Catheters Prepared with Nitric Oxide (NO) Releasing Lumen for Improved Hemocompatibility

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Statement of Purpose: Intravascular catheters suffer from two major clinical problems: 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 endogenous antimicrobial agent. Healthy endothelial cells exhibit a NO flux of 0.5-4x10^{-10} mol cm^{-2} min^{-1}, and materials that mimic this range of NO release rates are expected to have similar anti-thrombotic and antimicrobial 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. Here, initial studies were conducted with single lumen catheters to demonstrate a new approach to preparing NO-releasing catheters, where one lumen of the catheter is dedicated to the NO release chemistry.

Methods: Catheters (7 cm long) were prepared using silicone rubber tubing (Tygon 3350) with i.d. 0.8 mm and o.d. 2.4 mm. The inner lumen was filled with a methanol solution containing SNAP and poly(ethylene glycol) (PEG) (163 mg/mL and 666 mg/mL, respectively). Control catheters were prepared in a similar manner with PEG and N-acetylpenicillamine (NAP). After the methanol evaporated, the ends of the catheters were sealed with silicone rubber. Catheters were soaked in 10 mM PBS with 100 µM EDTA at 37°C. NO release from the catheters under physiological conditions was determined via a chemiluminescence NO analyzer (NOA) (Sievers, 280, Boulder, CO). Leaching of SNAP and its byproducts was monitored via LC-MS. A short-term (7 h) rabbit model was used to evaluate thrombus formation on the catheters. Catheters were positioned in jugular veins of rabbits. After 7 h in rabbits, 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.

Results: Single-lumen silicone rubber tubing was used for initial studies. The NO release from catheters prepared with various PEG species was monitored using chemiluminescence. The catheters prepared with PEG 4000 were able to release physiologically relevant levels of NO for up to 18 d (Fig. 1).

For the in vivo experiments, 5 cm of the SNAP and control catheters were placed in the jugular veins of rabbits. After 7 h implantation in, the catheters were explanted. The explanted SNAP-PEG catheters had a flux of ~2 x 10^{-10} mol cm^{-2} min^{-1}. The SNAP-based catheters exhibited significantly reduced thrombus area in comparison to E2As controls (see Fig. 2).

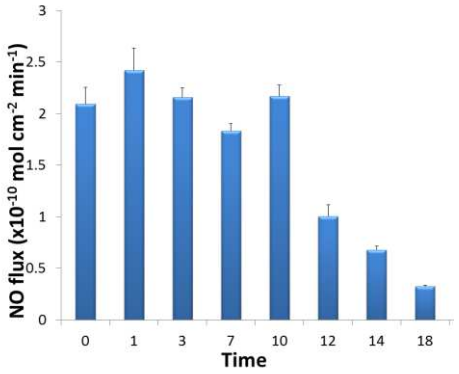

Fig. 1. NO release from silicone rubber catheters with SNAP-PEG 4000 filled lumen under physiological conditions (37°C in 10 mM PBS). (n=3)

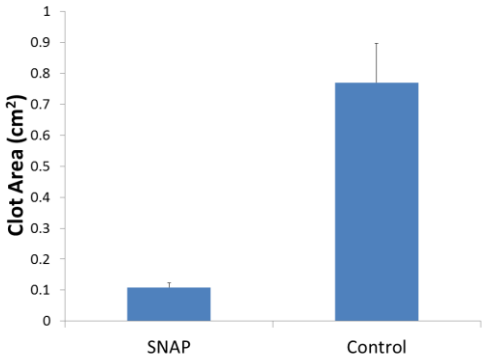

Fig. 2. Comparison of clot area on the SNAP and control catheters after 7 h implantation in rabbit veins. (n=4)

Conclusions: The NO release from the SNAP-PEG chemistry within the lumen reduced thrombus formation in a rabbit model. Based on recent studies with other NO release devices,[5-6] this level of NO release is also expected to have antimicrobial properties against common bloodborne pathogens (e.g., S. aureus, S. epidermidis). This study demonstrates the possibility of improving the hemocompatibility of commercial multi-lumen catheters by dedicating one lumen to SNAP-based NO release chemistry.

References:

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