Optimizing the Tensile Properties of Polyvinyl Alcohol Hydrogel for the Construction of a Bioprosthetic Heart Valve Stent

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Abstract: Although bioprosthetic heart valves offer the benefits of a natural opening and closing, better hemodynamics, and avoidance of life-long anticoagulant therapy, they nevertheless tend to fail in 10–15 years from tears and calcification. Several authors, including the present ones, have identified the rigid stent as a factor contributing to these failures. The ultimate solution is an artificial heart valve that has mechanical properties that allow it to move in conformity with the aortic root during the cardiac cycle, has superior hemodynamics, is nonthrombogenic, will last more than 20 years, and mitigates the need for anticoagulants. We have identified a polymer, polyvinyl alcohol (PVA) hydrogel, that has mechanical properties similar to soft tissue. The purpose of this research is to match the tensile properties of PVA to the porcine aortic root and to fabricate a stent prototype for a bioprosthetic heart valve with the use of the PVA hydrogel. Specimens of 15% w/w PVA were prepared by processing through 1–6 cycles of freezing (−20 °C) at 0.2 °C/min freeze rate and thawing (±20°C) at different thawing rates (0.2 °C/min and 1 °C/min), for different holding times (1 and 6 h) at −20 °C. Subsequently tensile tests and stress-relaxation tests were conducted on the specimens. The different holding times at −20 °C demonstrated no difference in the result. The slower thawing rate improved the tensile properties but did not produce significant changes on the stress-relaxation properties. The nonlinear stress-strain curve for the PVA after the fourth freeze–thaw cycle matched the porcine aortic root within the physiological pressure range. The stress-relaxation curve for PVA also approximated the shape of the aortic root. The complex geometry of an artificial heart valve stent was successfully injection molded. These results, in combination with other preliminary findings for biocompatibility and fatigue behavior, suggest that PVA hydrogel is a promising biomaterial for implants, catheters, and artificial skin.

Keywords: polyvinyl alcohol hydrogel; freeze–thaw; bioprosthetic heart valve; stent; tensile; stress relaxation

INTRODUCTION

Currently mechanical and bioprosthetic heart valves are the two types of artificial devices available for heart-valve re-
the tissue.\textsuperscript{3–5} Studies of the valve opening mechanism, dimensional change of the valve and distensibility of the aortic root have shown that abnormal stress on the valve cusps resulted from use of a rigid (nonexpansile) stent and contributes to the tearing mode of valve failure.\textsuperscript{6–12}

Although a stent with pivotal posts may alleviate the problem,\textsuperscript{13} the ultimate stent would be expansile moving in conformity with the expansion of the aortic root between systole and diastole. In addition, flexible cusps would permit a large central flow orifice with normal hemodynamic performance.\textsuperscript{6,7} Overall, the ideal heart valve material should behave in a manner mechanically similar to the natural tissue, durable, nonthrombogenic, as well as being resistant to calcification and nonantigenic. Although various expansible materials such as rubbers and polyurethane\textsuperscript{14–16} have been examined during the past four decades, their performance has not been satisfactory.

Polyvinyl alcohol (PVA) is a hydrogel with desirable properties for biomedical applications.\textsuperscript{17,18} In the late 1960s, PVA was crosslinked with formaldehyde to create a highly porous sponge that was marketed as Ivalon.\textsuperscript{17} It was used extensively in duct replacement, articular cartilage replacement,\textsuperscript{19} pharmaceutical release agent,\textsuperscript{17} and reconstructive (vocal cord) surgery.\textsuperscript{20} Although PVA can be crosslinked using glutaraldehyde, great care must be taken when choosing a crosslinking agent, because it can evoke an immune response within the body. Fortunately, PVA has unique properties that allow it to be crosslinked without the use of a chemical agent.

The ability to modify the nonlinear elastic modulus of PVA hydrogel by physical methods (e.g., freezing/vacuum cycles) has been investigated by several authors over the past 20 years.\textsuperscript{20–23} Watase et al.\textsuperscript{20} first investigated the effect of freezing and evacuating of PVA hydrogels on the complex Young’s modulus and concluded that the increase of the elastic modulus is due to increased crystallinity in the PVA hydrogel. Later, Peppas and Stauffer\textsuperscript{21} discussed how repeated thermal cycling of PVA hydrogels can increase the elastic modulus. These authors examined three main theories that model the effect of freezing and thawing on PVA: hydrogen bonding, polymer crystallite formation, and liquid–liquid phase separation. Stauffer and Peppas\textsuperscript{22} concluded that the strongest gels resulted from a 15%-by-weight PVA solution frozen at $-20^\circ$C for 24 h followed by thawing at $23^\circ$C for any period of time.

