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Mechanical properties and biocompatibility of plasma-nitrided laser-cut 316L cardiovascular stents

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Abstract The effect of surface modification of laser-cut 316L cardiovascular stents by low-T plasma nitriding was evaluated in terms of mechanical properties and biocompatibility of the stents. The plasma nitriding was performed at 400, 450 or 500 °C using various ratios of nitrogen–hydrogen gas mixtures. The flexibility and radial strength were measured in crimped and expanded state of the stents, respectively. The mechanical properties could be adjusted and improved by plasma nitriding conducted at temperatures lower than 450 °C and/or nitrogen content less than 10% in the treatment gas. An osteoblast cell culture model system was utilized to investigate the effect of plasma nitriding of the stents on the biological response towards the stents, using biological criteria such as cell viability, alkaline phosphatase and nitric oxide production. In terms of cell viability and alkaline phosphatase production, the plasma nitriding procedure did not appear to negatively affect the biocompatibility of the 316L steel stents. However, in terms of nitric oxide production that was slightly increased in the presence of the plasma-nitrided stents, an indirect improvement in the biocompatibility could possibly be expected.

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1 Introduction

The control of surface properties is very critical to improve biocompatibility and biofunctionality of implant materials [1]. There are several ways of optimizing mechanical and biological properties of laser-cut cardiovascular stents [2–6]. The surface may be coated with polymeric materials to eliminate or minimize imminent biological reactions such as thrombosis, inflammation and proliferation, following the installation of coronary stents [2]. However, the synthetic polymer films may induce an inflammatory reaction and their biocompatibility still remains as major concern. The mixed gas N_3O/O_2 plasma application on the surface of uncoated implants is also possible to reduce the formation of platelet and leukocyte attachments that initiate thrombosis [7]. Carbon atoms were introduced by ion implantation into the stent surface to form a barrier against the diffusion of heavy metal ions into the surrounding tissue [8]. Ion implanted stents were then placed in the lesions in human body and no apparent negative effects were observed. Among the plasma methods, plasma nitriding is the one used most for changing compositional, mechanical and biological properties of the stainless steel [9]. The plasma nitridation on the surface of stainless steel may increase the surface hardness, resistance to corrosive ambient, fatigue properties of material in the body fluids and biocompatibility.

The stents made of austenitic stainless steel (316L) are commonly used as cardiovascular stents [10, 11]. Late reliability problems of the stents are mainly related to mechanical and corrosive behaviour [5]. The blood environment is very hostile to induce corrosion by breaking the passivation oxide on the surface of the stent, thus, there is a high risk of thrombosis formation [12]. Not only the thrombosis is a very critical issue, but also the release

of potentially toxic metal ions must be prevented in the blood environment. It was found that the toxic compounds released via corrosion are accumulated in the tissues surrounding the stents, then migrating through blood to the vital organs in the body [13]. These corrosion products induce permanent changes in cell morphology and trigger necrosis [14]. To reduce the release of metal ions, the surface must be made corrosion resistant in the human body. One of the methods to prevent corrosion of the stents is to cover the surfaces with a polymeric material [2]. However, there are problems related to surface coverage and cracking of the polymer on the stent surface during stent deployment and excessive mechanical strains due to blood flow and wall shear stress [15]. A stent must possess less metal surface in contact with the artery, high radial strength, high flexibility and elasticity, yet, it is difficult to obtain all these properties in a particular type of stent [16]. The geometry of the stent, the thickness of the strut and the area of metal at the outer surface are all design parameters to control mechanical properties and biological response including the formation of thrombosis [17].

Biocompatibility of stents can be investigated in detail by monitoring the level of cellular viability, and metabolic activity and nitric oxide (NO) production in single cells, in model cell cultures, in vitro. Among the different cell lines, fibroblasts, enthothelial cells or osteoblasts from rat or human origin are commonly used for biocompatibility tests [18]. As a model system, they provide sufficient preliminary information for potential application of any material of organic or inorganic origin.

