

Chapter 13

On Accelerated Fatigue Testing of Prosthetic Heart Valves

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Abstract

Accelerated testing (AT) of prosthetic heart valves allows simulation of wear and fatigue sustained by the replacement heart valves, and to estimate the valves' life expectancy in human body. At accelerated test rates, sufficient amounts of data can be collected within a reasonably short time period, after repeated opening and closing cycles, to predict the valve durability. The U.S. Food and Drug Administration (FDA) Replacement Heart Valve Guidance (Version 4.1, 1994) requires that mechanical heart valves (MHV) must be tested at least 600 million cycles (equivalent to 15 years *in vivo*), while biological heart valve prostheses (BHV) must be tested at least 200 million cycles (equivalent to 5 years *in vivo*) in pulsatile flow simulators. The cyclic test must meet two basic FDA requirements: 1) the test valve open and close fully each cycle; and 2) the average transvalvular pressure is kept at least 100 mmHg at closure. At accelerated test rates, the valves were subjected to non-physiologic dynamic force loads and often damaged under excessive conditions, such as cavitation. AT may pinpoint early flaws in the design and in the manufacturing processes, and deflects regions of materials weakness. Hence the design of AT must follow the principles of engineering testing such as the law of dynamic similarities. One must first identify dimensionless parameters that are physiologically meaningful and those much be specific to heart valve testing. The main goal of this paper is to present an AT system and an experimental protocol so that *in vitro* accelerated testing may be carried out without creating these excess forces on the test valves and to predict the durability of prosthetic heart valves with physiological considerations.

1. Statement of Problem

The durability of a prosthetic heart valve (HVP) is directly related to the survival of the recipient. Accelerated testing (AT) of new artificial heart valves can significantly shorten the amount of time spent on research and development. The design of an adequate AT system has received much attention among industrial researchers and regulatory agencies. Various designs of accelerated pulse testers have evolved since the 1950s and much valuable data has been gathered (Xi *et al.*, 1995; Menzler *et al.*, 1997; Vivitro Systems Inc, Dynatek Laboratories Inc;

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Reul *et al.*, 1996; Mackay *et al.*, 1996; Reul *et al.*, 1998; Butterfield *et al.*, 2000; Iwasaki *et al.*, 2002).

Clinical experience compared with the results of accelerated HVP testing shows that: 1) the heart valve components that fail *in vitro* often fail also *in vivo*; 2) the sites of *in vitro* failures often coincide with those found in clinical explants; and 3) the more durable valves *in vitro* correspond to longer service life in patients (Clark *et al.*, 1978). Most of these correlations were very useful for the HVP manufacturers. While accelerated testing accumulates useful information on the durability of HVP in a short period of time, it can also help the manufacturers to refine their designs, manufacturing processes, and materials.

Some shortcomings of conventional AT have been recognized. First of all, the valve is less durable in accelerated testing than *in vivo* (Iwasaki *et al.*, 2002). Second, the same HVP tested in different ATs in independent studies may produce totally different results (Reul *et al.*, 1996, Iwasaki *et al.*, 2002). Certain studies actually unveiled new problems that arise only during high frequency accelerated testing and have not been experienced under normal physiologic circumstances (Reul *et al.*, 1996; Butterfield and Fisher, 2000; Iwasaki *et al.*, 2002).

At 10 to 20 times the normal heart rate, AT can operate at 600 ~ 1000 beats per minute (bpm) or faster. It should be noted that as long as the physiological transvalvular pressure difference of 100 mmHg were maintained at such high frequencies, the inertial forces on the test valves would increase significantly (Xi *et al.*, 1995; Reul and Potthast, 1998).

The International Standard Organization (ISO) points out in its ISO5840 guidelines that accelerated testing inherently imposes unrealistically severe conditions because of 1) the inability to achieve adequate system damping; and 2) high frequencies causing stresses that are not found at lower rates (International Standards Organization, 1984).

We present an AT system in this paper whose design is based on the principles of dynamic similarity and engineering parameters. The system can be used to predict accurately the durability of prosthetic heart valves *in vivo*.

