Paper No.
07674

NACE INTERNATIONAL CORROSION 2007 CONFERENCE & EXPO

AN ASSESSMENT OF ASTM F 2129 ELECTROCHEMICAL TESTING OF SMALL MEDICAL IMPLANTS - LESSONS LEARNED

Shari Nathanson Rosenbloom, Ph.D.
Corrosion Testing Laboratories, Inc.
60 Blue Hen Drive
Newark, DE 19713

Richard A. Corbett
Corrosion Testing Laboratories, Inc.
60 Blue Hen Drive
Newark, DE 19713

ABSTRACT

Much has been learned over a short period of time with respect to the corrosion assessment of small medical implant devices. Laboratory testing started with modifications of ASTM G 5 and G 61, which lead to the development of ASTM F 2129, and thence the fine-tuning of that specification to meet the intent of the FDA Guideline for non-clinical tests. The changes in electrochemical testing protocol with time are reviewed. Comparative data is presented addressing test environments, scan rates, statistical replication, alloy response, and acceptance criteria.

Keywords: ASTM F 2129, pitting corrosion, cyclic potentiodynamic polarization, *in vitro* testing

INTRODUCTION

The human body presents an aggressive environment for devices that are implanted within it. When developing a new device, the designers must not only assure that the device will function as intended, but also that it will tolerate the biological environment in such a way that it neither adversely impacts the host, nor is, itself, adversely impacted. Before getting approval to market a new device, a manufacturer must demonstrate to the Food and Drug Administration that, among other things, the implant will be able to withstand this environment, especially as related to corrosion. Corrosion in the body is particularly dangerous because it can affect the implant's ability to function (e.g. loss of mechanical integrity) and can evoke an unwanted, and potentially serious, host response (e.g. inflammation, allergy, toxicity). Pitting corrosion can be particularly dangerous for small devices (e.g. stents) whose functional integrity could be easily compromised by a single large pit. While there are several test methods used to determine corrosion resistance, one standard, ASTM F 2129, has been developed specifically to assess a small implant's resistance to pitting and crevice corrosion in its intended

environment. The development of this standard and some key issues with regard to testing protocol are discussed below. In addition, areas for continued research and discussion are highlighted.

DEVELOPMENT OF ASTM F 2129

ASTM F 2129 was developed as a tool to assess the susceptibility of small medical implant devices to localized corrosion (crevice and pitting) in a simulated physiological environment. Standards such as ASTM G 5[1] and ASTM G 61[2], which were used to standardize equipment and methods for making electrochemical measurements and for assessing corrosion susceptibility of various alloys, were determined to be too broad for practical use when assessing medical implant devices. Factors such as standardization of testing solution, relevant pH, and temperature needed to be addressed in order to assess the corrosion resistance of a device intended for service in the human body. In addition, certain alloys depend on the state of their surfaces for corrosion resistance. Therefore, processing conditions can greatly affect the performance of a material. ASTM F 2129 was developed in response to these specific issues. Whole devices, in their final form and surface finishes, are tested in a simulated physiological environment over a relevant range of potentials.

Overview of Testing Methodology

ASTM F 2129 is a cyclic potentiodynamic test. In this test, the implant (working electrode) is exposed to the test solution in a cell fitted with a reference electrode (saturated calomel electrode, SCE) and a counter electrode. A potentiostat is connected to these three electrodes, and the potential of the working electrode, with respect to the reference, is scanned through a voltage range from negative to positive, and then reversed to its starting potential. The resulting current between the working and counter electrodes is recorded. This scan is then plotted on a semi-log graph, which allows the resulting curve to be analyzed for key-point voltages and currents.[3]

In order to perform the test, an electrical wire is connected to the implant. This wire allows an electrical connection to the potentiostat, as well as suspension in the test solution. Partial masking of the specimen at the point of attachment is required to isolate the metal-to-metal contact of the device to the wire. This is intended to eliminate the possibility of any galvanic interference. The device is inserted into the test cell, which is filled with sufficient solution so that the suspended specimen remains below the surface. A simulated physiological solution is chosen for use as an electrolyte during testing, based upon the ultimate usage of the device in the body. pH is measured and recorded before and after the test.

