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*Original Article*

# Corrosive behaviour of Amplatzer® devices in experimental and biological environments

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**Abstract** *Purpose:* Nitinol, a nickel–titanium alloy, is a valuable material in the construction of interventional endoluminal devices because of its biocompatibility, super elasticity, high resiliency and shape memory. The possibility of nickel toxicity has been raised with devices constructed of Nitinol. Our investigation examines the long-term corrosive behavior of this alloy in experimental and biological environments. *Methods:* We performed three levels of study. Microscopic examination was made of 64 devices of various sizes, randomly selected from 240 Amplatzer® Septal Occluders that had been exposed to saline solution at 37°C for fourteen months. All samples were studied by electron microscopy ranging from 50 to 5000 times magnification. We also studied microscopically 3 Amplatzer® devices explanted 18–36 months after implantation in dogs, and 2 Amplatzer Septal Occluders removed from patients 18 months (cardiac transplant) and 19 months (died of causes unrelated to device placement) after implantation, which were examined grossly and by electron microscopy up to 5000 times magnification. We then measured the levels of nickel in the blood using inductive plasma mass spectroscopy in 19 patients with implanted Amplatzer® devices, making measurements before and 6 months after implantation. *Results:* Electron microscopy showed an intact titanium oxide layer with no evidence of corrosion in vitro and in vivo. One explanted device in direct contact with the platinum leads of a pacemaker for eighteen months showed minor pitting of the titanium oxide layer believed to be galvanic in nature. No wire fractures were found in vitro after cycle testing with 400 million cycles, nor in devices taken from the animals and humans. Biochemical studies showed no significant elevation of levels of nickel levels after implantation. *Conclusion:* Nitinol wire of Amplatzer® septal occlusion devices is resistant to corrosion when exposed to physiologic saline solution, and in experimental animals as well as humans. A device in contact with a platinum pacemaker electrode developed minimal pitting of the titanium oxide layer, believed to be galvanic in nature and of no structural or clinical significance. There is no increase of concentrations of nickel in the blood of patients who have received Amplatzer® nitinol devices. These favorable testing results reveal that nickel-titanium is an inert, corrosion resistant alloy.

Keywords: Nitinol; prosthesis; corrosion-biological

NITINOL, A NICKEL–TITANIUM ALLOY, HAS become a valuable material in the production of endoluminal devices because of its super elasticity/pseudo-elasticity, high resiliency, thermal shape memory, and fatigue resistance. Its nonferrous magnetic properties allow magnetic resonance imaging. These physical properties allow the construction of large devices that can be introduced through small catheters. The composition of nickel–titanium varies considerably, ranging from 54 to 60% of nickel per weight. Consequently, corrosion resistance may vary from one alloy to another.

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Investigators have shown corrosion on the surface of Nitinol wire after long term immersion in 1% sodium chloride solution at 37°C,[1,2] and when subjected to oral fluid.[3–6] This corrosion raised the question of nickel toxicity when the metal is implanted into the human body[7–9] even though no literature or case studies have reported such toxicity. The objective of this investigation is to evaluate for the first time the long-term corrosive behaviour of nickel in Amplatzer® devices in experimental and biological environments.

## Methods and materials

### *Experimental study*

We immersed 240 Amplatzer® Septal Occluder devices, AGA Medical Corp., Golden Valley, MN, of various sizes, and made from Nitinol wires 0.004–0.075 inch in diameter, in saline solution at 37°C, subjecting them to cycle testing of 400 million cycles for fourteen months. From the samples, 64 were randomly selected and cleaned in an ultrasonic bath before being examined by electron microscopy up to 5000 times magnification.

### *Biological studies*

Two Amplatzer® Muscular Ventricular Septal Occluders were used to close two surgically created defects in a dog. After eighteen months, a postmortem examination was performed. The completely epithelialized devices were explanted and cleaned by prolonged boiling in water and an ultrasonic bath. Both devices were examined by scanning electron microscopy. In a second dog, a surgically created abdominal aneurysm was repaired percutaneously by inserting a Nitinol graft composed of the same alloy used in all Amplatzer® devices. Follow-up angiography showed complete exclusion of the aneurysm with no endoleaks. The animal was sacrificed three years after placement of the graft and a postmortem examination performed. The graft was excised and cleaned by prolonged boiling in water and an ultrasonic bath. The device was examined by scanning electron microscopy.

