

Bioprostheses for Hemodialysis Access and Clinical Application of the ProCol® Graft

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Because of the unique requirements of the patient population the creation of a dialysis vascular access site and the paradigm related to choice of a conduit remains one of the more controversial issues in vascular surgery. It has long been noted that fistula hemodynamics, repeated cannulation, patient comorbidities, including diabetes, blood coagulopathies, immune complications and pathology associated with prior access modalities and the successive paucity of available access sites pose a significant challenge to maintaining successful and adequate hemodialysis. Added to this is the increasingly chronic condition of the prevalent dialysis population and the challenge of establishing hemoaccess with progressive venous pathology. This challenge has led to the development and use of various materials and conduits both synthetic and biological (Table I).

Table I
Biological Graft Materials

Allogenic	Xenogenic
Umbilical vein Saphenous Vein Femoral vein Cryopreserved superficial femoral vein	Preserved bovine mesenteric vein (ProCol®) Modified bovine carotid artery (Artegraft®)

The clinical consequences of these phenomena have been repeatedly demonstrated for various constructs of the most commonly utilized ePTFE prosthetic and biological grafts. Most of the sequelae have resulted in graft failure and/or abandonment attributable to the noncompliant character of the prosthetic materials, incompatibilities at the blood interface, material porosity and cannulation injury. At one year, primary patency rates for most prosthetic grafts average 40%-50% with cumulative patency rates ranging from 50% - 70%.¹ In the second and third subsequent years the significant reduction of the cumulative patency is accompanied by linearized intervention rates of approximately 1.5 – 2.0 per year.

Because several if not all of the unique dialysis fistula requirements can theoretically be accommodated by the biomechanic and blood interface properties of the native vasculature, the underlying rationale for the use of a native vein segment as part of an arteriovenous fistula, it would seem reasonable to assume that the ideal graft for fistula creation should be derived from a biological source.

Various early attempts to develop bioprosthetic conduits have included utilization of the human saphenous and umbilical veins and various xenogeneic carotid arteries; in all instances poor graft conservation; the paucity of extracellular proteins, especially elastin, and possible immune responses have resulted in aneurysmal degeneration and eventual graft failure. A similar immune sequela has been described for cryopreserved human allografts. Carotid artery grafts derived from bovine carotid arteries were first introduced prior to the FDA Device Amendment Act of 1976. Consequent to the ficin digestion incorporated in the processing of the carotid artery the smooth muscle cells and elastin are removed leaving a tubular scaffold essentially composed of collagen; also, histological evaluation of the remaining collagen demonstrates alterations most likely associated with the collagenase activity of the ficin used for decellurization. The minimal elastic properties of the carotid artery after modification by this process have been shown to be further reduced compared to the source material and reports of aneurysmal degeneration in clinical use may be related to the digestive nature of the process as well as to the choice of an artery as the source material.^{2,3}

Why is the mesenteric vein different and how does this translate into practical application? Excepting the elastic aorta, arteries are composed of mostly smooth muscle and collagen with elastin essentially limited to the internal elastic membrane. Conversely, larger caliber veins have a high elastin to collagen ratio related to the requirement to propagate flow. In a manner similar to the arguments for differences in ePTFE conduit architecture conclusions may be drawn from the differences in mural architecture between enzyme digested bovine carotid artery and bovine mesenteric vein derived conduits. The mesenteric vein in particular has a high ratio of extracellular proteins to cell

mass and a complete internal elastic membrane. Most importantly the mesenteric vein has a unique mural architecture consisting of an inner and outer media oriented approximately 90 degrees to each other providing for radial, circumferential and longitudinal compliance. For the ProCol[®] bioprosthesis a proprietary method of tissue preservation combines glutaraldehyde crosslinking, during which the vein is not subjected to distensive or other stresses, with gamma irradiation modification of the glutaraldehyde crosslinks geometry resulting in the morphologic conservation of the extracellular matrix proteins in their most favorable biomechanic state. This process allows for collagen and elastin function mimetic of native veins and also renders the cellular and extracellular components immunologically silent.

One of the most unique characteristics of the mesenteric vein is the rather robust internal elastic lamina. Subsequent to processing this structure serves as the blood interface. Elastin and elastin like polypeptides have been shown to provide a less thrombogenic blood interface surface⁴ which is most likely an important contributor to the overall patency results and may have especial import for patients with coagulopathies. The characteristics of the mesenteric vein result in a vascular bioprosthesis with a compliant mural response to native hemodynamics, especially at the anastomoses, mimetic of a native vein, multiaxial hysteric compliance including intimal compliance similar to native tissue, a thrombogenic resistant blood interface, low susceptibility to invasive stenotic healing, low porosity, low steal, amenability to various anastomotic geometries, resistance to cannulation injury and resistance to infection.