In the current study, the effect of low-T plasma nitriding on the mechanical and biological properties of laser-cut 316L stainless steel was investigated. Since the process parameters in plasma nitriding determine the state of nitridation, the experiments performed over a range of temperature, duration of nitridation and ratio of gases in the mixture of the plasma environment. The mechanical properties were determined by measuring the radial and flexibility strength of the stents. It was observed that the plasma nitriding by controlling process parameters significantly improves the mechanical properties of the stents. The surface roughness was also measured by Scanning Electron Microscopy (SEM) and appeared to be much lower than that of the nitrided plates processed in identical conditions. Finally, the biocompatibility tests were performed using the rat primary osteoblast cell culture, and assays for nitric oxide production, alkaline phosphatase production and cell viability were done. It was observed that the nitric oxide levels increased following the modification of the stent surfaces while cell viability and alkaline phosphatase level remains unchanged.

2 Experiments

2.1 Stent fabrication

The laser-cut stents were made of standard austenitic stainless steel containing only 0.01% C by weight (316L). The stents were manufactured from tubes with an outer diameter of 1.5 mm and a thickness of 0.15 mm. The stents were precisely cut by a Nd:YAG laser with the focal spot diameter in the range of 20–50 μms and the pulse repetition rates of 1 kHz. Following the cutting, pickling process was employed to remove the oxides from the surface. The stents were annealed in a high vacuum furnace to increase their ductility since they become brittle after the laser cutting. After the annealing process, electrochemical polishing was performed to remove the passivating oxide layer. Furthermore, the stents were later subjected to chemical passivation as well, to prevent oxidation in the corrosive biological environments. All details about the fabrication of stents used in this study may be found elsewhere [11].

2.2 Plasma nitriding

The plasma nitriding was carried on the stents in a dc-discharge plasma system consist of a 200-mm-diameter quartz glass vacuum tube. The samples first were exposed to H_2-rich plasma ambient to remove any dust or grease. The plasma nitriding was conducted at 1300 Pa for a period of 15–240 min at three different temperatures, 400, 450 and 500 °C with a maximum of 2 kW and cathode current densities ranging from 0.75 to 2.5 mA/cm^2. In the experiments, the gas mixtures containing 5, 10 and 25% nitrogen by volume and hydrogen in the rest were used for nitriding at all three temperatures. Surface quality was determined by scanning electron microscopy (SEM) following the plasma nitriding.

2.3 Mechanical tests

Mechanical properties were assessed by flexibility and radial strength tests. The number of stents in the mechanical tests used for different cases is six.

A testing device was used to measure the flexibility of stents in the crimped (on the balloon) state. The flexibility-testing device consists of a forcemeter that is positioned perpendicular to the stent, and an apparatus that determines the bending angle. A bending guide is also used to simulate the bending radius of the vessel while the probe of the forcemeter represents the contact point between the vessel and the stent where the bending force is applied. In these

tests, kink formation due to the bending guide is not observed. Each stent is bent from an angle of 0° to 70° by 1° increments, and the reaction forces are monitored. During all of these measurements, probe of the load cell is in contact with the stent surface in a perpendicular position. The sample stents were checked for any former damage using an optical microscope prior to be crimped on balloon catheters of 3 × 20 mm in size.

Radial strength measurement device consists of a radially enclosing system into the main axis of stent by a DC motor. There are eight contact points for the enclosing system on the stent surface. The ratio of applied force as an applied stress to the diameter change as a strain was monitored by a computer. All stents placed on the balloons were expanded to their application geometry by application of 12 atm air pressure in order for the stents with inflated balloons achieve a diameter of 3 and 20 mm in length. Then, the balloon was deflated and the expanded stent with a diameter of 3 mm was placed into the radial strength measurement device.

2.4 Biological tests

The effect of plasma nitridation on biological response of stents was then studied in osteoblast cell cultures using viability and metabolic response tests. The results were compared with those obtained using the unnitrided stent samples.

