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In Vitro Corrosion Behavior of Atrial Depressurized Device Made from Shape Memory Alloy for Heart Failure Treatment

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Abstract*— An atrial depressurized device (ADD) prototype has been designed and developed for HFpEF treatment. ADD prototype is categorized as a cardiovascular nitinol stent that utilizes superelasticity properties for its functions. However, some limitations are necessary, including prolonged implantation (10-15 years) in an aggressive corrosion environment, dissimilar metal contact (NiTi/Ti-6Al-4V), and risk of nickel ion release. Corrosion assessment is essential for predetermining the appropriate corrosion resistance of ADD prototypes prior to in vivo study. This study aims to assess the pitting corrosion, galvanic corrosion, and nickel release of ADD prototypes. Pitting and galvanic corrosion were tested following ASTM F2129 to determine corrosion susceptibility on the metal surface and corrosion tendency due to dissimilar metals in contact. Furthermore, nickel concentration released over 63 days of immersion in artificial plasma solution was measured following ASTM F3306. In addition, the acceptance criteria referred to the FDA draft guidance that recommends a tolerable intake value for non-oral exposure to nickel should not exceed 0.5 µg/day for 70 kg adult. The results showed that no pitting corrosion was found on the surfaces of NiTi wire and Ti-6Al-4V screw attachment when tested in an artificial plasma solution. Moreover, NiTi wire has the lowest corrosion rate ($14x10^5$ mm/year), followed by Ti-6Al-4V ($55x10^5$ mm/year) and SUS316L ($312x10^5$ mm/year). The pairing of NiTi/Ti-6Al-4V was not experienced corrosion due to their high corrosion resistance and low galvanic interaction. Finally, the maximum nickel release rates of the non-tested and fatigue-tested devices were approximately 875 times lower than the TI value for systemic toxicity. Consequently, using NiTi and Ti-6Al-4V as the main materials in ADD prototype, the device is safe in terms of strength and corrosion resistance.

***Index Terms*— Corrosion, Nickel ion released, NiTi wire, HFpEF, Cardiovascular stent.**

I. INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is when the heart is ineffectively supplying enough blood to the body due to the high stiffness of the left ventricle, resulting in increased pressure inside the heart. Currently, the number of HFpEF patients has continuously risen each year, and there is no effective treatment to cure HFpEF [1,2]. So instead, the doctor has reamed at the atrial septal to balance pressure between the high-pressure side (left atrium) and low-pressure side (right atrium). However, overtime passed, tissues can be regenerated to cover the channel, leading to the unbalance of pressure again.

In this study, a prototype of the atrial depressurized device (ADD) has been developed for HFpEF treatment. The ADD prototype is made by braiding NiTi superelasticity wire and formed into a double disc-liked device with central fenestration of 8 mm. The device can be loaded into and deployed from the catheter without any permanent deformation due to utilizing superelasticity. Moreover, a Ti-6Al-4V bush and screw attachment are joined at the left and right sides as components to connect with the delivery cable.

ADD prototype has been designed for long-term implantation, operating inside the heart. The body fluid acts as an aggressive environment for the device. It mainly contains water, dissolved oxygen, and various ions such as chloride and hydroxide [3,4]. Thus, corrosion resistance must be considered for biocompatibility assessment. Furthermore, ADD prototype has a braiding structure with a small and complex geometry that can be at risk of deteriorating the device's integrity and be susceptible to damage due to corrosion. Combining dissimilar metals with NiTi wire at proximal and distal ends may lead to galvanic corrosion. In addition, nickel ions released due to corrosion may affect patients with nickel allergies, and adverse event responses to nickel ion release should be considered [5].

The US FDA published a Technical Considerations for Non-Clinical Assessment of Medical Devices containing Nitinol, issued in April 2019. The guidance provides technical recommendations for manufacturing, mechanical

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testing, corrosion, nickel ion release, and biocompatibility of Nitinol devices. ASTM F2129 (Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices) is recommended to evaluate nitinol devices' localized corrosion susceptibility. In addition, immersion testing to determine nickel ions released from the device over a specified time under physiological conditions is assessed per ASTM F3306 (Standard Test Method for Ion Release Evaluation of Medical Implants) [6].

Pitting corrosion and nickel release of an electropolished Hydrus Microstent were investigated to determine the corrosion resistance of the nitinol microstent. The results report that the Hydrus microstent, which undergoes electropolishing, may improve pitting corrosion resistance and dissolution of nickel from the device [11]. In addition, the localized corrosion due to galvanic interaction between NiTi stent and noble markers such as Au, Pt, and Pd was investigated in NaCl 0.9% solution. The pairing of NiTi/Pt presented a significant potential for galvanic corrosion susceptibility [9].

