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Leading Opinion

Fatigue-life assessment and validation techniques for metallic vascular implants☆

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ABSTRACT

Vascular implants, such as cardiac valve prostheses, stents, and other devices are often subjected to complex loading conditions *in vivo*, which can include pulsatile pressure cycling, bending, torsion, tension, and compression, among others. At an average of 72 heartbeats per minute, pulsatile loading alone produces approximately 40-million cycles per year. With design lives of 10–15 years, fatigue performance assessment and validation of these devices are critical for the designer, as mechanical failure can have serious consequences. Historically, various fatigue life assessment approaches have been used to validate endovascular device fatigue performance, including durability testing, stress/strain-life analysis, and damage tolerance-based analysis. This paper explores the merits and shortcomings of each of these design approaches, and provides recommendations for fatigue-life validation of endovascular implants.

1. Background

Over one million vascular devices are implanted each year to provide relief to people with various medical conditions. Given that the US Food and Drug Administration (FDA), which has regulatory authority over such devices, recommends durability testing to the equivalent of 10–15 years of pulsatile loading [1] (400- to 600-million cycles at 72 heartbeats per minute), implant fatigue performance is of prime importance. The Bjork–Shiley Convexo–Concave heart valve failure issues experienced in the 1980s and '90s [2–4] underscore the importance of vascular implant fatigue performance and design validation. It has been estimated that fatigue fracture of various Bjork–Shiley design iterations resulted in approximately 600 fractures [3,4]. In 1990, it was estimated that approximately two-thirds of the failures resulted in patient death [2]. Given the large number of new vascular implant designs continually emerging on the market, appropriate fatigue assessment, and validation is critical for patient health and the vascular device industry.

The FDA provides guidance to medical device designers for non-clinical validation of intravascular stents and associated delivery systems [1]. This FDA stent-related guidance is also generally referenced for intravascular implants other than stents. The non-binding FDA recommendations include durability testing, typically conducted at a conservatively estimated *in vivo* loading condition, for the cyclic equivalent of 10–15 years (400- to 600-million cycles). At the end of durability testing, devices are examined to determine whether any fractures occurred; thus, resulting in a "pass/fail" acceptance criterion. The FDA guidance also recommends an analysis of stent fatigue resistance using "a Goodman analysis or another fatigue life analysis method" [1]. This process combines implant stress analysis results under estimated *in vivo* loading (typically obtained using the finite element method) with a stress- or strain-life fatigue analysis (e.g., Goodman analysis). The Goodman analysis (described in greater detail below) provides the designer a method to evaluate the combined effects of mean and alternating stresses on fatigue life.

Flaw-tolerant design, long used for large, easily inspectable components in industries such as power generation and aerospace, has occasionally been used for fatigue validation of specific implants such as heart valve struts and pyrolytic carbon occluder components [5–8]. Flaw-tolerant design incorporates linear-elastic fracture mechanics to predict whether or not flaws or defects will propagate as cracks and result in catastrophic fracture. Recently, journal articles have proposed damage-tolerant design approaches for small metallic vascular implants, such as stents [9–12].

This paper examines the benefits and shortcomings of the methods currently used by medical device manufacturers to assess and validate the fatigue performance of these long-term vascular implants.

☆ *Editor's Note:* This paper is one of a newly instituted series of scientific articles that provide evidence-based scientific opinions on topical and important issues in biomaterials science. They have some features of an invited editorial but are based on scientific facts, and some features of a review paper, without attempting to be comprehensive. These papers have been commissioned by the Editor-in-Chief and reviewed for factual, scientific content by referees.

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2. Component durability testing

Component durability testing is generally recommended by the FDA to help validate intravascular medical device designs [1]. Provided test loads adequately replicate *in vivo* conditions and sufficient specimens are tested to ensure statistical confidence, accelerated durability testing is an accepted means of demonstrating durability performance expected *in vivo*. In such tests, medical devices are typically deployed in a test fixture using a delivery process as close as possible to that expected in actual use. Because actual devices are used, implant conditions, such as surface roughness, heat treatment, plastic deformation during delivery, changes due to sterilization, etc., are incorporated in the test. Specimens are subjected to cyclic loads believed to represent *in vivo* conditions for the equivalent of 10–15 years of service. Cyclic loading imposed on test specimens is conducted at frequencies greater than the typical heart rate of 72 beats per minute (1.2 Hz). Test frequencies generally range from 20 to 100 Hertz, depending on specimen and test machine stability. Accelerated tests are often conducted in a simulated physiological environment, such as phosphate-buffered saline, Ringer's, or Hank's solution at 37 °C.

Ensuring that test loads adequately replicate *in vivo* conditions is one of the main challenges in design of durability tests. Limited availability of biomechanical data may lead to non-conservative assumptions regarding the mechanical environment facing an implanted device. Conversely, excessive conservatism in the design of durability tests may impose loads on test specimens far greater than those present *in vivo*, resulting in unrealistically low predictions of *in vivo* fatigue performance.