The purpose of this research is to match the tensile properties of PVA to the porcine aortic root determined from previous work\textsuperscript{23} with the use of a freeze/thaw technique, and to fabricate a stent prototype for a bioprosthetic heart valve with the use of PVA hydrogel.

### MATERIAL PROCESSING CONDITIONS AND TEST METHODS

#### Specimen Preparation

A 15% w/w PVA solution was prepared by heating and mixing with the use of a standard reflux column/flask combination. The PVA solution was poured into a cavity mold with dimensions of $120\times60\times3$ mm. The PVA in the mold was processed through freezing and thawing cycles between $-20$ and $20^\circ$C in a heated/refrigerated circulator. The preparation conditions (i.e., Series A, B, C, and D) for different holding times of 1 h or 6 h at $-20^\circ$C and thawing rates of 0.2 C/min or 1 C/min were compared to determine if the tensile elastic modulus or stress relaxation properties were affected. Table I lists the four series of specimen processing conditions. This study, does not assess the effect of freezing rate.

After each freeze/thaw cycle, one mold was removed from the circulator and the PVA sheet was extracted and punched into $20\times10$-mm rectangular-shaped specimens with the use of a special punch and die set. The thickness of each specimen was measured with the use of a custom-made thickness gauge consisting of a dial gauge that applies a consistent load to the specimen.

An additional set of specimens (designated validation V) was prepared for each of the series of A, B, C, and D listed above. The same tensile and stress-relaxation test described in the following sections were performed on each specimen ($n=10$). A two-way ANOVA (analysis of variance) was conducted on the validation set and on the original set for all six cycles for the stress and elastic modulus at strains of 20%, 40%, and 50% (three strain points were selected to test the curves within physiological range) as well as for the stress-relaxation parameters ($k_1$, $k_2$, and $\sigma_R$) to examine the reliability of the specimen preparation process and test methods.

#### Tensile Test

The material test system (MTS 858 Bionix) equipped with special grips\textsuperscript{23} was used for uniaxial tensile testing at a constant crosshead speed of 40 mm/s, to a maximum strain of 80%. All tests were carried out with the specimen immersed in distilled water, at a temperature of $37^\circ$C. Each of the 10

<table>
<thead>
<tr>
<th>Processing Conditions</th>
<th>Freeze Rate (°C/min)</th>
<th>Thaw Rate (°C/min)</th>
<th>Holding Time (h) at $-20^\circ$C</th>
<th>Holding Time (h) at $20^\circ$C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series A</td>
<td>0.2</td>
<td>0.2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Series B</td>
<td>0.2</td>
<td>0.2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Series C</td>
<td>0.2</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Series D</td>
<td>0.2</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
PVA specimens for each of the 1–6 freeze/thaw cycles, was preconditioned for five extension/return cycles. Raw data in the form of load-extension curves were converted into engineering stress–strain from the initial gauge length and sample dimensions. In order to obtain the elastic modulus at different strain, these stress–strain data were fitted by Eq. (1), and the incremental elastic modulus as a function of strain was calculated as the first derivative of Eq. (1):

\[ \sigma = a + b \varepsilon + c \varepsilon^2, \]

where \( \sigma \) is stress, \( \varepsilon \) is strain, and \( a, b, c, \) and \( k \) are constants.

### Stress-Relaxation Test

For the stress relaxation test, each of the 10 PVA specimens for each of the 1–6 freeze/thaw cycles for Series A, B, C, and D, immediately after the tensile test, was preconditioned for five extension/return cycles, then elongated to a strain of 0.8 and held constant for 100 s, while the load was recorded. Raw data in the form of load-time were converted into relative remaining stress (engineering) versus time, with respect to the stress at time zero. The stress-relaxation curve was fitted by Eq. (2) as described by Zhang et al.:

\[ \frac{\sigma_1}{\sigma_0} = \sigma_k + \alpha e^{-kt} + \beta e^{-kt}, \]

where \( \sigma_1 \) is remaining stress after time \( t \), \( \sigma_0 \) is initial stress, \( \sigma_k \) is final remaining stress or relaxed stress, \( \alpha \) and \( \beta \) are proportional constants for the crystalline and amorphous regions, where \( k_1 \) and \( k_2 \) are relaxation-rate fitting parameters for the initial and final regions.

