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Sustained Thromboresistant Bioactivity with Reduced Intimal Hyperplasia of Heparin-Bonded Polytetrafluoroethylene Propaten Graft in a Chronic Canine Femoral Artery Bypass Model

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Background: Bypass graft thrombosis remains a significant mode of failure in prosthetic graft revascularization. The purpose of this investigation was to evaluate the long-term thromboresistant effect of heparin-bonded expanded polytetrafluoroethylene (ePTFE) graft using Carmeda BioActive Surface technology in a canine model.

Methods: Bilateral femorofemoral artery bypass grafts with ePTFE grafts were performed in 25 adult grayhound dogs. In each animal, a heparin-bonded ePTFE graft (Propaten, WL Gore) was placed on one side, whereas a control nonheparin graft was placed on the contralateral side. The graft patency was assessed at 1, 6, 12, 18, and 24 months ($n = 5$ per group) following the bypass. Heparin bioactivity of the graft material was analyzed. The effect of intimal hyperplasia was also assessed.

Results: All bypass grafts were patent at 1 month. Significantly greater patency rates were noted in the Propaten group compared to the control group at 12, 18, and 24 months, which were 84%, 80%, and 80% vs. 55%, 35%, and 20%, respectively ($P < 0.02$). There was a significant reduction in the anastomotic neointimal area and neointimal cell proliferation in Propaten grafts compared with control grafts at all groups between 6 and 24 months ($P < 0.05$). Heparin bioactivity as measured by antithrombin binding assay was demonstrated in the Propaten graft between 1 and 24 months. Mean heparin activities on Propaten grafts ranged from 26.3 ± 6.4 pmol/cm^2 to 18.4 ± 8.7 pmol/cm^2 between 1 and 24 months, which were significantly greater than the control group ($P < 0.001$). Differences between mean heparin activities of explanted Propaten graft samples at the various time points were nonsignificant ($P > 0.05$).

Conclusions: Heparin-bonded ePTFE graft provides a thromboresistant surface and reduced anastomotic intimal hyperplasia at 2 years. The stable heparin bioactivity of the Propaten graft confers an advantage in long-term graft patency.

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INTRODUCTION

The prevalence of lower extremity arterial occlusive has risen steadily in recent decades due in part to the rise of the aging population. For patients with severe lower extremity arterial occlusive disease who require bypass reconstruction, the saphenous vein graft has long been considered as the ideal conduit of choice because of its autogenous property and proven patency. On the other hand, in patients who do not have adequate saphenous vein graft, prosthetic conduit such as expanded polytetrafluoroethylene (ePTFE) bypass graft has become a useful alternative conduit of choice. Although researchers have shown comparable patency rates of ePTFE bypass graft versus autogenous saphenous vein in above-knee femoropopliteal artery bypass grafting,[1] its clinical performance remains suboptimal when placed in small caliber vessels such as infrapopliteal or tibial artery due to graft thrombogenicity and graft-related intimal hyperplasia.

In an effort to improve the graft patency and enhance biomaterial thromboresistance, researchers have developed various heparin-bonding technologies by incorporating heparin to ePTFE biomaterial surface.[2,3] We have previously reported the beneficial role of heparin-coated ePTFE grafts and stents with reduced thrombogenicity, reduced intimal hyperplasia, and improved patency outcomes in both canine and baboon models.[4–7] Although these heparin-bonding modalities generally show excellent short-term thromboresistant properties, long-term benefits of graft patency is generally reduced due to the loss of heparin bioactivity on the biomaterial surface.[8–10] Scientists have made significant strides in the thrombosis research with biomaterial modification to improve the heparin retention efficacy to enhance prosthetic graft thromboresistance. A bioactive heparin-bonded ePTFE graft utilizing Carmeda BioActive Surface (CBAS) technology (Carmeda, WL Gore, Flagstaff, AZ), which utilizes a covalent end-point attachment method to bind heparin to the prosthetic graft surface, represents an exciting biomaterial strategy to provide a long-term heparin bioactivity.[11,12] Clinical studies have shown sustained functional heparin bioactivity with resultant reduction of platelet deposition and decreased thrombogenicity in oxygenator membranes, extracorporeal circuits, and heart-assist devices.[12–15]

In this present study, we hypothesized that CBAS heparin immobilization on an ePTFE vascular graft would result in stable and long-term heparin bioactivity. Specifically, we investigated the long-term effect of heparin-bonded ePTFE graft in thromboresistance, platelet deposition, and intimal hyperplasia in a canine model.