### *Human studies*

A sixty-year-old patient with dilated cardiomyopathy, severe left ventricular dysfunction and a moderate sized atrial septal defect was evaluated for cardiac transplantation. It was anticipated that his atrial shunt might lead to increased pulmonary hypertension, making the patient a less suitable candidate for cardiac transplantation. His atrial septal defect was successfully closed with a 20 mm Amplatzer® Septal Occluder device. Follow-up echocardiograms confirmed complete closure of the communication. He was placed on systemic anticoagulation of Warfarin and continued his congestive heart failure therapy. Despite medical and radiological interventions, his ventricular function deteriorated. In June 1999, cardiac transplantation was performed nineteen months after insertion of the septal occluder. The septal device was excised and cleaned by prolonged boiling in water and ultrasonic cleaning bath. It was carefully examined by scanning electron microscopy up to a magnification of 5000.

A second patient, 63 years old with coronary arterial disease and a large atrial septal defect underwent coronary arterial bypass in 1983. On February 26, 1998, further coronary arterial surgery was needed, along with replacement of the mitral valve, because of progressive coronary insufficiency with severe mitral insufficiency and congestive heart failure. His large atrial communication was closed surgically at the same time. A postoperative echocardiogram demonstrated a significant residual atrial shunt and marked tricuspid insufficiency. A Ventech ICD dual chamber pacemaker was placed on March 5, 1999, and functioned perfectly. A 20 mm Amplatzer® Septal Occluder device was placed in the residual defect without problems and with normal performance of the dual chamber pacemaker. There was no residual shunt after device placement. His cardiac condition worsened, however, and in June 1999, 18 months after implantation of the device, he died from underlying left ventricular dysfunction and the heart was obtained for autopsy. An experienced cardiovascular pathologist examined the excised heart grossly and microscopically. Several wires were removed from the device, which were cleaned by prolonged boiling in water and an ultrasonic cleaning bath. The wires were closely examined by scanning electron microscopy up to a magnification of 5000.

### *Bench testing*

Electrical bench testing was studied to explain the surface pitting encountered on one of the devices. Figure 1 shows the scheme of the equipment setup for measuring the open circuit potential.

The setup consisted of a Solartron, SI1287 Potentiostat and three-electrode test cells. The three electrodes included a Nitinol wire as the working electrode, a carbon counter electrode, and a saturated calomel reference electrode. The test cell contained about 300 ml of unbuffered Ringer's solution. The solution was maintained at 37°C with a water bath. The open circuit potential was measured between the Nitinol wire and the reference electrode. The polarization curve measured the currents of various

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potential while applied under a potential scanning rate of 2 mV/s.

*Biochemical study*

Amplatzer® Occluders were placed in 19 patients, aged from 2.3 to 34.5 years, with a mean of 11.3 years, standard error of the mean ± 1.9, and a median of 9.5 years. They weighed from 11.7 to 134.0 kg, with a mean of 39.4 kg, standard error of the mean ± 5.8, and a median weight of 32.7 kg. Of the devices, 3 were Amplatzer® Ductus Occluders, of sizes varying from 4 to 24 mm. One was in a patient with a patent arterial duct, and two in a patient with an axillary arterial fistula. We also placed 17 Amplatzer® Septal Occluders, 15 in patients with atrial septal defects, and two in patients with fenestrated Fontan circulations. Blood was collected prior to placement, and again six months later, for analysis of trace elements by inductive plasma mass spectroscopy.