In the biological experiments, osteoblasts were isolated from the calvaria of 1–3 days old neonatal Wistar rats and cultured according to the procedures explained elsewhere [18]. One 250 mL flask of confluent osteoblast cells was used to seed 12 well plates. Cells were washed with PBS and trypsinized with 1 mL of 1% trypsin and kept until they detach from the flask surface. Cells were then resuspended in 15 mL of culture medium to the density of ca. $\sim 2.3 \times 10^5$ per mL. Six hundred microliters of cell suspension were added into each well and allowed to settle for a few hours. Following settling of the cells at the bottom of the flask, stents (one into each well) were added and following the 72 h of incubation at 37 °C in RPMI-1640 medium with 5% CO_2 and 95% humidity, proceeded with the assays. Osteoblasts were incubated with the stents for 72 h and their viability was evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenlytetrazolium bromide) assay, based on the reduction of tetrazolium salt to formazan crystals by living cells [18]. The alkaline phosphatase production was investigated using BCIP–NBT assay (5-bromo-chloro-3-indolyl-phosphate–nitrobluetetrazolium) [18]. Nitrite quantification was done using Griess assay for indirect evaluation of osteoblast NO production. In a separate experiment, nitrided or non-treated stents were incubated for 72 h in the presence or absence of osteoblasts to check the NO levels possibly contributed by the stents themselves.

2.5 Statistical analysis

All data in graphs were expressed as the mean of three to six independent experiments. Upon the SPSS analysis, the results were considered significant at the level of $p < 0.05$.

3 Results

3.1 Mechanical properties

The effect of plasma nitriding conditions on flexibility was investigated by performing flexibility tests. Figure 1 shows the change of bending angle with an applied force for the samples nitrided at 450 °C in a gas mixture of 10% N_2 and 90% H_2 for different treatment durations. The flexibility of the stents was apparently reduced by plasma nitriding. In that respect, samples nitrided for 15 min only are very close to the pristine ones. The maximum reaction force occurred at the same bending angle for all samples except for those nitrided for 120 min. However, the reaction force was maximum and minimum for 30-min plasma nitrided and the unnitrided samples, respectively.