Initially, the test solution is purged with nitrogen for a minimum of 30 minutes. The test specimen is immersed in the solution, connected to the potentiostat and the test is started. After an equilibration period at open circuit (E_r)[(1)], a potentiodynamic scan is initiated at a pre-determined scan rate. The total potential is recorded throughout the scan and the potential vs. log current density data is plotted. At a predetermined maximum potential (E_v) or current density (caused by breakdown, E_b), the scan is reversed. The test is terminated when the current density during the reverse scan falls below the value measured in the passive state during the forward scan (repassivation, at E_p) or when the initial potential is reached.

After the test, the implants are microscopically examined to determine the presence of localized attack. Potential vs. log Current is plotted and E_r at the end of the equilibration period, as well as E_b, E_p, and E_v, as appropriate, are determined and reported, Figure 1.

The details of the testing protocol (such as equilibration time, starting potential, reversing potential, and scan rate) have been refined as the standard has been developed and are discussed below.

---

(1) All references to potential are vs. SCE

Early Versions of ASTM F 2129 up to –03

The standard was initially adopted in 2001[4] with a revision issued in 2003. An in-depth review of the initial standard and the 2003 revision was previously published[5]. A few relevant key points in the development of the standard, up to the 2003 revision, are presented below.

Initially, many testing laboratories used Hanks solution as an electrolyte. However, it was found that the pH of Hanks solution was not stable during the test and that calcium and magnesium precipitated out of solution onto the test specimen and the vessel. In the 2003 version, PBS (phosphate buffered saline) was specified as the standard solution for testing, although other solutions were allowed. The standard included formulations for PBS, Ringer's and Hanks solutions, as well as for two different simulated bile solutions. Testing parameters were as follows. The equilibration period at open circuit was set to one hour. The starting potential was fixed at 100 mV negative of open circuit, a remnant of other electrochemical testing methods in which Tafel curves were calculated (although Tafel calculation was never part of ASTM F 2129). A choice of scan rates was allowed: 0.167 mV/sec or 1 mV/sec, although users were cautioned not to compare data collected at different scan rates. The vertex potential (E_v), which would be used to define the potential reversal point in the absence of a breakdown, was fixed at 1V.

ASTM F 2129-04

The 2004 revision of the standard introduced two changes. Reference was made to ASTM F 1828[6], "Specification for Ureteral Stents", as an acknowledgement of the need to test devices intended for use in the urinary tract. In addition, two formulations for artificial urine as a testing solution were included in the standard.

In addition, the previous version of the standard, (2003), required a nitrogen purity (for gas purge) of 99.999%. In the 2004 revision, the minimum purity for nitrogen gas was specified at 99.99%.

ASTM F 2129-06

Three significant changes were made in the 2006 revision of the standard: a choice of open circuit hold time criteria was given, the starting potential was changed to be equal to the potential measured at the end of the open circuit hold time (as opposed to 100 mV cathodic to E_r), and the vertex potential was lowered to a minimum of +800 mV (from +1000 mV).

Previously, a one-hour hold at open circuit was specified prior to starting the test. The 2006 revision introduced a choice in protocols. While holding at open circuit for one hour is still allowed, an option of holding until the rate of potential change with time is less than 3 mV/minute is given. This option, if selected, can significantly decrease overall testing time.

Changing the start of the potential sweep to E_r instead of 100 mV cathodic to E_r, removed a vestige of this protocol that related to other electrochemical testing standards (e.g. ASTM G3)[7], in which Tafel slopes are calculated. These require both cathodic and anodic portions of the curve to be present. Tafel slopes are not calculated in ASTM F 2129, and therefore the cathodic portion of the curve is not needed for this purpose. In addition, an earlier version of ASTM F 2129 required the reporting of E_{zc} (zero current potential) and the corrosion current (i_{corr}), two parameters which are no longer reported. Therefore, the 100 mV cathodic polarization upon start up no longer served to generate data that was necessary to this testing protocol.

The 2006 version of the protocol also allows for reversal at a lower potential, in the absence of breakdown. Previously, the reversal potential was fixed at +1000 mV. As the purpose of this test is to determine the propensity for pitting in the biological environment, it is important to keep in mind what the realistic parameters are of that environment. A limited amount of data has been published for the

rest potentials of implant materials *in vivo*[8,9]. The published data suggests that rest potentials *in vivo* are less than +400 mV (much of the data was much lower than this value). In addition, oxygen evolution and hydrolysis of water may occur at potentials at about +800 mV, resulting in increases in current, which could be incorrectly interpreted as being related to breakdown. Since potentials at or above +800 mV are not physiologically relevant, it was determined that a reversing potential of +800 mV was sensible, although higher potentials are permitted.

