TRAITEMENT DE SURFACE PAR L'HEPARINE DES BIOMATERIAUX VASCULAIRES

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(Nice)

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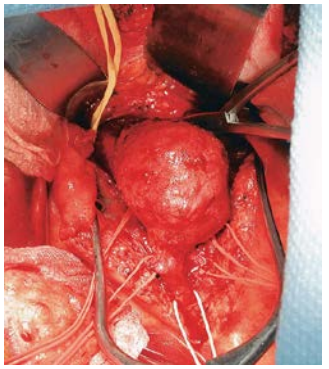
Faculté de Médecine

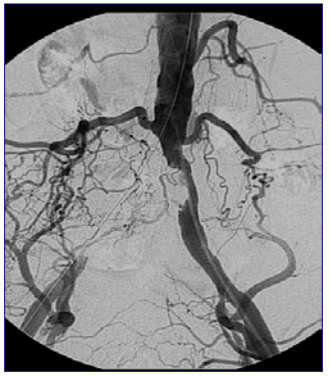
INTRODUCTION (1)

Les biomatériaux vasculaires

- **Utilisation**
  - Anévrismes
  - Maladies artérielles occlusives
  - Shunt A-V chez les hémodialysés chroniques



- **Matériaux**
  - PET (+++)
  - ePTFE (+++)
  - Polyuréthane (--)



- **Stents**

INTRODUCTION (2)

Les stents

- **Bare metal stent**
- **Drug eluting stent**

- **Stainless steel stent**
- **Nitinol stent**
- **Cobalt-chromium stent**

- **Uncovered stent**
- **Stent-graft**

- **Absorbable stents**

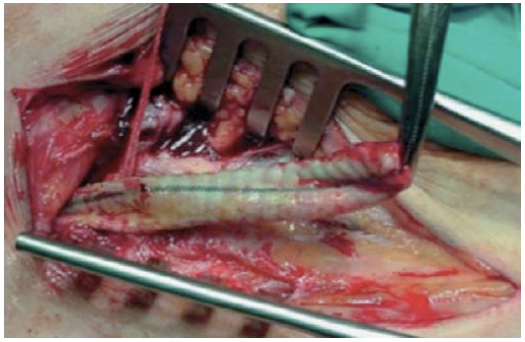
INTRODUCTION (3)

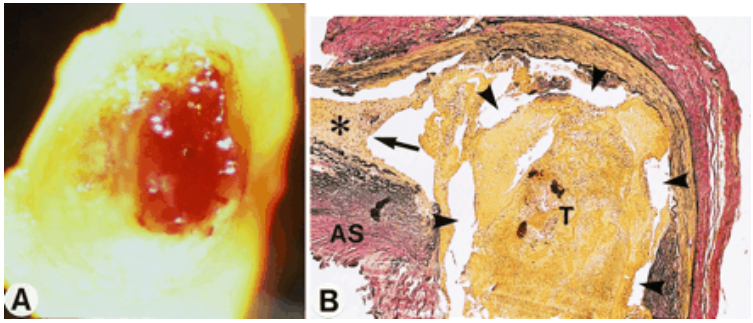
Les biomatériaux vasculaires

- **Principaux inconvénients**
  - Susceptibilité à l'infection
  - Thrombogénicité
  - Manque relatif de compliance

Problèmes cliniques divers

✓Infections prothétiques | ✓Thrombose précoce | ✓Hyperplasie myointimale





Stratégies d'optimisation des biomatériaux vasculaires

- **Carbon coating**
- **Fluoropolymer**
- **Modifications protéiques**
- **Incorporation de substances pharmacologiquement actives**

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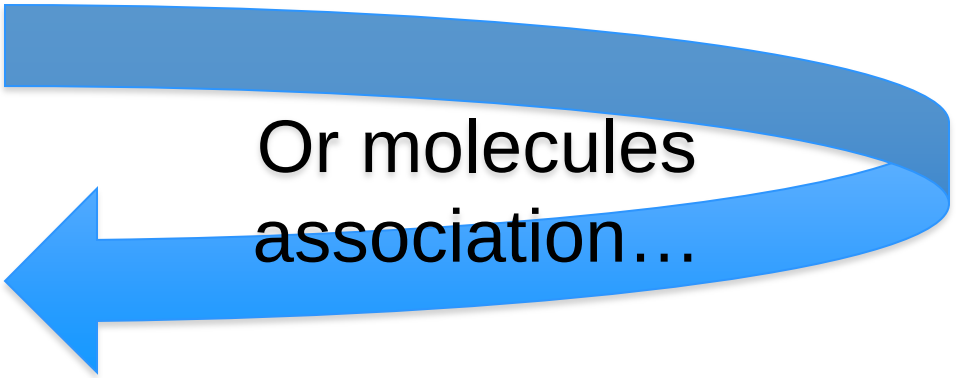
Drug immobilisation and drug delivery systems

- **Anticoagulant molecules**
  - Heparin
  - Thrombomodulin
  - Hirudin
- **Thrombolytic agents**
  - rTPA
- **Antiplatelet agents**
  - Iloprost
  - Dipyridamole
- **Antimitotic agents**
  - Rapamycin
  - Paclitaxel
- **Antibiotics**



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Modifications à l'héparine des biomatériaux vasculaires

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Faculté de Médecine

Historique

HEPARIN BONDING ON COLLOIDAL GRAPHITE SURFACES

Abstract

Experiments on clotting, both in vitro and in vivo, showed that a colloidal graphite surface, when rinsed with a cationic, surface-active agent, was capable of bonding heparin. The resistance of this graphite-heparin surface to the formation of clots was far greater than plastic or silicone surfaces in comparable studies.

- Significantly prolonged in vitro and in vivo clotting times on graphite-coated surfaces ionically bonded with heparin.

Gott VL, Whiffen JD, Dutton RC. Science 1963; 142: 1297-1298

Heparin-Bonded Surfaces in Extracorporeal Membrane Oxygenation for Cardiac Support

Ludwig K. von Segesser, MD

Clinic for Cardiovascular Surgery, University Hospital, Zürich, Switzerland

Development of increasingly complex perfusion devices with bonded heparin allowed for significant improvement of thromboresistance of most basic components required for cardiopulmonary bypass. In his recent review of heparin-coated cardiopulmonary bypass circuits, Gravlee cited 91 references dealing with heparin-coated surfaces, and far more can be found if the search includes material technology or heparin-coated devices not designed for cardiopulmonary bypass (eg, ventricular assist devices, hemofilters, catheters). The present review is focused on long-term application of heparin-coated equipment in conjunction with basic work on heparin bonding relevant for extracorporeal membrane oxygenation. Experimental open chest cardiopulmonary bypass using heparin-coated equipment without systemic heparinization up to 36 hours has shown improved thromboresistance, and better platelet preservation was demonstrated for perfusion with heparin-coated cardiopulmonary bypass equipment up to 5 days in the experimental set-up. Similar findings were reported for roller pump perfusion with heparin-coated tubing and centrifugal pump perfusion with heparin-coated pump heads More recently, heparin bonding was also made availabl for oxygenators with true membranes that preclud plasma leakage. The available knowledge on clinica applications of heparin-coated perfusion equipment i mainly based on short-term applications like ours, whic now includes more than 300 patients. Reduced postoper ative blood loss and as a result fewer transfusions wer the main benefits of heparin-coated equipment allowin for perfusion with low systemic heparinization. Ther are only a few reports on long-term use of heparin-coate equipment for prolonged circulatory support. However the longest clinical application of a single device is tha of an intravascular gas exchanger that remained full functional during a 29-day implantation period. Finally it appears, that circulating protamine interacts with sur face-bound heparin. Protamine administration shoul therefore be avoided during perfusion with heparin bonded equipment to maintain the improved thrombo resistance.

(Ann Thorac Surg 1996;61:330–5

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lowed the progress made in the experimental set-up, at least for short-term application [3]. In his recent review of

ing standard equipment with full systemic heparinizat
tion, we have evaluated the potential of open ches
perfusion with heparin-coated equipment in a canin
model [6, 7]. Duraflo II (Baxter-Bentley, Irvine, CA) hep
arin-coated tubing sets including a heparin-coated flexi
ble venous reservoir, a heparin-coated heat-exchange
hollow-fiber membrane oxygenator structure, and
heparin-coated arterial filter were used. Open chest per
fusion (right atrium to aorta) without systemic hepa

Presented at The Third International Conference on Circulatory Support Devices for Severe Cardiac Failure, Pittsburgh, PA, Oct 28–30, 1994.