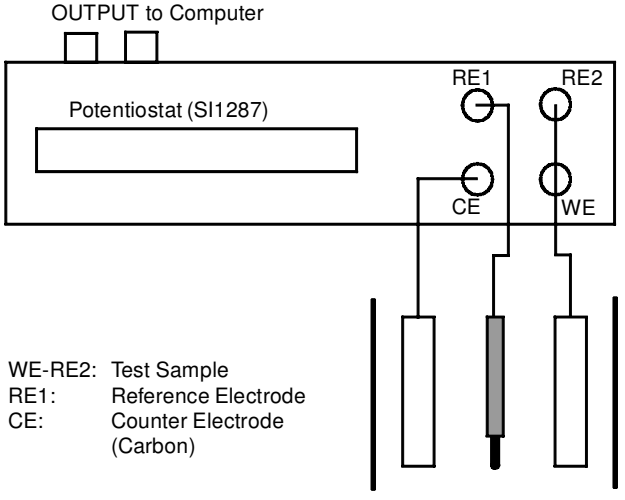


**Figure 1.**
*Scheme of the open circuit potential of Nitinol wire immersed in Ringer's solution at 37°C set for measuring/recording.*

## Results

*Experimental study*

After cleaning the devices, they appeared like new, with no evidence of corrosion or wire fractures. Scanning electron microscopy revealed an intact post and screw attachment of the device that is made of 316L stainless steel. Examination at 3000 times magnification showed an intact layer of titanium oxide indistinguishable from control (Fig. 2).

*Animal studies*

Gross examination of the heart from the first dog revealed complete closure and coverage of both devices by neoendocardium. Electron microscopic examination of the cleaned devices revealed an intact layer of titanium-oxide on the surface of both devices without evidence of corrosion or wire fractures (Fig. 3).

Gross pathologic examination of the second dog revealed the graft to be covered by a thin layer of neointima, with complete thrombosis of the abdominal aneurysm. After cleaning, the graft appeared intact. Scanning electron microscopy showed an intact layer of titanium oxide on the surface of the wires, with no corrosion, and no fractures.

*Human studies*

Upon gross examination in the first patient, the right atrial disc was completely epithelialized (Fig. 4a).

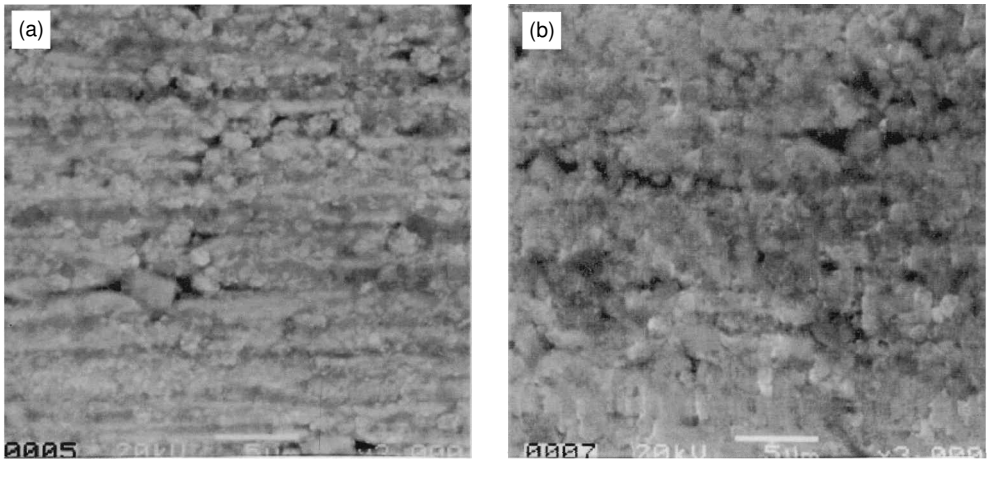


**Figure 2.**
*Scanning electron micrograph on the surface of (a) a test wire and (b) a new control wire. Magnification of 3000 times shows that both surfaces are indistinguishable, demonstrating the intact and characteristic layer of titanium oxide.*

