

## In vivo suppression of restenosis in rat abdominal aorta by nitric oxide-eluting stents

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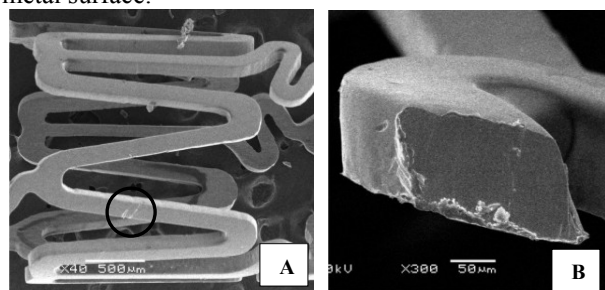
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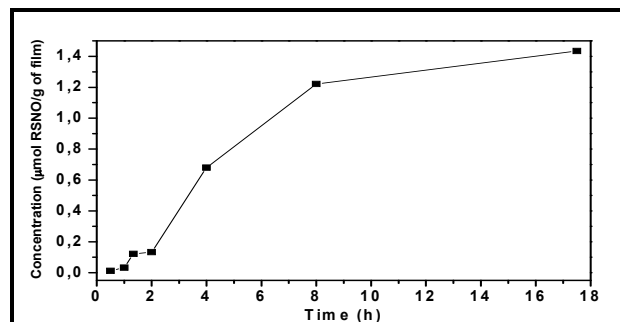
**Statement of Purpose:** Drug-eluting stents (DES), which deliver antiproliferative drugs, are well known to decrease intra-stent restenosis and repeated interventions by suppressing neointimal growth. Although clinically available Rapamycin and Paclitaxel-eluting stents have demonstrated great efficacy in the reduction of restenosis compared with bare-metal stents<sup>1</sup>, their efficacy has not been uniform across all patient and lesions subsets. This fact opens perspectives for the development of new therapeutic approaches in DES, with the use of alternative anti-restenosis drugs. Nitric oxide (NO) releasing drugs, as S-nitrosothiols (RSNOs), have already demonstrated to have potential for preventing thrombosis and for inhibiting restenosis<sup>1</sup>. These actions are partially associated with the ability of NO in inhibiting platelet adhesion, reducing smooth muscle cells proliferation and stimulating arterial reendothelization. In this work, stents were coated with hydrophilic RSNO releasing polymeric matrices and their morphology and elution behavior were analyzed. Moreover, in vivo RSNO-eluting stents were shown to inhibit intimal thickening in a rat aorta stent injury model.

**Methods:** Metallic stents (Inovatec) specially manufactured in the Incubation Center for Technological Interprises (Cietec, São Paulo, Brazil), were coated with hydrophilic polymeric films containing RSNOs by deep-coating with polymer/drug solutions. The morphology of the coated stents was analyzed by scanning electron microscopy (SEM). Coated and control (bare metal) stents were implanted in the abdominal aorta of Wistar rats. Seven days after implantation, the stents were removed from the artery, embedded in paraffin or epoxy resin, cut in slices of ca. 4  $\mu\text{m}$  and analyzed histologically and by immunohistochemistry for Proliferating Cellular Nuclear Antigen (PCNA).

**Results:** SEM micrographies of the coated stents showed that the immersion method used provides a continuous and uniform coating, which is highly adherent to the metal surface.

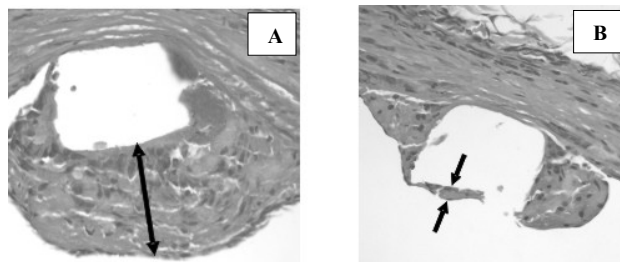


**Figure 1.** SEM micrographies of a stent coated with hydrophilic RSNO-releasing film. (A) Side view; (B) transversal section of a coated wire. The circle shows two scratches, done in order to reveal the polymeric coating.



**Figure 2.** Kinetic curve of RSNO release from stents coated with RSNO-containing hydrophilic films to PBS solution at 37 °C.

Figure 2 shows a representative kinetic curve for the elution of RSNO from a coated stent, immersed in PBS solution. The release profiles obtained indicate that the films release 40% of the total RSNO amount in ca. 15 h, allowing a sustained release for more than 24 h. Preliminary histological results of rat implants, showed that the SNO-releasing stents lead to a significant reduction in the PCNA counting and that this result is correlated to a reduction in intimal thickening (Figure 3). Moreover, a stimulation of arterial reendothelization was also obtained, compared to the bare metal stents.



**Figure 3.** Photomicrographies of stented rat abdominal aorta 7 days after stent implantation. (A) Bare metal; (B) NO-releasing stent with hydrophilic NO-releasing polymer (160 x).

**Conclusions:** Stents coated with hydrophilic NO-releasing polymer are able to provide a sustained release of NO for more than 15 h under physiological conditions. NO elution inhibited intimal thickening through the reduction of SMC proliferation and stimulated arterial reendothelization in a rat aorta stent injury model, suggesting that the coating used may be useful in preventing restenosis.

### References:

- West, J.L. Lipke, E.A., Acta Biomaterialia, p., 2005
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