According to technical guidance from the US FDA, this study aims to investigate corrosion susceptibility and nickel ion released from ADD prototype when exposed to an artificial plasma solution. The potentiodynamic test method was performed to assess pitting and galvanic corrosion on NiTi wire and Ti-6Al-4V screw attachment. Surface analysis by SEM was conducted to determine corrosion on metal surfaces. For nickel ion released, Immersion testing in an artificial plasma solution with a controlled temperature of 37C was implemented to prepare collected extracts (63 Days) then ICP AES was used to quantify the amount of nickel concentration. The nickel released rate per day per device and total cumulative nickel released were analyzed.

II. MATERIALS AND METHOD

Pitting corrosion

Pitting corrosion susceptibility was assessed following ASTM F2129 “Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices [7].” Five samples of NiTi wire from finished devices, Ti-6Al-4V, and SUS316L screw attachment were used in this experiment using Metrohm Autolab PGSTAT302N to accelerate the corrosion on metal surfaces. A saturated calomel electrode (SCE) was used as a reference electrode, and platinum wire was used as a counter electrode. Samples were tested in an artificial plasma solution (NaCl: 6.8 g/L, $CaCl_2$: 0.2 g/L, KCL: 0.4 g/L, $MgSO_4$: 0.1 g/L, $NaHCO_3$: 2.2 g/L, Na_2HPO4: 0.126 g/L, NaH_2PO_4: 0.026 g/L of DI water) [8] to simulate body fluid environments. Purged an artificial plasma solution (pH of 7.4) with nitrogen gas at 150 cm^3/min was performed for a minimum of 30 min prior to starting and continued purging throughout the test. Record the rest potential (E_r) after 1 hr immersed samples in the solution (37C). The potentiodynamic scan started with a scan rate of 1mV/s. To control the potentiostat, the minimum reversed scan potential was set to 800 mV (vs. SCE). Moreover, SEM analysis (JEOL JCM-7000 NeoScope) was carried out to determine pitting on metal surfaces.

Galvanic Corrosion

Potentiodynamic polarization was conducted using a method similar to pitting corrosion. NiTi wire, Ti-6Al-4V, and SUS316L screw attachment from finished devices were used as working electrodes. Record the corrosion potential (E_{corr})of the uncoupled anode and cathode samples prior to starting the galvanic corrosion test. The scan rate was set to 1 mV/s, scanning from Ecorr to 1 mV and Ecorr to -1 mV, to perform anodic and cathodic polarizations. Samples with higher corrosion potential, such as Ti-6Al-4V and SUS316L, were defined as cathodic curves which overlaid on the anodic curve of the lower corrosion potential sample (NiTi wire). The intersection point was used to determine the potential of the galvanic couple (E_{couple}) and the current of a galvanic couple (i_{couple}) based on the mixed potential theory [9].

Ni Ion release

Immersion testing in an artificial plasma solution was conducted to determine Ni ion released from non-tested and fatigue-tested (400 million cycles) devices. The test method was referred to as ASTM F3306 (Standard Test Method for Ion Release Evaluation of Medical Implants) [10]. Three devices from non-tested and fatigue-tested (n=3) were used in the experiment, and six wires were placed in 5 ml of an artificial plasma solution in each Polypropylene (PP) container. Test samples were incubated in a heating chamber operating at the temperature of 37°C throughout the experiment. The surface area-to-solution volume ratio of 0.23 cm^2/ml was calculated within the range recommended in the technical guidance for non-clinical assessment of medical devices containing nitinol [6]. In this study, sampling intervals were specified at 1, 3, 5, 7, 14, 21, 28, 35, 42, 49, 56, and 63 days. The collected extracts (blank and test samples) were diluted using trace-metal grade 2% nitric acid solution to ensure that nickel would be dissolved into the solution. An inductively coupled plasma atomic emission spectrometers (Shimadzu ICPE – 9800 Series) was used to determine the nickel concentration. A 5-point nickel calibration curve (0, 0.5, 1, 5, and 10 ppb) was performed with a linearity of greater than 0.999. To obtain the total mass of nickel (in ng), the nickel concentration (in ppb) was multiplied by the solution volume. The nickel release per device per day and the total cumulative release over a specified time were analyzed.

