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BLOOD COMPATIBILITY OF NITINOL COMPARED TO STAINLESS STEEL

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ABSTRACT

Because of its superelasticity, shape memory, corrosion resistance, and biocompatibility, Nitinol is becoming increasingly popular for minimally invasive devices such as endoluminal stents. Despite several studies on *in vitro* or *in vivo* biocompatibiliy of NiTi, few studies have been conducted on the interactions of the material with blood. In this study, blood compatibility tests were conducted on Nitinol and stainless steel stents using an *ex vivo*, AV-shunt porcine model. We have demonstrated that Nitinol is significantly less thrombogenic than stainless steel as indicated by ^{125}I-human fibrinogen ($p = 0.03$) and ^{111}I-platelets ($p = 0.01$) quantification. These differences may be related to the Nitinol titanium-oxide rich surface layer that may prevent denaturation of fibrinogen and minimize platelet-rich thrombus formation within the stent after implantation.

INTRODUCTION

Since the implantation of the first human coronary stent in 1986, many devices manufactured from different materials (stainless steel, tantalum, Nitinol, etc.), exhibiting various designs have entered the market. Along with the use of a better antiplatelet and anticoagulant therapy, optimal stent deployment has promoted stent implantation as a procedure of choice by reducing the risk of acute thrombosis and chronic restenosis. To achieve such an optimal deployment, conventional balloon-expandable stainless steel stents require high-pressure dilatation to plastically deform their structure in the atherosclerotic vessel, which may increase the level of vessel injury and endothelial denudation, and in turn enhance neointimal proliferation within the stents [1]. Moreover, longitudinal shortening during expansion and lack of elasticity remain limitations associated to the balloon-expandable stents. In contrast, Nitinol's superelastic properties can be favorably used to design self-expanding devices that minimize the need for balloon postdilatation and allow a good self-expansion ratio and a more uniform radial expansion with less longitudinal shortening [2–4]. In addition, Nitinol is characterized by biocompatibility and corrosion resistance comparable or superior to stainless steel [5–7]. These properties promote its uses

for stenting in peripheral artery disease (renal, carotid, iliac, and subclavian artery diseases, aortic intervention, and femoral PTA) through the development of such self-expanding devices.

Despite several studies on *in vitro* or *in vivo* biocompatibility of Nitinol, few studies have been conducted on the interactions of the material with blood. Even though clinical data are missing on this point, differences in haemocompatibility can be expected to have consequences on the clinical thrombogenic occlusion and/or restenosis rates. In the present study, we have investigated the thrombogenicity of NiTi stents in comparison to Stainless Steel (SS) stents. To achieve this goal, an *ex vivo*, AV-shunt porcine model was used to measure fibrinogen adsorption as well as platelet adhesion on both devices.

EXPERIMENTAL METHODS

STENTS

The NiTi stents were prototype devices manufactured by Cordis Corporation—Nitinol Devices & Components (Calif., U.S.). They consisted of 3 mm diameter by 30 mm long stents that were laser-cut from NiTi tubing to replicate the Palmaz 316L stainless steel stent geometry (P294M, Cordis Corp.). Palmaz 316L SS stents were used as reference.

EXTRA-CORPOREAL AV SHUNT

All procedures followed the American Heart Association Guidelines for Animal Research and were approved by the Animal Ethics Committee of the Montreal Heart Institute. Experiments were performed using six pigs weighing 25 ± 3 kg.

Animal platelets were isolated and radio labeled with Indium-111 (^{111}In oxine, Merck Frost Canada Inc., Canada) as described previously [8]. The quantification of fibrinogen deposition was done by injection of approximately 10 μCi ^{125}I-human fibrinogen (Amersham International, U.K.) one hour before the experiment.

Prior to each perfusion, two stents were inserted manually in two Silastic tubes using a sterile filament to position each device. The tubes were 1/8 inch Internal Diameter (ID) and 9 cm long. A 3 by 20 mm conventional semicompliant balloon catheter was then inserted in each tube and inflated at 12 atm to deploy the stent in the tubing. Even though the Nitinol stents were self-expanding devices and did not need to be deployed using a balloon catheter, they were inserted using the same method as the SS stents to avoid variation in manipulation of each device.

