BIOCOMPATIBILITY AND CORROSION RESISTANCE OF NiTi

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Summary

Nitinol is used in a wide variety of medical devices because of its excellent combination of mechanical and surface properties which include superelasticity, shape memory and corrosion resistance. Still, the biocompatibility has been questioned due to conflicting results in the literature. It is now recognized that this situation may be due to a variation in NiTi surface treatment. Indeed, through optimal surface treatments, corrosion resistance and thus, biocompatibility of the alloy can be enhanced. This paper reviews the results observed for corrosion resistance and biocompatibility of NiTi when the surface is passivated by different methods. Results show that NiTi is protected by a titanium-based oxide layer that is very efficient against bio-corrosion. Nickel release from NiTi alloys has been shown to be minimal and non-toxic in every study. Finally, *in vitro* and *in vivo* assays show that NiTi exhibits good biocompatibility.

Introduction

Equiatomic Nickel-Titanium (NiTi or Nitinol) is characterized by a unique combination of properties, including superelasticity and shape memory, that make it very attractive for biomedical applications. NiTi has been used for implants in orthopedics and orthodontics for several decades and is responsible for major improvements in these fields.[1,2] This alloy is also rapidly becoming the material of choice for self-expanding stents, graft support systems, filters, baskets and various other devices for minimally invasive interventional procedures.[1,3] The superior performance of Nitinol devices over devices manufactured from conventional engineering materials is documented in many references.[1,4,5] Nevertheless, some in the medical community are concerned because of publication of conflicting corrosion and biocompatibility data. The purpose of this paper is to focus on the bio-corrosion properties and to highlight the sources of the conflicting reports.

The primary concern about Nitinol is the high nickel content of the alloy (on the order of 55 weight %), and its possible influence on biocompatibility. Nickel is present in the human tissue in quantities close to 0.1 ppm, and is essential in nutrition for biological functionality of the human body.[6,7] However, there are concerns that if an implant material releases higher Ni concentrations it may generate harmful reactions.[7-9] For example, nickel may generate allergenic, toxic and carcenogenic reactions following skin contact or implantation of this material.[8,9] Other alloys which contain high levels of Ni, such as MP35N (an alloy with 35 weight % Ni), exhibit good biocompatibility, and are used as implants in orthodontics, orthopedics and cardiovascular applications.[10-12] Furthermore, it is important to recognize that intermetallic compounds, such as NiTi, will not produce the same reactions as pure metals or alloys. For example, the atomic bonding forces between Ni and Ti in intermetallic NiTi are considerably higher than in a Ti alloy

with a small amount of Ni.[13] These examples emphasize the importance of considering the complete alloy when evaluating biocompatibility testing and not only its elemental composition.

A major source of confusion about the use of NiTi as medical implants derives from some literature references that report moderate corrosion resistance and cell culture compatibility. A careful study of these references, however, reveals that the surface conditions of the samples are generally not well documented. It is now well known that NiTi requires controlled processing to achieve optimal mechanical and thermal properties. Optimization of the thermo-mechanical processing provides good fatigue life and general mechanical properties to meet the stringent structural requirements of medical implants. In the same way, surface processing is required in order to promote optimal corrosion resistance and biocompatibility of the material. Surface treatments to improve bio-corrosion response is not a new technique. For example, ASTM recommends a passivation procedure (ASTM-F86)[14] for metallic surgical implants. This standard recommends an appropriate chemical treatment of metallic implants to ensure passive surface condition. The treatments prescribed for stainless steel alloys consist of a nitric acid passivation or electropolishing to modify the oxide surface characteristics and therefore to improve their bio-corrosion responses. It is well established that NiTi is a passive alloy like titanium or stainless steel, with a stable surface oxide layer which protects the base material from general corrosion.[15] As in the case for other implant alloys, the passivity of NiTi may be enhanced by modifying the thickness, topography and chemical composition of the surface by selective treatments. [15-17]

This paper addresses the topics of corrosion resistance, Ni release and biocompatibility of NiTi alloys.