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III. RESULTS AND DISCUSSIONS

Pitting corrosion

The corrosion susceptibility of main components, including NiTi wire, Ti-6Al-4V, and SUS316L screw attachment when exposed to artificial plasma solution was assessed using cyclic potentiodynamic polarization following ASTM F2129 "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices." Potentiodynamic polarization plots are presented in overlaid format in Figure 1. NiTi wire and Ti-6Al-4V screw attachment show E_{corr} values of -268.32 and -359.11 mV (SCE) and represent the passive region with no breakdown point. However, the SUS316L screw attachment shows E_{corr} values of -104.08 mV (SCE) and exhibits a significant breakdown point at 303.93 mV (SCE). Moreover, NiTi wire and Ti-6Al-4V screw attachment show i_{corr} values of 0.019 and 0.065 µA/cm^2, whereas SUS316L screw attachment shows 0.26 µA/cm^2. Consequently, the corrosion rate (CR) is low for NiTi wire and Ti-6Al-4V screw attachment when used in an artificial plasma solution.

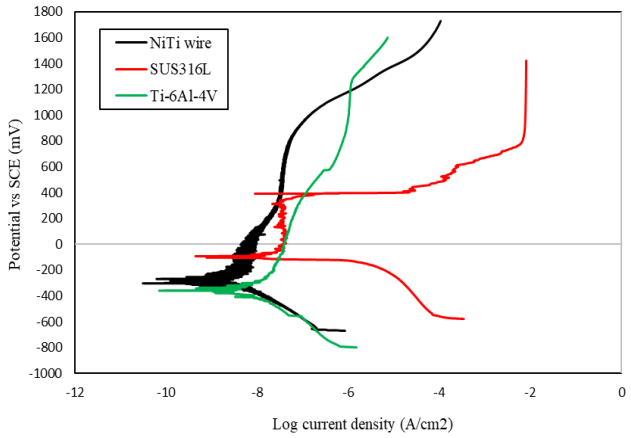

Fig. 1 The polarisation curves of NiTi wire, Ti-6Al-4V, and SUS 316L screw attachment in artificial plasma solution at 37°C.

The SEM images presented in Figure 2 depict the surface characteristics of NiTi wire, SUS316L, and Ti-6Al-4V screw attachment before and after undergoing potentiodynamic testing. The SEM analysis revealed that neither NiTi wire nor Ti-6Al-4V screw attachment exhibited any signs of pitting corrosion on their surfaces. Conversely, pitting corrosion was found on SUS316L screw attachment, as evidenced by the SEM images at a magnification of 60x. These observations agree with the polarization curve results shown in Figure 1, which demonstrate a breakdown point only in the case of SUS316L.

Table 1 Potentiodynamic polarisation test results for NiTi, SUS 316L, and Ti-6Al-4V screw attachment in artificial plasma solution at 37°C.

Sample	E_{corr} $(mV\ vs\ SCE)$	i_{corr} $(\mu A/cm^2)$	$CR \times 10^{-5}$ $(mm/year)$	E_b $(mV\ vs\ SCE)$
NiTi wire	-268.32	0.0196	14	N/A
SUS 316L	-104.08	0.2605	312	303.93
Ti-6Al-4V	-359.11	0.0652	55	N/A

The corrosion potential (E_{corr}) serves as an indicator of the stability of surface conditions. Therefore, less variability in E_{corr} values among different samples indicates more consistent surface processing. The corrosion current density (i_{corr}) and corrosion rate (CR) are relative measures of corrosion, illustrating how much material will be lost during the corrosion process. Thus, higher i_{corr} and calculated CR values indicate more material loss. Finally, the breakdown potential (E_{bd}) indicates the region where pitting initiates on the metal surface. Hence, a higher or more positive value of E_{bd} would indicate a larger region of corrosion resistance. The results are listed in Table 1.

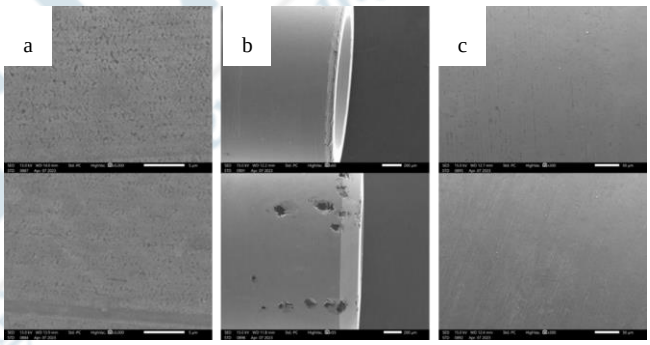

Fig. 2 SEM micrograph on the surface of a) nitinol wire (x5000), b) SUS316L screw attachment (x60), and c) Ti-6Al-4V screw attachment (x300)**.** Upper: Non-tested, Lower: after potentiodynamic test in artificial plasma solution.