MATERIALS AND METHODS

Bypass Grafts

Heparin-bonded prosthetic grafts used in this study were commercially available ePTFE grafts (internal diameter, 6 mm; length, 5 cm; Propaten, W.L. Gore & Associates, Inc. Flagstaff, AZ). These graft surfaces incorporated immobilized heparin using the proprietary CBAS technology, which produced a surface microstructure with stable and covalently bound heparin. With a single-point attachment method, the heparin active site was available for binding antithrombin III (AT-III) and contained catalytic function. The heparin activity and concentration on the ePTFE graft were approximately 53 pm AT-III uptake/cm^2 and 15 mg/cm^2, respectively.[8] Control or non–heparin-bonded grafts were also commercially available ePTFE grafts (internal diameter, 6 mm; length, 5 cm; GORE-TEX, W.L. Gore & Associates).

Femoral Artery Bypass Model

Twenty-five grayhound dogs weighing 32.7–38.6 kg (mean 36.7 kg) were used in this study. Anesthesia was induced with thiopental sodium (10–20 mg/kg intravenously). All procedures and care were performed in accordance with the *Guideline for the Care and Use of Laboratory Animals* (NIH publication No. 80-23, eighth edition, revised 2011) and the Food and Drug Administration's Good Laboratory Practice for Non-clinical Laboratory Studies Regulations (21 CFR, Part 58). Prophylactic cefazolin (1gm, Kefzol; Marsam Pharmaceuticals, Cherry Hill, NJ) was administered intravenously. Animals were given thiopental sodium (Pentothal; Abbott Laboratories, North Chicago, IL; 10 mg/kg IV). Endotracheal intubation was performed, and anesthesia was maintained with 1% isoflurane (Rhone-Poulenc, Bristol, UK). All animals underwent bilateral femorofemoral artery bypass grafting with heparin-bonded Propaten ePTFE graft on one side and control graft on the contralateral side. Propaten versus control grafts were randomly alternated between right and left femoral segments. All animals received systemic heparin (100 u/kg) during the time of anastomotic reconstruction. All anastomoses were created using end-to-side anastomoses and continuous 6-0 polypropylene sutures (Ethicon, Somerville NJ). Femoral arteries were then ligated at the regions immediately adjacent to the heels of proximal and distal anastomoses, with the restoration of blood flow through the grafted segments.

No anticoagulant medications were administered postoperatively. Graft implant durations were 1, 6, 12, 18, and 24 months. Arterial duplex ultrasound was performed on a biweekly basis following graft implantation to assess the graft patency.

Histology and Morphometry

Bromodeoxyuridine (BrdU; Sigma Chemical Co, St Louis, MO), 50 mg/kg dissolved in 50 mL of normal saline solution, was administered subcutaneously 24 hr before graft explanation using methods which we previously described.[4–7] Grafts, and adjacent 3-cm segments of attached vessel at each anastomosis, were harvested and fixed in 10% buffered formalin (Baxter Diagnostics Inc., McGaw Park, IL). Following fixation, the grafts were embedded in paraffin and sectioned at the midpoint between the heel and toe of each anastomosis at a distance of 2 mm from the heel of each anastomosis and at 5-mm intervals along the entire graft length. Five-micron sections were cut and stained with hematoxylin and eosin and with Verhoeff-Masson stain. Cell ingrowth overlying the luminal surface of the graft adjacent to the anastomosis was considered to be graft neointima. Cell proliferative tissue overlying the internal elastic lamina of native vessels was considered to be vessel neointima. Morphometric measurements of the area of anastomotic neointima were performed with computer image analysis software (Optimas, Bioscan, Inc., Edmonds, WA) on a magnified image relayed from a microscope-mounted video camera to a digitizing pad and video monitor (Thomas Optical, Columbus, GA) as previously described.[16,17] The graft and native vessel neointimal tissues at the anastomoses were measured separately. Three tissue blocks were generated between the heel and toe of each anastomosis. From the 3 tissue blocks, mean values of morphometric measurements and cell proliferation rates were reported. All the tissue samples were analyzed in a blinded manner with respect to whether they were derived from heparin-coated or control grafts.