COMPARATIVE DATA

Test Environment

The test method is intended to determine the susceptibility of an implant to pitting and/or crevice corrosion in its intended environment. As corrosion response is influenced by pH, temperature, and electrolyte, it is important to carefully consider the testing solution when designing a study. ASTM F 2129 allows for a variety of different testing solutions, depending on the final application. In addition, pH can be adjusted to better represent the final biological application. Temperature is fixed at 37 ± 1°C during testing.

Which simulated physiological solution will be the most aggressive is not always obvious. In addition, devices, such as stents, may be initially marketed for a particular end use (e.g. biliary) and, subsequently, used in another system (e.g. cardiovascular). Therefore, it is sometimes prudent to test in several different environments. An example of a testing program that highlights some of these concerns is given below.

A device manufacturer wanted to test the corrosion resistance of their nitinol stents, which would be used in both biliary and cardiovascular applications. Finished stents were submitted for testing in both PBS and reconstituted bile. Results from the testing were dramatically different for the each testing media (Table 1). Representative Potential vs. log Current curves are presented in Figure 2.

Scan Rates

One of the limitations in performing the ASTM F 2129 test on a large number of samples is the duration of the test. When first published, the standard recommended a scan rate of 0.1667 mV/sec, although a faster scan rate of 1 mV/sec was permitted. A typical test conducted using the slower scan rate could take as long as 6 hours for each sample. Given the need to test multiple samples (due to the statistical nature of pit initiation), this meant that testing a single sample set could take days or even weeks. Later versions allowed for either scan rate to be used, however a cautionary statement was included that warned against comparing data collected at different scan rates. Recently, a study was undertaken to better understand the influence of scan rate on breakdown potentials.[10] In this study, Type 316 LVM stainless steel and nitinol samples were tested in PBS at the two different scan rates. [Note: initial potential was also varied, according to the different versions of ASTM F 2129, such that the slower scan rate tests were started at 100 mV cathodic to open circuit and the faster scan rates tests were started at open circuit. Testing was performed at two different laboratories.] Statistical analysis of the data found that there were no statistically significant differences between the breakdown potentials measured at the different scan rates for either material tested.

Alloy Response

Corrosion of metals is an electrochemical process, which is dependent on a number of factors including testing media (electrolyte), temperature, pH, and potential. In a given solution and at a set temperature, a metal may exhibit immunity (non-corroding) or active (corroding) behavior, dependent on the potential.[11] In addition, there will be a range of potentials over which the material may exhibit passive behavior. Within this range of potentials, whether or not a material will behave as active or passive will depend on the quality of its protective surface oxide.

Materials such as gold and platinum will be immune to corrosion at the temperature, pH and range of potentials found in the biological environment, and would therefore not be expected to corrode. Other materials, such as zinc, will actively corrode in this environment, and would not be suitable for use in the human body. Materials, such as type 316 stainless steel and nitinol, fall into the category of "active/passive" materials, meaning that they may or may not corrode in the biological environment. A variety of results would be expected from the testing of these materials and these results would be highly dependent on the processing conditions and the integrity of the surface oxide.[12,13] ASTM F 2129 is an excellent tool for assessing the corrosion resistance of devices made from these materials, and is specifically designed to determine the potential at which breakdown will occur.

ACCEPTANCE CRITERIA

ASTM F 2129 does not include an acceptance criterion. It is up to the device manufacturer to interpret the results of the testing and justify their conclusions. The challenge is to determine how to interpret results gathered *in vitro* such that *in vivo* behavior can be predicted. Certainly, other assessment tools exist, such as the use of predicate devices, clinical trials, and explanted specimens. If a device is found to be acceptable in service through clinical trials, the ASTM F 2129 test can be performed on that material and a mean breakdown potential identified. Subsequently, material that would perform at or above this level in the testing could be considered acceptable. However, many device manufacturers do not have the ability to perform lengthy (and costly) clinical trials. In addition, sometimes a predicate device is not available for comparison. In those cases, the *in vitro* testing must be relied upon to determine suitability for implantation.

In order to determine an acceptance criterion, it is important that the biological environment be as completely understood as possible. Temperature and pH are reasonably well understood, and easily measured. However, the *in vivo* rest potential of various materials is not as readily determined, and a limited amount of published data exists. Furthermore, *in vivo* rest potential measurements will be dependent on the specific environment in which they were measured, e.g. within muscle or in the cardiovascular system. A comprehensive study has not yet been published. Hoar and Mears[6] and Shih[7] have published some data, although it was gathered in several different environments. This data suggests that rest potentials for type 316L stainless steel could be as low as –380 mV or as high as +300 mV, for cobalt-chromium alloys in the +250 to +350 mV range, for titanium in the +400 to +500 mV range, and for nitinol anywhere from –420 mV to +20 mV, depending on oxide film structure.