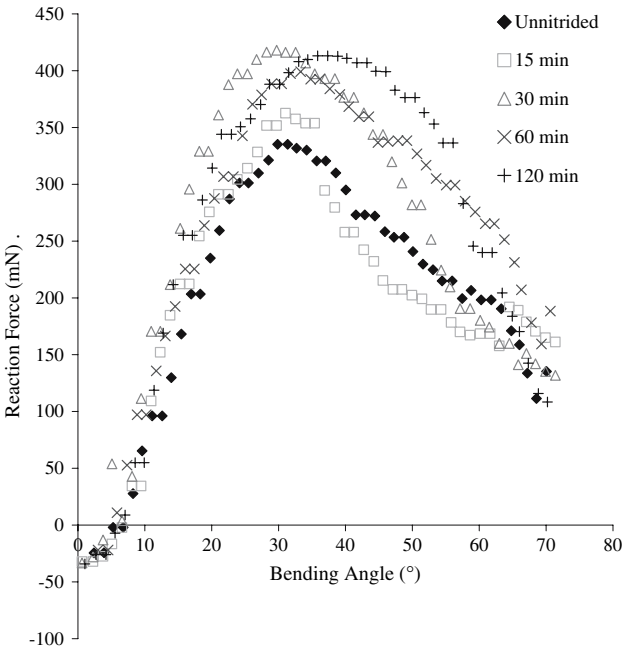

Fig. 1 Flexibility vs. plasma nitridation duration for 10% N_2 at 450 °C

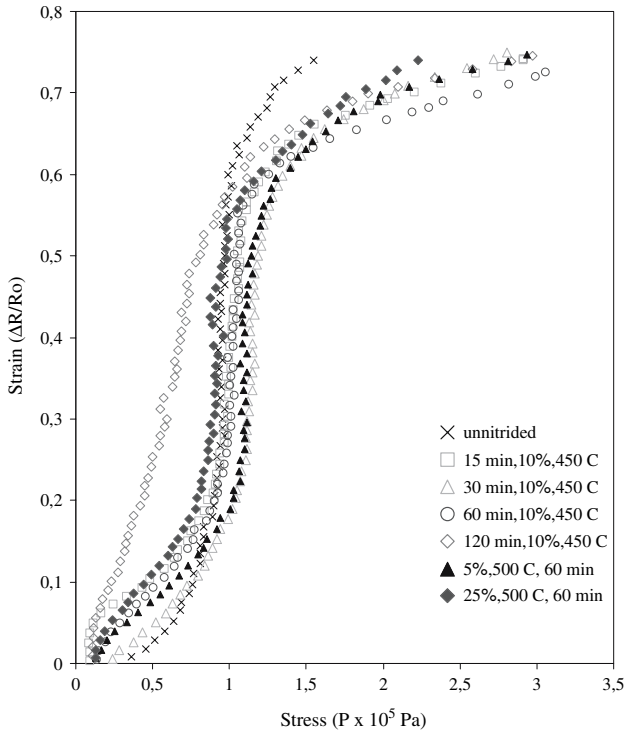

Fig. 2 Radial strength vs. different plasma nitriding conditions

In radial strength tests, the relationships between radial strength—nitridation temperature and radial strength—nitridation gas mixture ratio were studied. Stress-strain behavior of the samples processed for various durations at 450 °C with 10% N_2 containing gas in the plasma ambient (450 °C/10% N_2) and for 1 h at 500 °C with 5 or 10% N_2 was monitored and it appeared that the radial strength was improved by plasma nitridation (Fig. 2). In terms of radial strength, there was no obvious difference between the samples plasma nitrided for 15 min and the pristine ones, but there was a significant difference between the pristine ones and those plasma nitrided for 30 min at 450 °C with 10% N_2, and it was similar to the radial strength of the sample plasma nitrided at 500 °C with 5% N_2. Longer plasma nitridation procedure and higher nitrogen gas content in the plasma ambient resulted in lower radial strength as depicted by the samples plasma nitrided at 450 and 500 °C with 10 and 25% N_2 respectively.

The surface quality and roughness of the stents nitrided at 450 and 500 °C with 10 and 25% N_2 was shown in Fig. 3a, b, respectively. It was clear that the surface roughness and quality was better in the samples that were nitrided at the lower temperatures with low N_2 in the plasma nitriding ambient.

3.2 Biological response

The cell viability in the presence or absence of the untreated stents did not exhibit any difference (Fig. 4). However, in the presence of nitrided stents, cells exhibited slightly increased viability and proliferation capability. The increase was approximately 20% and did not differ significantly with the length of nitridation process. It appeared that the only noticeable difference was among the stents nitrided with various N_2 levels, i.e. 5% N_2 resulted in slightly higher effect on viability levels (Fig. 5).

Alkaline phosphatase activities showed a similar trend to those of viability experiments; a slightly higher activity was detected in the presence of plasma nitrided stents at 450 °C with 10% N_2 at all nitridation times (Fig. 6). Similar to the previous set of experiments, enzyme activity levels were improved with the stents treated at different temperatures and N_2 gas concentration (Fig. 7).

NO production by the osteoblasts was quantified by nitrite measurement in the extracellular medium, as nitrite is one of the two stable breakdown products of NO (Fig. 8). It was found that the presence of the nitrided stents (15 min, 450 °C/10% N_2) slightly increased the nitrite production by the cells. However, in the presence of the stents nitrided for longer periods, NO production by the cells increased proportionally with the length of nitridation procedure (data not shown). Therefore, the possibility of