The extracorporeal AV shunt consisted of a silicon tubing circuit connecting the left femoral artery to the right femoral vein through the perfusion channels (see Figure 1). The main extracorporeal AV shunt was divided in two parallel tubing systems inside the perfusion chamber and was connected to the stented tubes. During the experiment, the blood flow in the main circuit was maintained at a stable rate of 160 mL/min using a roller pump. The perfusion chamber was immersed in a 37± 1°C water bath. One hour after re-injection of the labeled platelets and fibrinogen, the stents (one SS and one NiTi) were set in each channel of the extracorporeal circuit and rinsed for 20 seconds using saline solution. Blood was then allowed to circulate for 15 minutes at a wall-shear rate of 456 s^{-1} (corresponding to 80 mL/min). This wall-shear rate represents the normal human shear rate in large- to medium-sized arteries [9]. At the end of the perfusion, circulation of saline solution was done to remove unattached cells and blood from the stents and the perfusion circuit. The stented tubing segments were cut at both ends and removed from the circuit. A 1.5 cm long segment at the distal end of each tube was cut and used as control. Before testing the next series of stents, the

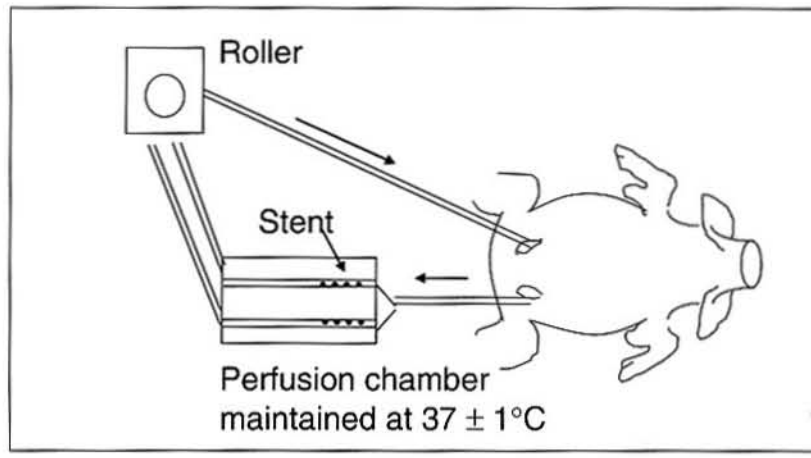

Figure 1 Schematic representation of the ex vivo *AV-shunt model.*

extracorporeal circuit was washed again with saline. All tubing segments were fixed in 1.5% glutaraldehyde solution and processed for quantification of platelet adhesion and fibrinogen adsorption. Using a gamma counter, the amount of ^{111}In-platelet and ^{125}I fibrinogen was quantified by measuring the radioactivity of each tubing segment [8].

STATISTICAL ANALYSIS

Results are expressed as mean value ± SD. The data in terms of fibrinogen adsorption and platelet adhesion were analyzed using paired Student-T tests. A p-value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

After the perfusion, macroscopic analysis of the stents revealed obvious differences between NiTi and SS. NiTi stents had only small amounts of white and/or red thrombus, principally located at the strut intersections. SS stents, however, clearly exhibited more thrombus. Typical thrombus observed on NiTi and SS stents is presented in Figure 2. Furthermore, one SS stent was occluded after 15 minutes of perfusion. These macroscopic observations were confirmed by subsequent quantification of the radio-labeled platelets and fibrinogen.

Results indicated that the nature of the stent material played a major role on the quantity of fibrinogen and platelets deposited on the devices. ^{125}I-fibrinogen adsorption was significantly lower on Nitinol than on SS ($p = 0.03$) (see Figure 3). The fibrinogen count averaged 3653 ± 913 cpm/stent on Nitinol stents and 5707 ± 1556 cpm/stent on SS stents. Nitinol devices had also significantly less platelet adhesion on their surface than had SS stents ($p = 0.01$) (see Figure 4). The mean quantity of platelets was 925 ± 248 x 10^6 platelets/stent for the Nitinol group while the quantity of platelet averaged 2526 ± 770 x 10^6 platelets/stent on SS. Control tubing segments did not promote significant fibrinogen adsorption (23.8 ± 7.3 cpm/tube) or platelets adhesion (2.96 ± 0.73 x 10^6 platelets/tube).