"Successful" accelerated durability tests do not result in device fractures or failures. Hence durability testing is "testing to success" rather than to failure. Incorporation of testing to failure allows the determination of important design information, such as safety factors, design margin, potential fracture locations, and unanticipated failure mechanisms. The high frequencies and shorter environmental exposure times inherent in accelerated tests may result in less corrosion fatigue damage than an equal number of cycles at a slower (physiological) frequency [13]. Therefore, tests for corrosion performance are recommended in addition to durability testing.

3. Stress/strain life

Wöhler, in the 1850s, first established that increased cyclic stress corresponded to decreased fatigue life, and created stress-life (S-N) curves [14]. In the mid-1950s, Coffin and Manson each independently developed essentially the same strain-life (ε-N) relationship for cyclic strains in the plastic regime [15]. Subsequently, many other investigators extended the Coffin–Manson relationship to separately account for the contributions of elastic and plastic strains in fatigue analysis for engineering design. Today, S-N and ε-N concepts are incorporated in the design process in nearly every industry where fatigue is an issue, including implantable medical devices. Stress- and strain-life testing involves both fatigue crack initiation and growth behavior, but generally does not distinguish the relative contributions of each to total fatigue life. However, in general, crack initiation accounts for the majority of fatigue life under high-cycle ($N > 10^5$) fatigue conditions. This is particularly true for implantable medical devices with small cross-sections that will require less crack growth to final failure than structures with thicker sections.

Traditional S-N analysis incorporates the use of stress-life test data obtained from smooth specimens in rotating bending. Rotating bending tests are conducted at zero mean stress. Samples are tested to failure at various cyclic stress amplitudes, and cycles to failure are counted. Specimens may also be tested with notches of various stress concentrations to ascertain their effect on fatigue life [15]. Since S-N fatigue data is often generated from rotating bending fatigue specimens with zero mean stress, consideration of the effect of positive mean stress on fatigue life of an engineering component requires further analysis. As stated above, the FDA recommends using a Goodman-type analysis to evaluate the effects of mean stress on fatigue life [1]. The linear Goodman equation is given by:

$$\frac{\sigma_a}{\sigma_N} + \frac{\sigma_m}{\sigma_{UTS}} = 1 \quad (1)$$

where σ_a is the amplitude ($\Delta\sigma/2$) of the applied cyclic stress, σ_m is the mean of the applied stress, σ_N is the fully reversed (zero mean stress) bending fatigue strength (in terms of stress amplitude) at a specified number of cycles, N (typically determined from rotating bending tests), and σ_{UTS} is the ultimate tensile strength. The parameters σ_a and σ_m characterize the fatigue loading conditions, and σ_N and σ_{UTS} are material-dependent parameters. A modified version of the Goodman relationship ("Modified Goodman") limits the maximum stress ($\sigma_a + \sigma_m$) in the fatigue cycle to the material yield strength. Other modifications to the Goodman line have been proposed over the years, such as using yield strength instead of ultimate tensile strength (Soderberg), squaring the σ_m/σ_{UTS} term (Gerber), or by using the true stress at fracture instead of the ultimate tensile strength (peak engineering stress). The Goodman relationship is generally thought to be conservative for ductile metals [14]. Improved agreement with fatigue performance of ductile metals may be achieved by replacing the ultimate tensile strength term with the true fracture strength or the Gerber relation. Comparison of the Goodman line with expected maximum mean and alternating *in vivo* stresses allows the determination of a fatigue safety factor or design margin. It is important to note that super-elastic nitinol, commonly used in medical devices, does not follow classic Goodman behavior [16].

4. S-N based component testing

Given the small size of many vascular implants, S-N or ε-N testing can be accomplished on actual devices (or representations thereof), rather than relying on data derived from rotating bending test specimens, as typically done with classical S-N testing for larger engineering components. In component-based S-N or ε-N testing, several devices are tested to failure at each of several specific loading/deflection conditions. Finite element analysis can be used to determine local stress and strain in specimens due to imposed test conditions. Given sufficient samples, statistical analysis can be conducted to determine statistical confidence in the test specimen failure rates, such as described in ASTM E739 [17]. The expected *in vivo* fatigue condition (mean and amplitude of stress or strain) can then be compared with the failure locus derived from specimen testing to determine fatigue design margins or safety factors.

Like the FDA-recommended durability testing, component-based S-N or ε-N testing is conducted on actual devices (or appropriate representations of the device); thus, accounting for actual material processing history, fabrication and deployment deformation history, residual stress, surface condition, etc., that may impact fatigue performance. However, unlike durability testing, component-based S-N and ε-N testing includes testing to failure, which allows the determination of failure modes and the determination of fatigue design margins. Done correctly, component-based S-N or ε-N testing provides better device fatigue performance information than the traditional S-N approach for medical device fatigue validation.