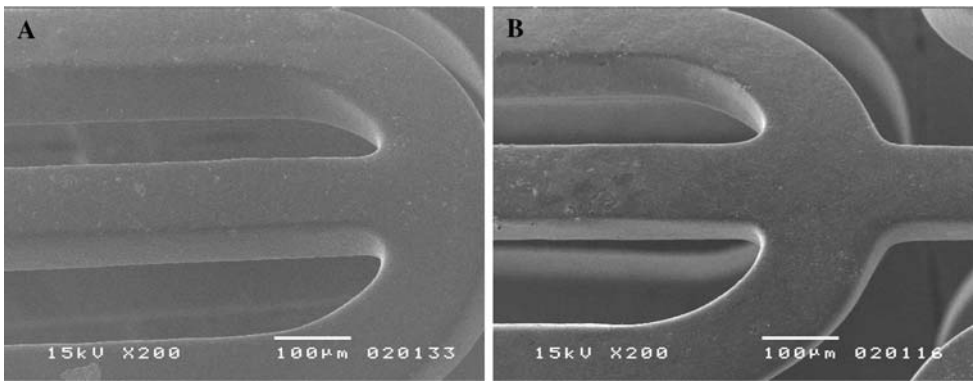

Fig. 3 The surface roughness by SEM (**a**) at 450 °C and 10% N_2 in the plasma ambient and (**b**) at 500 °C and 25% N_2 in the plasma ambient

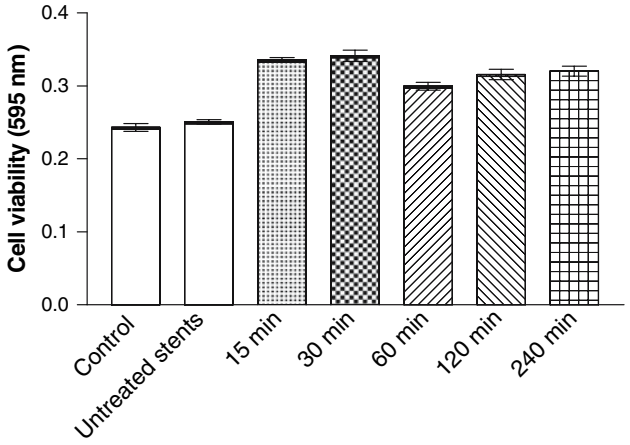

Fig. 4 Cell viability in the absence (control) or presence of stents nitrided at 450 °C, 10% N_2

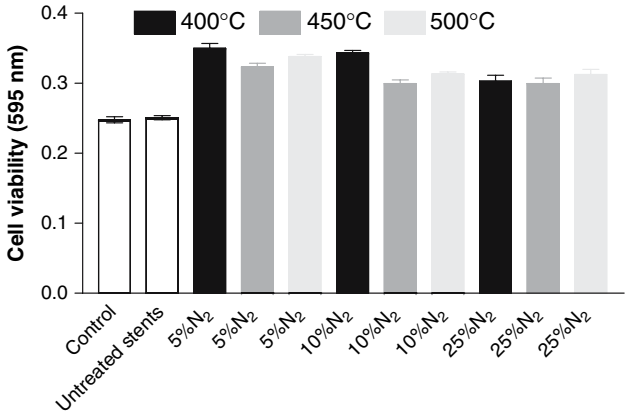

Fig. 5 Cell viability in the absence (control) or presence of stents nitrided at various temperatures and N_2 levels

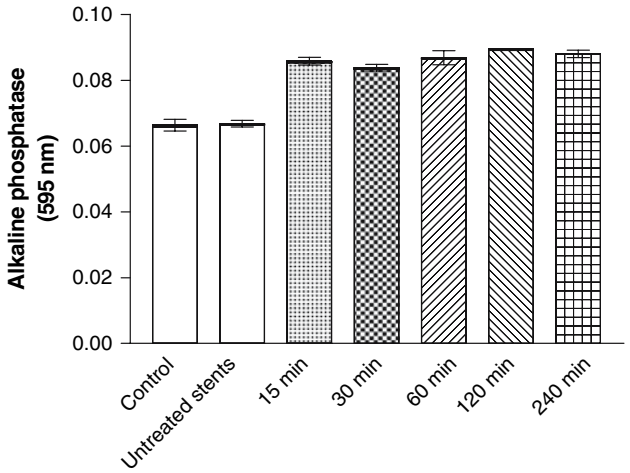

Fig. 6 Alkaline phosphatase activity in the absence (control) or presence of stents nitrided at 450 °C, 10% N_2