Based on our results, Nitinol exhibits a lower acute thrombogenicity than SS. Indeed, the amount of labeled fibrinogen adsorption and platelet deposition on Nitinol stents after 15 minutes of perfusion was significantly lower: 36% and 63%, respectively on Nitinol compared to SS stents. In our study,

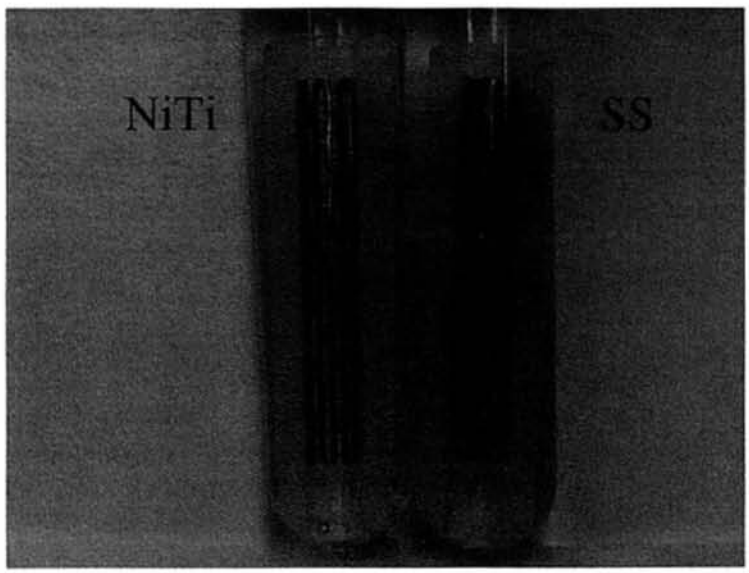

Figure 2 NiTi and SS stents after perfusion.

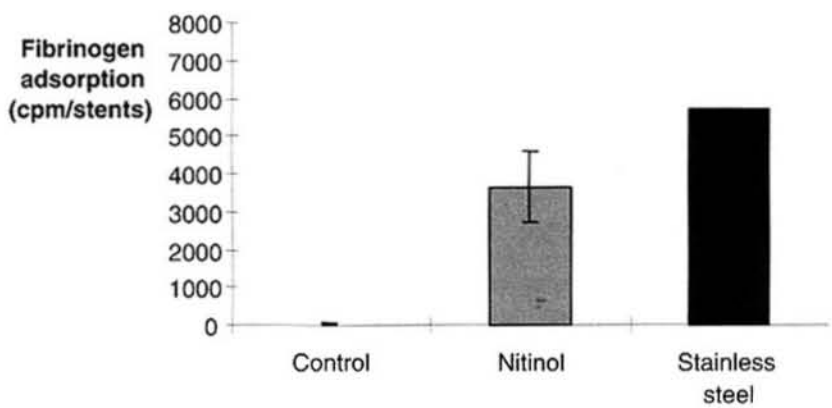

*Figure 3 ^{125}I-fibrinogen adsorption on Nitinol stents, SS stents, and Silastic tubes (control) after 15 minutes of perfusion (*p < 0.001 vs. control).*

the effect of the design and the surface finish were eliminated as device-related variables since both stents exhibited the exact same geometry and similar smooth and uniform electropolished surface.

Stent surface composition and topography will determine the nature of the protein-adsorbed layer, which will affect thrombus formation following stent implantation [10]. Previous studies have reported that the surface of electropolished SS is mainly covered by a chromium- and iron-rich oxide [7]. On the other hand, electropolished Nitinol has been shown to be covered by a titanium-rich oxide layer (mainly TiO_2) similar to the oxide on titanium alloys, which is recognized for its good haemocompatibility [7,11]. Nygren, et al. have shown that depending on the characteristics of the TiO_2 surfaces, the levels of surface-adsorbed plasma proteins such as fibrinogen and of platelets were significantly different. Furthermore, thrombus formation on biomaterial surfaces is also con-

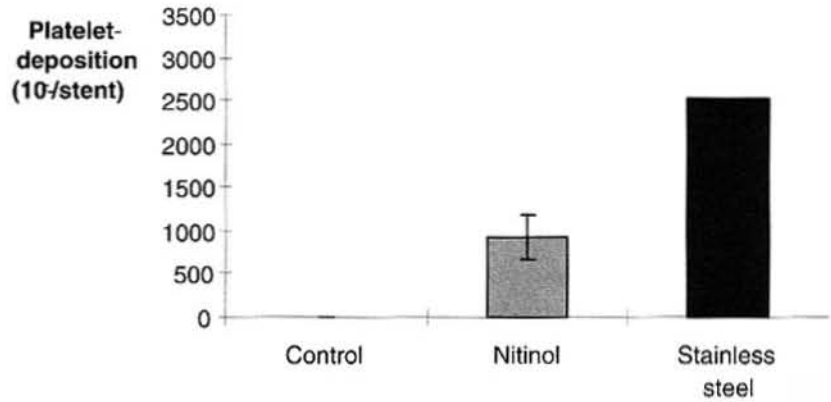

*Figure 4 ^{111}In-platelet deposition on Nitinol stents, SS stents, and Silastic tubes (control) after 15 minutes of perfusion (*p < 0.001 vs. control).*

trolled by the denaturation of fibrinogen into fibrin monomers and fibrinopeptides [10]. This event may rely on an electron exchange from occupied valence band states of the fibrinogen to the surface of the stent [12].