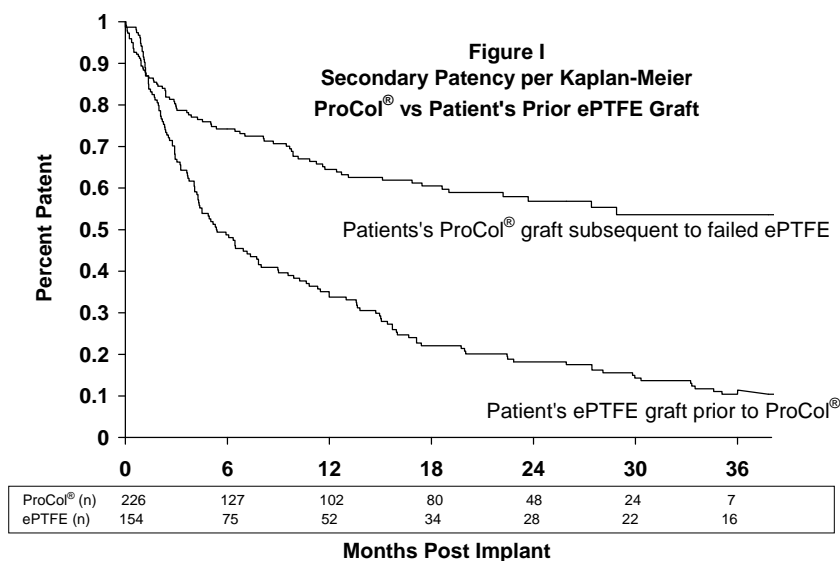
Clinical experience with the ProCol[®] graft demonstrates that with the proper choice of tissue source and processing designed to maintain the characteristics of the native tissue the objective of providing a conduit with broad application and filling the requirements of an ideal access site can be achieved. These characteristics are shown in Table II.

Table II
Ideal Access Graft Characteristics

Physical Characteristics	Functional Characteristics
Available in appropriate dimensions Can be cut or shaped during implantation Accommodates suturing and/or clips Can be passed through a tunnel Can be revised Resistant to infection Does not illicit an immune response	Maintains patency No weeping Resists infection No suture hole bleeding Ability to evaluate flow Easy to cannulate No needle puncture bleeding

The safety and efficacy of ProCol[®] as a vascular access graft has been established and its versatility in providing a site for hemoaccess with particular success in patients representative of the vast majority of the hemodialysis population has been repeatedly demonstrated.^{1, 5, 6, 7, 8, 9, 10, 11, 12} Upon completion of a multicenter clinical investigation the ProCol[®] Vascular Bioprosthesis was approved by the United States Food and Drug Administration for patient implants in 2003. It is important to recognize that the method of preservation allows all patients to remain candidates for future transplant after receiving a ProCol[®] bioprosthesis in contrast to patients receiving cryopreserved allograft vascular conduits which can illicit an antibody response.¹³ ProCol[®] has demonstrated particular success in the following patient populations.

Redo Patients – It has been reported that a history of a prior failed ePTFE graft is the only significant risk factor for failure of a subsequent ePTFE graft at a new site and the risk of failure for a new ePTFE graft increases with the number of previously failed grafts.¹⁴ In a prospective, multicenter study of patients with at least one prior failed synthetic graft, results for 183 ProCol[®] grafts were compared to ePTFE grafts. The ProCol[®] graft provided the patient with superior secondary graft patency (60% at 24 months and 54% at 36 months) over both the same patient's own prior synthetic graft (18% at 24 months and 10% at 36 months) (Figure I) and a ePTFE reference group (42% at 24 months).



Patients receiving the ProCol® graft experienced significant reductions in incidences of thrombosis, infection and interventions and because the wall of this bioprosthesis is nonporous there were no occurrences of seroma. The ProCol® graft provided a means of extending vascular access to this challenging patient population.⁸ Similarly, results from a subset of 74 patients with three or more prior failed ePTFE grafts showed a statistically significant benefit to the patient with ProCol® compared to ePTFE in both assisted primary patency and secondary patency rates with fewer thrombotic events, fewer infectious events, and fewer interventions required to maintain their permanent dialysis access.⁶

Thigh Access Grafts - The thigh area is often the last resort after other sites have failed. When this position is not utilized, patients may be left with long term catheter dialysis as their only dialysis option. Secondary patency at 24 months was 71% in 50 patients receiving the ProCol® bioprostheses as an access graft in the thigh position. This patency with the low incidence of infection suggests that for patients with a thigh graft option, ProCol® should be utilized to obtain acceptable patency and complication rates.⁷

Hypercoagulable Patient History - ProCol® has performed well in patients with diagnosed hypercoagulopathies including lupus. Published results show that with postoperative low molecular weight heparin therapy these patients have maintained access via their ProCol® graft without recurrent thrombotic events or episodes of bleeding.⁹

Patients at High Risk of Infection – In a study of 23 ProCol® and 23 ePTFE patients serious infections occurred significantly more often in the ePTFE group. Of the 7 ePTFE graft infections 6 resulted in explantation with two patient deaths from sepsis. The two infections in the ProCol® group were successfully treated by antibiotic therapy and, in one case, incision and drainage. The author concluded that the difference in infection rate and its consequences was the most important result in the investigation.¹² In a larger study involving 183 ProCol® grafts the risk of infection in the reference group of patients receiving ePTFE was 4.4 fold greater than in the ProCol® cohort.⁸ Anecdotal experience has similarly reported success using ProCol® to replace or repair previously infected hemoaccess conduits.

Size Mismatch – Anastomotic challenges found in the very young, thin or elderly patients, particularly women, are not infrequent. In many instances the major vessel difficulty is the arterial inflow where most conduits present a significant mismatch in size and compliance. The ProCol® graft is well suited to deal with these issues as it can be tapered, crimped or easily banded at the time of implant. Adjustment to the setting can be managed on an intuitive basis due to the tissue characteristics, particularly the accommodating nature of the compliant graft wall.

In summary, the foregoing discussion has outlined the current status of bioprostheses for dialysis access and the rationale for ProCol®. It has detailed multiple applications and data supporting the utility of these applications. In recognizing the physiology of the blood flow of the ProCol® graft, the basic science of graft preservation and the results of clinical application, the validity of the concept that structure does influence function is supported.

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