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The effects of surface processing on *in-vivo* corrosion of Nitinol stents in a porcine model

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ABSTRACT

A major limitation with current assessments of corrosion in metallic medical devices is the lack of correlation between *in-vitro* and *in-vivo* corrosion performance. Therefore, the objective of this study was to elucidate the relationship between pitting corrosion measured by breakdown potentials (E_b) in ASTM F2129 testing and corrosion resistance *in-vivo*. Four groups of Nitinol stents were manufactured using different processing methods to create unique surface properties. The stents were implanted into iliac arteries of minipigs for six months and explanted for corrosion analysis. Scanning electron microscopy and energy dispersive X-ray spectrometry analyses indicated that stents with a thick complex thermal oxide (420 nm) and high corrosion resistance *in-vitro* (E_b = 975 ± 94 mV) were free from detectable corrosion *in-vivo* and exhibited no changes in Ni/Ti ratio when compared to non-implanted controls. This result was also found in mechanically polished stents with a thin native oxide (4 nm; E_b = 767 ± 226 mV). In contrast, stents with a moderately thick thermal oxide (130 nm) and low corrosion resistance *in-vitro* (E_b = 111 ± 63 mV) possessed corrosion with associated surface microcracks *in-vivo*. In addition, Ni/Ti ratios in corroded regions were significantly lower compared to non-corroded adjacent areas on explanted stents. When stents were minimally processed (i.e. retained native tube oxide from the drawing process), a thick thermal oxide was present (399 nm) with low *in-vitro* corrosion resistance (E_b = 68 ± 29 mV) resulting in extensive *in-vivo* pitting. These findings demonstrate that functional corrosion testing combined with a detailed understanding of the surface characteristics of a Nitinol medical device can provide insight into *in-vivo* corrosion resistance.

Statement of Significance

Nitinol is a commonly used material in the medical device industry. However, correlations between surface processing of nitinol and *in-vivo* corrosion has yet to be established. Elucidating the link between *in-vivo* corrosion and pre-clinical characterization can aid in improved prediction of clinical safety and performance of nitinol devices. We addressed this knowledge gap by fabricating nitinol stents to possess distinct surface properties and evaluating their corrosion susceptibility both *in-vitro* and after six months of *in-vivo* exposure. Relationships between stent processing, surface characterization, corrosion bench testing, and outcomes from explanted devices are discussed. These findings highlight the importance of surface characterization in nitinol devices and provide *in-vitro* pitting corrosion levels that can induce *in-vivo* corrosion in nitinol stents.

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1. Introduction

The corrosion resistance of medical implant alloys has increased over the past few decades due to advancements in manufacturing technologies. Even with these improvements, corrosion of biomedical materials has been reported for both orthopaedic and cardio-

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vascular devices. Several recent research studies found corrosion damage in titanium and cobalt-chromium alloys from explanted metal-on-metal hip replacement devices [1–5]. Corrosion has also been observed in other orthopaedic implants such as screws and wires made from stainless steel alloys [6–8]. Corrosion in cardiovascular devices has been documented to a lesser extent mainly due to difficulties in obtaining explants for these life supporting implants. Two studies reported severe pitting corrosion in first generation Nitinol endovascular grafts in as little as 5 months of implantation time [9,10]. Brott and colleagues recently found corrosion in explanted cardiovascular stents made of Nitinol, stainless steel, and cobalt based alloys [11–13]. However, these studies predominantly identified corrosion qualitatively through microscopy and did not have matched controls to definitively distinguish *in-vivo* corrosion from pre-existing features from the manufacturing process.

Significant corrosion from medical implant material may not only adversely affect the structure or function of the device, but also provoke a biological response. Corrosion in orthopaedic metallic hip replacement devices has resulted in pseudotumors and adverse local tissue reactions [14–18]. For cardiovascular devices, the biological consequences of corrosion byproducts are less clear as metal ions may be transported systemically by blood flow or remain locally within the vascular tissues. Corrosion byproducts in cardiovascular stents can elicit an inflammatory cell response that increases neointimal growth in the vessel that results in restenosis [19,20]. This is especially important for Nitinol implants because approximately half of the elemental composition is nickel which has been shown to cause allergic reactions, nephrotoxicity, and carcinogenicity at various doses [21–24]. It should be noted that while hypersensitivity-related adverse events (e.g. contact dermatitis) have been reported in cardiovascular implants [25–32], a direct causal link between corrosion and these adverse events has yet to be established. Research studies that can more directly identify the ramifications of corrosion in medical implant biomaterials, particularly those that contain nickel, would help address this critical knowledge gap.

