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Biologic vascular grafts in the venous position

To the Editor:

The recent article by Ratto and colleagues (*J THORAC CARDIOVASC SURG* 1991;102:440-7) demonstrated a new application of heterologous connective tissue tube grafts (glutaraldehyde-treated, ovine grafts) as vascular substitutes in the venous system. Previously, good results after implantation of these grafts in animals were reported by Perloff and colleagues,¹ but other investigators were not as successful. Although the graft itself is interesting and may be a step in the right direction toward finding a suitable material for venous replacement, the provocative findings of Ratto and colleagues raise some important concerns.

With light microscopy, Ratto and colleagues noted that the grafts were covered with a network of fibrin fibers, enmeshing platelets, and blood cells at 7 and 14 days after implantation. After only 2 more weeks, however, they suddenly noticed complete and regular endothelialization (day 28). Although the speed of endothelialization in venous grafts may be rapid because of good anchoring of endothelial cells in slow blood flow, their findings in only two grafts explanted at 1 month may not have been representative of the entire population. Because this is the most important period in the development of endothelialization, more observations may have been warranted. In addition, explanations between 14 and 28 days would have better defined how this rapid endothelialization may have occurred.

In the study of Ratto and colleagues, a staining method specific to endothelial cells would have identified the inner layer as endothelial. Peroxidase-antiperoxidase methods, which use a factor VIII-related surface antigen, are relatively easy to perform and have been used to correctly identify endothelial cells. This would have differentiated their findings of "completely and regularly endothelialized" connective tissue grafts from the expanded polytetrafluoroethylene graft neointima, which was "uniformly thinner than 200 μ m and . . . completely lined with an endothelium-like layer."

Three possible sources of endothelialization have been suggested: (1) endothelial cell migration from the anastomosis, (2)

circulating endothelial cells, and (3) migration of capillary endothelial cells through the graft from the perigraft tissue. In 1964, Wesolowski and associates² demonstrated that endothelialization from the anastomoses is slow, and it has also been shown that glutaraldehyde-treated biologic materials have a diminished affinity for cells on the luminal surface. More recently, Noishiki and coworkers³ demonstrated limited endothelialization (only 4 to 8 mm from the anastomoses) in heparinized, glutaraldehyde-treated ureteral grafts implanted into the canine inferior vena cava as long as 878 days after operation. The possibility of endothelial cell migration through the graft wall seems unlikely for similar reasons. Even though Ratto and colleagues implanted short grafts (3.8 cm) into the venous system of growing pigs, the source of the rapid endothelialization remains a mystery.

Ratto and colleagues did not discuss the cause of graft occlusion at 56 days in one of their collagen grafts. Was it intimal hyperplasia? Was it graft degeneration? Intimal hyperplasia is the main cause of graft occlusion in venous conduits in both the intermediate and long term. It therefore would not be surprising to see a short-term patency rate of 100% decrease significantly through the long term in the clinical setting. If the cause of graft occlusion was intimal hyperplasia or graft degeneration, this graft may not be as advantageous in clinical use, where long-term patency is the goal.

The report also raises some concerns with graft design and preimplantation treatment. Their Fig. 3 demonstrates multiple areas of thrombus deposition on the exposed Dacron polyester fibers only 1 hour after implantation. The origin of this phenomenon needs to be identified, but possible explanations can be suggested: (1) The graft was not fully matured or was injured during preparation. (2) The graft could not support the surrounding blood pressure adequately, even though it was in a low-pressure system. (3) The graft was extremely thrombogenic. Previous studies with similar grafts have also demonstrated important problems with connective tissue tube grafts implanted into the canine arterial system. For example, endothelialization is limited to the anastomoses at 12 months, and thrombus formation is common on the luminal surface.⁴ In the study of Christie, Ketharanathan, and Perloff,⁵ the cross-sectional area of the grafts increased during the long term; this may have been a result of their mesh framework with hexagonal interstices, which predisposed the grafts toward formation of pseudoaneurysms. Finally, glutaraldehyde-treated ovine connective tissue grafts have been found to be of limited usefulness because of bioincompatibility and degenerative changes.⁴

Glutaraldehyde treatment may not be as appropriate for the loosely arranged collagen fibers of a connective tissue tube as it is for biomaterials made of dense collagen fibers (heart valves and pericardium). Although dense connective tissue becomes strong after glutaraldehyde treatment because of the organization of its collagen fibrils, loose connective tissue tends to become rigid and brittle with glutaraldehyde treatment. In addition, glutaraldehyde is toxic and makes a biomaterial hydrophobic and bioincompatible. Alcohol-treatment may therefore be a better option to reduce antigenicity and maintain the graft's hydrophilic properties and cell affinity. In a study by Yamane,⁶ ethanol-treated bovine connective tissue tube grafts were implanted into the canine arterial system. Yamane demonstrated endothelial cells on the surface of the graft both extending from the anastomoses and appearing sporadically at the center of the graft 30 days after implantation.⁶ These findings suggest

a possible future for these grafts in both the arterial and venous systems.