A method of determining the susceptibility to breakdown has been proposed that relies on the difference between measured *in vitro* corrosion potential and breakdown potential.[14] However, when applied to the biological environment, this method does not address the *in vivo* potential that may be seen by an implant. As an independent laboratory, relying solely on *in vitro* tests, we have developed a conservative acceptance criteria, which we apply broadly to all materials tested according to ASTM F 2129[5, 12]. The criterion is based on the fact that the published *in vivo* data suggests that most biological rest potentials fall somewhere below 300 mV. Material to be implanted in the body must be able to withstand potentials as high as might reasonably be expected. In addition, given the gravity of the consequences of a failure due to corrosion, including a safety margin is appropriate. Therefore, it is our opinion that material that consistently exhibits resistance to breakdown at or above +600 mV should be considered acceptable with regards to its corrosion resistance. Considering that, much above this potential, oxygen evolution and hydrolysis of water occurs, we feel that this represents a very conservative threshold criterion. Material that exhibits breakdown potentials below +300 mV is considered unacceptable, as this material might reasonably be expected to perform in an environment where such potentials could exist. Material that exhibits breakdown potentials below +600 mV, but above +300 mV, would be considered marginal and more testing would be required in order to determine whether it would truly be fit for service in the biological environment.

It should be noted that the repassivation potential is not addressed in either of the two proposed acceptance criteria discussed above. The data gathered thus far has shown wide variability in the repassivation potentials recorded for material in a single sample set, with some specimens showing repassivation and others, whose current densities remain high during the entire reverse scan, showing no repassivation. In addition, repassivation potentials often fall within the range of potentials that we would consider "unacceptable" (based on the published *in vivo* rest potential data). The interpretation of repassivation potential, vis a vis the ASTM F 2129 standard, and its significance to a material's performance in the biological environment require further investigation and discussion.

STATISTICAL REPLICATION

It has long been recognized that pitting is a stochastically controlled phenomenon.[15,16] Because of this, and because ASTM F 2129 is specifically designed to test for pitting, multiple samples must be run in order to gain an understanding of the behavior of the material being tested. Once an acceptance criterion has been established, the goal of the testing program would be to characterize the implant material and determine whether it meets the criteria. Presently, just as the standard does not address a specific pass/fail acceptance criterion, neither does it address the issue of sample set size. The burden falls on the device manufacturers to justify their conclusions as to the biocompatibility (vis a vis corrosion resistance) of the material. A large sample set would give a higher degree of confidence in the calculated values for mean E_b, standard deviation, and the observed range of values. However, it can be costly to run very large sample sets, and, from an economic point of view, it would be prudent to determine the smallest sample set that would yield statistically valid data.

Presently, we recommend a starting sample set size of seven (7) replicates. Many times, the data gathered from a sample set of this size yields highly reproducible results, with reasonably low scatter and a small standard deviation, Figure 4. Other times, however, the data shows a great deal of scatter, Figure 5. In these instances, even if some of the breakdown potentials are high and would be considered acceptable, we would recommend either further testing to determine whether some of the lower values were outliers, or process changes in order to help make the material more uniform and/or more corrosion resistant.