To aid medical device manufacturers in non-clinical corrosion assessment of cardiovascular metallic stents, the US Food and Drug Administration recently published an update to the guidance document (Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems: Guidance for Industry and Food and Drug Administration Staff). The *in-vitro* testing paradigm outlined in the guidance document recommends cyclic potentiodynamic polarization testing per ASTM F2129 (Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices). This bench test method evaluates the voltage required to initiate pitting on the device surface (i.e. breakdown potential). If the pre-specified acceptance criterion is not met, additional *in-vitro* testing such as nickel leach testing or surface characterization is recommended. In 2007, acceptance criteria for ASTM F2129 testing were proposed by Rosenbloom and Corbett, suggesting that implants with a breakdown potential exceeding 600 mV have acceptable performance, potentials below 300 mV are unacceptable, and potentials between 300 and 600 mV may be acceptable if certain conditions are met [33]. These criteria were based primarily on previous studies that found rest potentials varied for stainless steel alloys (−380 to 290 mV) [34,35], Nitinol (−400 to −100 mV) [35,36] and cobalt-chromium alloys (−100 to 150 mV) [37] in various anatomic locations. Although rest and breakdown potentials from ASTM F2129 are used to assess pitting corrosion resistance during regulatory review of medical device applications, there is considerable debate within the medical device community regarding the relevance of the proposed acceptance criteria [38,39]. In fact, members of the cardiovascular implant community cited the lack of *in-vivo* performance correlation with current bench corrosion testing (e.g. ASTM F2129 testing) as a major limitation [40]. This is especially important for Nitinol implants because the corrosion resistance of Nitinol is highly dependent on the manufacturing processes. Therefore, the objective of this study was to characterize the relationship between *in-vitro* performance and *in-vivo* corrosion for Nitinol stents manufactured to span the full range of ASTM F2129 breakdown potentials. The selected stent groups included contrasting *in-vitro* performance to elucidate potential disparities *in-vivo*.

2. Methods

2.1. Stent manufacturing and characterization

Nitinol stents (8 mm × 30 mm length) were manufactured using a generic design by Confluent Medical Technologies. To investigate the effects of surface finish on *in-vitro* and *in-vivo* corrosion, four unique surface conditions were created using different processing methods: Salt Pot (SP), Mechanical Polish (MP), Air Furnace (AF), and Oxidized Tube (OT). Table 1 provides a summary of these methods that have been previously described in detail [41]. Depth profiles of surface constituents (n = 1 stent/group) were captured through Auger Electron Spectroscopy (PHI 680, Physical Electronics, East Chanhassen, MN) by alternating an acquisition cycle with a sputter cycle. The oxide layer thickness was determined by using the full width at half maximum method.

2.2. Potentiodynamic polarization testing

In-vitro pitting corrosion resistance of stents (n = 14 for SP, MP, and AF stent groups and n = 8 for OT stents) was characterized per ASTM F2129. Gamry (Interface 1000, Warminister, PA) or Princeton Applied Research (Model 263A, Oak Ridge, TN) potentiostats were used for all corrosion susceptibility assessments. Saturated Calomel Electrode (SCE) was used as a reference electrode and graphitic carbon was used as an counter electrode. Stents were tested in phosphate buffered saline (PBS, deaerated with nitrogen gas at 150 cm^3/min for 30 min) at a temperature of 37 ± 2 °C. The rest potential (E_r) was recorded after the stents had been submerged in PBS for one hour and then the potentiodynamic scan was initiated in the positive direction at a scan rate of 1 mV/s. The potential at which the current rapidly increases by 100× was established as the breakdown potential (E_b). If the stent did not experience breakdown during testing, the E_b was considered to be the vertex potential (1000 mV). The scan was reversed at 1000 mV or if the current densities exceeded 25 mA. The over potential was calculated as the difference between the breakdown potential and the rest potential (E_b–E_r).

2.3. Stent implantations

Stent implantations and animal husbandry were conducted at MedStar Health Research Institute (MHRI) under an approved Institutional Animal Care and Use Committee (IACUC) protocol (#2012-022) in accordance with the principles of the Animal Welfare Act and the NIH guidelines established for the Care and Use of Laboratory Animals. Female Yucatan miniature swine (minipigs, Sinclair BioResources, Auxvasse, MO) approximately 1 year of age and 50 kg were chosen for use in this study due to their established suitability as a long term animal model for cardiovascular device implantation [42–45]. All stents used for implantation were sterilized using Ethylene Oxide (EtO) as it is commonly used to sterilize stents and has been shown not to impact the corrosion resistance

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