Bound to Perform: GORE PROPATEN Vascular Graft and CBAS Heparin Surface Technology

The role of grafts having end-point attached heparin in maintaining patency.

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The Fistula First initiative mandates the construction of an autogenous arteriovenous fistula (AVF) as the primary choice for hemodialysis access. However, certain clinical scenarios remain that are best suited for a prosthetic arteriovenous graft (AVG). These scenarios include patients lacking suitable vein for or lack of maturation of an AVF. In these cases, a prosthetic AVG, most commonly expanded polytetrafluoroethylene (ePTFE), is indicated to establish permanent hemodialysis access despite a historic record of inferior primary and secondary patency compared to AVFs. Prosthetic AVGs are prone to thrombosis due to increased thrombogenicity and stenosis or occlusion as a result of an accelerated myointimal hyperplastic response. This myointimal hyperplastic occlusive process most commonly forms at the AVG-venous anastomosis due to hemodynamic flow disturbances, as well as the biologic response to the anastomotic construction.

The reasons for suboptimal performance with prosthetic grafts are biological and hemodynamic. Expanded PTFE grafts are more thrombogenic than autogenous conduits, with increased platelet adhesion and activation of the coagulation cascade.[1] Increased thrombogenicity at the graft surface results in thrombosis especially when blood flow falls below the critical thrombotic threshold. Late graft failure due to myointimal hyperplasia usually occurs 6 to 24 months after graft implantation. This hyperplastic response is the result of smooth muscle cell migration and proliferation, primarily at the toe and heel of the anastomosis, causing a reduction in lumen area, reduction in flow, and subsequent graft occlusion. The hemodynamic factors of shear stress and compliance mismatch have been implicated in prosthetic graft failure. However, an animal study addressing compliance did not prove compliance to be a significant factor in the formation of the hyperplastic response.[2] Anastomotic turbulence, oscillating shear forces, near wall residence time, and flow separation have been suggested as mechanisms of graft failure due to hyperplasia.[3]

IMPROVING PROSTHETIC GRAFT PERFORMANCE

The major cause of failure for prosthetic AVGs is thrombosis or significant stenosis due to neointimal hyperplasia. There have been biological and hemodynamic manipulations used in attempts to affect these failure mechanisms. In terms of hemodynamics, cuffed AVGs have been used involving stretch or non-stretch AVGs with the addition of a vein cuff. In terms of biological manipulation, AVGs having end-point attached heparin (CBAS Heparin Surface; Gore & Associates) have been utilized for hemodialysis access and reported better clot free survival than standard ePTFE alone. Even though follow-up in the series by Davidson et al was short, at less than 6 months for 38% of patients, 78% clot-free survival for the AVGs having the CBAS Heparin Surface versus 58% clot-free survival for the standard ePTFE at 1 year follow-up was reported.[4] There have been differences in

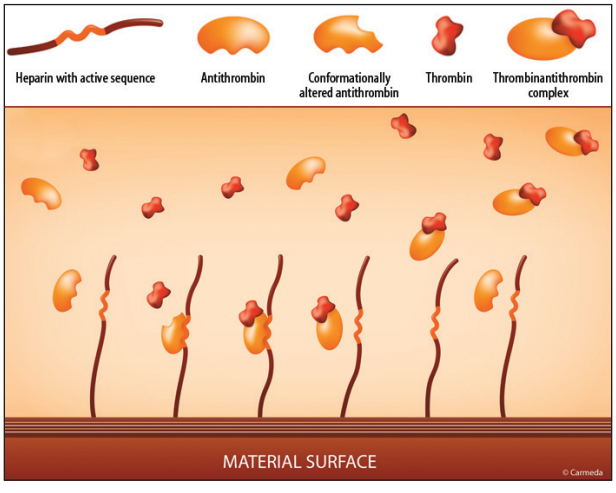

Figure 1. Illustration of CBAS Heparin Surface showing the material surface, base coating, and end-point attached heparin. Also shown are the reactants antithrombin, conformationally altered antithrombin, thrombin, and the inactive thrombin antithrombin complex.

neointimal hyperplasia between standard and heparin bonded graft use for dialysis access documented in animal models showing that compliance may play a role as shown by Gessaroli et al.[5] Therefore, potential solutions to improve the performance of a prosthetic graft for dialysis access includes affecting thrombogenicity through heparin bonding or affecting the development of myointimal hyperplasia by optimizing anastomotic compliance and hemodynamics.