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Thrombin During Cardiopulmonary Bypass

L. Henry Edmunds, Jr, MD, and Robert W. Colman, MD

Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, and The Sol Sherry Thrombosis Research Center, Hematology Division, Department of Medicine, Temple University, Philadelphia, Pennsylvania

Cardiopulmonary bypass (CPB) ignites a massive defense reaction that stimulates all blood cells and five plasma protein systems to produce a myriad of vasoactive and cytotoxic substances, cell-signaling molecules, and upregulated cellular receptors. Thrombin is the key enzyme in the thrombotic portion of the defense reaction and is only partially suppressed by heparin. During CPB, thrombin is produced by both extrinsic and intrinsic coagulation pathways and activated platelets. The routine use of a cell saver and the eventual introduction of direct thrombin inhibitors now offer the possibility of completely suppressing thrombin production and fibrinolysis during cardiac surgery with CPB.

(Ann Thorac Surg 2006;82:2315–22)

Blood is a tissue designed to sustain all cells by continuous circulation within a vast labyrinth paved with endothelial cells. These unique cells simultaneously maintain the fluidity of blood and ensure integrity of the vascular system. Contact with the surgical wound and diversion of blood into the heart-lung machine trigger an angry defense reaction that evolved to protect the body from pathogens, injuries, and noxious substances. The major participants are blood cells and five plasma protein systems, which generate a massive reaction by upregulating cellular receptors and by releasing a potpourri of vasoactive, cytotoxic, and cell-signaling substances into the circulation. Platelets, neutrophils, monocytes, and

Methods

An Internet search was made using the keywords *thrombin*, *thrombosis*, *tissue factor*, and *fibrinolysis* on Google, Ovid, Pub Med, and Scirus. The number of hits for *tissue factor* varied between 4826 (Ovid) and "about 24,900,000" (Google). The other keywords produced hits within this range. Thus, we retreated to traditional sources, which included textbooks [2, 3]; original references and reviews (see subsequent sections); and more than three decades of collaborative, government-funded, active research.

Heparin

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n [6].
hibition

Instead we concentrate on the primary mechanisms involved in the generation of thrombin, which is the key enzyme involved in the thrombotic portion of the defense reaction during CPB.

of thrombin and factors IXa and Xa more than 1000-fold, but the mechanisms of inhibition differ. In the case of thrombin, a bridging effect predominates, whereas with factor Xa and factor IXa, the major effect is an allosteric expanse of a reactive loop [7].

Heparin has advantages and disadvantages. The most notable advantages are rapid thrombin inhibition and reversal by protamine. Protamine does not reverse low-

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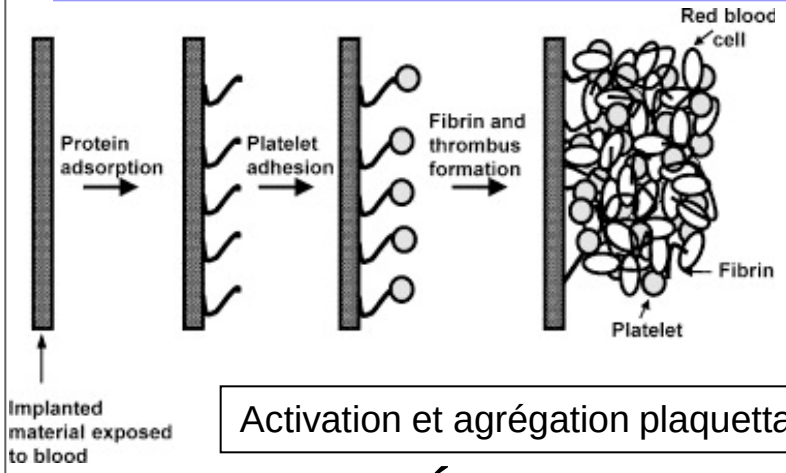
doi:10.1016/j.athoracsur.2006.06.072

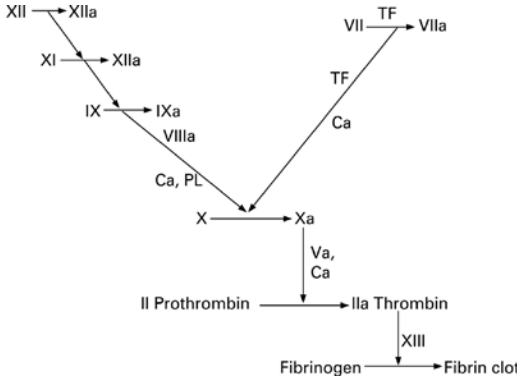
- **Development of heparin coating for a number of blood-contacting devices**
- **Most extensive use in cardiopulmonary bypass circuits**

Intérêt théorique de la fixation de l'héparine

La thrombogénicité intrinsèque des biomatériaux vasculaires



Activation et agrégation plaquettaires



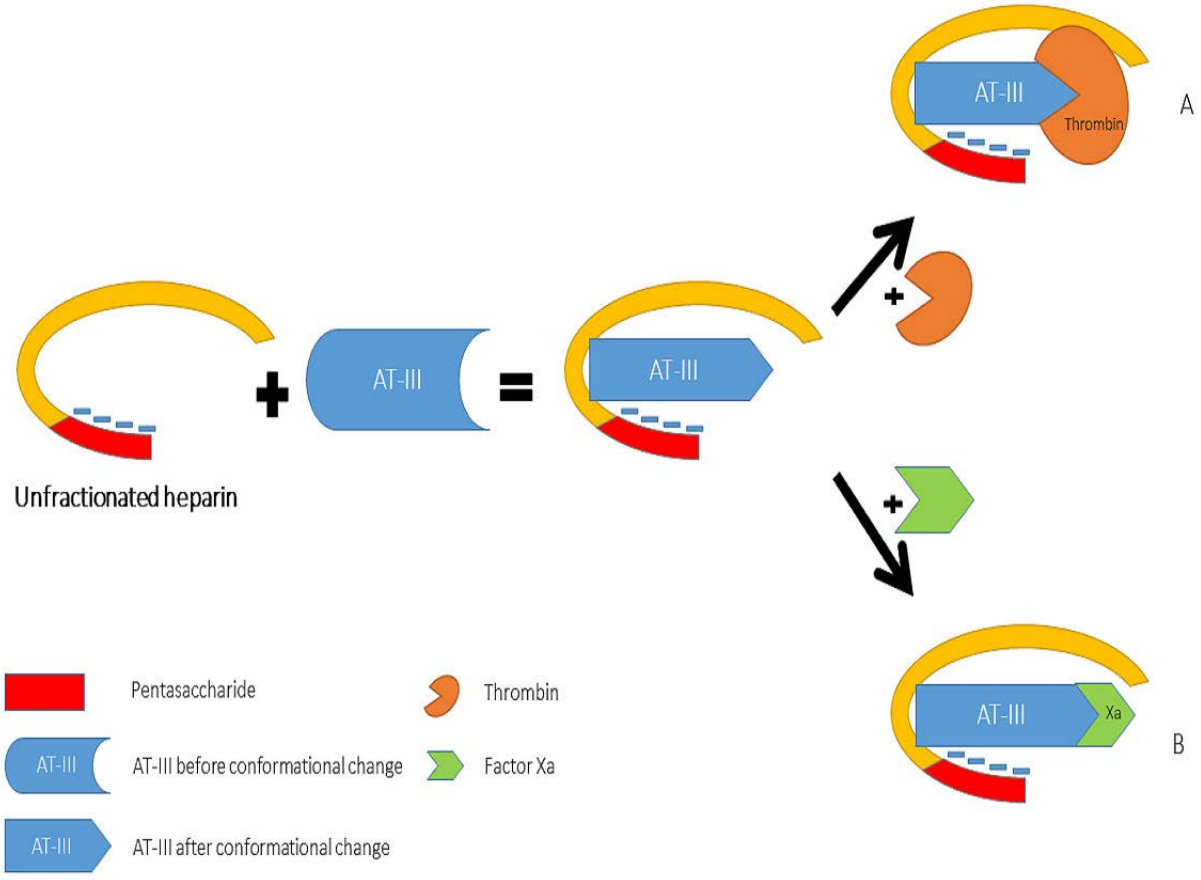
Activation de la voie intrinsèque de la coagulation

Élévation de promoteurs prothrombotiques

- ❑Thrombomoduline
- ❑thromboxane B2
- ❑facteur XIIa
- ❑éléments du complément
- ❑leucocytes circulants