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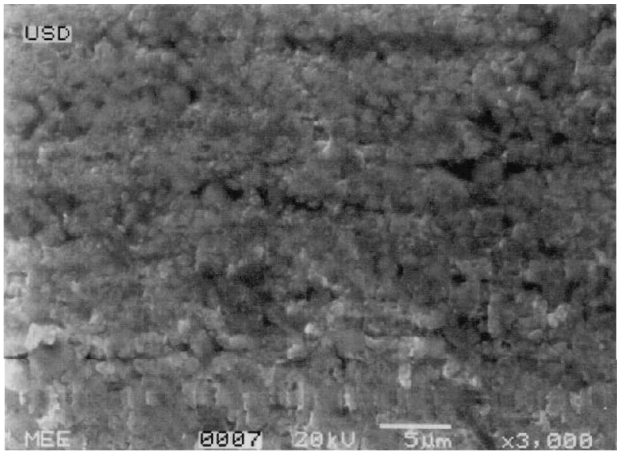


**Figure 3.**
*Surface of an explanted Amplatzer® Muscular Ventricular Septal Occluder from a dog shows no evidence of corrosion, with an intact layer of titanium oxide seen at a magnification of 5000 times.*

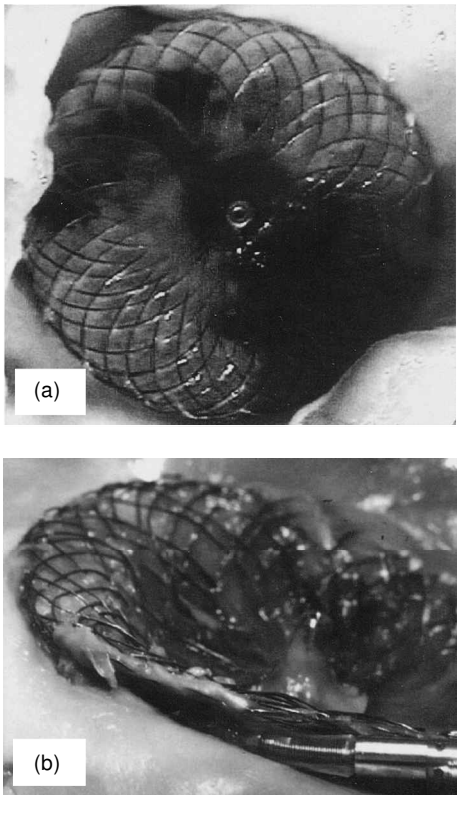


**Figure 4.**
*(a) Close-up view of an Amplatzer® Septal Occluder Device in place 19 months after implantation in our first patient. The device is covered by a thin layer of neoendocardium except for the small central post. (b) Close-up view of the Amplatzer® Septal Occluder Device implanted in our second patient. The prosthesis is completely endothelialized except for the small central post, where it is in close contact with the platinum pacemaker lead. The pacemaker functioned normally.*

The left atrial disc was covered with well formed pannus around the periphery. Towards the center, the epithelium was much thinner and around the central "post" there was an area of about 1 cm where the Nitinol wires were exposed and still "free" from the underlying organized tissue on the polyester disc within the device. Scanning electron microscopy revealed an intact layer of titanium oxide with no evidence of corrosion.

The device inserted in the second patient was completely epithelialized on gross inspection. The right atrial disk was in intimate contact with the bipolar electrode of the pacemaker (Fig. 4b). After cleaning, the device appeared mechanically intact with no wire fractures and no evidence of surface corrosion. At 5000 times magnification, however, "pitting" was found on the surface of the wires, indicating localized breakdown of the layer of titanium oxide typical for corrosion (Fig. 5).

### *Bench testing*

The open circuit potential E of the Nitinol wire was found to be −0.05 V, and the E value of the platinum wire was 0.25 V. The pitting potential of Nitinol was 0.08 V. The negative E value of the Nitinol wire relative to the platinum indicates that a galvanic cell can be formed with the Nitinol wire being the base and the platinum being the noble metal. When the platinum electrode was placed in contact with the Nitinol wire, a sudden increase of current resulted, which indicates the start of pitting corrosion.