Since thrombus growth depends on the polymerization of fibrin monomers incorporating activated platelets, prevention of such denaturation can improve the haemocompatibility. It has been recently suggested that a TiO_{2-x}-oxide film may prevent the denaturation of fibrinogen in a similar way [13]. Based on our results, the titanium-rich oxide surface of Nitinol stents may have minimized the formation of fibrin-platelet rich thrombus. Previous *in vitro* studies have reported similar quantities of platelet adhesion between NiTi and SS in contact with platelet-rich plasma in absence of fibrinogen [14,15]. These results may be explained by the different test models that were used in these studies. They also emphasize the important role of fibrinogen and its denaturation to fibrin in the thrombus-formation processes in dynamic flow condition.

Our results are in agreement with those obtained by Sheth, et al. using a rabbit carotid artery model [2]. They reported lower thrombogenicity of Nitinol stents compared to SS stents. Still, because stent surface finish, design, and deployment mechanism were different for the Nitinol and SS stents, their results could not clearly show the individual effect of the material composition on thrombogenicity. Indeed, all these parameters have been shown to be very important factors in the modulation of blood-biomaterial response [16]. It is important to emphasize that in our study use of similar stent geometry and surface finish allowed us to isolate the effect of material composition on blood interaction.

CONCLUSIONS

This study was conducted to assess the relative thrombogenicity of Nitinol and SS stents in an *ex vivo*, AV-shunt porcine model. NiTi stents manufactured to replicate the geometry and the surface finish of the Palmaz stainless steel stent were tested. Our results show that Nitinol is significantly less thrombogenic than SS-based on ^{125}I-human fibrinogen ($p = 0.03$) and ^{111}I-platelets ($p = 0.01$) quantification. These differences may be related to a Nitinol titanium-oxide rich surface layer that may prevent denaturation of fibrinogen and minimize platelet-rich thrombus formation within the stent after implantation.

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REFERENCES

1. S. L. Goldberg, et al., *Am. J. Cardiol.* **81** (1998), 708.
2. S. Sheth, et al., *Circulation* **94** (1996), 1733.
3. E. Rechavia, et al., *Cath. Cardiovasc. Diagn.* **41** (1997), 85.
4. A. J. Carter, et al., *Cath. Cardiovasc. Diagn.* **44** (1998), 193.
5. J. Ryhanen, *Biocompatibility evaluation of nickel-titanium shape memory metal alloy* (Oulu, Finland: Oulu University Press, 1999).
6. R. Venugopalan and C. Trepanier, *Min. Inv. Ther. and Allied Tech.* (forthcoming).
7. B. Thierry, et al., *J. Biomed. Mater. Res.* (forthcoming).
8. Y. Merhi, M. King, and R. Guidoin, *J. Biomed. Mater. Res.* **34** (1997), 477.
9. S. R. Hanson and K. S. Sakariassen, *Am. Heart J.* **135**, no. 5, pt. 2, suppl. (1998), S132.
10. H. Nygren, C. Erikson, and J. Lausma, *J. Lab. Clin. Med.* **129** (1997), 35.
11. C. Trepanier, et al., *J. Biomed. Mat. Res.* **43** (1998), 423.
12. P. Baurschmidt and M. Schaldach, *J. Bioengineering* **1** (1977), 261.
13. H. Nan, et al., *Biomaterials* **19** (1998), 771.
14. C. S. Sutton, P. M. Consigny, and M. Thakur, *Circulation* **90**, suppl. 1 (1994), I-9.
15. D. A. Armitage, et al., in *SMST-97: Proceedings of the Second International Conference on Shape Memory and Superelastic Technologies*, ed. A.R. Pelton, et al. (Pacific Grove, California: International Organization on SMST, 1997), 411.
16. C. R. Rogers and E. R. Edelman, *Circulation* **91** (1995), 2995.