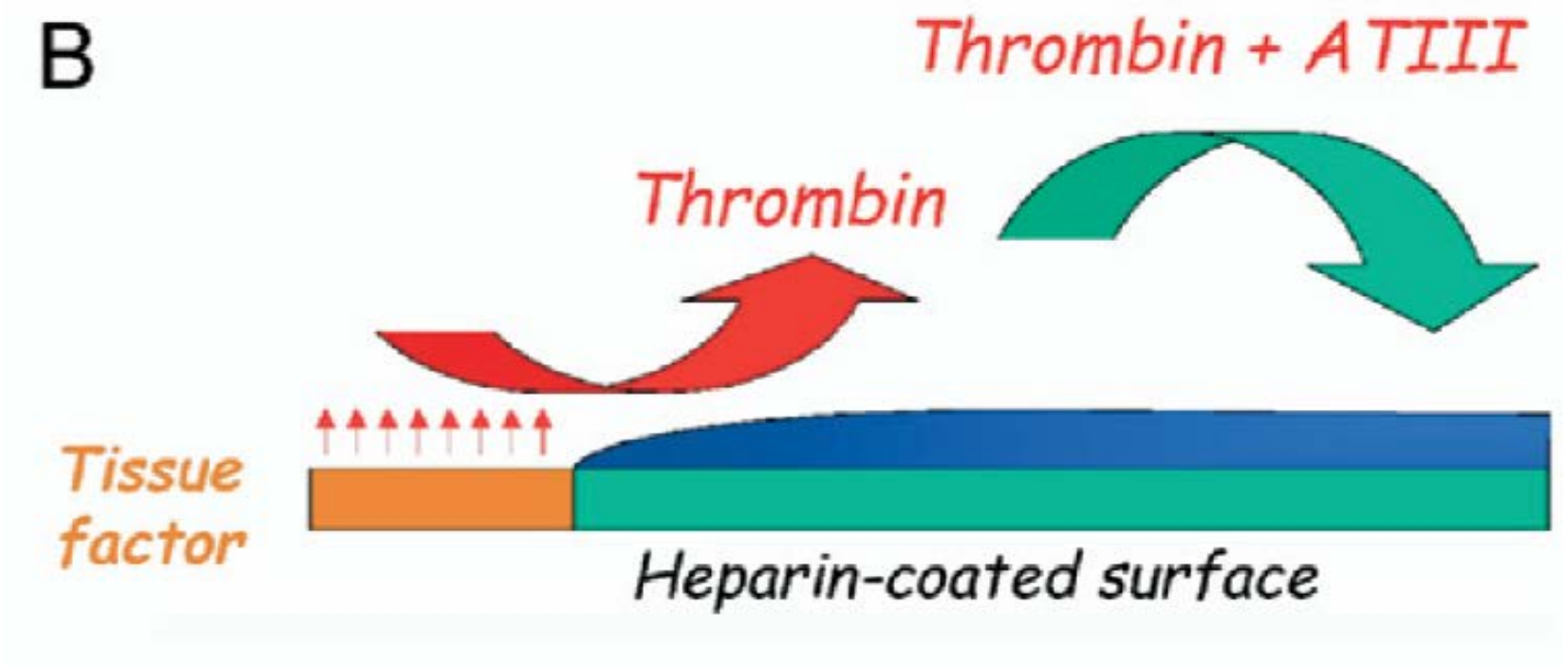
✓Incapacité d'avoir des substituts < 6mm

Mécanismes d'action de l'héparine



Membrane–mimetic films containing thrombomodulin and heparin inhibit tissue factor-induced thrombin generation in a flow model

Tseng et al. *Biomaterials* 2006; 27(12):2637-50



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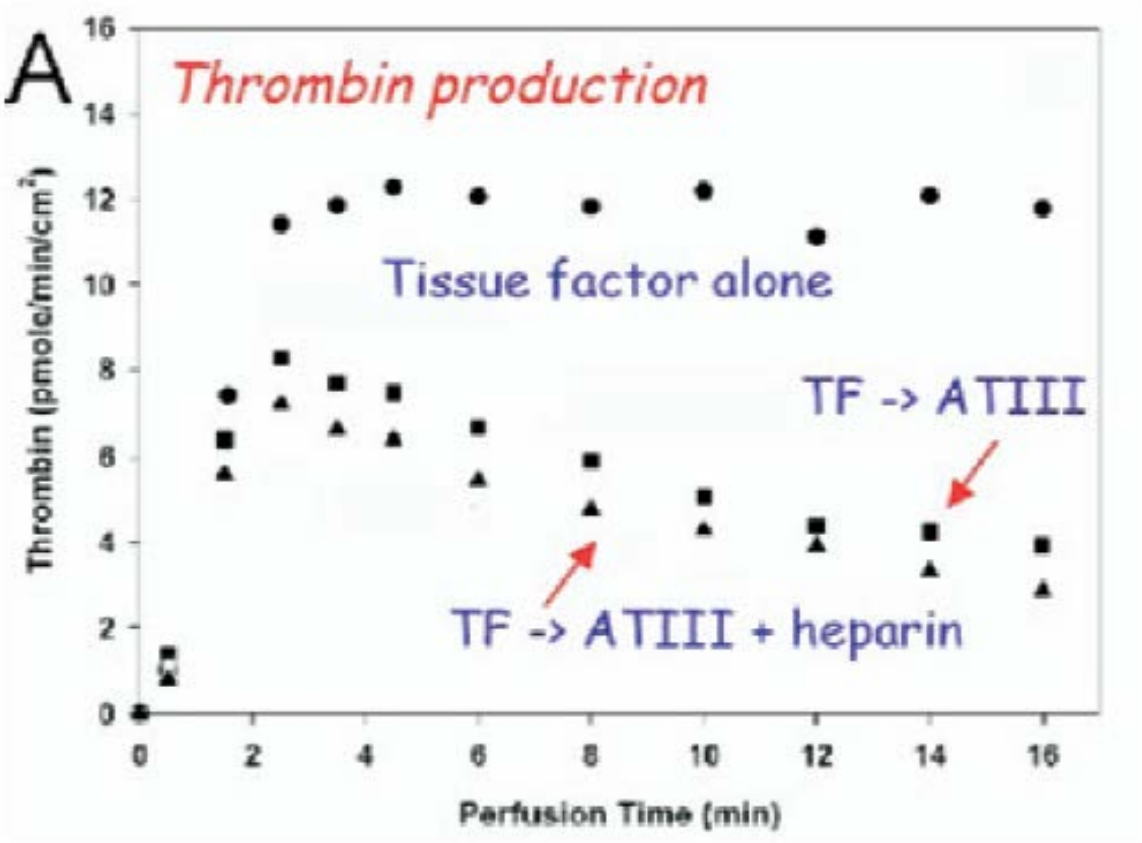
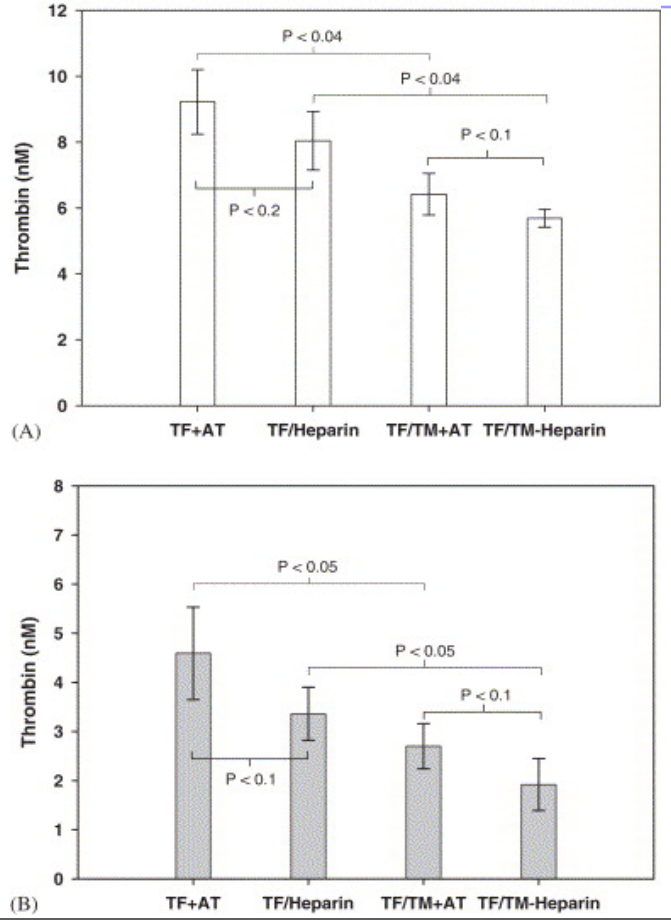