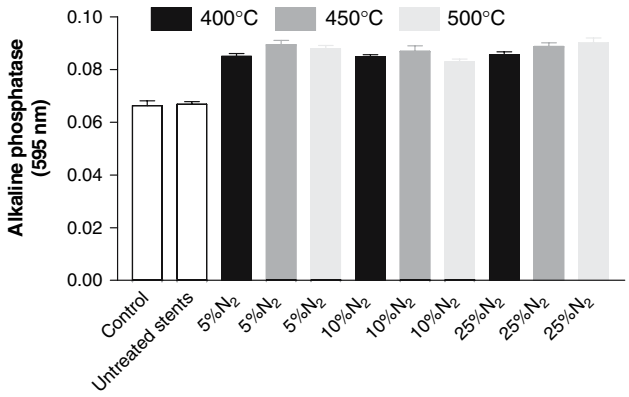

Fig. 7 Alkaline phosphatase activity in the absence (control) or presence of stents nitrided at various temperatures and N_2 levels

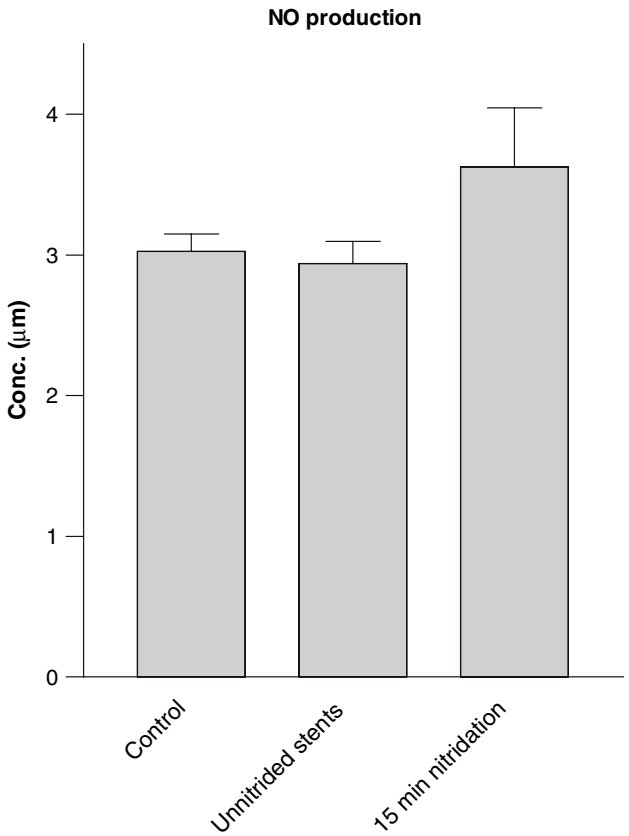

Fig. 8 NO production by the osteoblasts in the absence (control) or presence of unnitrided or 15 min-nitrided stents at 450 °C, 10% N_2

the stents to act as NO donors was investigated in the absence of the cells. An external contribution of NO into the medium from the nitrided stents was not detected.