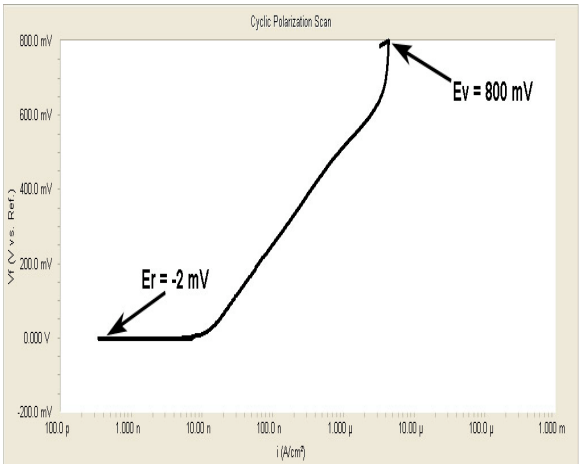
AREAS FOR FUTURE WORK

ASTM F 2129 has come a long way in its development as a standard for testing for implantable devices. As laboratories have gained experience working with the standard, running many hundreds of tests, much knowledge has been gained. Many issues, such as scan rate, testing environment, and open circuit equilibration time, have been refined as a result of discussion at the ASTM governing committee. However, there is still much work to be done. In particular, areas for future concentration would be sample set size, gaining a better understanding of the *in vivo* behavior of materials to help refine a universally recognized acceptance criteria, and gaining a better understanding of the significance of the repassivation potential. In addition, two issues which were not addressed in the present paper, but deserve attention nonetheless would be standardization of reference electrodes and gaining a better understanding of the effect of specimen size on E_b (given the stochastic nature of pitting) and, possibly, statistical scatter.

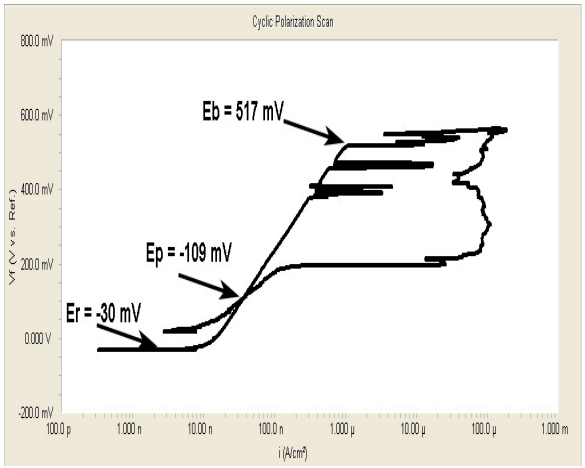
SUMMARY

ASTM F 2129 has been developed as a tool to assess the pitting and crevice corrosion propensity of small medical devices. Changes to the standard have been made as a result of practical experience and continued research, including Round Robin testing. The protocol attempts to address the realities of *in vitro* simulation of an *in vivo* application. Parameters such as appropriate testing media (simulated physiological fluids), scan rates, potential sweep range, and equilibration prior to testing have been studied and discussed at length in technical committee meetings. These discussions have guided the

revision process. The standard, however, is still evolving. Areas for future work include gaining a better understanding of *in vivo* behavior and relating that behavior to the results and interpretations of the ASTM F 2129 test, coming to terms with the issues related to standardization of reference electrodes, and determining an appropriate sample set size that would yield statistically significant results. In addition, the actual specimen size may have an effect on the testing results, and needs to be better understood. The standard does not address the issue of an acceptance criteria. Further discussion and research is still needed in order to better understand these issues and to continue to develop the standard to best serve the purpose for which it was intended.



No breakdown.



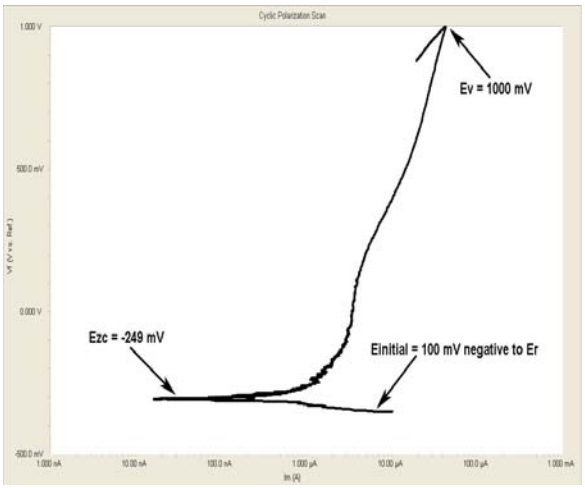
Breakdown at +517 mV.

FIGURE 1 - Typical Potential vs. log Current curves for Type 316L stainless steel. Note: testing conducted according to ASTM F 2129-06.

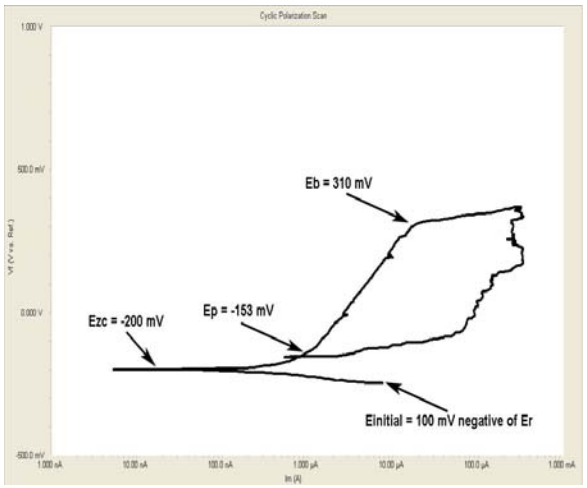
TABLE 1
RESULTS OF TESTING IN BILE AND PBS

Testing Media	pH (before/after test)	# Samples Tested	Average Eb*	Standard Deviation
Bile	6.2/5.2	7	1000 mV	0
PBS	7.4/7.4	7	266 mV	62

* Note: ASTM F 2129-04 protocol was used in this test. E_V = 1000 mV.