CBAS Heparin Surface Technology and Benefits

One of the most clinically successful and innovative heparin bonding methodologies has been the CBAS Heparin Surface.[6,7] It is based on covalent end-point attached heparin to a biomaterial surface, enabling maintenance of functional heparin bioactivity. The end-point attachment mechanism, used in the CBAS Heparin Surface, preserves the heparin-active site and thus enables binding of the clotting factor inhibitor, antithrombin III (Figure 1).[7] Just as heparin functions in the solution phase, immobilized CBAS heparin is also catalytic. It is not consumed in the reaction by which antithrombin inhibits clotting factors such as thrombin. This retention of catalytic activity and the fact that the heparin is covalently attached and noneluting provides the potential for long-term immobilized heparin functionality clinically. The CBAS Heparin Surface can be applied to most medical device materials.[8] The coating is thin yet durable, usually in the range of hundreds of nanometers. When stored properly, CBAS-coated devices have an acceptable shelf life of at least 4 years. The CBAS coating can be sterilized by ethylene oxide, one of the common methods of device sterilization, without losing its mode of action. Furthermore, some of the key clinical performance benefits of end-point attachment of heparin on the CBAS Heparin Surface have been demonstrated in broad application, including extracorporeal circuits, vascular stents, ventricular assist devices, and ePTFE vascular grafts. The CBAS Heparin Surface has clinically shown a reduction of platelet deposition, a decrease in inflammatory responses,[9-11] and a reduction of thrombogenicity.[12-16]

Although there are many approaches for binding heparin to devices,[17] different immobilization techniques can affect the functional activity of the immobilized heparin. Immobilization of heparin to the surface alone does not necessarily ensure thromboresistance of that surface. Heparin can be bound by covalent attachment to material surfaces in different ways that adversely affect heparin's functional properties.[18] In contrast to covalent end-point attachment as employed in the CBAS Heparin Surface, heparin covalently bound by multipoint attachments along the heparin molecule can interfere with the critical pentasaccharide sequence in heparin known to be essential for its anticoagulant activity. Even end-point attachment of heparin can be performed in different ways and, generally, will not result in the unique functional properties[19] of the CBAS Heparin Surface. Each heparin-coating technology is individual and must therefore be judged according to its specific clinical performance. Tanzi[20] and Jordan[21] provide a relevant review of heparin and alternative technologies for improving biocompatibility of device materials.

The CBAS Heparin Surface has been in clinical use for nearly 25 years. It is the most widely published of all commercially available technologies of its type, providing evidence of the CBAS Heparin Surface hemocompatibility and biocompatibility benefits for short-term and permanent product applications, with few if any adverse events reported. More than 400 publications and studies have examined the hemocompatible properties of the CBAS Heparin Surface in controlled in vitro blood contact models or in vivo animal models and clinical studies. The continued commercial clinical application of this surface is based on a decade long track record of proven usefulness of this technology for improving the hemocompatibility of devices used for cardiovascular treatment.

The GORE ePTFE Vascular Graft with the CBAS Heparin Surface, the GORE PROPATEN Vascular Graft, was designed to improve the properties of vascular grafts with regard to thrombosis and, as a result, the clinical patient outcomes for cardiovascular disease treatment. The CBAS Heparin Surface is bound to the luminal surface of the GORE PROPATEN Vascular Graft. The CBAS Heparin is retained on the graft flow surface, is uniform in nature, and its functionality is maintained. With several hundred thousand GORE PROPATEN Vascular Grafts implanted worldwide, this graft has been reported to be widely used in contemporary practice.[22] In animal models and clinical applications, evidence has suggested that the GORE PROPATEN Vascular Graft is superior to uncoated grafts with patency rates comparable to autologous veins in humans.[23-26] By substantially reducing acute graft thrombosis within weeks after implantation, the CBAS Heparin Surface on the GORE PROPATEN Vascular Graft provides beneficial effects that standard ePTFE, control grafts do not.[27] The CBAS Heparin Surface has improved the clinical performance of prosthetic small-caliber vascular graft bypasses and has an important role in the management of lower extremity occlusive disease, with up to 4-year primary patency and limb salvage rates for the GORE PROPATEN Vascular Graft approaching historical results achieved with autologous vein conduits.[28-31] Furthermore, the CBAS Heparin Surface on the GORE