Immunocytochemistry

The avidin-biotin complex immunoperoxidase procedure (LSAB Kit, Dako Co., Carpenteria, CA) was used to identify determinants characterizing neointimal cell types and proliferating cells as previously described.[16,17] Briefly, immunostaining for α-actin and factor VIII–related antigen was performed to identify smooth muscle cells and endothelial cells, respectively. Proliferating cells were identified with anti-BrdU monoclonal antibody (Dako CO). BrdU-positive cells were quantified manually with a cell counting technique on a calibrated micrometer grid with microscopy (×400). In each field, all the cells were counted, and the number of positively stained cells was expressed as a percentage of total cells to arrive at the BrdU index. A minimum of 10 fields was quantified per section.

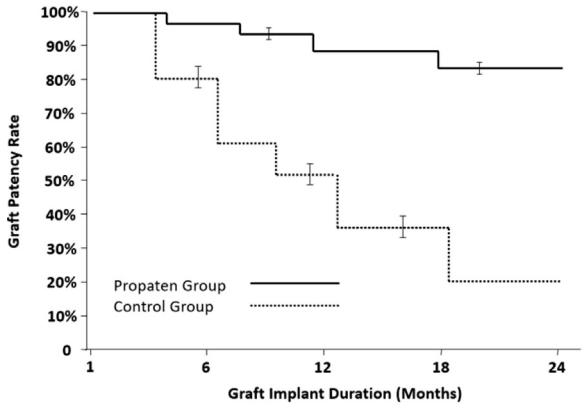

Fig. 1. Graft patency rates between the Propaten and control group.

Heparin Bioactivity Assay

Heparin bioactivity was measured as the capacity of the surface-bound heparin to bind antithrombin.[18] At the time of graft harvest, 2 representative 2-cm segments from the midsegment of each graft were rinsed in isotonic saline, cleared of endogenous heparin in buffered 0.6-M borate in 0.01-M NaCl (pH 9), and rinsed again with deionized H_2O. Samples then were assayed for luminal-surface heparin activity measured as capacity to bind antithrombin and expressed as antithrombin bound per unit surface area (pmol/cm^2) as described.[18]

Statistical Analysis

All statistical analyses were performed using a statistical software program JMP 10 (SAS Institute, Gary, NC). Bypass graft patency rates as assessed by arterial duplex ultrasound between the Propaten and control grafts were evaluated with Kaplan-Meier life table analysis and compared with a log-rank test. One-way analysis of variance was used to compare mean heparin activities on the Propaten and control graft samples from the *in vivo* heparin function study. Comparisons of neointimal areas and cell proliferation between the heparin-treated grafts and the control grafts were made with the Student's *t*-test (2-tailed) for paired data. The values are given as the mean ± the standard error. The results were considered significant if the *P* value was less than 0.05.