4 Discussion

To interpret the findings in characterization of the laser-cut stents, the effect of plasma nitriding on the materials

properties of 316L must be revisited. We studied the development of microstructure of austenitic stainless steel (316L) under the plasma nitriding using a glancing angle XRD [9]. It was found that the microstructure was dependent on the processing temperature and the amount of nitrogen in the N_2–H_2 gas mixture. CrN precipitations were observed at temperatures higher than 450 °C and/or in gas mixtures containing more than 10% nitrogen by volume. CrN formation makes the material brittle and vulnerable to corrosion [19, 20]. Since the CrN formation was visible at high temperature plasma nitriding, a strong diffusion of N atoms into the material must have occurred during the processing. The case depth is a measure of nitrogen diffusion into the steel, thus it is a figure of merit to determine the degree of plasma nitriding. The case depth is deeper in the case of CrN formation due to high temperature processing and in plasma nitriding conditions with longer processing. Hardness of the materials is another important property in plasma nitriding and it is studied extensively via nano-indentation measurements. It was reported that there was a significant improvement in the hardness irrespective of the temperature and gas composition of the plasma nitriding conditions, if the coating-only hardness was assessed [9]. Since the processing conditions do not affect the surface hardness, the case depth becomes a critical parameter to determine the degree of rigidness for a stent geometry.

Flexibility of the stent on the balloon is its capacity—in the unexpanded state—to navigate tortuous anatomy en route to its destination [21]. A stent with low flexibility may cause damage to vessel walls. It is important to optimize the stent geometry and rigidness to increase the variety of stent applications. The rigidness may be optimized without changing the geometry of the stent by plasma nitriding via adjusting the case depth. In Fig. 1, the samples nitrided for 30 min have the highest reaction force at a given bending angle. On the other hand, the samples nitrided for 120 min exhibit lower flexibility than all the other samples including the unnitrided ones. In the evaluation of samples after the flexibility test, some of the struts and links in the samples nitrided for 120 min appeared to be broken, since longer plasma nitriding makes the stents more brittle due to the deeper case depth. The nominal thickness of the struts and links in the stent geometry is 100 μm. A deeper case depth is corresponding to higher portion of struts and links of stent that is plasma nitrided, thus its rigidness is increased by a longer plasma nitriding. The samples nitrided for 30 min at 450 °C with 10% N_2 were intact in geometry and had improved mechanical properties. The case depth for those samples from the surface was about 3 μm, therefore only 6% of total thickness of the strut of stent was plasma nitrided. If the plasma nitrided part of the strut is thicker than 10 μm (i.e. in the case of 120 min nitriding), the stent geometry is broken due to the increase in rigidness. Using the same approach, the results from radial tests were evaluated. The radial strength of a stent is its resistance against variable dynamic forces applied throughout the vessel wall, both in the expanded and emplaced state [20, 21]. A stent damaged by plastic deformation may become a vital threat, thus, it is critical to improve the radial strength of the stents. As seen in Fig. 2, no such improvement was obtained in the samples nitrided for 15 min, due to low level of plasma nitridation. On the samples plasma nitrided for 120 min, there were broken struts and links. Therefore, radial as well as flexibility test results proved the procedure unsuccessful. The samples plasma nitrided at 500 °C with 25% N_2 appeared to have CrN formation in their microstructure, thus they became brittle and some of the links and struts were also damaged during the tests [9]. Therefore, the radial strength of such samples were even lower than pristine samples. The microstructure of the samples also contained CrN if they were plasma nitrided at 500 °C with 5% N_2. These samples exhibited a radial strength comparable to the samples plasma nitrided at 450 °C with 10% N_2 for 30 min. Therefore, inducing rigidness at the optimum level with shorter processing times might be possible even with CrN formation. However, the samples contaminated with CrN precipitations are not favored in corrosive body fluids [19].

To reduce the blood clotting initiated by the formation of the first cell layer on the stent surface, it is crucial to obtain a surface roughness as low as 100 nm [3]. As seen in SEM examinations, the quality of the surfaces after plasma nitriding is within the acceptable limits, i.e., burr free and no dross build-up with flat inner walls [12]. Surface roughness was as high as 500 nm in the nitriding experiments performed on steel plates under the identical conditions with stent plasma nitriding [22]. However, the apparent roughness on the stent surface after plasma nitriding is very low when the plasma nitriding conditions do not induce CrN precipitations (Fig. 3a). On the other hand, surface roughness of the samples containing CrN after plasma nitriding appears to be acceptable for the stent applications (Fig. 3b).