PROPATEN Vascular Graft has evolved to a clinically powerful technique for the hemodialysis patient resulting in a 20% improved clot-free survival at 1 year.[4] Other medical devices having the CBAS Heparin Surface that are used in peripheral vascular reconstruction and/or dialysis applications include the GORE ACUSEAL Vascular Graft, the GORE HYBRID Vascular Graft, and the GORE VIABAHN Endoprosthesis.

LOWER LIMB EXPERIENCE WITH CBAS HEPARIN: GORE PROPATEN VASCULAR GRAFT

The available worldwide experimental evidence and published clinical results point to significant durable clinical benefits of the CBAS covalent end-point attached heparin on the GORE PROPATEN Vascular Graft, imparting improved thromboresistance to the graft surface. The CBAS Heparin Surface may improve prosthetic graft performance by decreasing luminal thrombosis and the formation of myointimal hyperplasia. Reduced platelet deposition has been demonstrated in animal and human models as well as reduced thrombus formation on the inner surface of the graft.[25-27,32] A reduction in myointimal hyperplasia at the anastomotic site has also been demonstrated in animal models.[25,32,33]

Clinical trials in the lower extremity have supported these findings with improved patency rates as compared to historic controls of standard ePTFE. This is especially important in the below-knee position for tibial bypass in the lower extremity. Clinical bypass results with GORE PROPATEN Vascular Grafts have been described in nonrandomized, retrospective trials from Europe.[34,35] Although these trials included a limited experience with tibial bypass, they reported results superior to those obtained using standard ePTFE with 1 year patency for below knee popliteal bypass in the 80% range and 68% patency at 3 years. A retrospective comparison between the GORE PROPATEN Vascular Graft and saphenous vein grafts (SVG) for below-knee bypass demonstrated higher patency rates for the GORE PROPATEN Vascular Graft conduit although without reaching statistical significance, and concluded that the GORE PROPATEN Vascular Graft should be routinely considered for below-knee bypass.[28] Peeters reported 2 year patency rates of 73% for below-knee bypass and 69% for tibial bypass using heparin bonded ePTFE.[36] Patency specifically for tibial bypass was reported by Lösel-Sadée and Alefelder, who found 64% patency at 1 year for tibial bypasses using the GORE PROPATEN Vascular Graft.[37] Comparing the GORE PROPATEN Vascular Graft and vein for below-knee bypass, Battaglia and colleagues noted that vein graft patency was significantly better in patients with single-artery runoff and more severe symptoms at initial presentation.[38] Dorigo et al compared primary patency for in situ vein, standard PTFE, and the GORE PROPATEN Vascular Graft in a below knee bypass experience with patency rate at 18 months of 75% for vein, 40% for standard PTFE, and 53% using the GORE PROPATEN Vascular Graft. Early thrombosis was not significantly different between vein and the GORE PROPATEN Vascular Graft. However, patency results remained inferior compared to saphenous vein conduit.[39] Similar results were obtained on a larger scale as reported by the Italian Registry Group, with GORE PROPATEN Vascular Graft patency of 75% at 1 year and 61% at 3 years.[40]

