

CARMEDA® BioActive Surface - Features & Benefits

selected references

The CARMEDA® BioActive Surface is a clinically proven and lasting thromboresistant heparin coating technology that actively prevents platelet adhesion and thrombus formation on medical device surfaces.

The following features and benefits of the CARMEDA® BioActive Surface have been shown in published clinical studies and scientific papers:

Thromboresistant - By suppressing the coagulation mechanism the CARMEDA® BioActive Surface reduces or eliminates thrombotic complications related to the exposure of blood to artificial materials (1, 2). The CARMEDA® BioActive Surface has been shown to effectively neutralize activated coagulation factors such as thrombin (3) and FXa (4). Studies have also revealed that the initiation mechanism of the coagulation system is suppressed by the bound heparin (5, 6). The CARMEDA® BioActive Surface has in certain applications reduced the risk of thrombosis-related complications to a degree that allowed decreased systemic anticoagulation (7, 8).

Platelet compatible - The CARMEDA® BioActive Surface causes minimal activation and adhesion of platelets as demonstrated by *in vitro* (9, 10), *in vivo* (10, 11) and clinical studies (12, 13).

Decreased inflammatory response - Several preclinical studies have shown near-elimination of complement activation in blood exposed to the CARMEDA® BioActive Surface (14, 15). The CARMEDA® BioActive Surface has also been demonstrated to effectively prevent complement-dependent as well as complement-independent activation of cells such as leukocytes and platelets (16) along with inhibition of increases in chemokines and growth factors (17). Clinical studies have confirmed that medical devices with the CARMEDA® BioActive Surface cause less complement activation and subsequent cell activation than uncoated devices (18, 12).

Reduced infection rates - Clinical studies have indicated a reduced infection rate in patients treated with central venous catheters with CARMEDA® BioActive Surface compared to uncoated catheters (19, 20). Hypothetically, due to the thromboresistant properties of the CARMEDA® BioActive Surface, the catheter surface is less likely to be fouled by clot-related material, making it less prone to support microbial growth.

Reduced neointimal hyperplasia – Several studies in animal models have shown that vascular grafts coated with the Carmeda heparin technology delay and reduce anastomotic intimal hyperplasia, both short- and long term at 2 years (10, 11, 21, 22).

Lasting performance - The CARMEDA® BioActive Surface is a long-term, highly robust thromboresistant coating able to withstand all expected fluid flow conditions and many mechanical challenges. For example, the coating has been shown to remain bound and functional with sustained heparin bioactivity on explanted devices after months or even years of blood flow contact (23, 24, 25). It also withstands, e.g. the mechanical challenge of balloon expansion of coronary stents in stenosed arteries (10, 26).

Improved clinical outcome - Numerous studies have shown improved clinical outcome for devices featuring the CARMEDA® BioActive Surface. Direct comparison of uncoated and coated ventricular assist devices (VADs) have shown that those with the CARMEDA® BioActive Surface significantly reduce the replacement rate of the pumps, mainly due to decreased thrombus deposition and thromboembolic complications (27). The clinical benefit of vascular grafts has similarly been investigated in lower extremity revascularization, where ePTFE grafts coated with the Carmeda heparin technology have superior primary patency rates in both above-knee and below-knee grafts when compared to non-heparin coated grafts (28, 29). These grafts configured for pediatric shunts have also been shown to reduce mortality in neonates and infants receiving systemic-to-pulmonary shunts (30). Compared with non-heparin coated ePTFE grafts they have had fewer shunt occlusions/thromboses and desaturation or arrest events, resulting in significantly lower shunt-related as well as overall 30-day mortality. Another example is coronary stents, where stents coated with the CARMEDA® BioActive Surface reduced subacute stent thrombosis in coronary interventions compared to bare metal stents (31). An extensive number of clinical references categorized into type of product/application can be found in the CARMEDA® BioActive Surface reference list.