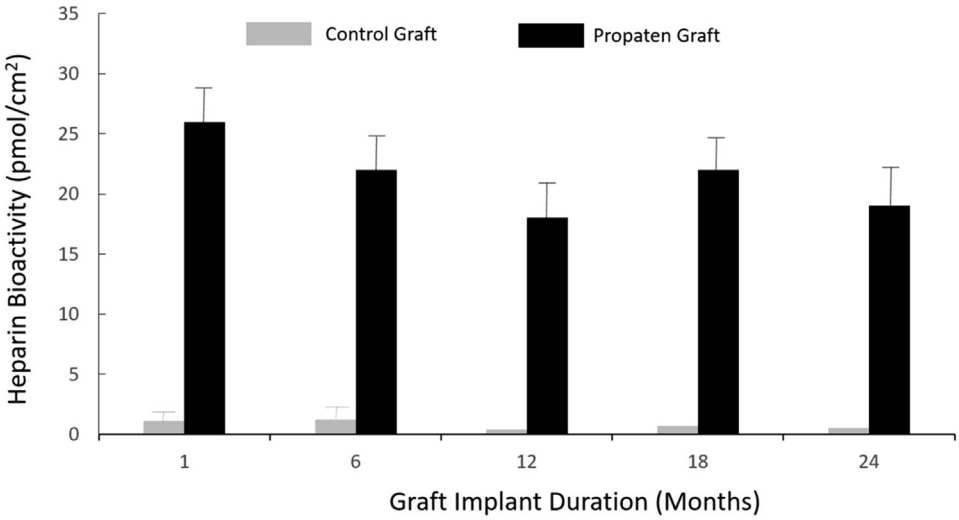

Fig. 2. Comparison of heparin bioactivity between the Propaten and control group.

RESULTS

Graft Patency and Heparin Bioactivity Assay

All animals survived the duration of the study. Significantly greater patency rates were noted in the Propaten group compared to the control group at 12, 18, and 24 months, which were 84%, 80%, and 80% vs. 55%, 35%, and 20%, respectively ($P < 0.02$; Fig. 1). Heparin bioactivity was detected on all explanted Propaten grafts at each time point throughout the study duration. Comparison of the heparin activities between the 2 groups was displayed in Figure 2. Significantly greater mean heparin bioactivity was detected in the Propaten group at each explant period compared with the control group ($P < 0.001$). Mean heparin activities on the Propaten graft samples ranged from 26.3 ± 6.4 pmol/cm^2 measured at 1 month to 18.4 ± 8.7 pmol/cm^2 at 24 months. The mean heparin activity at 24 months was 19.4 ± 8.3 pmol/cm^2. Mean heparin activities of control grafts were near or below the lower detection limit of the assay. Differences between mean heparin activities of explanted Propaten graft samples at the various time points were nonsignificant ($P > 0.05$).

Neointimal Hyperplasia and Neointimal Cell Proliferation

Measurable neointimal hyperplasia was present at both proximal and distal anastomoses of the grafts in both Propaten and control grafts. Smooth muscle cells were the major type of anastomotic neointimal cells identified by α-actin immunostaining. Endothelial cells covered the surfaces of all the anastomotic neointima as shown with factor VIII—related antigen immunohistochemical staining. Results of neointimal hyperplasia at the anastomoses between the Propaten and the control groups are shown in Table I. Significant reduction of graft intima hyperplasia at both proximal and distal anastomoses in the Propaten grafts was noted as compared with proximal and distal anastomoses in the control grafts at 6, 12, 18, and 24 months ($P < 0.05$). However, there was no difference in vessel neointimal area at anastomoses between the Propaten and the control groups.

Neointimal cell proliferation was evaluated by BrdU incorporation staining, and the results are displayed in Table II. Smooth muscle cells were the major type of anastomotic neointimal cells identified by α-actin immunostaining. No difference in neointimal BrdU-labeling index between proximal and distal anastomoses of grafts was found. However, when comparing the cell proliferation between the graft neointima between the Propaten and control grafts, the BrdU-labeling index was significantly less in the Propaten grafts as compared with the control grafts at 6, 12, 18, and 24 months ($P < 0.05$, Table II). There was no significant difference in BrdU-labeling index in the native vessel at the anastomoses between the Propaten and control groups at the various time points during the study (Table II).

DISCUSSION

The introduction of ePTFE bypass graft in the 1970s revolutionized the field of lower extremity

Table I. Effects of heparin-bonded Propaten grafts versus control grafts on anastomotic neointimal areas of canine femoral artery bypass grafting