In more recent podium presentations and publications, it was reported that GORE PROPATEN Vascular Grafts had improved clinical performance over standard ePTFE, especially in the most challenging patient populations.[41,42] Prospective and retrospective studies have led to the conclusion that peripheral arterial disease treatment using the GORE PROPATEN Vascular Graft is a clinically acceptable, safe alternative to treatment with native vein, especially disadvantaged vein.[29] The Scandinavian GORE PROPATEN Trial prospectively evaluated the GORE PROPATEN Vascular Graft across 11 centers in patients with chronic limb ischemia.[42] The GORE PROPATEN Vascular Graft was randomized against Stretch ePTFE Vascular Grafts in femoropopliteal (above-knee and below-knee) or femoral-femoral bypasses and demonstrated statistically significant improvement versus ePTFE in primary patency, secondary patency, and in patients with critical limb ischemia. It was determined that as severity of disease increases, the benefit of the GORE PROPATEN Vascular Graft increases.[42]

In a retrospective analysis of prospectively collected data, 112 tibial bypasses (62 GORE PROPATEN Vascular Graft, 50 SVG) were compared.[43] All GORE PROPATEN Vascular Graft bypasses were performed using an autologous vein patch at the distal anastomosis. At 1 year, the GORE PROPATEN Vascular Graft had a primary patency of 75.4% and SVG patency of 86.0% with the GORE PROPATEN Vascular Graft group including more reoperative procedures (45% vs 26%). There was no significant difference in primary patency due to gender, race, or diabetes mellitus. Results showing comparable primary patency and limb salvage rates with SVG at one year demonstrate that the GORE PROPATEN Vascular Graft is an effective alternative choice for patients with absent or poor quality saphenous veins that need a tibial bypass. The GORE PROPATEN Vascular Graft has emerged as the choice over arm vein, especially in the ESRD patient who needs upper extremity vein for dialysis access, and over composite short saphenous vein given the increased dissection required and length of conduit.

CONCLUSION

End-point attachment of heparin on ePTFE grafts using the CBAS Heparin Surface technology carries much promise to improve the clinical performance of prosthetic small-caliber bypasses, approaching the historical results achieved with autologous vein conduits. The available experimental evidence and emerging clinical results point to significant clinical benefits of the stable CBAS Heparin Surface immobilization on the GORE PROPATEN Vascular Graft. The CBAS Heparin Surface provides important beneficial effects, which include sustained thromboresistance and reduced platelet attachment. These benefits may explain the promising below-knee and dialysis access clinical results attained with the GORE PROPATEN Vascular Graft, as well as the potential of other products utilizing the CBAS Heparin Surface technology. ■