Galvanic corrosion

The galvanic interaction of NiTi wire, when coupled to Ti-6Al-4V, and SUS316L screw attachment in artificial plasma solution, was assessed by potentiodynamic polarization. The anodic and cathodic polarization curves of Ti-6Al-4V, and SUS316L screw attachment overlaid with the anodic polarization curve of NiTi wire are shown in Figures 3 and 4, respectively. Values from the intersection points, corresponding to the potential of the galvanic couple (E_{couple}), current of the galvanic couple (i_{couple}), and potential difference, are listed in Table 2. The potential difference between the paring of NiTi/Ti-6Al-4V and NiTi/SUS316L in artificial plasma solution was 53.40 and 98.24 mV. The galvanic interaction demonstrated by E_{couple}, i_{couple}, and potential difference of the paring of NiTi/Ti-6Al-4V is lower

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than the pairing of NiTi/SUS316L. These results indicate that the pairing of NiTi/Ti-6Al-4V has a low risk in terms of corrosion induced by galvanic interactions. The potential difference is the main factor strongly affecting the magnitude of galvanic corrosion. Thus, the galvanic interaction of NiTi/Ti-6Al-4V in an artificial plasma solution is low compared to the paring of NiTi/SUS316L.

Table 2 Galvanic current and potential of NiTi wire, SUS 316L and Ti-6Al-4V screw attachment in artificial plasma solution at 37℃.

Sample	E_{couple} $(mV\ vs\ SCE)$	i_{couple} (A/cm^2)	Potential difference $(mV\ vs\ SCE)$
NiTi / Ti-6Al-4V	-379.18	2.40	53.40
NiTi / SUS 316L	-325.77	4.66	98.26

Moreover, NiTi alloys have similar electrochemical behavior to titanium alloys, reducing susceptibility towards galvanic corrosion. In addition, the passive oxide layer that forms on the surface of titanium and NiTi alloys provides further protection against galvanic corrosion. The results reveal that pairing NiTi wire and Ti-6Al-4V screw attachment, as the main components in ADD prototype, has a low risk of corrosion caused by galvanic interactions. Therefore, galvanic corrosion should be carefully considered when combining cardiovascular devices with other types of components or radiopaque markers with ADD prototypes.

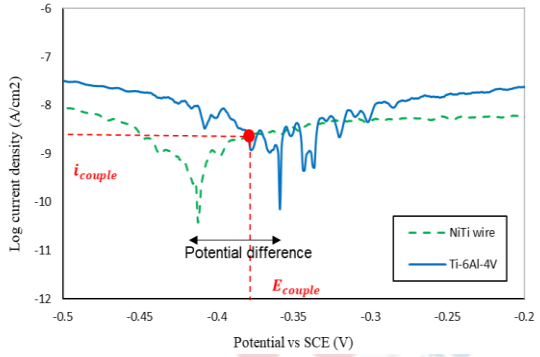

Fig. 3 Anodic polarization curve of Ti-6Al-4V screw attachment and NiTi wire in artificial plasma solution.

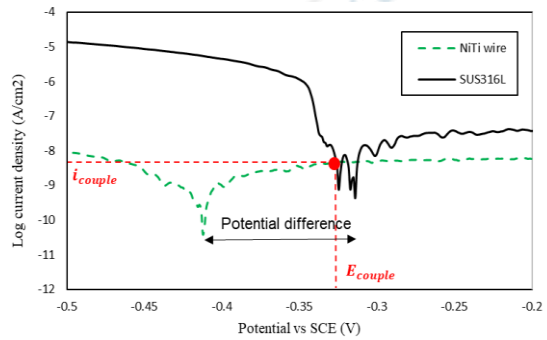

Fig. 4 Anodic polarization curve of SUS 316L screw attachment and NiTi wire in artificial plasma solution.

Nickel ion release

In vitro nickel release testing was performed to assess the amount of nickel released from the ADD compared to a Tolerable Intake (TI) value for nickel which is defined in ISO 10993-17 (Biological evaluation of medical devices -- Part 17: Establishment of allowable limits for leachable substances). Control artificial plasma blanks solution (n = 12 total) were all below the detection limit (0.3 ppb) of the ICP-AES system. The cumulative nickel release of the ADD prototype for each immersion time point is shown in Figure 5. The maximum nickel release of non-tested and fatigue-tested devices were 41.4 and 35.6 ng/device, respectively. The nickel release rates were determined for each time point, as shown in Figure 6. The maximum release rates were 21.2 and 16.5 ng/device/day for non-tested and fatigue-tested samples, respectively. Moreover, nickel release rates after Day 14 were significantly low compared to Day 1-13 and dropped to a constant level until Day 63.