Testing in bile. No breakdown.



Testing in PBS. Breakdown at +310 mV.

FIGURE 2 - Potential vs. log Current curves for nitinol tested in bile and PBS solutions. Note: testing conducted according to ASTM F 2129-04.

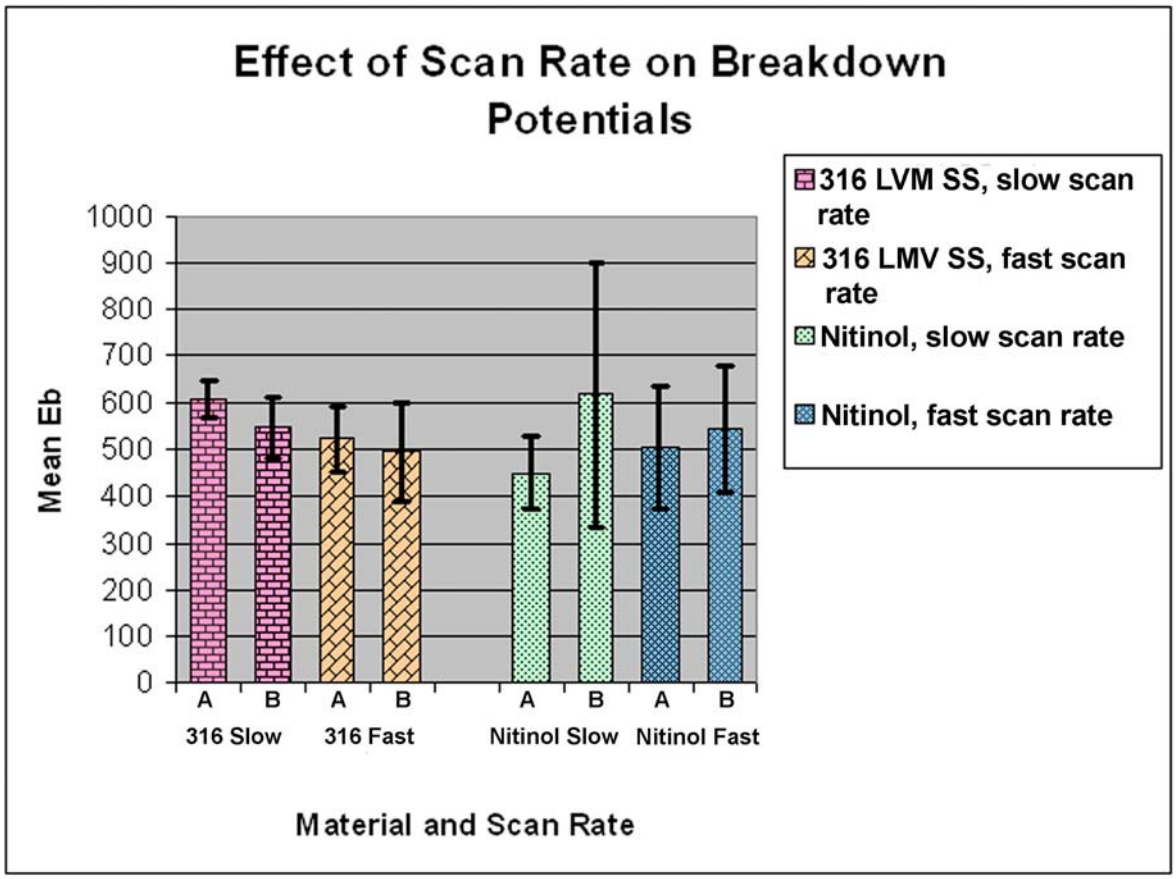


FIGURE 3 - Mean breakdown potential for Type 316 stainless steel and nitinol tested at different scan rates. Note: testing was done at two different laboratories, denoted A and B. Data adapted from [10].