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1. Heyligers JM, Arts CH, Verhagen HJ, et al. Improving small diameter vascular grafts: from the application of an endothelial cell lining to the construction of a tissue-engineered blood vessel. *Ann Vasc Surg*. 2005;19:448-456.
2. Norberto JJ, Sidawy AN, Trad KS, et al. The protective effect of vein cuffed anastomoses is not mechanical in origin. *J Vasc Surg*. 1995;21:558-566.
3. Neville RF, Elkins CJ, Alley MT, Wicker R. Hemodynamic comparison of differing anastomotic geometries using magnetic resonance velocimetry. *J Surg Res*. 2010;169: 311-318.
4. Davidson I, Hackerman C, Kapadia A, et al. Heparin bonded hemodialysis e-PTFE grafts result in 20% clot free survival benefit. *J Vasc Access. 2009*;10:153-156.
5. Gessaroli M, Bombardi C, Giunti M, Bacci ML. Prevention of neointimal hyperplasia associated with modified stretch expanded polytetrafluoroethylene hemodialysis grafts (Gore) in an experimental preclinical study in swine. *J Vasc Surg*. 2012;55:192-202.
6. Matheve C. Clinical evidence of improved biocompatibility using heparin-coated surfaces. *Perfusion*. 1996;11:264-269.
7. Riesenfeld J. Olsson P, Sanchez J, et al. Surface modification with functionally active heparin. *Med Device Technology*. 1995;6:24-31.
8. CBAS: Carmeda Bioactive Surface. Available at http://carmeda.com/upl/files/31627.pdf. Accessed May 13, 2014.
9. Bozdayi M, Borowiec J, Nilsson L, et al. Effects of heparin coating of cardiopulmonary bypass circuits on in vitro oxygen free radical production during coronary bypass surgery. *Artif Organs*. 1996;20:1008-1016.
10. Fukutorni M, Kobayashi S, Niwaya K, et al. Changes in platelet, granulocyte, and complement activation during cardiopulmonary bypass using heparin-coated equipment. *Artif Organs*. 1996;20:767-776.
11. Borowiec J, Thelin 5, Bagge L, et al. Heparin-coated circuits reduce activation of granulocytes during cardiopulmonary bypass. *J Thoracic Cardiovasc Surg*. 1992;104:642-647.
12. Kaufmann F, Hennig E, Loebe M, et al. Improving the anti-thrombogenicity of artificial surfaces through heparin coating—Clinical experience with the pheumatic extracorporeal Berlin Heart assist device. *Cardiovasc Engineering*. 1996;1:40-44.
13. Serruys PW, Ensanuelsson H, van der Giessen W, et al. Heparin-coated Palmaz-Schatz stents in human coronary arteries. *Circulation*. 1996;93:412-422.
14. Serruys PW, Grines CL, Stone GW, et al. Stent implantation in acute myocardial infarction using a heparin-coated stent: A pilot study as a preamble to a randomized trial comparing balloon angioplasty and stenting. *Int J Cardiovasc Intervent*. 1998;1:19-27.
15. Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (BENESTENT II). *Lancet*. 1998;352:673-681.
16. Dzavik V, Carete RG, Teo KK, et al. An open design, multi-centre, randomized trial of percutaneous transluminal coronary angioplasty versus stenting, with a heparin-coated stent, of totally occluded coronary arteries: Rationale, trial design and baseline patient characteristics. *Can J Cardiol*. 1998;14:825-832.
17. Murugesan S, Xie J, Linhardt RJ. Immobilization of heparin: approaches and applications. *Curr Top Med Chem*. 2008:8:80-100.
18. Gore S, Andersson J, Biran R, Underwood C, et al. Heparin surfaces: Impact of immobilization chemistry on hemocompatibility and protein adsorption. *J Biomed Mater Res B Appl Biomater*. Published online ahead of print April 18, 2014.
19. Wendel HP, Ziemer G. Coating-techniques to improve the hemocompatibility of artificial devices used for extracorporeal circulation. *Euro J Cardiovasc Surg*. 1999;16: 342-350.
20. Tanzi MC. Bioactive technologies for hemocompatibility. *Expert Rev Med Devices*. 2005;24:473-492.
21. Jordan SW, Chaikof EL. Novel thromboresistant materials. *J Vasc Surg*. 2007;45:suppl 1:A104-A15.
22. Twine CP, McLain AD. Graft type for femoropopliteal bypass surgery (review). Cochrane Database Syst. 2010.
23. Veith FJ, Gupta K, Samson RH, et al. Superficial femoral and popliteal arteries as inflow site for distal bypasses. *Surgery*. 1981;90:980-990.
24. Devine C, McCollum C. Heparin-bonded Dacron or polytetrafluorethylene for femoropopliteal bypass: Five-year results of a prospective randomized multicenter clinical trial. *J Vasc Surg*. 2004;40:924-931.