### *Biochemical study*

The mean level of nickel before placing the devices was 65.8 nmol/L, with a standard error of the

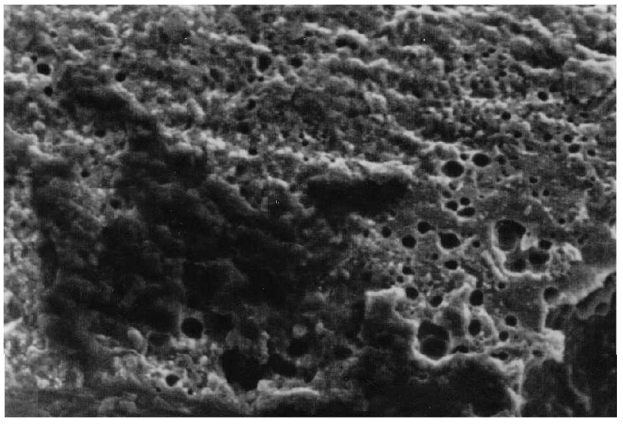

**Figure 5.**
*Scanning electron micrograph of the explanted Amplatzer® Septal Occluder Device in our second patient. Scanning electron micrographic study of the surface of the wire demonstrates tiny "pits" typical for minimal corrosion of the superficial layer of titanium oxide.*

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mean ± 6.3, and a median of 71.0 nmol/L. Six months later, the level was was 68.3 nmol/L, with the standard error of the mean ± 4.8, and the median 71.5 nmol/L. There was no significant difference in these levels before and after placement of the Amplatzer® Occluders. There was no clinical evidence of nickel toxicity in any patient.

## Discussion

Metallic implants are by far the oldest materials used in medicine, going back to the sixteenth century. For the past one hundred years, nickel-containing alloys including stainless steel have been part of the daily surgical armamentarium. Examples of the use of stainless steel in surgery are pacemaker wires, vascular clips, cardiac valves, all surgical instruments, orthopedic prostheses, Harrington rods, inferior caval venous filters, and so on. Since the mid 1970s, such devices have gained application in interventional radiology, including vascular occlusion coils, vascular stents, aneurysm prostheses, and venous filters. Toxicity to stainless steel has not been an issue. Nitinol, a nickel–titanium alloy, has now replaced stainless steel in some devices. The unique properties of nickel–titanium, such as its super elasticity and pseudo-elasticity, allow the introduction of large devices through small catheters without deformation. The thermal shape memory provides reconfiguration of the original shape at body temperature. The nickel content of this alloy varies from 54% to 60%, compared to 14% for stainless steel. The considerably higher content of nickel has raised the question of biocompatibility and nickel toxicity.

Contact allergic dermatitis to nickel is common in the general population, with an incidence ranging from 9 to 28.5%.[10,11] In the worldwide implantation of more than 6500 Amplatzer® devices, at least 600 patients would be expected to be allergic to nickel. To date, nonetheless, there has not been one single documented case in which the device had to be explanted because of nickel allergy. Documented allergy, therefore, is not a contraindication for implantation.

It was the resistance to corrosion which led the United States Navy to develop this alloy in the early 1960s, hence the acronym Nitinol: NIckel-TItanium-Naval-Ordinance-Laboratory. This resistance to corrosion limits its dissemination in the body. This is due to formation of a layer of oxide of titanium and nickel on the surface of the alloy. A new diamond drawn Nitinol wire has a very thin amorphous homogenous non-porous surface layer of titanium oxide, and to a lesser degree nickel oxide. The binding forces of titanium and nickel in Nitinol are very strong, effectively preventing release of more nickel ions into the body.[12] In laboratory testing, nickel–titanium has the same chemical stability and prominent anticorrosive property as titanium.[13] Results from cell cultures have shown that the toxicity of Nitinol is virtually identical to pure titanium.[13,14] In the heat treatment of Nitinol in Amplatzer® devices, a fairly thick oxide layer is formed on the surface.