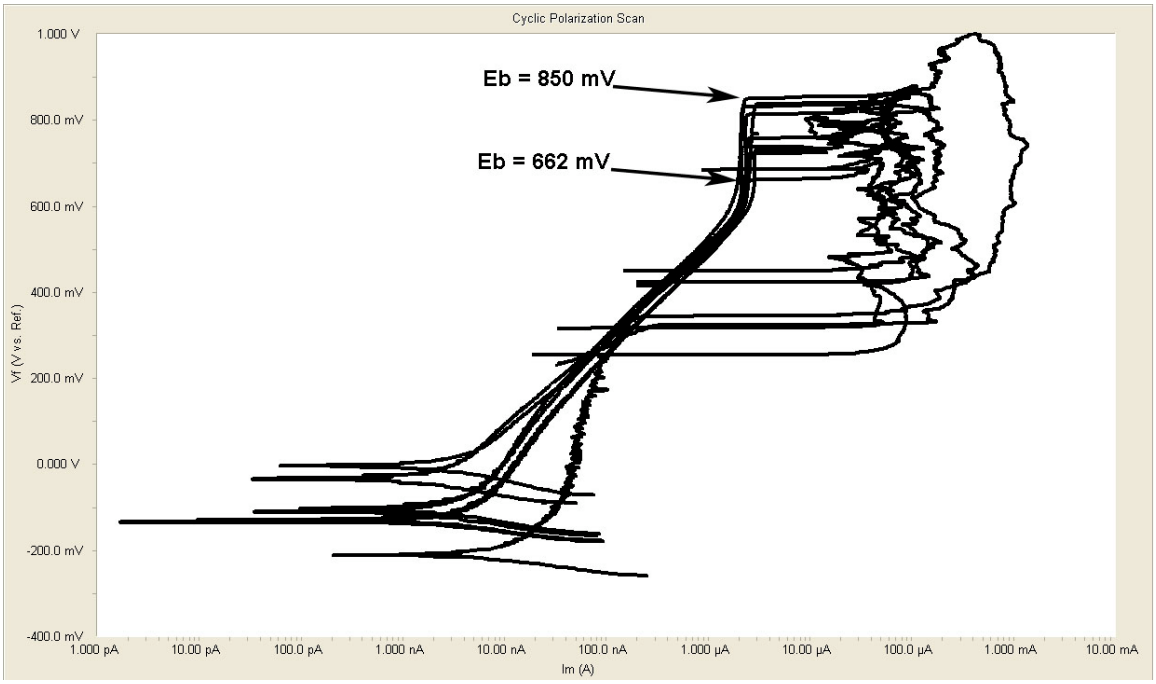


FIGURE 4 - Seven (7) tests with good reproducibility. Eb ranged from 662 mV to 850 mV. Mean was 783 mV and standard deviation was 69.
Note: tested conducted according to ASTM F 2129-04.