Surface Layer and Corrosion Resistance of NiTi

Several studies have demonstrated that after an appropriate passivation of its surface, NiTi surface layers consist mainly of a titanium-oxide layer (TiO_2)[15-18] similar to that found on Ti alloys.[19] This finding corroborates basic thermodynamics data which specify that the free energy of formation of TiO_2 is favored over other nickel or titanium oxides.[18]

This oxide layer serves two purposes:

- Increase the stability of the surface layers by protecting the bulk material from corrosion.
- Create a physical and chemical barrier against Ni oxidation and modify the oxidation pathways of Ni.[20]

The stability of the surface layer on NiTi and its ability to protect the material from corrosion was investigated in several studies by electrochemical experiments.

Early studies performed by Kimura and Sohmura[21] showed that a passivation treatment that promotes the growth of an oxide layer improved the corrosion resistance of NiTi in 1% NaCl solution at 37°C. Furthermore, it was demonstrated that a thin oxide layer was able to sustain the large deformation induced by the shape memory effect.

More recently, Trepanier, et al.[16] investigated the effects of electropolishing and heat treatments of NiTi stents on their corrosion resistance in Hank's physiological solution at 37°C. Figure 1 below illustrates anodic polarization curves of stents with different surface treatments. These results indicated a significant improvement of the corrosion resistance of NiTi stents that was attributed to the promotion of a thin and very uniform Ti-based oxide layer. The authors concluded that uniformity of, rather than thickness of, the oxide is most important to protect the material from corrosion. Furthermore, as was shown by Kimura and Sohmura[21], a thin oxide layer is preferable to maintain the integrity of the surface layer in the advent of large deformations due to shape memory or superelasticity.

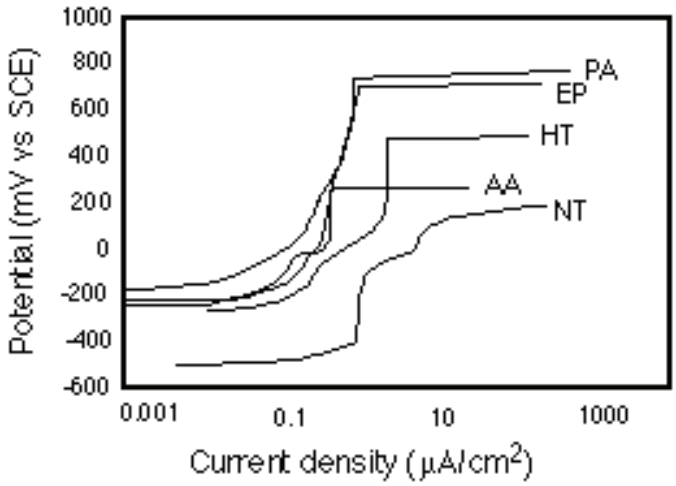

Figure 1 Potentiodynamic anodic polarization curves for surface treated NiTi stents (NT: non-treated, AA: air-aged, HT: heat-treated, EP: electropolished and PA: passivated)[16]

A comparative study of the corrosion resistance of passivated Ti-6Al-4V, 316L stainless steel and NiTi was performed in Hank's physiological solution by Wever, et al.[15] Their results show that while Ti-6Al-4V was the most corrosion resistant, NiTi samples were more resistant to chemical

breakdown of their passive film than 316L stainless steel samples. Figure 2 shows the anodic polarization curves of the three materials.