Superiority compared to other commercial heparin coatings - Central to the design of a functional heparin surface is to retain the anticoagulant activity of heparin, i.e. by preserving its ability to bind antithrombin and catalyze the inhibition of coagulation factors. Of the various approaches and methods used to bond heparin permanently, very few achieve this prerequisite of preserving antithrombin binding. It is thus important to recognize that not all heparin coatings are equivalent (32). Of commercialized non-eluting heparin coating technologies developed for use in the medical device industry, few technologies except the CARMEDA® BioActive Surface have publications showing biochemical evidence of surface heparin functionality (33). The CARMEDA® BioActive Surface has an impressive pre-clinical and clinical track record, and undoubtedly an extensive publication history describing both basic biochemical mechanisms and clinical applications (see CARMEDA® BioActive Surface reference list).

Reference list

- 1) Olsson P, Sanchez J, Mollnes TE, et al. On the blood compatibility of end-point immobilized heparin. *J Biomater Sci Polym Ed* **2000** 11(11): 1261-1273.
- 2) Weber N, Wendel HP, Ziemer G, et al. Hemocompatibility of heparin-coated surfaces and the role of selective plasma protein adsorption. *Biomaterials* **2002** Jan 23(2): 429-439.
- 3) Pasche B, Kodama K, Larm O, et al. Thrombin inactivation on surfaces with covalently bonded heparin. *Thromb Res* **1986** Dec 44(6): 739-748.
- 4) Kodama K, Pasche B, Olsson P, et al. Antithrombin III binding to surface immobilized heparin and its relation to FXa inhibition. *Thromb Haemost* **1987 Dec** 58(4): 1064-1067.
- 5) Sanchez J, Elgue G, Riesenfeld J, et al. Control of contact activation on end-point immobilized heparin: the role of antithrombin and the specific antithrombin-binding sequence. *J Biomed Mater Res* **1995** May 29(5): 655-661.
- 6) Sanchez J, Elgue G, Riesenfeld J, et al. Studies of adsorption, activation, and inhibition of factor XII on immobilized heparin. *Thromb Res* **1998** Jan 89(1): 41-50.
- 7) Mottaghy K, Oedekoven B, Pöppel K, et al. Heparin-coated versus non-coated surfaces for extracorporeal circulation. *Int J Artif Organs* **1991** Nov 14(11): 721-728.
- 8) Øvrum E, Tangen G, Tølløfsrud S, et al. Heparinized cardiopulmonary bypass circuits and low systemic anticoagulation: An analysis of nearly 6000 patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* **2011** May; 141(5): 1145-1149.
- 9) Mollnes TE, Videm V, Christiansen D, et al. Platelet compatibility of an artificial surface modified with functionally active heparin. *Thromb Haemost* **1999** Sep 82(3): 1132-1136.
- 10) Kocsis JF, Llanos G, Holmer E. Heparin-coated stents. *J Long Term Eff Med Implants* **2000** 10(1-2): 19-45.
- 11) Lin PH, Bush RL, Yao Q, et al. Evaluation of platelet deposition and neointimal hyperplasia of heparin-coated small-caliber ePTFE grafts in a canine femoral artery bypass model. *J Surg Res* **2004** May 118(1): 45-52.
- 12) Fukutomi M, Kobayashi S, Niwaya K, et al. Changes in platelet, granulocyte, and complement activation during cardiopulmonary bypass using heparin-coated equipment. *Artif Organs* **1996** Jul 20(7): 767-776.
- 13) Gurbel PA, Bliden KP. Platelet activation after stenting with heparin-coated versus noncoated stents. *Am Heart J* **2003** Oct 146(4): E10.