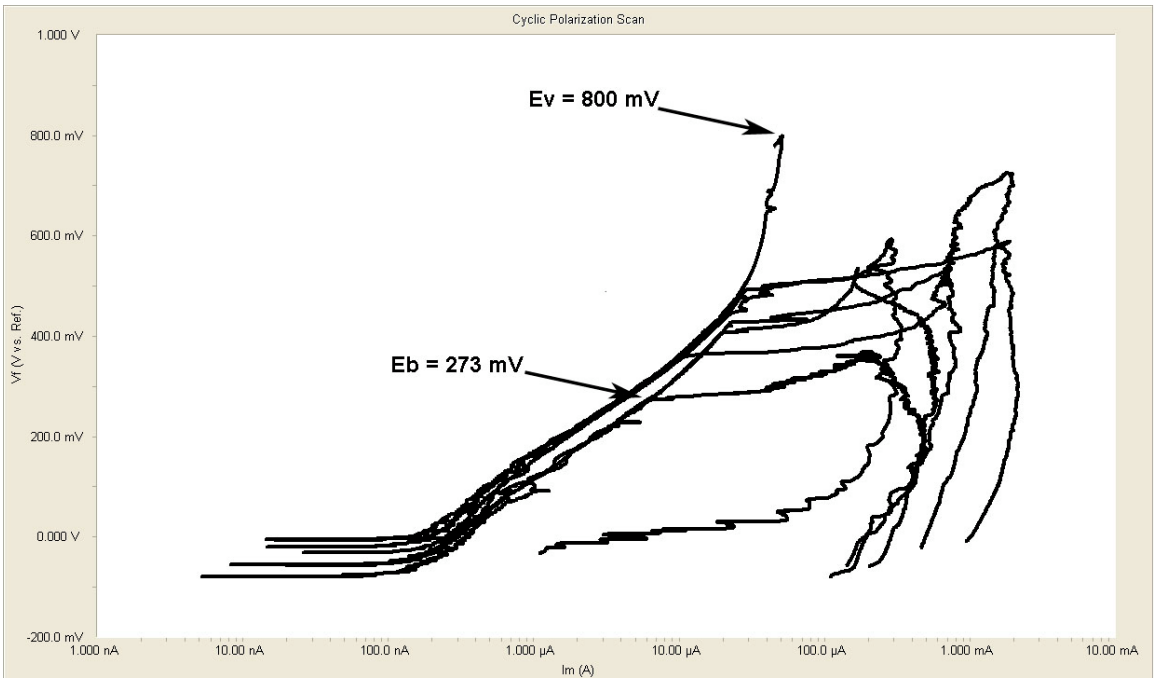


FIGURE 5 - Seven (7) tests with highly variable results, with breakdown as low as 273 mV. One sample was completely passive, going all the way to Ev = 800 mV. Mean was 466 mV and standard deviation was 167.
Note: tested conducted according to ASTM F 2129-06.

REFERENCES

[1] ASTM G 5-94 (2004). "Standard Reference Test Method for making Potentiostatic and Potentiodynamic Anodic Polarizaiton Measurements." West Conshohocken, PA: ASTM International; 1994 (Reapproved 2004).

[2] ASTM G-61-86 (2003). "Standard Test Method for Conducting Cyclic Potentiocynamic Polarization Measurements for Localized Corrosion Susceptibility of Iron-, Nickel-, or Cobalt-Based Alloys." West Conshohocken, PA: ASTM International; 1986 (Reapproved 2003).

[3] Report of ASTM F 2129 Testing, Corrosion Testing Laboratories, Inc., Newark, DE, 2006.

[4] ASTM F 2129-01. "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices." West Conshohocken, PA: ASTM International; 2001.

[5] Corbett, R.A. "*Laboratory Corrosion Testing of Medical Implants*" In: Shrivastava S, editor. Proc. Materials and Processes for Medical Devices Conf., Materials Park, OH: ASM International; 2004. p. 166-171.

[6] ASTM F 1828, "Specification for Ureteral Stents." West Conshohocken, PA: ASTM International.

[7] ASTM G-3-89 (2004), "Standard Practice for Conventions Applicable to Electrochemical Measurements in Corrosion Testing." West Conshohocken, PA: ASTM International; 1989 (Reapproved 2004).

[8] Hoar, T.P. and Mears, D.C., *"Corrosion-Resistant Alloys in Chloride Solution: Materials for Surgical Implants"*, Proc Royal Soc A, 294(1966)pp. 486-510.

[9] Shih, C.C., et al., *"Increased Corrosion Resistance of Stent Materials by Converting Current Surface Film of Polycrystalline Oxide into Amorphous Oxide"*, J. Biomed. Mater. Res., 52(2000)pp. 323-332.

[10] Warner, C.P. and Corbett, R.A., "*The Impact of Testing Methodology on Breakdown Potentials,*" in SMST 2006: Proceedings of the International Conference on Shape Memory and Superelastic Technologies. In Press.

[11] Pourbaix, M., *Lectures on Electrochemical Corrosion,* Plenum Press, New York, 1973.

[12] Corbett, R.A. and Rosenbloom, S.N.,*"An Assessment of ASTM F 2129 Test Results Comparing Nitinol to Other Implant Alloys",* in SMST 2006: Proceedings of the International Conference on Shape Memory and Superelastic Technologies. In Press.

[13] Trepanier, C., et al., *"Corrosion Resistance of Oxidized Nitinol"*, in SMST-2003: Proceedings of the International Conference on Shape Memory and Superelastic Technologies, Pacific Grove, California, 2003.

[14] Pound, B.G. *"Susceptibility of Nitinol to Localized Corrosion",* J. Biomed. Mater. Res., 77A(2006)pp. 185-191.

[15] Shibata, T., *"Statistical and Stochastic approaches to Localized Corrosion"*, Corrosion Science, 52:11(1996), pp. 813-830.

[16] Shibata, T. and Taketama, T., *"Stochastic Theory of Pitting Corrosion"*, Corrosion Science, 33:7(1977), pp. 243-251.