S-Nitroso-*N*-acetylpenicillamine (SNAP)-doped Elast-eon Catheters Reduce Thrombosis and Bacterial Adhesion

Elizabeth J. Brisbois[1], Hitesh Handa[2], Ryan Davis[2], Anna Jones[2], Robert H. Bartlett[2], Mark E. Meyerhoff[1].
[1] Department of Chemistry, [2] Department of Surgery, University of Michigan, Ann Arbor, MI USA

Statement of Purpose: Two major clinical problems associated with intravascular catheters are clotting and infection. One approach to improving the hemocompatibility of blood-contacting devices is to develop materials that release nitric oxide (NO), a known potent inhibitor of platelet adhesion/activation and also an antimicrobial agent. Healthy endothelial cells exhibit a NO flux of 0.5-4x10^{-10} mol cm^{-2} min^{-1}, and materials that mimic this NO release rate are expected to have similar anti-thrombotic properties. Incorporation of NO donor molecules such as *S*-nitrosothiols (RSNOs) into polymers, either non-covalently dispersed or covalently bound, have been reported.[1-4] NO release from these RSNO-based materials can be initiated via heat, metal ions, or light. However these materials have suffered due to RSNO leaching, low RSNO conversion during synthesis, and thermal instability that would limit their shelf-life. Recent work has shown that the *S*-nitroso-*N*-acetylpenicillamine (SNAP)-doped Elast-eon E2As polymer creates an inexpensive NO releasing material which exhibits remarkably stability during storage, even after 2 months at elevated temperatures.[5] In this study, SNAP-doped Elast-eon E2As catheters were prepared and implanted in sheep veins for 7 d to observe effects on thrombus and bacterial adhesion.

Methods: Catheters were prepared by dip coating polymer solutions (100 mg/mL in THF) on stainless steel mandrels (d=2 mm, McMaster Carr). SNAP-doped E2As catheters had a trilayer configuration consisting of 5 base coats of Elast-eon E2As, 25 active coats of 10 wt% SNAP in E2As, and 5 top coats of E2As. Control catheters were prepared in a similar manner with E2As only (no SNAP added). Catheters were soaked in 10 mM PBS at 37°C. NO release from the catheters under physiological conditions was determined via a chemiluminescence NO analyzer (NOA) (Sievers, 280, Boulder, CO). Under sterile conditions, catheters were positioned in jugular veins of sheep. Catheter patency was tested each day by drawing blood. After 7 d in sheep, catheters were explanted. Pictures were taken of the whole catheter and the 2D representation of the thrombus area was determined with the NIH ImageJ software. To quantitate the adhered bacteria, 1 cm sections of catheters were homogenized in sterile PBS buffer, serially diluted in PBS, and plated on agar plates. The agar plates were incubated at 37°C for 24 h to determine the number of colony forming units per catheter surface area (CFU/cm^2).

Results: Prepared catheters were 15 cm long and had an i.d. of 2 mm and o.d. of 3 mm. SNAP-doped catheters had a higher NO flux on the first day of soaking (due to the initial water uptake of the E2As polymer and leaching of SNAP) followed by a sustained NO flux of ~1x10^{-10} mol cm^{-2} min^{-1} (Fig. 1). Top and base coats of E2As were employed to reduce SNAP leaching and control NO release.

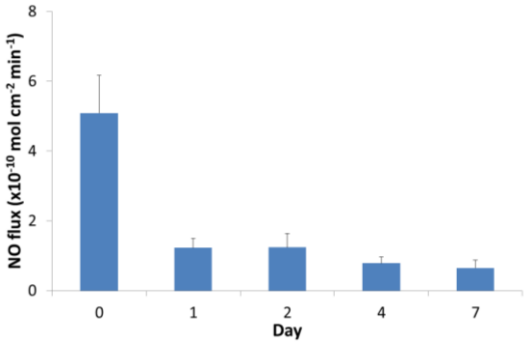

Fig. 1. NO release from SNAP-doped E2As catheters under physiological conditions (37°C in 10 mM PBS). (n=3)

The SNAP-doped catheters remained patent during the 7 d implantation period, while E2As control catheters typically clotted after 24 h. After 7 d implantation in sheep veins, the catheters were explanted. The explanted SNAP-doped catheters had a flux of ~0.6x10^{-10} mol cm^{-2} min^{-1}. The SNAP-doped catheters exhibited significantly reduced thrombus area in comparison to E2As controls (see Fig. 2). The SNAP-doped catheters had ~85% less bacterial adhesion in comparison to E2As controls.

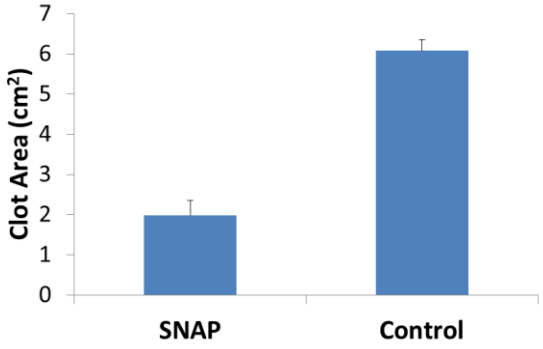

Fig. 2. Comparison of clot area on SNAP-doped E2As and E2As control catheters after 7 d implantation in sheep veins. (n=3)

Conclusions: The SNAP-doped Elast-eon E2As polymer creates catheters that can release physiologically relevant levels of NO for up to 7 d. After 7 d implantation in sheep veins, the SNAP-doped catheters have significantly reduced thrombus area and bacterial adhesion, in comparison to the E2As control catheters, demonstrating their potential for improving the hemocompatibility of blood-contacting devices.

References:

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