- 14) Mollnes TE, Riesenfeld J, Garred P, et al. A new model for evaluation of biocompatibility: combined determination of neoepitopes in blood and on artificial surfaces demonstrates reduced complement activation by immobilization of heparin. *Artif Organs* **1995** Sep 19(9): 909-917.
- 15) Kopp R, Mottaghy K, Kirschfink M. Mechanism of complement activation during extracorporeal blood-biomaterial interaction: effects of heparin coated and uncoated surfaces. *ASAIO J* **2002** Nov-Dec 48(6): 598-605.
- 16) Lappegård KT, Fung M, Bergseth G, et al. Effect of complement inhibition and heparin coating on artificial surface-induced leukocyte and platelet activation. *Ann Thorac Surg* **2004** Mar 77(3): 932-941.
- 17) Lappegård KT, Bergseth G, Riesenfeld J, et al. The artificial surface-induced whole blood inflammatory reaction revealed by increases in a series of chemokines and growth factors is largely complement dependent. *J Biomed Mater Res A* **2008** Oct 87(1): 129-135.
- 18) Fosse E, Moen O, Johnson E, et al. Reduced complement and granulocyte activation with heparin-coated cardiopulmonary bypass. *Ann Thorac Surg* **1994** Aug 58(2): 472-477.
- 19) Appelgren P, Ransjö U, Bindslev L, et al. Surface heparinization of central venous catheters reduces microbial colonization in vitro and in vivo: results from a prospective, randomized trial. *Crit Care Med* **1996** Sep 24(9): 1482-1489.
- 20) Jain G, Allon M, Saddekni S, et al. Does heparin coating improve patency or reduce infection of tunneled dialysis catheters? *Clin J Am Soc Nephrol* **2009** Nov 4(11): 1787-1790.
- 21) 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** Jun 39(6): 1322-1328.
- 22) Freeman J, Chen A, Weinberg RJ, et al. Sustained Thromboresistant Bioactivity with Reduced Intimal Hyperplasia of Heparin-Bonded PTFE Propaten Graft in a Chronic Canine Femoral Artery Bypass Model. *Ann Vasc Surg* **2017**, Nov 29. Epub ahead of print.
- 23) Riesenfeld J, Ries D, Hetzer R. Analysis of the heparin coating of an EXCOR Ventricular Assist Device after 855 days in a patient. *Society for Biomaterials Transactions of the 32rd annual meeting* **2007**.
- 24) Begovac PC, Thomson RC, Fisher JL, et al. Improvements in GORE-TEX Vascular Graft Performance by Carmeda BioActive Surface Heparin Immobilization. *Eur J Vasc Endovasc Surg* **2003** May 25(5): 432-437.
- 25) Werkkala K, Jokinen JJ, Soininen L, et al. Clinical Durability of the CARMEDA BioActive Surface in EXCOR Ventricular Assist Device Pumps. *ASAIO J* **2016** Mar-Apr 62(2): 139-142.
- 26) Hårdhammar PA, van Beusekom HM, Emanuelsson HU, et al. Reduction in thrombotic events with heparin-coated Palmaz-Schatz stents in normal porcine coronary arteries. *Circulation* **1996** Feb 93(3): 423-430.
- 27) Kaufmann E, Hennig M, Loebe, et al. Improving the antithrombogenicity of artificial surfaces through heparin coating - Clinical experience with the pneumatic extracorporeal Berlin Heart assist device. *Cardiovascular Engineering* **1996** Dec 1(1): 40-44.
- 28) Samson RH, Morales R, Showalter DP, et al. Heparin-bonded expanded polytetrafluoroethylene femoropopliteal bypass grafts outperform expanded polytetrafluoroethylene grafts without heparin in a long-term comparison. *J Vasc Surg* **2016** Sep 64(3): 638-647.

- 29) 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. *Eur J Vasc Endovasc Surg* **2011** May 41(5): 668-673.
- 30) Ashfaq A, Soroya MS, Iyengar A, Federman M, Reemtsen BL. Heparin-Coated Grafts Reduce Mortality in Pediatric Patients Receiving Systemic-to-Pulmonary Shunts. *Pediatr Cardiol* **2018** Jan 13. Epub ahead of print.
- 31) Gupta V, Aravamuthan BR, Baskerville S, et al. Reduction of subacute stent thrombosis (SAT) using heparin-coated stents in a large-scale, real world registry. *J Invasive Cardiol* **2004** Jun 16(6): 304-310.
- 32) Gore S, Andersson J, Biran R, et al. Heparin surfaces: Impact of immobilization chemistry on hemocompatibility and protein adsorption. *J Biomed Mater Res B Appl Biomater* **2014** Nov 102(8): 1817-1824.
- 33) Biran R, Pond D. Heparin coatings for improving blood compatibility of medical devices. *Adv Drug Deliv Rev* **2017** Mar 112: 12-23.