



Plasma-induced nanopillars on bare metal coronary stent surface for enhanced endothelialization

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ABSTRACT

An increased risk of late stent thrombosis associated with polymer carriers on the surface of drug-eluting stents remains one of the challenges in cardiovascular stent technology, which has instigated a renewed interest in the polymer-less, bare metal stent approach. As thrombus formation is most likely augmented by the lack of endothelial cell coverage at the exposed stented site, an improved stent surface that enhances cell coverage is essential for viable polymer-less all metal stents. We demonstrate superior endothelial cell growth, more continuous monolayer formation and overall improved endothelialization with nanopillar arrays created via radio frequency plasma surface texturing on our all metallic stent surface of MP35N stent alloy. It is shown that the nanotextured surface significantly up-regulates primary bovine aortic endothelial cell (BAEC) functionality when compared with unprocessed, smooth MP35N surfaces without a nanopillar topography. The desirable presence of transmembrane tight junctions and highly organized monolayer formation was induced by the presence of the nanopillar surface texture. The nanopillar structure also produced a reduced level of oxidative stress in the BAECs. These findings may contribute to new nanotechnology-based surface design concepts for bare metal stents producing advanced cardiovascular implants which mitigate late stent thrombosis.

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1. Introduction

The treatment of coronary and peripheral artery disease using metallic stents has been one of the most revolutionary and rapidly adopted medical interventions of our time [1]. The use of metallic stents in general, and in particular polymer-coated, drug-eluting metallic stents (DES), have contributed greatly to reducing the scope of such cardiovascular problems [2,3]. However, the current most significant issue is concern about the increased occurrence of late stent thrombosis, the formation of a blood clot inside the vessel wall at the stented site, when using drug-eluting stents because of potential polymer by-products from delamination, under-endothelialization and other complications due to the surface properties [5,6]. More specifically, late stent thrombosis may occur months or even years after implantation and has become a complex clinical problem due to a lack of endothelial cell coverage over the inner stent wall, where the stent fails to be fully integrated in the vessel [7,8]. In a current study of stent behavior DES thrombosis rates in patients observed in clinical trials was significantly higher than in patients with bare metal stent (BMS) devices (without polymer drug carriers) [9], thus making bare metallic stents a more attractive option for the next generation of stent designs. In

fact, as we move forward in cardiovascular stent technology there are several reasons why the focus of stent development is likely to return to BMS technologies, where progress is being made in improving stent biomaterials and surface modifications on the nanoscale [1].

Surface roughening modifications, for example using sol-gel coated hydroxyapatites, polymer nanostructure coatings or sand-blasted stainless steel stents, have been recognized as somewhat enhancing endothelialization of stent struts [10,11]. However, available data for polymer-less, all metallic textured surfaces are less common and recent studies were mostly based on polymer coating studies rather than bare metallic surfaces. Surface roughening has been shown to improve the cellular response of smooth muscle and endothelial cells in the vessel wall, as observed on poly(lactic-co-glycolic acid) films possessing increased nanometer surface roughness [4], however, these areas were not polymer-less.

Despite a substantial return of interest in bare metal stents, little documented research can be found on bare metallic surfaces of the most widely used stent metal alloy MP35N. MP35N (Co–20 Cr–35 Ni–10 Mo) alloy possesses closer to optimum properties as a stent base material with excellent biocompatibility and a higher strength than traditional 316L stainless steel alloys [1]. However, MP35N surface modifications, such as induced topological nanostructures, have yet to be understood in terms of cellular responses and endothelialization capability, as we have recently reported

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[12]. In the present study we have investigated the cellular response of primary bovine endothelial aortic cells (BEACs) on our uniquely modified MP35N stent surface, with vertically aligned (i.e. radially aligned on the stent strut wire) nanopillar arrays created via radio frequency (RF) plasma treatment. By creating nano-textures on the MP35N stent wire we sought to enhance endothelialization of the stent wall.

The bare metallic nanotextured surface that we produced and employed in this study is a completely “polymer-less” approach to surface modification, and a “coating-less” approach as well, as surface addition of foreign materials such as by chemical vapor deposition (CVD), physical vapor deposition (PVD), sol-gel processing or electrochemical plating is also avoided. Such metallic nanostructures on stent wire surfaces may be useful for enhanced and safe stent performance, as a polymer-less option potentially reducing thrombus rates in patients having implanted coronary stents.