Non-tested and fatigue-tested ADD were selected from different production batches, utilizing distinct types of templates in the fabrication process leading to variations in wire length and total surface area. Prior to conducting immersion tests, the weights of the non-tested and fatigue-tested devices were measured and found to be 0.246 g and 0.237 g, respectively. The calculated surface areas of the non-tested and fatigue-tested devices were 13.6 cm^2 and 12.44 cm^2, respectively. Consequently, the nickel release rates for both conditions were normalized based on the release rates per unit of surface area. The results indicated that the normalized nickel release rates for non-tested devices ranged from 0.01-1.56 ng/cm^2/day and 0.06-1.33 ng/cm^2/day for fatigue-tested devices. The wide range of release rates observed in non-tested ADD can be attributed to more surface area than fatigue-tested devices. These suggest that the manufacturing process significantly influences the variability in nickel release rates.

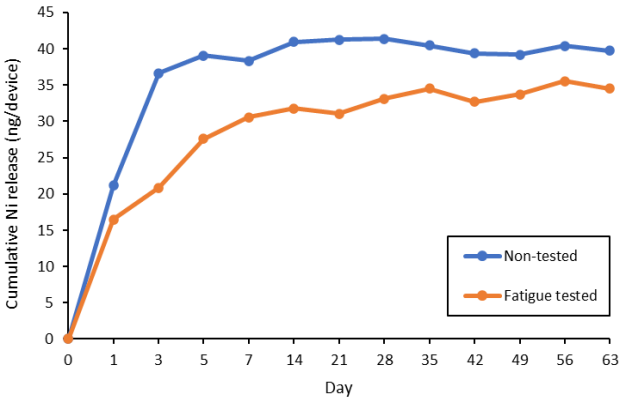

Fig. 5 Nickel ion release rates of ADD over 63 days immersion testing.

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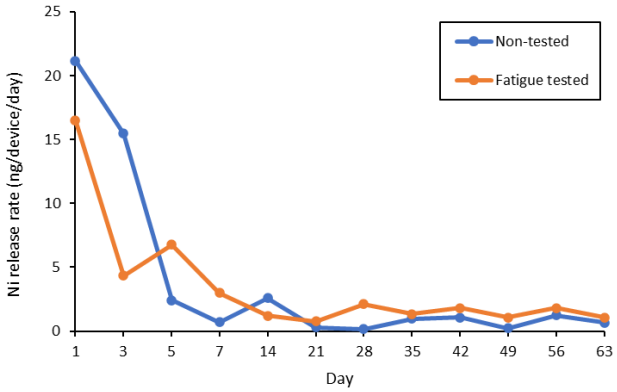

Fig. 6 Cumulative nickel ion release of ADD over the 63days immersion duration.

The FDA technical draft guidance recommends a parenteral Permitted Daily Exposure (PDE) [6] should not exceed 35,000 ng/day for a 70 kg adult, based on systemic toxicity data from experimental animals following administration of nickel salts by parenteral routes of exposure (e.g., intravenous, intraperitoneal) followed the outlined in the ISO 10993-17 standard (Biological evaluation of medical devices—Part 17: Toxicological risk assessment of medical device constituent. As the results mentioned above, non-tested and fatigue-tested ADD had a maximum Ni release of 41.4 and 35.6 ng/device, which is approximately 875 times lower than the PDE value. Therefore, ADD prototype shows a low risk of systemic toxicity when implanted in an artificial plasma solution.

Table 3 Maximum Ni release per device and per day of non-tested and fatigue tested ADD.

Ni release	Non-tested	Fatigue tested
Maximum release (ng/device)	41.4	35.6
Maximum release rates (ng/device/day)	21.2	16.5

IV. CONCLUSION

This study aims to investigate the corrosion susceptibility and nickel ion released from ADD prototype when exposed to an artificial plasma solution. The following conclusions are obtained from this study.

1. No pitting corrosion was found on NiTi wire and Ti-6Al-4V screw attachment surfaces when exposed to an artificial plasma solution.
2. Low galvanic interaction when NiTi wire and Ti-6Al-4V screw attachment are in contact.
3. Low risk of systemic toxicity due to low Ni release rate referred to ISO 10993-17.
4. The ADD prototype is safe due to comprise NiTi and Ti-6Al-4V as the main components.

V. ACKNOWLEDGMENTS

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