In summary, no commercially available synthetic or biologic graft is adequate for venous replacement. We remain cautiously optimistic, however, that with significant improvements, collagen tube grafts may be of value in the future.

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Reply to the Editor:

In their letter, Drs. Tomizawa, Moon, and Noishiki raised some criticisms regarding the results we have obtained with glutaraldehyde-treated ovine collagen grafts implanted in the inferior vena cava of pigs (*J THORAC CARDIOVASC SURG* 1991;102:440-7).

They noted that only two grafts were removed 28 days after operation and there were no explantations between 14 and 28 days. They concluded that our findings may not precisely depict the phenomenon of graft endothelialization. However, the exact definition of the period during which ovine collagen grafts were completely endothelialized in growing pigs has little clinical concern. Great differences exist between human beings and experimental species with regard to the healing of vascular grafts. In particular, it has been suggested that 1-month results with the prosthesis in pigs may be considered to correspond to 3-month prosthesis results in the dog and 21-month results in human beings. Further, human beings have limited capacity for development of a complete endothelial lining. Data in the growing pig may thus be useful only as preliminary and general indicators of the prosthesis' potential. Because results cannot be extrapolated to human beings, chronologic elucidation of the endothelialization phenomenon did not seem essential.

Similar considerations could be applied to the interesting suggestion of using a staining method specific to endothelial

cells. In our article, we always called the cells covering the inner graft surface "endothelium-like cells," never "endothelial cells".

Tomizawa, Moon, and Noishiki also discussed our early findings after implantation. One hour after blood contact, multiple areas of thrombus deposition have been observed on the exposed Dacron polyester fibers of the ovine collagen prostheses. Three possible explanations of this phenomenon have been proposed by Tomizawa, Moon, and Noishiki: (1) The graft was not strong enough to withstand injuries during preparation. (2) The graft could not tolerate blood pressure. (3) The graft was extremely thrombogenic. Because fibrin deposition was limited to defects in the inner collagen layer (exposing the underlying Dacron polyester fibers), graft surface thrombogenicity cannot explain inner thrombus formation. We assumed that the intimal graft defects were caused by the thinness and inadequate mechanical strength of the inner collagen cover, making it easily damaged by handling and manipulation during implantation. Accordingly, a new ovine collagen prosthesis with improved structural characteristics was developed. A thicker inner tissue layer was obtained without changing the graft's biophysical properties. We tested the new biosynthetic graft in the inferior vena cava of growing pigs, according to the same experimental protocol described in our previous article. One hour after implantation, neither disruptions of the inner graft components nor fibrin deposits were found. These findings confirmed the following statements: (1) The intact intimal graft surface was not thrombogenic. (2) The inner layer defects were traumatic in nature. (3) The defects were due to a structural deficiency. Despite such improvements, however, long-term patency of the newer grafts was not superior to that of the older ones. The reason for these late failures remained unclear.

Because Tomizawa, Moon, and Noishiki pressed us to discuss this subject, we state that, under microscopic examination of both types of failed grafts, the most remarkable finding was uniform mononuclear cell infiltration of the prosthetic wall. The widely known procoagulant activity exerted by white blood cells may support the immunologic hypothesis for long-term thrombosis of either the older or the newer ovine collagen grafts. Variable degrees of intimal hyperplasia were also observed in the failed grafts. Whether intimal hyperplasia depends on the immunologic response intensity remains to be investigated. Our results further emphasize the importance of Tomizawa, Moon, and Noishiki's suggestion to use alcohol instead of glutaraldehyde for ovine collagen tube treatment. A greater reduction of the graft antigenicity (with maintenance of hydrophilic properties) could make ovine collagen tubes a more reliable venous substitute.

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The New York Society for Thoracic Surgery: Seventy-five years, 1917-1992

To the Editor:

On February 20, 1917, in prescient recognition of thoracic surgery as a newly emerging specialty area of surgical endeavor, Dr. Willy Meyer (Fig. 1) of New York City convened a meeting in his office for the dual purpose of founding a New York Society for Thoracic Surgery and creating a national