2. Materials and methods

2.1. MP35N substrate preparation and RF processing

For the cell culture experiments on the stent substrate surface 250 μm diameter surface electropolished medical grade MP35N alloy wires (composition 35% Co–35% Ni–20% Cr–10% Mo in wt.%) were commercially procured (Fort Wayne Metals, Fort Wayne, IN) and cut into 10 cm lengths. This 250 μm diameter dimension is comparable with the strut diameter used in some medical stent applications. For the purpose of convenient cell culture, the round wires were press deformed prior to RF plasma processing in a laboratory hydraulic press to flat ribbon-like wires with a width of $\sim 400 \mu\text{m}$ and thickness of $\sim 50 \mu\text{m}$. The wires were then placed in the RF plasma chamber for surface texturing treatment. Nanotextured surfaces were created using a custom built RF plasma system, with the RF cathode operated at 100–200 W power and using 30 s.c.c.m. of Ar gas with a base operating pressure around 2.0×10^{-2} Torr [12]. The wire samples were mounted vertically at the cathode plate base spaced 2.5 cm apart from neighboring wires, as illustrated in Fig. 1a. A general schematic of our experimental procedure steps is shown in Fig. 1b. The temperature rise of the MP35N wire and ribbon samples on RF plasma processing was monitored using visual inspection and infra-red pyrometer. After RF plasma processing the surface nanostructure of the MP35N wire samples was examined by scanning electron microscopy (SEM).

2.2. Surface characterization

2.2.1. SEM and energy dispersive X-ray analysis (EDXA) for surface analysis

A Phillips XL30 FEI scanning electron microscope was used to visualize the surface morphology of the non-textured (unprocessed smooth) and textured (RF processed) MP35N samples. An Oxford EDXA attachment and Inca software were used to determine the elemental make-up and composition of the sample surfaces.

2.2.2. Atomic force microscopy (AFM)

An atomic force microscope was used to characterize the three-dimensional (3D) topography and surface roughness of the MP35N wire samples. The AFM apparatus was a Veeco scanning probe multi-mode microscope with a nanoscope IV controller. The average roughness (R_a) was measured for the non-textured vs. textured MP35N surface in tapping mode using MikroMasch tapping cantilever tips (NSC15/NoAl) over a $1.0 \mu\text{m}^2$ scan area. For AFM analysis four areas on the sample surface were measured and the average was taken.

2.2.3. Contact angle measurement

The measurement of water droplet contact angle for the cell culture substrates was carried out with a video contact angle measurement system in a commercially available contact angle measurement device (model VSA 2500 XE, AST Products Inc.).

2.3. Cell culture

The nanopillar textured alloy wire ribbon samples were sterilized by standard autoclaving before cell culture experiments. Unprocessed, non-textured MP35N wires (similarly flattened) cut into identically sized pieces and autoclaved in the same manner were used as a comparison sample for the cell culture data. BAECs were seeded onto MP35N non-textured and textured ribbon surfaces in order to compare and analyze endothelial cell response to the unique surface modification.

Primary BAECs were purchased from Cell Applications (San Diego, CA). The cell culture growth medium was optimized by Cell Applications and was ready for use as purchased. The cells were cultured in a humidified 95% air/5% CO_2 incubator at 37°C . All experiments were conducted with BAEC cultures between passages 2 and 3. For the experimental assays cells were plated at a

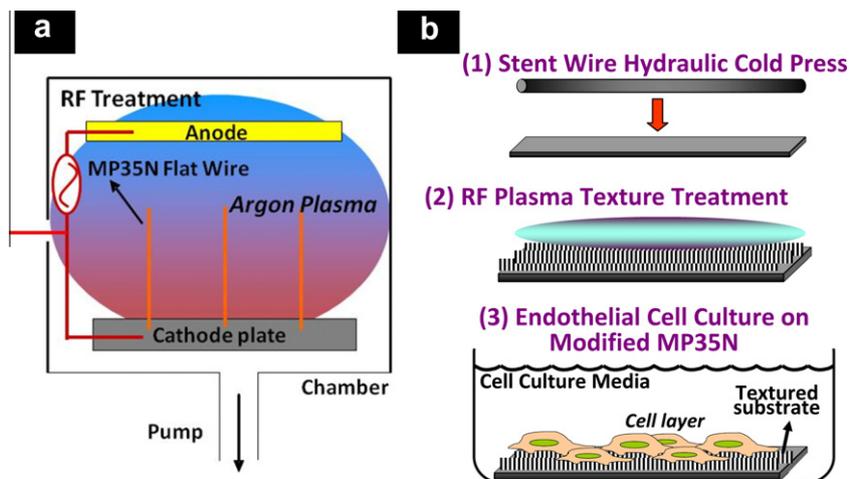


Fig. 1. (a) Schematic illustration of RF plasma processing of MP35N alloy bare metal wire for nanopillar formation. (b) Schematic of substrate preparation and usage. (1) The round MP35N wire is cold pressed into a flat ribbon wire, followed by (2) RF surface sputter treatment in Ar at 200 W, 2×10^{-2} Torr operating pressure, 10 min process time, 30 s.c.c.m. Ar flow. (3) Cell culture of endothelial cells on the nanopillar textured MP35N flat wire.

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