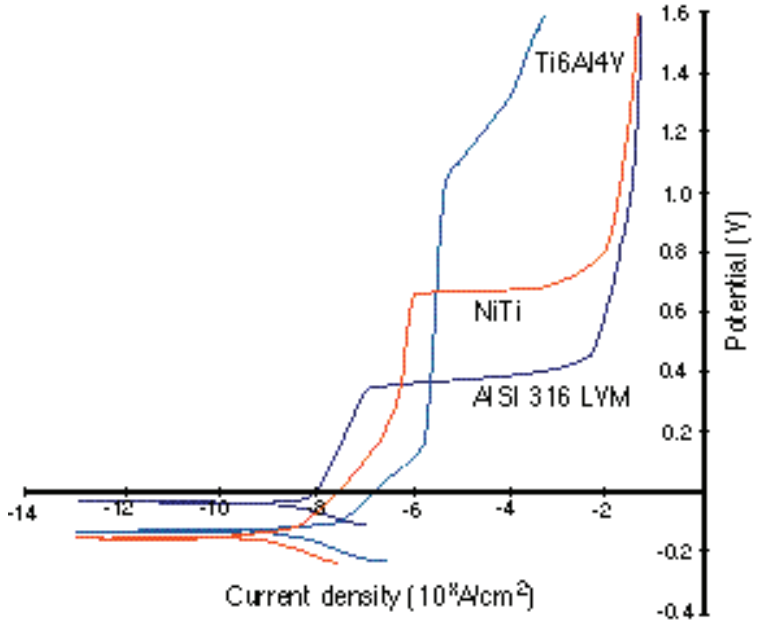

Figure 2 Anodic polarization curves of NiTi, Ti-6Al-4V and 316L stainless steel[15]

Nickel Release from NiTi

Since Nickel release during the bio-degradation of NiTi is an important concern for its use as an implant, several studies have been undertaken to measure this value. For example, Barret, et al.[22] and Bishara, et al.[23] investigated nickel release from NiTi archwires (processed by the manufacturer) in saliva. During an *in vitro* dissolution study, they found that NiTi appliances released an average of 13.05 µg/day, which is significantly below the estimated average dietary intake of 200-300 µg/day.[22] In a second study, orthodontic patients with NiTi appliances had Ni-concentration in their blood measured during a period of 5 months.[23] Results show no significant increase in the nickel blood level throughout this study.

A comparative *in vitro* cell culture study was undertaken by Ryhanen, et al.[24] in which they measured Ni released from NiTi and 316L stainless steel in a fibroblast and osteoblast cell culture media. In both media, Ni levels were higher in the NiTi group the first day and decreased rapidly as a function of time to achieve similar levels as 316L after 8 days. It is important to highlight the fact that even though Ni release was higher in the NiTi group, it did not reached toxic values and cell

proliferation or cell growth near the implant surface was not affected. Furthermore, in this study, NiTi was only mechanically polished while stainless steel was electropolished according to the guidelines of the manufacturer. Ryhanen, et al. anticipate a decrease in Ni release if further passivation treatments, such as electropolishing, are performed on NiTi.

Wever, et al.[15] conducted a similar comparative study with passivated NiTi and 316L stainless steel in Hank's solution. They also found that Ni release from NiTi was maximum the first day ($14.5X10^{-7}$ $\mu g/cm^2 sec$) and reached undetectable levels similar to 316L after 10 days.

Biocompatibility of NiTi

Biocompatibility of a material may be simply defined as its ability to be well accepted by the body. Since every material will generate a "foreign body reaction" when implanted in the body, the degree of biocompatibility is related to the extent of this reaction. In order to study this phenomena, *in vitro* testing with cell cultures allows isolation of the reaction from each cell and physiological media, whereas, *in vivo* testing provides a more complete response involving the biological environment and immune system. Both types of tests were undertaken to better understand the biological response to NiTi.

In vitro studies

Recently, a study revealed no significant differences between the cell growth behavior near the surfaces of different implant materials (mechanically polished Ti and NiTi, electropolished 316L stainless steel).[24] A microscopy study also showed that the cells had grown very near to Ti and NiTi alloys while they were less close to the stainless steel samples. The authors concluded that NiTi showed very good biocompatibility and that it had an excellent potential for clinical applications.

Also, based on a MEM extract cytotoxicity test, a guinea-pig sensitization test and genotoxicity testing, passivated NiTi showed no cytotoxic, allergic or genotoxic activity.[25] In this study, similar results were obtained for the control group composed of passivated 316L stainless steel samples. In a different study that addressed only the genocompatibility of the material, NiTi exhibited a good biocompatible behavior similar to Ti and 316L stainless steel on cellular chromatin.[26] Based on these results, genocompatibility of NiTi is very promising.