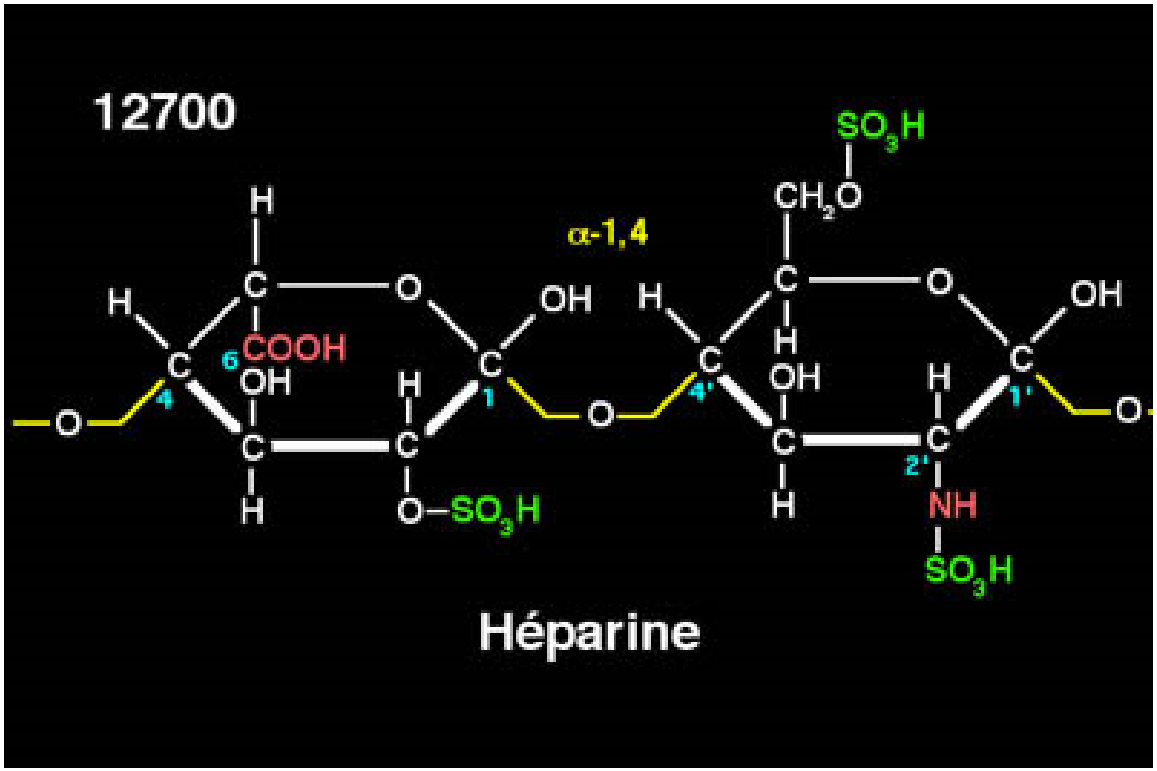
Membrane–mimetic films containing thrombomodulin and heparin inhibit tissue factor-induced thrombin generation in a flow model

Tseng et al. *Biomaterials* 2006; 27(12):2637-50



Additive effect of surface bound HP and TM to limit TF-induced thrombin formation

Méthodes de fixation de l'héparine sur les biomatériaux vasculaires



J Nanosci Nanotechnol. 2006 Sep-Oct;6(9-10):3163-70.

Hemocompatibility of layer-by-layer hyaluronic a
nanostructure coating on stainless steel for card
its use for drug delivery.

Huang LY[1], Yang MC.

Author information

Abstract

In order to develop **drug**-eluting **cardiovascular stents**, **stainle**
were coated with **hyaluronic** acid (HA) and heparin (HEP), and
and **dru**
with nit
HA was covalently immobilized onto the surface. Heparin was th
HA-immobilized SS substrate. After repeating 1 to 5 cycles, 1 to
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the in vitro **drug delivery** study showed that release of sirolimus
stainless steel was able to maintain more than 30 days. Thus I
can improve the **hemocompatibility** of SS surface and control
multiple layers of HA/HEP PEC. These results indicate that the
coated **stainless steel** would be suitable for **drug** eluting **stents**

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In vitro hemocompatibility of self-assembled monolayers displaying various functional groups

Claudia Sperling[a], Rüdiger B. Schweiss[a], Uwe Streller[a], Carsten Werner[a,b,*]

[a]*Department of Biocompatible Materials, Leibniz Institute of Polymer Research Dresden, The Max Bergmann Center of Biomaterials Dresden, 01069 Dresden, Germany*
[b]*Department of Mechanical and Industrial Engineering, University of Toronto, Toronto ON, Canada*

Received 5 November 2004; accepted 15 April 2005
Available online 4 June 2005

Mécanismes de fixation de l'héparine

- electrostatic self-assembly through heparin's negatively charged sulfate groups

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blood.
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surface chemical–physical properties on distinct blood activation cascades, i.e. to analyze –OH surface groups vs. complement activation, acidic surface sites vs. contact activation/coagulation and surface hydrophobicity vs. thrombogenicity. Blood and model surfaces were analyzed after incubation for the related hemocompatibility parameters. Our results show that the adhesion of leukocytes is abolished on a $-CH_3$ surface and greatly enhanced on surfaces with –OH groups. The opposite was detected for the adhesion of platelets. A strong correlation between the activation of the complement system and the adhesion of leukocytes with the content of –OH groups could be observed. The contact activation for hydrophilic surfaces was found to scale with the amount of
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hydrophilicity/hydrophobicity, interfacial adaptability and surface roughness are considered to determine the fate of blood proteins, enzymes and cells interacting

theories concerning the initiation of coagulation processes. One claims that blood coagulation could be initiated through an autoactivation process of FXII to FXIIa [4–6] on negatively charged surfaces. Yet as newer research displays the role of FXIIa in vivo is rather controversial and it is disputed if its activation really is one of the main elicitors for thrombotic and immunologic processes on the biomaterials surface. The focus of coagulation activation has now shifted to the role of tissue factor (TF) for in vivo situations. TF which

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doi:10.1016/j.biomaterials.2005.04.042

BASIC RESEARCH STUDIES

From the Midwestern Vascular Surgical Society

Silyl-heparin bonding improves the patency an vivo thromboresistance of carbon-coated polytetrafluoroethylene vascular grafts

James Laredo, MD, PhD,[a,c] Lian Xue, MD, PhD,[a,c] Vicki A. Husak, BS,[c] Joan Ellinger, BS,[c] Gu Singh, MD,[c] Paul O. Zamora, PhD,[d] and Howard P. Greisler, MD,[a,b,c] *Maywood and Hines, Ill; a College Park, Md*

Objectives: Our purpose was to improve the performance of carbon-coated expanded polytetrafluoroethylen grafts by bonding the grafts with silyl-heparin, a biologically active heparin analog, using polyethylene g cross-linking agent.
Material and method: Silyl-heparin–bonded carbon-coated expanded polytetrafluoroethylene vascular gra Peripheral Vascular, Tempe, Ariz), were evaluated for patency and platelet deposition 2 hours, 7 days, and 30 graft imp autologo Histolog activity o
Results: C versus 68.7% for control (11/16) grafts ($P = .045$). Acute 2-hour graft patency was 100% for the silyl-hepari (6/6) grafts versus 83.3% for control (5/6) grafts. Radiolabeled platelet deposition studies revealed a significa amount of platelets deposited on the silyl-heparin grafts as compared with control grafts in the 30-day grou 7.18 vs 28.4 ± 9.73, CPM per cm2 per million platelets, mean ± SD, $P = .0451$, Wilcoxon rank sum test). In t group of dogs, a trend towards a lower deposition of platelets on the silyl-heparin grafts was observed. The significant difference in platelet deposition between the two grafts in the 7-day group. Histologic studies significant re in the 30-day types in the (internationa time points (2 ± 0.001, n = Conclusion: S improved gra thrombus. Th

Clinical Relevance: Expanded polytetrafluoroethylene (ePTFE) remains the most commonly used prosth material in infrainguinal arterial reconstructions. Reported long-term patency rates of ePTFE bypass grafts a to those observed with autogenous vein. Modification of the luminal surface of ePTFE bypass grafts may pr graft failure and ultimately improve long-term graft performance. Silyl-heparin is a biologically active heparin a is readily adsorbed onto hydrophobic surfaces while retaining its anticoagulant properties. Silyl-heparin bon carbon-coated ePTFE grafts improves the patency and in vivo thromboresistance and results in a decrease in int graft thrombus. This graft may be useful in the clinical setting.

From the Departments of Surgery,[a] and Cell Biology, Neurobiology and Anatomy,[b] Loyola University Medical Center, Maywood, Ill, the Department of Surgery,[c] Edward Hines VA Hospital, Hines, Ill, and Biosurface Engineering Technologies,[d] College Park, MD.
Competition of interest: Dr Greisler has been a consultant to Bard Peripheral Vascular.
Presented at the Twenty-seventh Annual Meeting of the Midwestern Vascular Surgical Society, Chicago, Ill, Sep 18-20, 2003.

Reprint requests: Howard P. Greisler, MD, Division of cular Surgery, Department of Surgery, Loyola Un Center, 2160 South First Avenue, Maywood, IL hgreisl@lumc.edu).