2. Current AT Systems and the Design Parameters

In order to meet the FDA requirements, researchers have continuously devised AT systems of different designs. Currently on the market, the most common models are the HIA and HIA-2 (Helmholtz Institute, Aachen, Germany), the Shelhigh FTS300 (Shelhigh Inc., Springfield, NJ, USA), and the Dynatek (Dynatek Dalta, Galena, MO, USA). In all these systems, the test valves are immobilized on a stationary platform while pulsatile fluid flows by the test valve. The other types are the Rowan-Ash (Rowan Ash Ltd., Sheffield, UK) and the TH2200 (Tsinghua University, Beijing, China) testers which place the test valves on a mobile platform that moves at a desirable test frequency and the test valves moves through the otherwise stationary testing fluid, back and forth, to stimulate valve opening and closing. The Rowan-Ash tester placed the driving power unit near the base of the system, while the TH2200 tester placed the drive unit on the top. It thus requires less force and avoided leaking problems. All these accelerated testers are each different in their designs, but all of them meet the basic FDA testing requirements. The systems all have adjustable resistance, compliance, amplitude, and cycle rate.

Test results from these AT systems are generally found inconsistent in at least two categories: First of all, there is the inconsistency where accelerated testers either significantly overshoot or underestimate the actual fatigue lifetime of the valve (Vesely *et al.*, 1995; Reul and Potthast, 2000; Butterfield and Fish, 2000; Iwasaki *et al.*, 2002). Secondly, different accelerated testers produce different fatigue results for the same valve (Reul *et al.*, 1996, Iwasaki *et al.*, 2002). These discrepancies are observed mainly because these testers do not have adequate relaxation time, and that they all experience additional impact loading forces

which do not exist under physiological (lower) frequency operations.

Under accelerated conditions, the valve loading force is a non-linear function of the compliance, frequency, amplitude, and transvalvular pressure. Earlier AT test results, obtained by various research groups, that are related to each of these parameters are presented as follows:

2.1 Compliance

Iwasaki *et al.*, (2001, 2002) pointed out that if the accelerated tester lacks the compliance component, the tested Jellyfish valve couldn't open fully. The water hammer effect can be reduced with a built-in compliance in the pulsatile flow simulator (Xi *et al.*, 1995). When performing accelerated testing of the St. Jude Medical (St. Jude Medical Inc., St. Paul, MN) artificial valve (SJM) under fixed frequency and varying amplitudes, Reul and Potthast (1998) showed that the loading force on the valve decreased linearly with increasing compliance. When observing localized valve wear and damage, Iwasaki *et al.*, (2002) reported increasing compliance may absorb some of the pressure in the field. In order to maintain 120 mmHg transvalvular pressure, the driving motor had to exert more force to compensate the lever as it moves with increasing amplitude. Consequently, the occluder of the test valves exhibited obvious signs of wear and damage. The system compliance can also affect the pressure waveforms both upstream and downstream of the test valve after closing, creating an excessive pressure difference that contributes to leaflet damage.

2.2 Frequency

Mechanical and biological prosthetic heart valves behave differently under increased operational frequencies in accelerated testing. Mechanical valves may create cavitations that may be harmful to the valve surfaces. The threshold for cavitation is represented by dP/dt . They found that $(dP/dt)_{\max}$ rises as the frequency increases (Reul *et al.*, 1996). The valve damage and fatigue observed in AT are primarily due to the excessive forces from accelerated flow and cavitations. Similarly, biological valves may experience varying turbulent stresses with increasing frequency (Reul and Potthast, 2000). This group further observed during the closing phase that biological valves receive an impact force one magnitude less than that of mechanical valves (Reul and Potthast (1998). Selwayn *et al.*, (2001) observed that when the plastic leaflets of a trileaflet artificial valve open, they experience higher angular strain but this was unaffected by the operational frequency.

Butterfield and Fish (2000) tested biological valves on the Rowan-Ash accelerated tester for 200 million cycles (5 years *in vivo*) and still maintained normal function. They were unable to replicate the clinical observations of *in vivo* valve failure after 2-3 years. However, the etiology behind the clinically observed valve failure cannot be accurately predicted under *in vitro* accelerated testing. The valve does not exhibit normal creep movements that it would under *in vivo* physiological conditions.

2.3 Amplitude

The transvalvular pressure can be adjusted through the amplitude of the driving piston of the accelerated tester. Increased amplitude (stroke volume) may create faster fluid inertial speed and leaflet acceleration, which in turn may enhance the extent of leaflet damage (Iwasaki *et al.*, 2002).