The constituent elements of most so-called non-corrosive implants can be demonstrated in the surrounding tissue, even if microscopic corrosion of the implant is not demonstrable. The fibrotic tissue reaction around the implant is directly proportional to the amount of ions released from the implant. Stainless steel may result in a fibrotic capsule up to 2 mm, while nickel–titanium causes only a minimal fibrotic layer, suggesting that more nickel ions are released from steel. Slow passive dissolution of nickel ion from the protective oxide layers takes place in even the most corrosion resistant, passivated metals.[13,15–18] This is so minimal that it is of no clinical significance.

To determine whether or not nickel toxicity is an important consideration for Nitinol devices, we performed four separate studies: experimental testing of corrosion, scanning electron microscopy of explanted animal devices, scanning electron microscopy of explanted human devices, and changes in concentration of nickel in the blood six months after implantation of Amplatzer® devices.

Our experimental study clearly demonstrates that Nitinol in Amplatzer® devices is resistant to corrosion when exposed to 0.9% saline solution for a prolonged period of time. Our findings are different from those of published studies.[1,2] The composition of Nitinol in Amplatzer® devices and these previous studies is similar, 55% nickel, although the suppliers are different. We speculate that the improved resistance of Amplatzer® devices to corrosion is related to surface properties of the metal. The wire tested for corrosion in the published studies[1,2] was polished, which removes much of the titanium and nickel oxides coating Nitinol wires after normal wire-drawing and -pickling processes. The heat curing which shapes Amplatzer® devices further thickens the oxide coating, and may provide additional protection against corrosion. Whatever the cause, Amplatzer® devices clearly have superior resistance to corrosion following long-term immersion.

The data from our implants in dogs and one of our patients clearly prove there is no corrosion of this alloy in a biologic environment. Even after three years, the layer of titanium oxide on the implants was found to be completely intact when examined at 5000 times magnification. It is, therefore, reasonable to assume that this alloy will never corrode once implanted in the body. This assumption is also supported by the fact that the difference between the

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resting potential and breakdown potential of the layer of titanium oxide is so great that this alloy, or other titanium containing alloys, should never corrode in body fluids.[6,16,19]

The results from our second patient were a surprise. Although the device was covered by a thin layer of neoendocardium, and looked normal and intact upon examination at low magnification, localized "pitting" considered to be corrosion was observed at 5000 times magnification. The difference between this case and all other implants was contact with a pacemaker lead. The leads of this particular pacemaker are made of 90% platinum and 10% iridium. It was logical to assume a causative connection of this pitting with the metal-to-metal contact of the implant and the electrodes.

It is well known that two metals of different potential immersed in an electrolyte solution form a galvanic cell, with the less noble metal being the base or anode, and the noble metal being the cathode. For example, if a stainless steel wire is gold plated, it is protected from corrosion. If the gold layer is severed by a crack or scratch, a galvanic corrosion of stainless steel will occur, and the gold plating may then make the stainless steel wire more corrosive.[19] In the case of Nitinol, a breakdown of the layer of titanium oxide may also occur, but this breakdown is not uniform and results in typical local corrosion referred to as "pitting". In order to prove this hypothesis and that the results in our second patient are indeed of galvanic origin, laboratory tests were carried out.

These showed that, when a Nitinol stent contacts platinum, a galvanic cell is formed between them. The galvanic cell results in an anodic current in Nitinol, which may cause the Nitinol to corrode if the current exceeds the tolerance level of the material. These results indicate that the contact with platinum could induce pitting corrosion by pushing the potential of Nitinol to a value above its pitting potential. Even if this minimal surface corrosion is estimated to be about 1%, certainly an enormous over-estimation, the daily additional nickel burden would be only 0.007 mg since the 20 mm Septal Occluder device weighs only 714 mg. This is 1.4% of our daily nickel intake.

Finally, biochemical studies carried out in 19 patients showed no change in concentration of nickel in the blood 6 months after implantation of Amplatzer® devices. This strongly supports the results of the experimental studies in dogs and humans.

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