Duration	Location	Propaten graft (mm^2)	Control graft (mm^2)	*P* value
1 month	Proximal anastomosis			
	Graft neointima	0.47 ± 0.27	0.53 ± 0.24	NS
	Vessel neointima	0.29 ± 0.19	0.31 ± 0.16	NS
	Distal anastomosis			
	Graft neointima	0.37 ± 0.18	0.36 ± 0.08	NS
	Vessel neointima	0.37 ± 0.159	0.35 ± 0.11	NS
6 months	Proximal anastomosis			
	Graft neointima	0.38 ± 0.21	1.01 ± 0.28	0.02
	Vessel neointima	0.28 ± 0.17	0.29 ± 0.14	NS
	Distal anastomosis			
	Graft neointima	0.35 ± 0.09	0.46 ± 0.15	NS
	Vessel neointima	0.34 ± 0.16	0.36 ± 0.12	NS
12 months	Proximal anastomosis			
	Graft neointima	0.45 ± 0.23	1.31 ± 0.29	0.02
	Vessel neointima	0.31 ± 0.18	0.33 ± 0.17	NS
	Distal anastomosis			
	Graft neointima	0.36 ± 0.17	0.73 ± 0.23	0.04
	Vessel neointima	0.36 ± 0.19	0.38 ± 0.18	NS
18 months	Proximal anastomosis			
	Graft neointima	0.43 ± 0.24	1.41 ± 0.32	0.02
	Vessel neointima	0.34 ± 0.22	0.36 ± 0.16	NS
	Distal anastomosis			
	Graft neointima	0.38 ± 0.24	1.15 ± 0.25	0.03
	Vessel neointima	0.35 ± 0.19	0.39 ± 0.18	NS
24 months	Proximal anastomosis			
	Graft neointima	0.53 ± 0.27	1.53 ± 0.32	0.01
	Vessel neointima	0.36 ± 0.17	0.38 ± 0.15	NS
	Distal anastomosis			
	Graft neointima	0.42 ± 0.25	1.21 ± 0.31	0.02
	Vessel neointima	0.36 ± 0.18	0.39 ± 0.19	NS

NS, not significant.

revascularization as the prosthetic conduit became a viable graft alternative particularly in patients who did not have adequate or available autogenous vein conduits.[19] Despite advances in biomaterial science, prosthetic graft occlusion remains a significant challenge in clinical practice. It is well acknowledged that bypass graft failure can be caused by early thrombotic occlusion, neointimal hyperplasia, or late atherosclerotic disease progression. Heparin bonding of ePTFE biomaterial has been shown to reduce thrombotic formation and improve graft patency rate in multiple studies.[2,4,5,8,9,13] The findings of our study are distinctive as it demonstrated that heparin-bonded ePTFE graft provided a thromboresistant bioactivity and reduced intimal hyperplasia compared with non–heparin-bonded graft. Furthermore, our study represents the longest *in vivo* study to date which validated the sustained heparin bioactivity with persistent thromboresistance and reduced intimal hyperplasia in a chronic canine bypass model.

The formation of thrombus on the graft luminal surface by the circulating blood represents the most immediate mode of graft failure. Researchers have attempted to reduce graft surface thrombogenicity by coating anticoagulant or antiplatelet drug to the graft biomaterial.[8,10,20] However, early reports of such efforts have produced suboptimal results with inconsistent bioactivity of the anticoagulant molecule secondary to a widely varied degree of drug elusion once the bypass graft is exposed to the circulating blood. The CBAS heparin ePTFE graft uses a polymeric base matrix, which binds the heparin molecule to the graft surface in a manner that preserves the anticoagulant activity using a covalent end-point linking technology.[21] The anticoagulant activity of the end-point bonded heparin, referred to as bioactivity, is measured as the capacity to bind

Table II. Effects of heparin-bonded Propaten grafts versus control grafts on neointimal cell proliferation at the femoral bypass graft anastomosis

Duration	Neointimal cell proliferation	Propaten graft (mm^2)	Control graft (mm^2)	*P* value
1 month	Graft neointima (BrdU%)	3.08 ± 0.42	4.83 ± 0.82	0.04
	Vessel neointima (BrdU%)	3.75 ± 0.54	3.62 ± 0.45	NS
6 months	Graft neointima (BrdU%)	3.28 ± 0.37	6.24 ± 0.72	0.02
	Vessel neointima (BrdU%)	4.12 ± 0.57	4.43 ± 0.47	NS
12 months	Graft neointima (BrdU%)	3.48 ± 0.38	6.37 ± 0.79	0.02
	Vessel neointima (BrdU%)	3.95 ± 0.56	4.02 ± 0.42	NS
18 months	Graft neointima (BrdU%)	4.23 ± 0.46	7.21 ± 0.86	0.02
	Vessel neointima (BrdU%)	4.21 ± 0.68	4.38 ± 0.65	NS
24 months	Graft neointima (BrdU%)	4.76 ± 0.47	7.42 ± 0.85	0.02
	Vessel neointima (BrdU%)	4.17 ± 0.78	4.25 ± 0.39	NS

