Methods: The graft comprised an interior of knitted polyglycolic acid compounded with collagen to supply a scaffold for tissue growth and an exterior of woven poly-L-lactic acid for reinforcement. All components were biocompatible and biodegradable, with excellent cellular affinity. The grafts, measuring 10 mm in internal diameter and 30 mm in length, were implanted into porcine aortas, and their utility was evaluated to 12 months after grafting.

Results: All explants were patent throughout the observation period, with no sign of thrombus formation or aneurysmal change. Presence in the neomedia of endothelialization with proper integrity and parallel accumulation of functioning smooth muscle cells, which responded to vasoreactive agents, was confirmed in an early phase after implantation. Sufficient collagen synthesis and lack of elastin were quantitatively demonstrated. Dynamic assessment and long-term results of the in vivo study indicated adequate durability of the implants.

Conclusion: The graft showed morphologic evidence of good in situ cellularization, satisfactory durability to withstand arterial pressure for 12 postoperative months, and the potential to acquire physiologic vasomotor responsiveness. These results suggest that our tissue-engineered vascular graft shows promise as an arterial conduit prosthesis.

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We developed a tissue-engineered vascular graft for arterial reconstruction to facilitate renewing of autologous tissue without pretreatment and evaluated its utility in a porcine model. The graft showed morphologic evidence of good in situ cellularization, satisfactory durability against arterial pressure for 12 months, and potential to acquire vasomotor responsiveness.

Supported by a grant from the Ministry of Economy, Trade, and Industry in the Japanese government.

Received for publication Dec 29, 2006; revisions received May 15, 2007; accepted for publication June 25, 2007.

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J Thorac Cardiovasc Surg 2008;136:37-45

0022-5223/$34.00

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doi:10.1016/j.jtcvs.2007.06.039

Artificial vascular grafts manufactured from synthetic materials, for example polyester and expanded polytetrafluoroethylene (ePTFE), have been routinely used to reconstruct blood flow in patients with various cardiovascular disorders. Conventional grafts have clinically shown satisfactory durability; however, they still have several disadvantages, such as thrombogenicity, late stenosis and occlusion from intimal hyperplasia (especially in small caliber grafts), susceptibility to infection, and lack of growth potential.[1,2] To overcome these limitations in the search for an ideal artificial graft, various tissue-engineered vascular grafts (TEVGs) have been developed.[3] The utility and the clinical experience of these new grafts have been reported.[4-6] In TEVGs, a biodegradable polymer or a decellularized biomaterial is commonly used as a scaffold to enable host cells to rebuild the vessel architecture, and autologous cell seeding and culture or growth with bioreactors before the operation is usually necessary to improve their antithrombogenicity and performance.[1,2,7-11] These pretreatments involve complicated and invasive procedures, potentially leading to infection, and also require a certain period to complete, which means that pretreated TEVGs are not always available or may be unsuitable for an emergency

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Abbreviations and Acronyms

ePTFE = expanded polytetrafluoroethylene
HUVEC = human umbilical vein endothelial cell
PGA = polyglycolic acid
PLLA = poly-L-lactic acid
SMC = smooth muscle cell
SNP = sodium nitroprusside
TEVG = tissue-engineered vascular graft

case.[5] Furthermore, use of TEVGs has been mostly limited to low-pressure conditions because of their poor durability.[5,6,12]

For these reasons, we focused on the concept of in situ cellularization, whereby a population of living host cells is achieved in situ without any pretreatment by supplying a scaffold to support tissue self-renewal. This scaffold acts as an in situ incubator and bioreactor. Chen and colleagues[13] realized this concept in the regeneration of bovine chondrocytes by using a biocompatible material with excellent cellular attachment properties. We recently developed two promising novel patches for cardiovascular repair, a poly(lactic-co-glycolic acid) and collagen patch[14] and a tissue-engineered patch,[15] both of which showed good in situ cellularization in vessel wall reconstruction of large animal models. We hypothesized that an entire tubular graft fabricated from our patch would be an ideal vascular prosthesis that could acquire favorable morphologic features and also intrinsic vascular function matched to the native artery by means of in situ cellularization. This kind of TEVG has not yet been reported.

In this study, we designed a TEVG for arterial reconstruction that was expected to facilitate regeneration of autologous tissue without any pretreatment and assessed in situ cellularization after implantation in a porcine model. We also evaluated whether the implanted TEVG possessed adequate durability to withstand the hemodynamic stress of the systemic circulation in a long-term follow-up model and had acquired the physiologic vasoreactivity inherent in an artery.