2.4 Transvalvular Pressure

Transvalvular pressure is defined as the pressure difference between the upstream and downstream regions of a valve at closure. At the instant of valve closing, the water hammer effect due to reversed fluid flow increases downstream pressure and decreases upstream pressure. At the higher frequencies of accelerated testing, the inertial acceleration and transvalvular pressure both increase. In order to maintain a constant transvalvular pressure, the compliance component can reduce the effects of the water hammer but the amplitude must be increased. Chandran *et al.*, (1995) measured an upstream pressure of 500 mmHg during valve at closure, they found a loading force significantly larger than the normal 100 mmHg.

2.5 Valve Loading Force

The inertial forces and system compliance exist in equilibrium under normal physiological conditions (Xi *et al.*, 1995). But when performing accelerated testing, the inertial effects of the valve leaflets and fluid both increased rapidly and, when coupled with the transvalvular pressure, created a significant loading force on the test valves. When trying to maintain the transvalvular pressure at physiological values under accelerated testing conditions, the loading forces and valve damage are expected to increase. Consequently, accelerated tests generally yielded shorter valve lifetimes than observed in the body. Reul *et al.*, (1996) tested the Bjork-Shiley CC (Shiley Inc., Irvine, CA) mechanical valve on the Rowan-Ash accelerated tester, maintained transvalvular pressure at 100 mmHg, and observed increasing valve loading force with increasing frequency. Reul and Potthast (1998) observed similar results when testing the SJM valve on the HIA-2 tester. In addition, mechanical valves experience impact forces at closing which may be orders of magnitude greater than that experienced by the natural heart valves.

In animal experiments performed by Rau *et al.*, (1995), the valve loading force was found to increase rapidly with higher dP/dt . Schreck *et al.*, (1995) further showed the loading force rises linearly with the 3rd power of left ventricular dP/dt , and square root of the left ventricular pressure.

Overall, excessive valve loading force is artificially exerted on the test valves under accelerated testing conditions when transvalvular pressure is maintained at constant 100 mmHg level. Transvalvular pressure should not be the only factor considered in simulating the physiological conditions, when accelerated testing is performed. Reul and Potthast (1998, 2002) and Xi *et al.*, (1995) measured the valve loading forces under normal physiological conditions in a circulatory mock flow loop. Using these loading forces as reference as opposed to the transvalvular pressure when performing accelerated testing, these researchers concluded that they could obtain more accurate results and evaluations. The main purpose of this paper is to identify the interaction between the control parameters and valve forces under accelerated testing conditions, and to show that there is an alternative approach for the testing standard other than the transvalvular pressure that FDA requires.

3. Dynamic Similarity of AT

In vitro testing tries to predict the working conditions and lifetime of artificial heart valves inside the human body. From an engineering point of view, the artificial heart valve structure is very complex. The problem with accelerated testing is the correlation and required similarities of dynamic parameters between *in vitro* accelerated conditions and *in vivo* physiological conditions, which in fact is difficult to achieve. The forces on the artificial valve under accelerated testing can be represented by the unsteady momentum equation of the control volume with

only one inlet and outlet (Cheon and Chandran, 1994):

$$F = A_i P_i - A_o P_o + \dot{m}_i U_i - \dot{m}_o U_o - \frac{d(MU)}{dt} \quad (1)$$

The first two terms are the pressure force, the third and fourth terms are momentum flux, and the last term is the rate change of the momentum, where:

A_i, A_o – areas of the cross section in the control volume

$\dot{m}_i, \dot{m}_o$ – fluid masses flow rate

P_i, P_o – pressure at the cross-sections

U_i, U_o – flow velocities

M – mass of the control volume

U – mean velocity of the control volume

i – inlet section

o – outlet section

Assuming a harsh boundary and M is a constant, the last term in the above equation represents the closing of the valve leaflets.

$$\frac{d(MU)}{dt} = M \frac{dU}{dt} \quad (2)$$

This equation also includes the loading force as a result of the water hammer effect (Hwang and Houghtalen, 1996). We represent the valve displacement with x :

$$x = A \sin \omega t + B \sin^2 \omega t + C \sin^3 \omega t + \dots \quad (3)$$

To simplify the analysis, we use the first term

$$x = A \sin \omega t \quad (4)$$

$$U(t) = \frac{dx}{dt} = \omega A \cos \omega t \quad (5)$$

$$\frac{dU(t)}{dt} = -\omega^2 A \sin \omega t \quad (6)$$

Under accelerated conditions, the inertial effects of the valve and fluids are significantly enhanced and directly proportional to the square of the frequency. When the valve closes, the increase in pressure is

$$\Delta p = E_c \frac{\Delta Vol}{Vol} \quad (7)$$

where E_c is the composite modulus of elasticity of the boundary walls and the fluid within, Vol is the original volume of the control volume, and ΔVol is the extra volume. correlates to the E_c compliance. When the valve closes, the force is

$$F_c = \Delta p \cdot A_s = M \frac{dU}{dt} \quad (8)$$

where A_s is the area of the valve.