NS, not significant.

antithrombin, which is not only a natural coagulation inhibitor in the circulating blood but also a key protein for the heparin-mediated control of blood coagulation.[18] The CBAS-immobilized heparin biosurface previously has been shown to catalyze the rate of inactivation of thrombin by antithrombin effectively blocking the conversion of fibrinogen to fibrin, as well as block Factor XII initiation of the coagulation cascade.[22,23] In addition, the CBAS heparin surface is known to influence initial protein deposition on various biomaterials.[24] Consequently, the CBAS-treated ePTFE heparin surface is more hemocompatible due to its influence on protein adsorption during initial blood contacting events.[25] Clinical applications of the CBAS immobilized heparin surface include cardiovascular biomaterials such as cardiopulmonary bypass circuitry,[26] ventricular assisted device,[12] vascular graft,[11,27] and stent graft.[28] Our laboratory has previously reported the antithrombotic characteristics of heparin-coated ePTFE grafts and stents in canine and baboon models.[4–7] The effectiveness in reducing surface-induced thrombus formation has been linked to reduction in inflammatory cytokine activation in numerous *in vitro* studies.[29,30] In a clinical study which evaluated an extracorporeal Berlin Heart assist device, CBAS-immobilized heparin biomaterial has been shown to reduce the frequency and thickness of thrombotic deposits, thereby likely reducing complications related to thromboembolism.[31]

The finding of reduced thrombus formation in our study is consistent with other reports, which showed reduced platelet deposition on CBAS-immobilized devices, including cardiopulmonary bypass circuitry and oxygenator membrane.[12,32] Improved graft patency and reduced thrombogenicity with sustained heparin bioactivity at 6 months was also reported in a sheep carotid artery bypass model using heparin-coated ePTFE graft.[33] The bioactivity of heparin-bonded ePTFE surface with resultant decreased platelet adherence, decreased thrombus formation, and reduced inflammatory response has also been shown in extracorporeal circuits, and heart-assist devices up to 2 years.[12,34,35] Kocsis et al.[25] analyzed CBAS-heparin treated coronary stents in a baboon *ex vivo* model and reported a significant decrease in platelet deposition on heparinized stents compared to untreated control stents. In addition, the decreased platelet deposition in heparin-treated stents was correlated with the immobilized high AT-affinity heparin fraction. These researchers noted that significantly reduced platelet deposition corresponded with heparin activity as low as 7 pmol/cm^2.[25] Begovac and coworkers tested CBAS immobilized heparin ePTFE graft in a canine carotid artery bypass model, and demonstrated sustained antithrombin bioactivity was present at 12 weeks in the heparinized grafts.[11] Furthermore, significantly greater thrombus-free luminal surface was found on the heparin treated grafts when compared to non-heparin treated grafts. The authors reported a stable heparin activity in all CBAS-ePTFE surfaces with levels ranging between 15 and 25 pmol/cm^2 up to 12 weeks, which were well above the activity shown to reduce platelet deposition on the CBAS-treated surface. These results are consistent with our results in which we showed sustained heparin bioactivity between 18.4 ± 8.7 pmol/cm^2 and 26.3 ± 6.4 pmol/cm^2 during the 2 years of graft implantation duration.