Materials and Methods

Graft Design and Cellular Affinity

The new vascular prosthesis was made from a tissue-engineered patch[15] recently developed in our laboratory with greater biocompatibility and mechanical strength than previous materials used for cardiovascular repair. The patch has a three-layered structure: the interior (luminal side) is composed of knitted polyglycolic acid (PGA) compounded with collagen microsponge, the middle layer is polycaprolactone, and the exterior is composed of woven poly-L-lactic acid (PLLA; Figure 1A). It was provided by Senko Medical Instrument Mfg Co Ltd (Tokyo, Japan). All these materials are biocompatible and biodegradable and have received Food and Drug Administration clearance. The internal 3-dimensional porous structure of knitted PGA and collagen microsponge is expected to play a crucial role as a scaffold promoting in situ cellularization. The tightly woven layer of PLLA on the outside reinforces the patch,

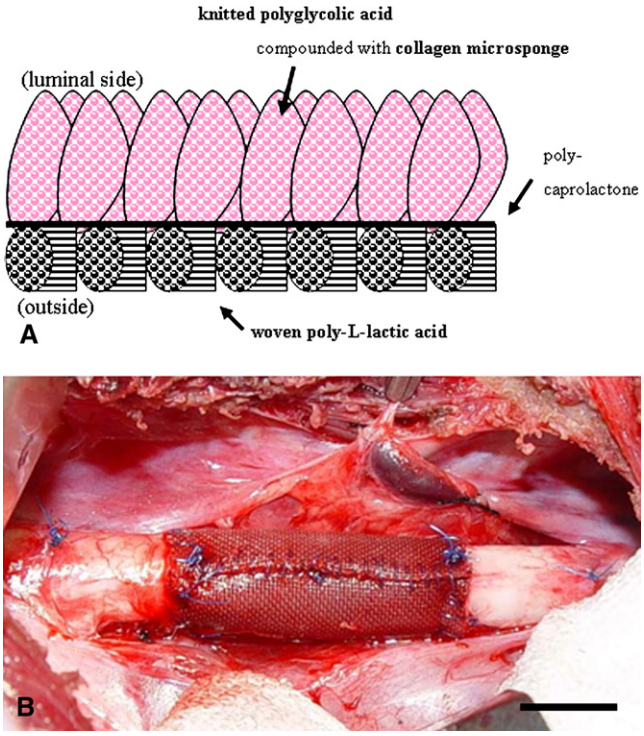

Figure 1. A, Scaffold design of polyglycolic acid/poly-L-lactic acid graft. Graft wall had three-layered structure: luminal side, knitted polyglycolic acid compounded with collagen microsponge; middle layer, polycaprolactone; outside, woven poly-L-lactic acid. B, Implantation of graft into porcine aorta. *Scale bar* represents 10 mm.

and a polycaprolactone film binds the PGA and PLLA layers to each other. Degradation tests (37°C) of the synthetic polymers, mainly involving hydrolytic reactions, demonstrated that the mechanical strength of PGA was no longer adequate by 3 weeks, whereas PLLA was degraded so slowly that its strength was maintained through 6 months.

Cell culture tests were performed to evaluate cellular affinity and proliferation in the materials used in this study. Two lines of cells, human umbilical vein endothelial cells (HUVEC; Cambrex Corporation, East Rutherford, NJ) and murine fibroblasts (NIH3T3; American Type Culture Collection, Manassas, Va) were seeded at a density of 300 cells/mm^2 onto knitted PGA with or without collagen microsponge, woven PLLA, and ePTFE (GoreTex; Japan GoreTex Inc, Tokyo, Japan) (n = 6), then cultured at 37°C at 100% humidity and in a 5% carbon dioxide atmosphere. The culture medium was Dulbecco modified Eagle medium (Gibco; Invitrogen Corporation, Carlsbad, Calif) supplemented with 10% fetal bovine serum (Sigma Chemical Co, St Louis, Mo) and 1% penicillin and streptomycin (Invitrogen). After 3 days of culture, the number of cells attached to each material was counted by a water-soluble tetrazolium assay (Dojindo Laboratories, Kumamoto, Japan).

Implantation in Porcine Models

A tissue-engineered patch was manually formed into a tubular shape with continuous 5-0 Prolene sutures (Ethicon, Inc, Somerville,NJ).

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