0741-5214/$30.00

doi:10.1016/j.jvs.2003.12.025

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Immobilization of heparin on a silicone surface through a heterobifunctional PEG spacer

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[b]*Departments of Chemistry, McMaster University, 1280 Main St. W., Hamilton Ont., Canada L8S 4L7*

Available online 27 July 2005

Abstract

eld well density silicone icity for heparin heparin
modified surfaces was demonstrably greater as measured by a chromogenic thrombin generation assay. The results suggest that the heterbifunctional PEG linker results in a high density of active heparin on the surfaces.

Keywords: Silicone; PEG spacer; Heparin; Thrombogenic; Fibrinogen; Antithrombin III

plasma mediate ects with is neces- order to

biocompatibility, processability and low cost. However, the relatively high surface hydrophobicity of these materials, which results in the adsorption of significant amounts of protein [1], constrains their use in biomedical applications. While potentially desirable in some applications [2,3], the non-specific adsorption of proteins is generally considered detrimental to performance, as it has been widely demonstrated that the initially adsorbed protein layer is responsible for mediating subsequent biological effects [4]. In blood contacting

render the material more biocompatible.

Heparin, a heterogeneous extended polymer of repeating sugar units with molecular weight ranging from 3000 to 30,000 and an average molecular weight of 15,000, and related compounds are among the most frequently used therapeutic agents for thrombin regulation. The utility of heparin-modified surfaces including heparin-modified silicone surfaces, however, has been mixed [5,6]. Heparin contains a key pentasaccharide sequence that binds to the inhibitor antithrombin; this complex has a significantly increased reaction with serine proteases including thrombin compared with free heparin [7]. The maintenance of an intact three-dimensional structure, particularly one in which the accessibility of the key active pentasaccharide is maintained, is necessary for activity of the heparin molecule.

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doi:10.1016/j.biomaterials.2005.05.053

Mécanismes de fixation de l'héparine

- covalent grafting often by a spacer arm

Covalently-Bound Heparin Makes Collagen Thromboresistant

Jeffrey F.W. Keuren, Simone J.H. Wielders, Anita Driessen, Michel Verhoeven, Marc Hendriks, Theo Lindhout

Objective—Blood compatibility of artificial surfaces depends on their immunogenic and thrombogenic properties. Collagen's weak antigenicity makes it an attractive candidate for stent coatings or fabrication of vascular grafts. However, the thrombogenic nature of collagen limits its application. We examined whether heparinization can make collagen more thromboresistant.

Methods and Results—Collagen was heparinized by crosslinking collagen with extensively periodate oxidized heparin and/or by covalently bonding of mildly periodate oxidized heparin. Both ways of heparinization have no effect on platelet adhesion and could not abolish induction of platelet procoagulant activity. However, thrombin generation was completely prevented under static and flow conditions. The functionality of immobilized heparin was confirmed by specific uptake of antithrombin, 13.5±4.7 pmol/cm^2 and 1.95±0.21 pmol/cm^2 for mildly and heavily periodated heparin, respectively.

Conclusions—These results indicate that immobilization of heparin on collagen, even as a crosslinker, is a very effective way to prevent surface thrombus formation. These data encourage the application of heparinized collagen as stent-graft material in animal and eventually human studies. (***Arterioscler Thromb Vasc Biol*. 2004;24:613-617.)**

Key Words: collagen ■ heparin ■ thrombogenicity ■ thrombosis ■ blood flow

Cardiovascular disease, including vascular stenosis, is still the leading cause of death in Western society. Obstructive atherosclerotic disease, causing angina pectoris or even myocardial infarction, is currently treated by the implantation

functionally active as it accelerated the thrombin-antithrombin (AT) reaction. In addition, this group demonstrated that crosslinking of collagen had an adverse effect on the antigenicity and degradation rate of collagen, but stimu-

Mécanismes de fixation de l'héparine

sistant. Collagen has been widely used in medical applications, including skin replacement, bone substitutes, and artificial valves.[7,8] Recently, a number of investigators attempted to use modified collagen as a vascular graft material.[9–12] Potential advantages of the natural biological polymer collagen are its weak antigenicity and high tensile strength, which can resist high arterial blood pressures. Furthermore, collagen

This study was undertaken to get a better understanding of the precise antithrombotic functions of immobilized heparin. Three types of heparinized collagen (heparin-crosslinked collagen, heparinized heparin-crosslinked collagen, and heparinized EDC/NHS-crosslinked collagen) were evaluated for their thrombogenicity by measuring platelet adhesion, platelet activation, and thrombin generation.

- integration into a hydrogel network

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From the Department of Biochemistry (J.F.W.K., T.L.) and the Cardiovascular Research Institute (S.J.H.W., T.L.), Maastricht University, 6200 MD Maastricht, The Netherlands; and the Medtronic Bakken Research Center B.V. (A.D., M.V., M.H.), 6229 GW Maastricht, The Netherlands.

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Controlled release of heparin from poly(ε-caprolactone) electrospun fibers

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Received 4 July 2005; accepted 31 October 2005
Available online 21 November 2005

Abstract

Sustained delivery of heparin to the localized adventitial surface of grafted blood vessels has been shown to prevent the vascular smooth muscle cell (VSMC) proliferation that can lead to graft occlusion and failure. In this study heparin was incorporated into electrospun poly(ε-caprolactone) (PCL) fiber mats for assessment as a controlled delivery device. Fibers with smooth surfaces and no

Mécanismes de fixation de l'héparine

Keywords: Polycaprolactone; Electrospinning; Drug release; Heparin; Pro-inflammatory response; Vascular smooth muscle cells

1. Introduction

- loading into a bulk polymer for controlled release

vessel, heparan sulfate glycosaminoglycans present in the vessel wall help maintain VSMCs in a contractile, non-

infiltration [5]. These changes can lead to the proliferation of vascular smooth muscle cells (VSMCs) in the vessel media and the subsequent migration of these cells into the intima causing arterial stenosis. In an uninjured blood

genes [7], inhibition of production of matrix-degrading proteases important for cell migration and proliferation [8], and inhibition of mitogen-activated protein kinase [9]. The local delivery of heparin to the site of vascular injury could be used to prevent the myoproliferative response whilst avoiding the associated problems of systemic drug delivery. Application of anti-proliferative agents to the localized adventitial surface of injured blood vessels has been

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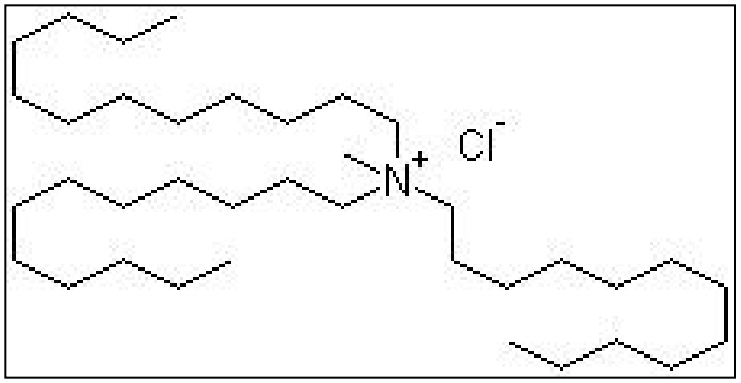
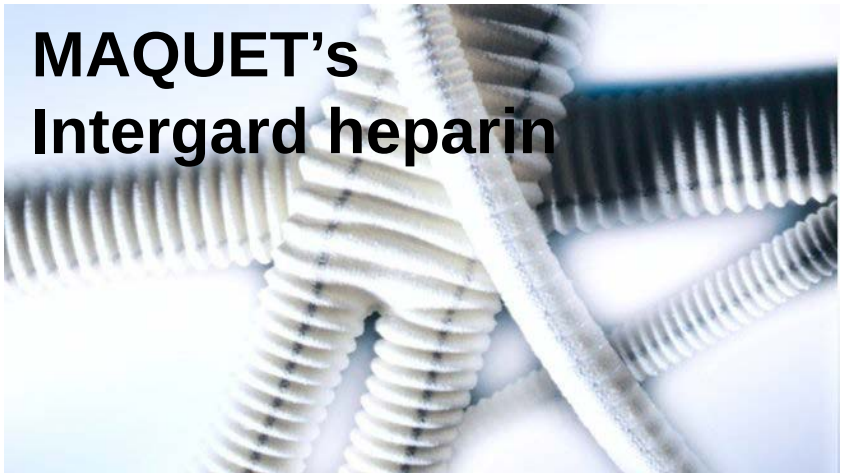
Mécanismes de fixation de l'héparine sur les prothèses vasculaires

- **MAQUET'S Fusion Bioline©**
- **Double couche**
  - Interne: ePTFE
  - Externe: PET
- **Fixation via l'albumine**
- **Niveaux de preuve**
  - Aucun
  - Extrapolation de l'utilisation du procédé dans les circuits de CEC

Mécanismes de fixation de l'héparine sur les prothèses vasculaires

Fixation par le Tri-Dodécyl-méthyl-ammonium-chloride (TDMAC)