The inertial forces and transvalvular pressure comprise the total loading force on the valve. Current technology only considers the similarity of the transvalvular pressure to physiological conditions. Consequently, the valve undergoes significant loading forces under accelerated conditions and damages quickly. The tested lifetime of the valve is much shorter

Petitioner's Exhibit 1005

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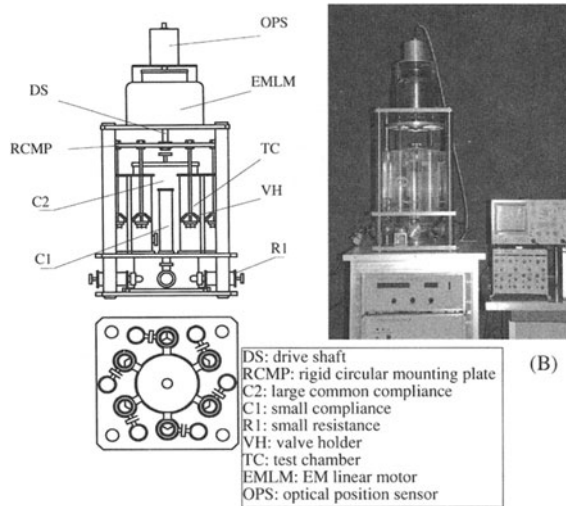


Fig.1 Schematics (A) and Photograph (B) of the TH 2200 Accelerated HVP Tester

than the actual lifetime in the body. The real problem with accelerated testing lies in trying to maintain similar valve loading forces and their distributions under both accelerated and physiological conditions. Therefore, we suggest that the ratio of valve loading force and water hammer force (F_c) remain constant,

$$\frac{F}{F_c} = C = \text{constant} \quad (9)$$

$$\frac{F}{M\omega^2 A \sin \omega t} = C \quad (10)$$

By maintaining conditions identical or similar to physiological conditions under constant C , increasing the frequency ω after acceleration requires adjusting the amplitude A and loading force to guarantee full valve opening and closing. Under these testing conditions, the accelerated tester should be able to more accurately reflect the lifetime of the artificial valve under normal physiological usage.

4. Methods and Procedures

4.1 The Accelerated Testing Systems

Based on the preceding discussion, we designed an AT that can monitor the dynamic load acting on the test valve with a specially designed load cell. The apparatus, as shown in **Fig. 1**, consists of four basic parts: the actuator, the circulatory flow loop, the test section, and the monitoring system.

The actuator uses an electromagnetic linear motor as the power source and random wave generator to create the driving waveform, which then produces 200 W of power from a power amplifier. A horizontal circular plate with 6 vertical mounting rods is attached to the actuator, which produces the sinusoidal movement. The amplitude and frequency of the movement are adjustable from 0 ~ 3 cm and 0 ~ 20 Hz and above, respectively. The whole system is notable for its small size, large driving force, simple transmission, minimal mechanical friction and low

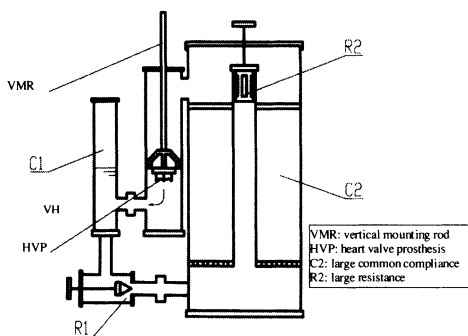


Fig.2 Schematics of Individual Circulatory Flow Loop

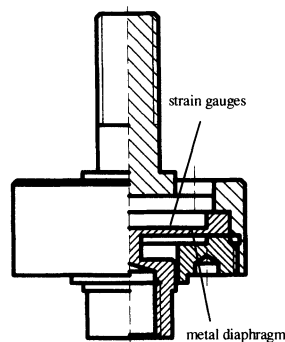


Fig.3 The Load Cell Transducer

noise. Since the driving waveform directly effects the loading on the test valve, it must be adjustable and is normally set to operate in the range of the physiological heart rate.