A previous study demonstrated that plasma-nitrided 316L steel plates exhibit high corrosive resistance against blood environment and saline fluids [19]. The plasma nitriding of the stents is also expected to improve the corrosion resistance properties of stents so that there is a minimum risk of thrombosis due to an active surface and no risk of toxicity of metals because of no metal release into the body. Thus, plasma nitriding of stents is a very powerful method to eliminate one of the important long-term reliability problems of stents. The fatigue life of steel is enhanced after plasma nitriding due to compression

stress on the surface Therefore, plasma-nitrided austenitic stainless steel stents exposed to cyclic forces in the veins are expected to be more reliable and possess longer lifetime in the service. The risk of restenosis is related to the stent structure and increase with thicker struts and the presence of higher metal area exposed on the surface [17]. Occurrence of restenosis is less probable with the use of thinner but high strength struts provided by low-T plasma nitriding.

It is a usual practice to study in biological systems the biocompatibility of the novel materials to be utilized as implants. The behavior of osteoblasts in the presence of ionic compounds possibly contributed by a material is a suitable experimental model for the evaluation of biocompatibility. In these experiments, a material in question might be considered biocompatible when no significant change in the physiological functions of the cells is observed in the presence of the material in question. In our study we used such a model system, where cell viability/proliferation capability, alkaline phosphatase production and NO production by the cells were measured in the presence of the plasma-nitrided stents against negative and positive controls.

Cell viability was not impeded by the presence of the stents, in contrast, it was slightly enhanced. It appeared that the treatment time or conditions did not significantly affect the biocompatibility of the stents.

Alkaline phosphatase production by the osteoblasts is an indication of biological activity of these cells. The growing bones need alkaline phosphatase [18]. The results indicated that alkaline phosphatase production was not hindered by the stents, yet, its induction was slightly enhanced. This is another indication that the osteoblasts continue their physical functions normally in the presence of the plasma-nitrided stents.

The last group of tests consisted of monitoring of NO production by the osteoblasts. The NO production may be an indication of the early bone mineralization, or homeostatic and development functions or immune response of the mammalian cells. Moreover, it was previously reported that NO has various other functions in vascular tissues, such as inhibition of platelet and inflammatory cell adherence, and protection of endothelial cells from apoptosis [23]. Therefore, an increase in NO production promoted by nitrided stents might not be considered as a negative result. Examining the results obtained in this study, it could be clearly stated that the NO production response of the osteoblasts towards the stents treated for 15 min at 450 °C and 10% N_2 were not even significantly higher than that against the untreated stents. Yet, as the nitridation process was longer than 15 min, higher NO levels were obtained in the culture medium. To eliminate the possibility that nitrite could have been contributed directly by the stents, control measurements were done in the media containing only the nitrided or unnitrided stents, but no osteoblasts. Any additional nitrite production was not observed. It appeared that nitridation processes longer than 15 min induced NO production. As mentioned above, in the light of the current knowledge, an increased NO production appears to be in favor of the endothelial cells. Nevertheless, it would be wise to perform more detailed experiments, to elucidate whether a significant increase in NO levels would be considered as a problem or a favored event, particularly since the mechanical properties of the stents increase with the duration of nitridation process.

5 Conclusion

We examined the effects of low-T plasma nitriding on the mechanical and biological response of laser-cut austenitic stainless steel cardiovascular stents. The plasma nitriding of the stents at 450 °C with 10% N_2 gas provided an enhanced flexibility and radial strength.

As far as the biological compatibility of the stents was concerned, the viability and metabolic activity studies proved acceptable results, i.e. all the plasma-nitrided stents performed similar to unnitrided ones. In terms of NO production, only the stents subjected to 15-min plasma nitriding appeared to elicit native responses, while longer nitriding increased the NO production, which could be postulated as an indication of improved biocompatibility.

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