- Liaision ionique entre l'ammonium quaternaire (NH_4+) et le groupe sulfate (SO4-) de l'Héparine
- Adsorption sur la prothèse par liaisons hydrophobes avec les longues chaines alkyles du TDMAC
- Imprégnation de la prothèse modifiée dans du collagène bovin en vue de l'étanchéification

Heparin-bonded Dacron or polytetrafluorethylene for femoropopliteal bypass: Five-year results of a prospective randomized multicenter clinical trial

Carol Devine, BA, and Charles McCollum, MD, FRCS, on behalf of The North West Femoro-Popliteal Trial Participants, *Manchester, England*

Objective: Dacron was largely abandoned for femoropopliteal bypass 30 years ago, because better patency rates were achieved with saphenous vein. Despite the range of potential prosthetics, polytetrafluoroethylne (PTFE) clearly predominates in current femoropopliteal practice. We compared heparin-bonded Dacron (HBD) with PTFE in a randomized multicenter clinical trial.
Method: Over 28 months, 209 patients (179 above-knee disease, 30 below-knee disease) were randomized to receive HBD (n = 106) or PTFE (n = 103) grafts. Aspirin, 300 mg/d, was started before surgery, and was continued if tolerated.
Results: At follow-up for a minimum of 5 years (mean, 76 months; range, 60-89 months), 37 patients (17.7%) had died with patent grafts and 121 (58%) grafts were occluded. Primary patency rate, measured with Kaplan-Meier survival analysis, was 46% (95% confidence interval [CI], 35%-57%) at year 5 for HBD, compared with 35% for PTFE (CI, 25%-45%; $P < .055$). Long-term patency was achieved in only 4 of 78 interventions performed in 55 thrombosed grafts. Secondary patency rate for HBD was 47% (CI, 36%-58%), and for PTFE was 36% (CI, 26%-46%). Risk factors for arterial disease did not significantly influence prosthetic patency. Major limb amputation was necessary in 9 patients with HBD grafts and 20 patients with PTFE grafts ($P < .025$). Two amputations in the HBD group and 8 amputations in the PTFE group were in patients undergoing bypass surgery to treat claudication only. Limb salvage rate was 86% (CI, 77%-95%) and 74% (CI, 64%-84%), respectively.
Conclusions: Significantly better patency rates were achieved with HBD than with PTFE at 3 years ($P < .044$), but the difference was no longer statistically significant at 5 years ($P < .055$). The incidence of major limb amputation, however, was significantly greater ($P < .025$) in the PTFE group compared with the HBD group at both 3 and 5 years of follow-up.
(J Vasc Surg 2004;40:924-31.)

Controversy still exists regarding material and tech-

gen-coated, heparin-bonded Dacron (HBD) prostheses

- At 5 years, Heparin-bonded Dacron grafts showed no significant improvement compared with uncoated ePTFE in the femoropopliteal position

From the Department of Surgery, Wythenshawe Hospital, Manchester, England.
Competition of interest: none.
Presented at the Twenty-eighth Annual Meeting of the Southern Association for Vascular Surgery, Rio Grande, Puerto Rico, Jan 14-17, 2004.
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0741-5214/$30.00

doi:10.1016/j.jvs.2004.08.033

Dacron grafts were, for the most part, abandoned for femoropopliteal bypass, because early experience proved disappointing. At the time, neither the role of platelets in generating thrombus on the luminal surface of prosthetic grafts nor the value of platelet inhibitory drug therapy was appreciated. This left the choice between PTFE and human umbilical vein. In randomized trials better patency rates tended to be achieved with human umbilical vein compared with PTFE,[5,14-16] but clinical practice changed little, presumably because surgeons were unconvinced that this small

Mécanismes de fixation de l'héparine sur les prothèses vasculaires

- Modification de surface par le procédé dit de « Carmeda Bioactive » ou technique d'immobilisation en « end-point »
- Générer une fonction aldéhyde sur l'unité saccharidique terminale de l'héparine
- Réaction avec une fonction amine présente sur la surface de l'implant via une base de Schiff
- Réduction pour obtenir une liaison covalente plus stable

Eur J Vasc Endovasc Surg **25**, 432–437 (2003)
doi:10.1053/ejvs.2002.1909, available online at http:/

Improvements in GOR Carmeda® BioAct

P. C. Begovac[*1], **R. C. Thor**

[1]*W. L. Gore & Associates, Inc., 3250*
[2]*Carmeda AB, Kana*

- **Greyhound dogs : significant reduction in acute and chronic thrombogenicity of heparin-bonded grafts with retention of heparin bioactivity at 12 weeks**

Small-caliber heparin- platelet deposition an baboon model

Peter H. Lin, MD,[a,b] Changyi Chen, MD, Ph
Alan B. Lumsden, MD,[a,b] and Stephen R. Ha

Purpose: Intimal hyperplasia and graft thrombosis
inhibits neointimal hyperplasia in animal models. T
expanded polytetrafluoroethylene (ePTFE) graft
aortoiliac bypass grafting in a baboon model.
Methods: Heparin-coated ePTFE grafts (4-mm di
shunts placed in five baboons. Platelet deposition

and did not differ significantly ($p > 0.05$).
Discussion: *these results support the conclu*
and improved patency in canine interposition
likely contributes to this outcome and holds

Key Words: ePTFE; Heparin; Vascular graf

- **Platelet deposition and anastomotic neointimal hyperplasia were reduced in ex vivo femoral arteriovenous shunt and chronic aortoiliac bypass models, respectively.**

Introduction

Improved patency of synthetic vascular
been a sought-after clinical goal since
duction nearly four decades ago. Expa
tetrafluoroethylene (ePTFE) vascular
demonstrated a long history of good clinic
ance as vascular conduits. While ePTFE
patency performance comparable to saph
in above-knee clinical applications,[1–4] ther
to be room for performance improveme
used for ≥6-mm diameter applications
diameter applications (<6mm diamete
below-knee bypass, however, all prosthe
graft materials are less than desirable
performance relative to autologous vein.
has gone into development of prosth
diameter grafts; but, due to the complex

*Please address all correspondence to: P. C. Begovac
Associates, Inc., 3250 West Kiltie Lane, P.O. Box 300
86002-0300, U.S.A.

1078–5884/03/050432+06 $35.00/0

neointima (3.47% ± 0.43%) in heparin-coated graf
control grafts ($P < .05$).
Conclusions: Small-caliber heparin-coated ePTFE g
timal hyperplasia and cell proliferation, without n
small-caliber ePTFE grafts is useful for improving

It is widely accepted that an autologous vein graf
ideal bypass conduit in peripheral arterial bypass
dures. However, nearly a third of patients who un
peripheral arterial reconstructive operations do no
adequate or available autologous vein graft, as a re
either previous vein harvest or poor vein quality.[1]

From Division of Vascular Surgery & Endovascular Therapy, Mi
DeBakey Department of Surgery, Baylor College of Medicine,[a] M
ist Hospital,[b] and Department of Biomedical Engineering,
Health & Science University.[c]
Competition of interest: none.
Presented at the Thirty-first Annual Meeting of the Association
demic Surgery, Sacramento, Calif, Nov 13-15, 2003.
Reprint requests: Stephen R. Hanson, PhD, Department of Bio
Engineering, Oregon Health & Science University, 20000 NW
Rd, Beaverton, OR 97006 (e-mail: shanson@bme.ogi.edu).
0741-5214/$30.00

doi:10.1016/j.jvs.2004.01.046

From the Peripheral Vascular Surgery Society

Heparin immobilization reduces thrombogenicity of small-caliber expanded polytetrafluoroethylene grafts

Jan M. M. Heyligers, MD,[a,b] Hence J. M. Verhagen, MD, PhD,[a] Joris I. Rotmans, MD, PhD,[c]
Cees Weeterings, Msc,[b] Philip G. de Groot, PhD,[b] Frans L. Moll, MD, PhD,[a] and Ton Lisman, PhD,[b]
Utrecht, The Netherlands