Six valves may be simultaneously tested with each one installed in an independent circulatory flow loop as shown in **Fig.2**. Each valve holder, shaped like a flower basket, is connected to the lower end of one of the six vertical mounting rods, which are all connected to the bottom side of a flat, rigid, horizontal circular plate and the common drive shaft. This allows the 6 independent valves to move together but each one operates independently in its separate testing loop.

When the valve holder moves down in the plexiglass cylinder filled with the testing fluid, the valve closes due to fluid resistance and simultaneously pushes the fluid through the circulatory loop. Each loop consists of two resistor units and two compliance chambers, as shown in **Fig.2**. The small compliance (C1) and resistance (R1) are found in each of the 6 loops, while the large common compliance (C2) and resistance (R2) are shared by all six flow loops. The compliance and resistance units simulate the human systemic circulation for blood flow. These may be adjusted to represent the afterload on aortic valves.

4.2 The Monitoring System

The monitoring system includes three basic sensors for the loading force of the valve, the displacement, and the back pressure. The time course of loading on the test valve, $F(t)$ is measured under accelerated testing conditions, to adjust properly the driving waveform signal and afterload, and to maintain physiological loading. For this purpose, we designed the loading force sensor (Load Cell, LC) as shown in **Fig.3**.

Two identical LC transducers are placed symmetrically on the upper end of the valve mounting rods (**Fig.4**). The loading force generated by the system itself was first measured without placing the test valves in the valve holder. Since the LC transducers are placed symmetrically, their signals tend to cancel each other as shown in **Fig.5**. A test valve was mounted on one of the rods, while the valve loading force was measured. The loading forces from the empty mounting rods are subtracted from the loading force on the test valve to obtain the valve loading, $F(t)$. By adjusting the afterload and amplitude of the loading force, the valves can be maintained within the physiologic range even under accelerated testing conditions (**Fig.6 and 7**).

4.3 Accelerated Test Procedures

Three Edwards Pericardial bioprosthetic heart valves (size 29mm) served as test samples in our

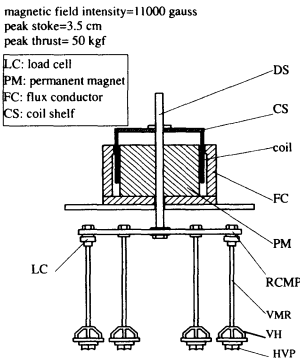


Fig.4 AT Actuator and HVP Mounting Mechanism

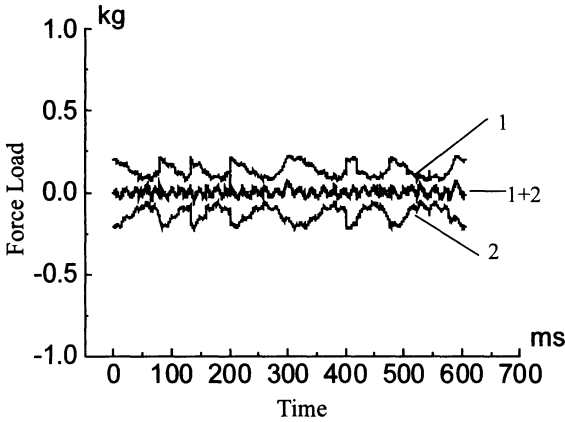


Fig.5 Inertia Force of the Valve Holder and Its Mounting ROD

experiments. The accelerated tests procedures were all carried out at room temperature ($22\pm 2^{\circ}\text{C}$) using an aqueous glycerin solution, 33% by volume, with $3.3\times 10^{-3}\text{N/s/m}^2$ (or 3.3CP) viscosity, and 1100kg/m^3 density, as the analog test fluid.

Valve displacements were continuously monitored and the actuator signal was controlled by feedback to maintain the amplitude at a fairly constant value. We utilized an electro-optic position detector for this purpose that does not make physical contact with the test valve and allows long-term, continuous operation.

We also measured the back pressure waveform on the valve, which is the standard guide for adjusting the afterload. A physiologic pressure transducer was connected to the bottom of the test section via a 3-way stopcock, which can be opened for the pressure measurement whenever desired, and otherwise kept closed. A computer continuously monitors and controls the entire apparatus over any desirable long period of time, using the measured valve loading force, displacement, and back pressure values as inputs.