In vivo studies

Cutright, et al.[27] have studied the tissue response of subcutaneous implantation of NiTi wire sutures in rats for a period of 9 weeks. Their study illustrated that the inflammatory response was minimal starting 3 days after implantation. The healing process initiated after 1-2 weeks consisted of a fibrous capsule formation around the implant. The reaction was similar to the one generated by similar stainless steel wires.

In addition, Castleman, et al.[28] evaluated the biocompatibility of chemically passivated NiTi by inserting plates into beagle's femur for a period ranging from 3 to 17 months. The histological analysis of muscular tissue surrounding the implantation site showed no significant difference between NiTi and Cr-Co plates. Furthermore, neutron activation analyses have shown that there was no significant dissolution of metallic Ni in muscle near the NiTi implants. Based on their observations, they concluded that the material was safe to conduct further testing.

More recently, Trepanier, et al.[29] performed an *in vivo* study on passivated NiTi stents. Implantation of the material in rabbit paravertebral muscles and study of the inflammatory reaction for periods ranging from 3 to 12 weeks demonstrated good biological response to NiTi. Analysis of the fibrous capsule surrounding NiTi stents revealed a decrease of the thickness as a function of time. Figure 3 illustrates the typical fibrous capsule surrounding the implants after 12 weeks.

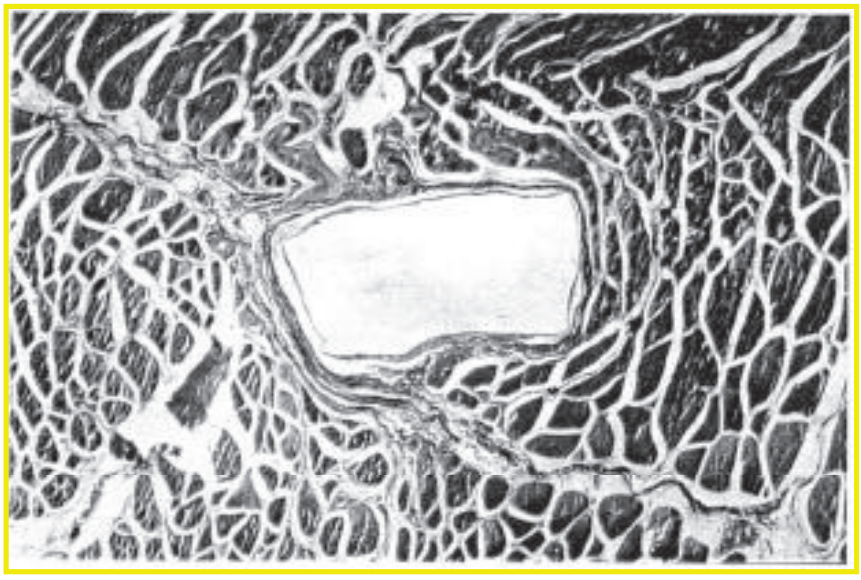

Figure 3 Thin fibrous capsule surrounding passivated NiTi stent after a 12-week implantation period[29]

In a comparative study, a 26-week follow-up on rats was done to assess the effect of different materials on soft tissues.[30] In this study, short-term biocompatibility of polished NiTi was found similar to polished Ti-6Al-4V and electropolished stainless steel when in contact with muscle and perineural tissue. These results indicate promising soft tissue compatibility of NiTi.

Conclusion

Based on the abundance of literature reports, NiTi has good corrosion resistance and biocompatibility, and minimal Ni release. From the literature review presented in this paper:

- NiTi is protected from corrosion by a highly stable and biocompatible Ti-based oxide layer (mainly TiO_2). This good corrosion behavior will prevent degradation of the material in the physiological environment and therefore will promote biocompatibility.

- Corrosion resistance of NiTi is enhanced by different surface treatments such as electropolishing which promote a very uniform oxide layer.

- Ni release from NiTi has been shown to be minimal in every study. From well below dietary levels, Ni dissolution decreases rapidly to nearly non-detectable levels in the first few days following NiTi immersion in a physiological media.

- *In vitro* and *in vivo* studies show that NiTi exhibits good biocompatibility and does not promote toxic or genotoxic reactions when in contact with a physiological environment.

Therefore, properly treated NiTi can be considered a biologically safe implant material with unique mechanical properties.

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