Objective: The patency of small-diameter expanded polytetrafluoroethylene (ePTFE) grafts for vascular reconstruction is impaired by acute thrombotic occlusion. Prosthetic materials are thrombogenic and cause platelet adhesion and activation of the coagulation cascade. Heparin is a potent anticoagulant drug widely used to prevent and treat thrombosis. A new ePTFE
ith long-term bonding of heparin is now commercially available in several European countries, but a basic analysis of
hanism of action in humans has never been performed. This study was performed to evaluate the thrombogenicity of
-bonded ePTFE grafts compared with standard ePTFE in a newly developed human ex vivo model.
s: Nonanticoagulated blood was drawn from antecubital veins of 10 healthy donors with a 19-gauge needle. The
al end of a 60-cm ePTFE vascular graft with a diameter of 3 mm was connected to the needle while the distal end
nnected to a syringe, which was placed in a syringe pump. Every volunteer served as his or her own control by using
in-bonded ePTFE graft on one arm and a standard ePTFE graft on the other arm. The perfusions were performed
minutes with a flow rate of 20 mL/min, corresponding to a shear rate of 74/s. Serial samples were taken at the
nd of the graft for determination of prothrombin fragment 1 + 2, fibrinopeptide A, and P-selectin expression on
d platelets. Fibrin deposition and platelet deposition were studied by using scanning electronic microscopy.
: Fibrinopeptide A production over time was significantly reduced on the heparin-bonded ePTFE grafts compared with standard ePTFE grafts ($P < .05$). There was no increase in the production of prothrombin fragment 1 + 2 or P selectin over time on either type of graft. Scanning electronic microscopy scanning showed platelet deposition and fibrin formation on standard ePTFE grafts, whereas no platelets or fibrin were observed on heparin-bonded ePTFE grafts.
Conclusions: Heparin immobilization substantially reduces the thrombogenicity of small-diameter ePTFE in a newly developed human ex vivo model. In this study, we provide evidence that the mechanism of action of the heparin bonding
may be an important improvement of
rg 2006;43:587-91.)

ll-caliber expanded polytetrafluoroeth-
r reconstruction is impaired by acute
dhesion and activation of the coagula-
treat thrombosis. A new ePTFE graft
analysis of its mechanism of action in
mbogenicity of heparin-bonded ePTFE
odel. We demonstrated that heparin
-bonded ePTFE grafts might therefore
result in better patency rates for vascular reconstructions with vascular grafts.

- **Reduction of fibrinopeptide A production, with absent platelet or fibrin adhesion, when non-anticoagulated blood from healthy donors was drawn directly into heparin-bonded grafts**

doi:10.1016/j.jvs.2005.10.038

(or heparinized) grafts have shown favorable results in

Heparin-bonded expanded polytetrafluoroethylene vascular graft for femoropopliteal and femorocrural bypass grafting: 1-year results

Marc Bosiers, MD,[a] Koen Deloose, MD,[a] Jürgen Verbist, MD,[b] Herman Schroë, MD,[c] Geert Lauwers, MD,[c] Wouter Lansink, MD,[c] and Patrick Peeters, MD,[b] *Dendermonde, Bonheiden, and Genk, Belgium*

Objective: Several prosthetic materials have been used for femoropopliteal bypass grafting in patients with peripheral vascular disease in whom a venous bypass is not possible. Expanded polytetrafluoroethylene (ePTFE) is the most commonly used, but patency results have not always equaled those achieved with vein, especially in below-knee reconstructions. This study assessed the performance of a new heparin-bonded ePTFE vascular graft that was designed to provide resistance to thrombosis and thereby decrease early graft failures and possibly prolong patency.
Method: From June 2002 to June 2003, 86 patients (62 men and 24 women; mean age, 70 years; 99 diseased limbs) were enrolled prospectively in a nonrandomized, multicenter study of the heparin-bonded ePTFE graft. Fifty-five above-knee and 44 below-knee (including 21 femorocrural) procedures were performed. Follow-up evaluations consisted of clinical examinations, ultrasonographic studies, and distal pulse assessments. Patency and limb salvage rates were assessed by using life-table analyses.
Results: All grafts were patent immediately after implantation. There were no graft infections or episodes of prolonged anastomotic bleeding. During the 1-year follow-up, 10 patients died, 15 grafts occluded, and 5 major amputations were performed. The overall primary and secondary 1-year patency rates were 82% and 97%, respectively. The limb salvage rate in patients with critical limb ischemia (n = 41) was 87%. Primary patency rates according to bypass type were 84%, 81%, and 74% for above-knee femoropopliteal, below-knee femoropopliteal, and femorocrural bypasses, respectively; the corresponding secondary patency rates were 96%, 100%, and 100%.
Conclusions: In this study, the heparin-bonded ePTFE graft provided promising early patency and limb salvage results, with no device-related complications, in patients with occlusive vascular disease. Longer-term and randomized studies are warranted to determine whether this graft provides results superior to those achieved with other prostheses, especially in patients at increased risk of early graft failure, such as those undergoing below-knee bypass and those with poor run-off or advanced vascular disease. (J Vasc Surg 2006;43:313-9.)

Patients with severe peripheral arterial occlusive disease may require bypass surgery to relieve symptoms, restore their ability to walk, or avoid foot amputation. Autologous

grafts used for infrainguinal bypass applications, especially infragenicular bypasses.

Prosthetic graft occlusion has several related causes

- 1-year primary patency rates of 84% to 91% for above knee bypass grafts and 81% to 92% for below knee bypass grafts.
- Two-year primary patency rates are 68% to 76% for above knee bypasses and 73% to 81% for below knee bypasses.

Competition of interest: none.
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0741-5214/$32.00

doi:10.1016/j.jvs.2005.10.037

hemocompatibility and improved patient outcome. The optimal method for attaching heparin to a prosthetic surface must provide long-term retention of the agent on that surface as well as sustained heparin activity.[6] Several attachment techniques have been developed, but one of the most common and successful is the Carmeda BioActive Surface

Eur J Vasc Endovasc Surg (2011) 41, 668–673

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☆

J.S. Lindholt [a,*], B. Gottschalksen [b], N. Johannesen [c], D. Dueholm [d], H. Ravn [e], E.D. Christensen [f], B. Viddal [g], T. Flørenes [h], G. Pedersen [i], M. Rasmussen [j], M. Carstensen [k], N. Grøndal [a], H. Fasting [a]

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[d] Department of Vascular Surgery, Kolding Hospital, Kolding, Denmark
[e] Department of Vascular Surgery, Eksjö District Hospital, Eksjö, Sweden
[f] Department of Vascular Surgery, Aabenraa Hospital, Aabenraa, Denmark
[k] Department of Vascular Surgery, Rigshospitalet, Copenhagen, Denmark

« Carmeda bioactive »

– A 1 an, diminution de 37% du risque d'échec primaire des pontages prothétiques Allergies à l'héparine: risque de TIH?

Femoropopliteal with adequate follow-up.

☆ The article was presented at the XXIV annual ESVS meeting in Amsterdam, 18 September 2010.
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E-mail address: jes.s.lindholt@viborg.rm.dk (J.S. Lindholt).

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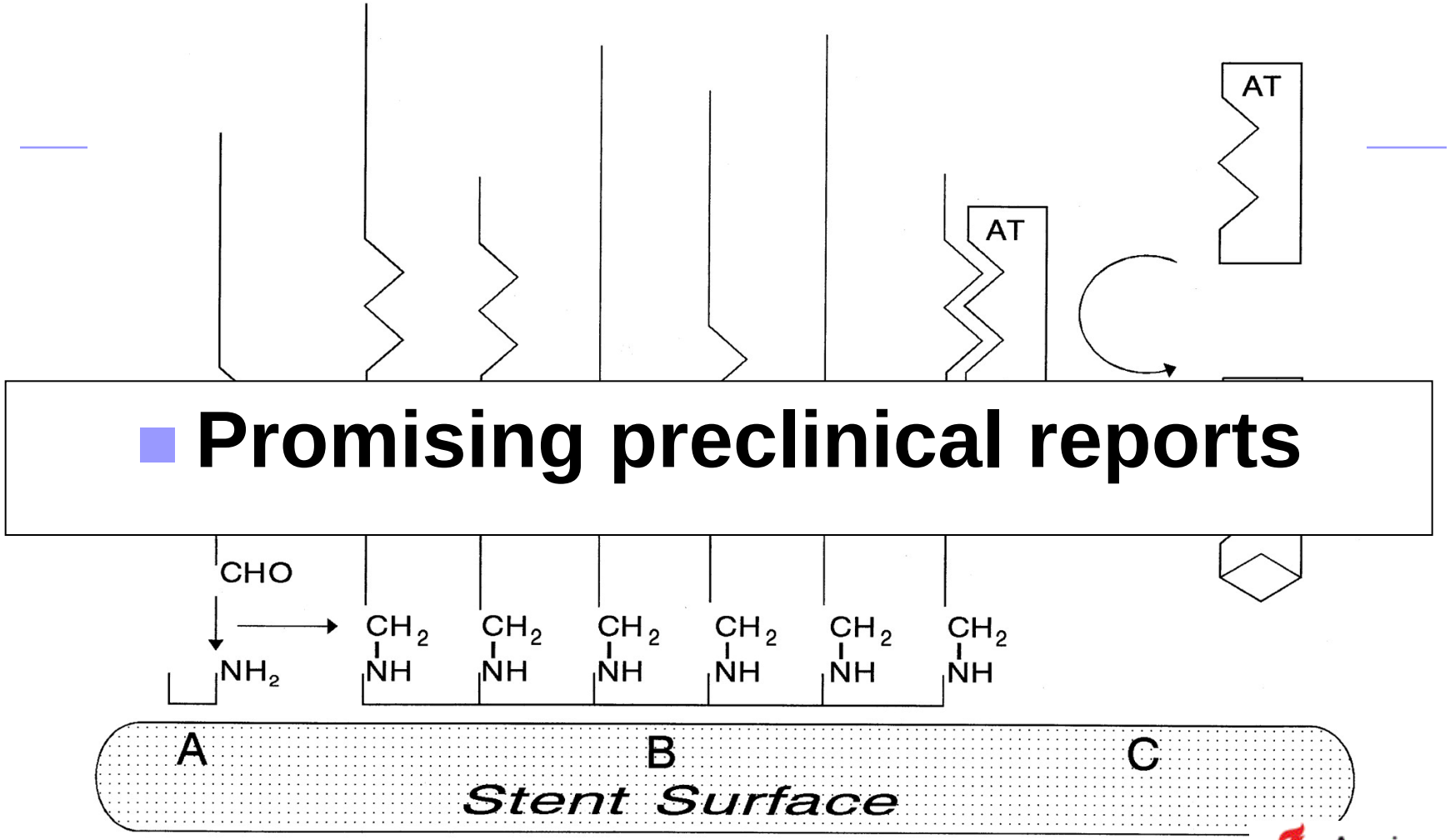
doi:10.1016/j.ejvs.2011.01.021