The AT system is driven by an electromagnetic linear actuator to simulate the physiological characteristics of the human systemic circulation. The system produces a pressure waveform that closely mimics the physiologic aortic pressure waveform even under accelerated testing conditions (**Fig.6 and 7**). A particular advantage of the mock loop system is that the amplitude and the afterload can be adjusted precisely to maintain a fairly constant loading force on the heart valves being tested.

The dynamic loading on the valves needs to be measured over a wide range of pulse rates. It is necessary to obtain the inertial loading force on the apparatus and subtract it, as described previously. Two equally responsive load cell transducers were mounted in opposite positions on the horizontal mounting plate in the apparatus, without any valves, to measure the loading forces generated by the mounting rods and valve holders. Since the transducers are placed symmetrically, the waveforms cancel each other, as shown in **Fig.5**. This test was carried out at all 6 positions around the horizontal mounting plate, and the results showed that the dynamic characteristics throughout the apparatus remain symmetrical in the range of the frequencies used for the tests.

4.3.1 AT Experiment with Fixed Transvalvular Pressure, ΔGP

The loading forces on the test HVP are determined by the measured pressure waveforms when the valves are mounted in the valve holders. **Fig.8 through 13** show valve loadings at test frequencies of 78, 500, and 1,134 bpm, while the transvalvular pressure was held constant at

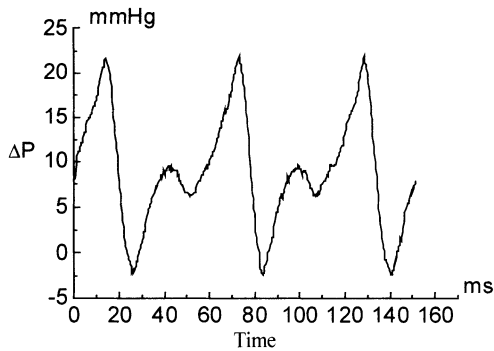


Fig.6 Tranvalvular Pressure Measurement (pulse rate: 1000 bpm)

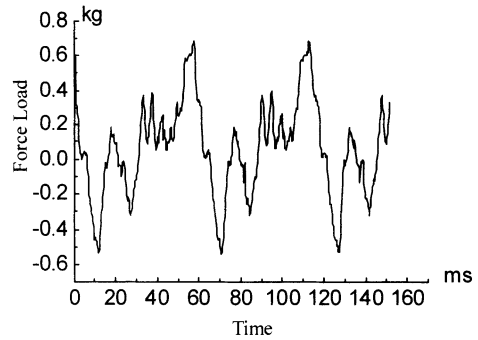


Fig.7 Force Load on Test HVP (pulse rate: 1000 bpm)