25. Lin PH, Chen C, Bush RL, et al. Small caliber heparin coated ePTFE grafts reduce platelet deposition and neointimal hyperplasia in a baboon model. *J Vasc Surg*. 2004;39:1322-1328.
26. Begovac PC, Thomson RC, Fisher JL, et al. Improvements in GoreTex vascular graft performance by Carmeda bioactive surface heparin immobilization. *Eur J Vasc Endovasc Surg*. 2003;25:432-437.
27. Heyligers JM, Verhagen HJ, Rotmans J, et al. Heparin immobilization reduces thrombogenicity of small caliber expanded polytetrafluoroethylene grafts. *J Vasc Surg*. 2006;43:587-591.
28. Daenens K, Schepers S, Fourneau I, et al. Heparin bonded ePTFE grafts compared with vein grafts in femoro-popliteal and femorocrural bypasses; 1 and 2 year results. *J Vasc Surg*. 2009;49:1210-1216.
29. Dorigo W, Raffaele P, Piffaretti G. Results from an Italian multicentric registry comparing heparin-bonded ePTFE graft and autologous saphenous vein in below-knee femoro-popliteal bypasses. *J Cardiovasc Surg*. 2012;53:187-193.
30. Samson RH, Morales, L. Improved three year patency rates for heparin-bonded PTFE femoropopliteal bypass grafts vs. ePTFE grafts without heparin, Presented at the 35th International Charing Cross Symposium (CX 35); April 6-9, 2013; London, UK. In: Greenhalgh RM, ed. Vascular and Endovascular Challenges Update, BIBA Publishing, London, UK, 2013, pp. 315-320.
31. Veith FJ, Gupta SK, Ascer E. Six year prospective mulitcenter randomized comparison of autologous saphenous vein and expanded PTFE in infrainguinal reconstruction. *J Vasc Surg*. 1986;3:104-114.
32. Lin PH, Bush RL, Yao Q, et al. Evaluation of platelet deposition and neointimal hyperplasia in heparin coated small caliber ePTFE grafts in a canine femoral artery bypass model. *J Surg Res*. 2004;118:45-52.
33. Pedersen G, Laxdal E, Ellensen V, et al. Improved patency and reduced intimal hyperplasia in PTFE grafts with luminal immobilized heparin compared with standard PTFE grafts at six months in a sheep model. *J Cardiovasc Surg*. 2010;5:443-448.
34. Walluscheck KP, Bierkandt S, Brandt M, Cremer J. Infrainguinal ePTFE vascular graft with bioactive surface heparin bonding; first clinical results. *J Cardiovasc Surg*. 2005;46:425-430.
35. Bosiers M, Deloose K, Verbist J, et al. Heparin bonded expanded polytetrafluoroethylene vascular graft for femoropopliteal and femorocrural bypass grafting; 1 year results. *J Vasc Surg*. 2006;43:313-319.
36. Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded polytetrafluoroethylene grafts for femorodistal bypasses. *J Cardiovasc Surg*. 2006;47:407-413.
37. Losel-Sadee H, Alefelder C. Heparin bonded expanded polytetrafluoroethylene graft for infragenicular bypass; five year results. *J Cardiovasc Surg*. 2009;50:339-343.
38. Battaglia G, Tringale R, Monaca V. Retrospective comparison of a heparin bonded ePTFE graft with saphenous vein for infragenicular bypass; implications for standard treatment protocol. *J Cardiovasc Surg*. 2006;47:41-47.
39. Dorigo W, Pulli R, Alessi Innocenti A, et al. Lower limb below knee revascularization with a new bioactive prosthetic graft. A case control study. *Ital J Vasc Endovascul Surg*. 2005;12:75-82.
40. Pulli R, Dorigo W, Castelli P, et al. Midterm results from a multicenter registry on the treatment of infrainguinal critical limb ischemia using a heparin bonded ePTFE graft. *J Vasc Surg*. 2010;51:1167-1177.
41. Samson RH, Morales L. Improved three year patency rates for heparin-bonded ePTFE femoropopliteal bypass grafts vs ePTFE grafts without heparin, Presented at the 35th International Charing Cross Symposium (CX 35); April 6-9, 2013; London, UK. In: Greenhalgh RM, ed. Vascular and Endovascular Challenges Update. London, UK: BIBA Publishing, 2013:315-320.
42. Lindholt JS, Gottschalksen B, Johannesen N, et al. The Scandinavian Propaten® Trial–1-year patency of PTFE vascular prostheses with heparin-bonded luminal surfaces compared to ordinary pure PTFE vascular prostheses–a randomised clinical controlled multi-centre trial. *Euro J Vasc Endovasc Surg*. 2011;41:668-673.
43. Neville RF, Capone A, Amdur R, et al. A comparison of tibial artery bypass performed with heparin-bonded expanded polytetrafluoroethylene and great saphenous vein to treat critical limb ischemia. *J Vasc Surg*. 2012;56:1008-1014.