Quid des stents coatés à l'héparine?

Reduction in Thrombotic Events With Heparin-Coated Palmaz-Schatz Stents in Normal Porcine Coronary Arteries



- **Promising preclinical reports**

Peter A. Hårdhammar et al. Circulation. 1996;93:423-430

American Heart Association.

Centre Hospitalier Universitaire de Nice

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

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UMET Unité des Matériaux Et Transformations Université Lille 1

Faculté de Médecine

Heparin-Coated Wiktor Stents in Hum Coronary Arteries (MENTOR Trial)

Matty C.M. Vrolix, MD, Victor M. Legrand, MD, Johan H.C. Reiber, MD, PhD, Gille Grollier, MD, Martin J. Schalij, MD, Philippe Brunel, MD, Louis Martinez-Elba Manuel Gomez-Recio, MD, Frits W.H.M. Bär, MD, Michel E. Bertrand, MD, Ph Antonio Colombo, MD, PhD, and Johannes Brachman, MD, for the MENTOR Trial Investigators

The purpose of this study was to determine the feasibility, safety, and efficacy of elective stenting with heparin-coated Wiktor stents in patients with coronary artery disease. In experimental studies, heparin coating has been shown to prevent subacute thrombosis and restenosis. Recently, a new method of heparin coating was developed, resulting in a more stable and predictable heparin layer on stent devices. This trial constitutes the first in-human use of this coating procedure, applied on the well-known Wiktor stent device. Heparin-coated Wiktor stent implantation was performed in 132 consecutive patients (132 lesions) in a multicenter international trial from September 1996 to February 1997. Forty-three percent of patients had unstable angina, 33% had previous myocardial infarction, and 10% had diabetes mellitus. Patients were followed for 12 months for occurrence of major adverse cardiovascular events, and 96% of the eligible patients underwent quantitative angiographic control at 6 months. Stent deployment was successful in 95.5% of lesions. Minimal lumen diameter increased by 1.67 ± 0.48 mm (from 1.02 ± 0.38 mm before to 2.69 ± 0.37 mm after the stent implar Mean percent diameter stenosis decreased from 11.3% before to 18.9 ± 7.7% after the interve successful intervention (<50% diameter stenosis major adverse cardiac events within 30 days) o in 97% of the patients. The subacute thrombo was 0.8%, which compares favorably with h controls of this stent, and a low incidence of po dural increase in creatine kinase-MB was note months, event-free survival was 85% and angio restenosis rate was 22% with late loss of 0.78 mm and a loss index of 0.48 ± 0.44. Heparir Wiktor stents appeared to be an efficacious d treat Benestent-like lesions, yielding angiograp clinical results comparable to a heparin-coated Schatz stent. Despite its use in more complex lesi incidence of subacute thrombosis appeared to b than historical controls with a similar noncoate

(Am J Cardiol 2000;86:38

European Heart Journal (2001) **22**, 1808–1816
doi:10.1053/euhj.2001.2608, available online at http://www.idealibrary.com on IDEAL®

Comparison of the heparin coated vs the uncoated Jostent® — no influence on restenosis or clinical outcome

J. Wöhrle, E. Al-Khayer, U. Grötzinger, C. Schindler, M. Kochs, V. Hombach and M. Höher

Department of Cardiology, University of Ulm, Ulm, Germany

Aims Heparin coating of stents is thought to reduce stent thrombosis and restenosis rates. However, clinical data comparing coated and uncoated stents of the same model are lacking. We compared the heparin coated (C) and the uncoated (U) version of the Jostent® stent with regard to the clinical and angiographic outcome after 6 months.

Methods and Results Provisional stenting was done in 277 patients and 306 lesions; only 40 were Benestent-II like lesions. Delivery success rate was 98·4%. Both groups (C/U: n=156/150 lesions) were comparable in clinical and procedural data. Post stenting, reference diameter (C/U: 2·68 ± 0·56/2·66 ± 0·53 mm) and minimal lumen diameter did not differ (C/U: 2·48 ± 0·47/2·48 ± 0·52 mm). During follow-up the rate of subacute stent thrombosis (C/U: 1·9%/1·3%) and myocardial infarction did not differ. Angiography at the 6-month follow-up (79·4%) revealed no factors for restenosis were a type B2/C lesion (P<0·02), a stented segment longer than 16 mm (P<0·006) and a stent inflation pressure <14 bar (P<0·0063).

Conclusion Corline heparin coating of the Jostent® has no impact on the in-hospital complication rate, stent thrombosis or restenosis. The Jostent® design gives a high procedural success rate and satisfying result at 6 months in an everyday patient population undergoing provisional stenting.

(Eur Heart J 2001; 22: 1808–1816, doi:10.1053/euhj.2001.2608)

Key Words: Stent, restenosis, heparin coating, thrombosis.

See page 1766 for the Editorial comment on this article

- **Disapointing outcomes when heparin-coated stents were compared with bare-metal stents in two prospective, randomized clinical studies.**

Despit… coron… tions to t… Even with… and ticlop… remains i… dine carri… cations.[2] … of stent s… less thron… medicatio… indicate th… less acute thrombus formation, both in rabbit iliac arteries[3] and in a porcine coronary model.[4,5] Previous human coronary artices.

METHODS

Wiktor GX balloon-expandable intracoronar

The balloon-expandable Wiktor stent used present study is constructed of a single tantalu (diameter 0.127 mm) that is formed into a sin wave and wrapped into a helical coil structu prosthesis, 16 mm long, is premounted on a p ylene balloon of a standard angioplasty cathet device was used under the Food and Drug A tration investigational device exemption status of a multicenter study. The study was approve ethical committee of each participating institu

From the AZ St Jan, Genk, Belgium; CHU Sart Tilman, Liège, Belgium; Heart Core, Leiden, The Netherlands; CHU, Caen, France; LUMC Leiden, Leiden, The Netherlands; CHU de Nantes, Nantes, France; Hospital de la Princesa, Madrid, Spain; Academisch Ziekenhuis, Maastricht, The Netherlands; Université de Lille, Lille, France; Casa Di Cura Columbus, Milan, Italy; and Medizinische Universitäts Klinik, Heidelberg, Germany. The study was supported in part by Medtronic Inc., Minneapolis, Minnesota. Manuscript received December 22, 1999; revised manuscript received and accepted March 1, 2000.

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0002-9149/00/$–see front matte
PII S0002-9149(00)00951-

…enosis, …s was …rming …fy the vascular response following angioplasty injury and to reduce the amount of intimal hyperplasia. In addition, coating can decrease the surface roughness and thus may reduce the thrombotic properties of the stent struts and consequently the need for adjunctive antiplatelet therapy. Despite the reduced rate of stent thrombosis with the combined treatment of acetalsalicylic acid and ticlopidine or clopidogrel[2], these medical regimes still contain the risk of haematological complications[3].

It has been suggested that heparin coating of stents lowers the stent thrombosis rate, reduces the proliferative vascular response by minimizing the adhesion and activation of platelets and granulocytes, and decreases the activation of coagulation and complement. Experimental studies have demonstrated the ability of heparin

Revision submitted 16 January 2001 and accepted 17 January 2001.

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0195-668X/01/191808+09 $35.00/0

CONCLUSION

- **Faisabilité éprouvée de la fonctionnalisation des biomatériaux vasculaires par l'héparine**
- **Preuves encore insuffisantes des bénéfices à long terme**
- **Nécessité de poursuivre les recherches**