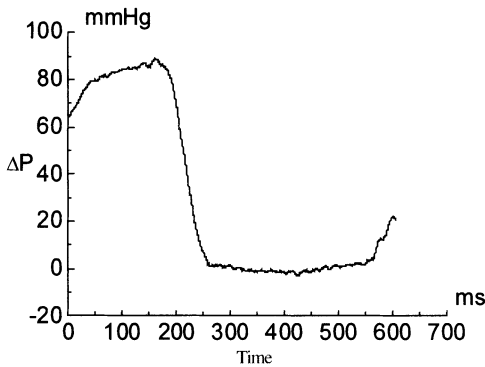


Fig.8 Tranvalvular Pressure (95 ± 5 mmHg) at 78 bpm

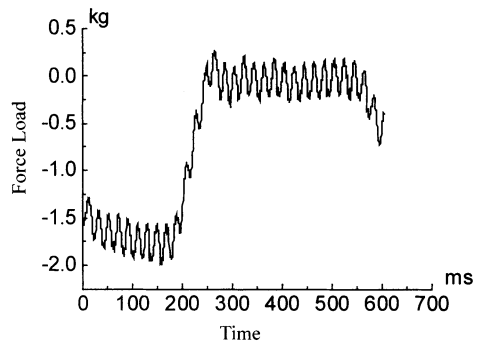


Fig.9 Force Load on HVP at 78 bpm

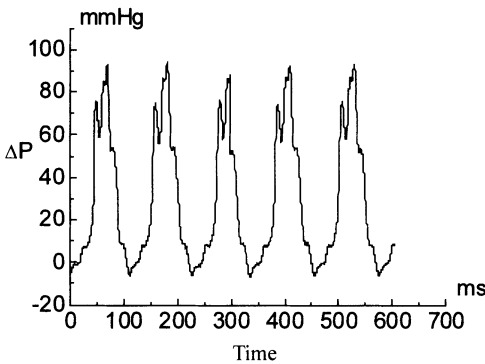


Fig.10 Tranvalvular Pressure (95 ± 5 mmHg) at 500 bpm

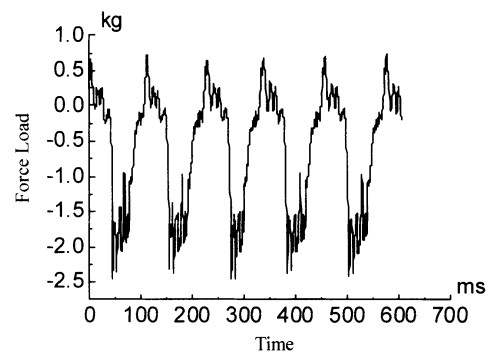


Fig.11 Force Load on HVP at 500 bpm

95 ± 5 mmHg as required by the FDA. The measured force load on the test valves increases drastically with frequency, as shown in **Fig.14**.

4.3.2 AT Experiment with Fixed Stroke Amplitudes

A second AT flow loop was constructed with a rigid crank shaft drive mechanism (**Fig.15**) to investigate accelerated HVP testing at fixed stroke volume. Without feedback control, the open loop system can operate at practically any frequency (pulse rate) and amplitude (stroke

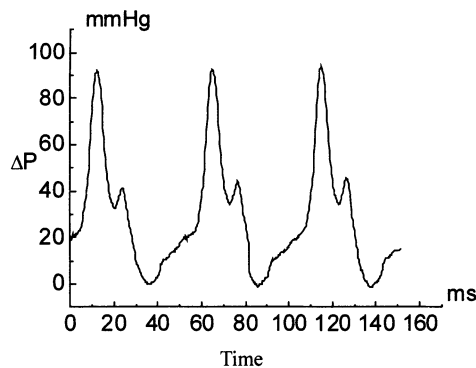


Fig.12 Transvalvular Pressure (95 ± 5 mmHg) at 1134 bpm

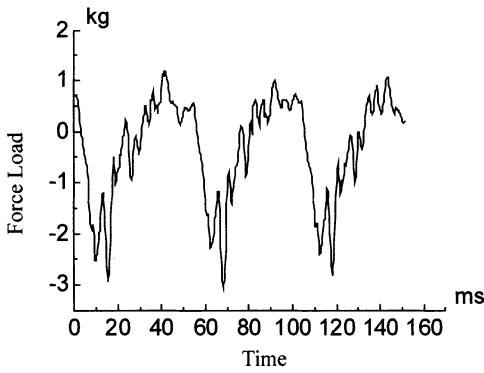


Fig.13 Force Load on HVP at 1134 bpm

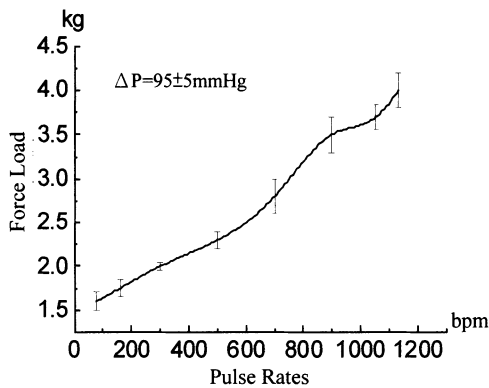


Fig.14 Measured Force Load on HVP at Different Pulse Rates

volume). **Fig.16** is typical of the measured force loading on a given test valve at pulse rates from 120 to 500 bpm. For this experiment the stroke amplitude was set at $A=\pm 3$ mm.

4.3.3 AT Experiment at Fixed Valve Load

The experiment was carried out while the valve load was carefully kept constant over a broad range of operating frequencies (pulse rates). The complete opening and closure of the test valve in each cycle was verified visually.

Fig.17 shows the results of one such experiment conducted by keeping the valve load constant at 1.90 ± 0.15 kg. Transvalvular pressure measurements were made at various pulse rates between 60 and 1,120 bpm. The results indicate that the transvalvular pressure decreases at higher operating frequencies.