Our study showed that CBAS-immobilized heparin graft resulted in significantly less anastomotic neointimal hyperplasia when compared to non–heparin-treated grafts, based on the evidence of

reduced cell proliferation and medial thickness (Tables I and II). These results are in line with our previous reports in terms of reduced intimal hyperplasia in heparinized grafts compared with nontreated grafts in animal models.[4,5] The antiproliferative effect of heparin on smooth muscle cell has been proven in multiple *in vitro* studies using human, baboon, bovine, and rat cell cultures.[36,37] Studies have demonstrated that the inhibitory effect of heparin on cultured smooth muscle cell proliferation is mediated via inhibition of DNA synthesis and by downregulation of the transcription gene necessary for cell passage from G_0 through G_1 and into the S phase.[38,39] Researchers have also discovered other possible mechanisms by which heparin inhibits neointimal proliferation. For instance, the antiproliferative properties of heparin may in part be mediated through inhibition of a second messenger pathway resulting in proto-oncogene expression in cell cycling.[40] Heparin not only inhibits intracellular protein kinase activity during signal transduction[41] but also downregulate transcription activator proteins.[42] Moreover, it can modulate the function and expression of numerous growth factors. It has also been shown that heparin can inhibit basic fibroblast growth factor (bFGF)—mediated growth responses of both endothelial and smooth muscle cells as well as downregulate the bFGF expression in the wall of injured arteries.[43] Heparin similarly can inhibit epidermal growth factor receptor expression and potentiates the inhibitory properties of transforming growth factor β by releasing it from a carrier protein.[44,45] Finally, heparin selectively inhibits the production of certain proteases that are critical for degrading extracellular matrix which can diminish cellular proliferation. These proteases include tissue-type plasminogen activator, interstitial collagenase, stromelysin, and gelatinase.[46] These results suggest that heparin plays a vital role in modulating smooth muscle cell migration and neointimal proliferation via a complex biochemical and cellular cascade. Therefore, new treatment strategies which target these cellular pathways by incorporating heparin on prosthetic vascular biomaterial may potentially improve the graft patency and clinical outcome.

The beneficial effect of CBAS-immobilized heparin in cardiovascular application has been validated by numerous clinical investigators.[12,25,47–50] Studies have shown CBAS-coated heparinized coronary stents can reduce subacute thrombosis,[51] decrease major adverse events compared to coronary balloon angioplasty,[52] and result in superior patency rates.[48] Kaufmann et al.[53] analyzed CBAS-heparin coated EXCOR ventricular assist device pumps up to 190 days of clinical use and found that the replacement rate of pumps with the CBAS heparin treatment was significantly reduced compared with uncoated pumps, due in part to decreased thrombus deposition and thromboembolic complications. In a similar study which analyzed CBAS treated ventricular assist device pump, Werkkala et al.[12] showed sustained heparin bioactivity up to 461 days of clinical usage. The clinical benefit of CBAS-heparinized ePTFE graft, or Propaten graft, has similarly been investigated in lower extremity revascularization. Samson et al.[54] reported a large clinical study in which they analyzed the outcomes of femoropopliteal artery bypass between 234 Propaten grafts and 123 standard ePTFE grafts and found superior primary patency rates in both above-knee and below-knee Propaten graft when compared to non-heparin—treated grafts. The Propaten European Product Evaluation II multicenter prospective European registry observed 12-month primary patency rates of 82.7% in above-knee and 74.2% in below-knee heparin-bonded femoropopliteal grafts.[49] A prospective randomized multi-institutional Scandinavian study documented a 12-month primary patency rate of 80.4% in the heparin-bonded femoropopliteal grafts, which was significantly higher compared to 69.6% rate observed in the standard ePTFE group of that study.[50] Dorigo et al.[55] reported their institutional experience of femoropopliteal below-knee bypass using standard PTFE versus heparin-bonded Propaten graft. Their results showed significantly improved 18-month patency rate of Propaten graft compared with the standard graft, which were 40% and 53%, respectively. Taken altogether, these clinical reports underscored the superior clinical outcome of CBAS-heparin treated vascular biomaterials in terms of superior patency and improved outcomes compared to non—heparin-treated biosurface.

In conclusion, this study demonstrated long-term thromboresistant property of heparin-bonded Propaten graft, which incorporates CBAS-ePTFE heparin surface to provide stable and sustained heparin bioactivity. In addition, reduced graft neointimal hyperplasia was demonstrated in heparin-bonded Propaten graft compared with the control untreated graft in our chronic animal bypass model. Our data support the use of CBAS-ePTFE heparin-bonded bypass in clinical application due to the long-term thromboresistant bioactivity.

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