4.3.4 Changes in Transvalvular Pressure and Loading Across the Test HVP

As mentioned earlier, the loading sustained by the artificial heart valves increases significantly as the frequency rises, while the pressure is maintained at 95 ± 5 mmHg (**Fig.12**).

5 Conclusions

In vitro accelerated testing allows the study of the long-term performance of prosthetic heart valves in significantly less time. The FDA requires that physiologic conditions be simulated

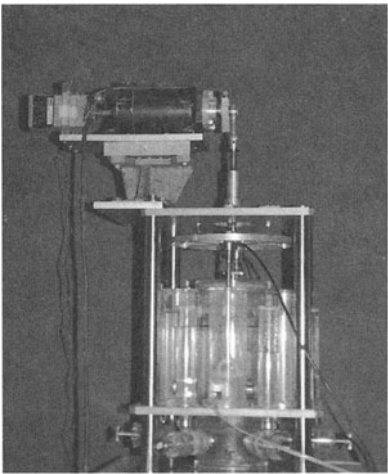


Fig.15 AT with Rigid Crank Shaft Drive Mechanism

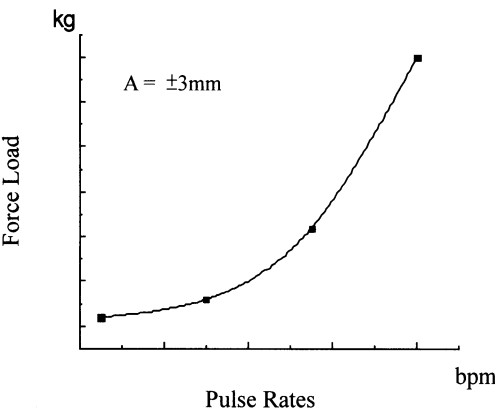


Fig.16 Fixed Stroke ($A=\pm 3$ mm) Measurement of HVP Force Load at Different Pulse Rates

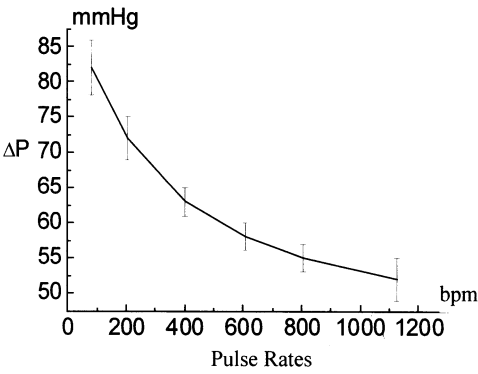


Fig.17 Transvalvular Pressure at Different Pulse Rates (Force Load on HVP at Constant Level: 1.90 ± 0.15 kg)

and the pressure across the test heart valves must be maintained at 80 ~ 100 mmHg at closure. From an engineering viewpoint, it is irrational to hold the transvalvular pressure constant at accelerated test rate. When valve displacement is constant in an open loop system, the valve loading force increases rapidly and non-linearly with test frequency (**Fig.16**). Despite adjustments for the afterload, this nonlinear trend persists, as shown in **Fig.14**.

When the pressure is held constant, the loading sustained by the valves during accelerated testing increases with the test frequency. This excess load on the test valves accelerates wear and fatigue. This method does not reflect long-term performance accurately as it underestimates the valve's durability (Reul and Potthast, 1998).

In contrast, when the force load on the test valve is held constant, the transvalvular pressure decreases in a non-linear fashion as the test frequency increases. These non-linear relationships arise from taking the time derivative of the momentum in Equation 8. The ratio of the loading F and $M \, dU/dt$, should be considered simultaneously during accelerated HVP testing by implying the relationship:

$$C = \frac{F(t)}{M \omega^2 A \sin \omega t}$$

We propose that the loading, rather than the pressure difference, should be held constant when performing accelerated testing. As the heart rate or frequency (ω) increases, the amplitude and afterload should be decreased to maintain constant loading. Consequently, the loading sustained by the artificial heart valves remains within the physiologic range (**Fig.8**) even when the pressure difference is not maintained within 80 ~ 100 mmHg (**Fig.7**). At constant loading, the artificial valves can undergo accelerated testing while simulating physiological conditions.

Accelerated testing of prosthetic heart valves needs further studies. The suggestions we made in this paper should introduce a new approach to accelerated HVP testing.

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