### RESULTS

#### Process Optimization

**Specimen Process Validation.** The stress–strain, elastic modulus–strain and stress relaxation–time curves were prepared between the original set and the validation set for each process condition (Series A, B, C, and D). Figure 1 is an example of the validation for the stress–strain relationship between Series A and Series B. For the validation data set (designated A1–A6-V) and Series A processing condition. Figure 1 shows the effect of the thawing rate on stress–strain curves of Series A and C. Series B and

**Holding Time.** Figure 2 illustrates the effect of the holding time on stress–strain relationship between Series A and Series B. Series A, B, C, and D showed similar results. Two-way ANOVA on the stress at strains of 20%, 40%, and 50%, the elastic modulus at strains of 20%, 40%, and 50%, and stress-relaxation parameters (\( k_1 \) and \( k_2 \) and \( \sigma_R \)) for each process condition showed that there is no significant difference (\( P>0.05 \)) between the original and validation preparations for all six cycles. This result confirms that the processes for preparing and testing the specimens are consistent. A significant difference observed among the six cycles for the stress–strain, elastic modulus and stress relaxation (\( k_1 \), \( k_2 \), and \( \sigma_R \)) was confirmed by the ANOVA (\( P<0.05 \)).

**Thawing Rate.** Figure 3 shows the effect of the thawing rate on stress–strain curves of Series A and C. Series B and
D were not assessed because of the similar results obtained in the previous section. Changes in stress–strain and elastic modulus–strain were observed and confirmed by a two-way ANOVA analysis ($P<0.05$). The fitting parameter for stress relaxation did not change ($P>0.05$). A fast thawing rate (Series C) resulted in a lower incremental elastic modulus. The significant differences observed among the six cycles were confirmed for the stress–strain, elastic modulus, and fitting parameter $k_1$ for stress relaxation, but not fitting parameters $k_1$ and $k_2$.

**Tensile Properties**

**Stress–Strain Relationship.** Figure 4 shows the stress–strain relationships of 15% PVA, through 1–6 freeze/thaw cycles for Series A specimens. (Series B, C, and D showed a similar trend). The porcine aortic root result obtained previously is also plotted in this figure in order to illustrate the close match between PVA and porcine aortic root.

A nonlinear, gradual then rapid increasing slope of the stress–strain relationship was observed for the PVA hydrogel. This shape for the stress–strain relationship is unique compared to other polymers and rubbers, and matches the shape for the porcine aortic root. The PVA hydrogel exhibited an increase in stiffness with an increasing number of freeze/thaw cycles. The stress–strain curve of PVA at freeze/thaw cycle 4 was comparable to that of porcine aortic root within the physiological strain range of 0.17 to 0.49, which is equivalent to the range of distension of the human aorta within the cardiovascular pressure range of 45 mmHg to 163 mmHg.

**Incremental Elastic Modulus–Strain Relationship.** Due to the nonlinear stress–strain relationship of PVA, the elastic modulus of PVA is not a constant. Therefore, incremental elastic modulus was adopted here to describe the varying modulus at different strains. Figure 5 shows modulus–strain relationships of 15% PVA through 1–6 freeze/thaw cycles for a Series A specimen compared to the porcine aortic root. (Series B, C, and D showed similar trends). A nonlinear, gradually increasing relationship between modulus and strain was observed. The moduli increased with increasing freeze/thaw cycles. It can be seen that the incremental elastic modulus of PVA material at freeze/thaw cycle 4 closely matches that of porcine aortic root within the range of physiological strain. A typical elastic modulus value for PVA at freeze/thaw cycle 4 at a systolic pressure of 120 mmHg is about 350 KPa.

**Stress-relaxation Behavior**

Values of the fitting parameters for Eq. (2) are shown in Table II. A comparison of the stress relaxation behavior between Series A at four freeze/thaw cycles and porcine aortic root shows comparable curves for the relative remaining stress of PVA and porcine tissue. The fitting parameters of $k_1$ and $k_2$ represent the slopes of the relaxation curve in the initial and final regions, respectively. There was no signifi-
significant increase ($P>0.05$) in $k_1$ and $k_2$ values for increased freeze/thaw cycles for Series A. There were no significant differences ($P>0.05$) in $k_1$ and $k_2$ between Series A and Series C. However, the $k_1$ values of PVA for cycle 2, 4, and 6 were significantly ($P \leq 0.001$) less than that of porcine tissue. Similarly, PVA hydrogel had a significantly ($P \leq 0.001$) lower $k_2$ value than porcine aortic root.

<table>
<thead>
<tr>
<th>Fitting Parameters</th>
<th>$\sigma_R$</th>
<th>$k_1$ (1/s)</th>
<th>$k_2$ (1/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series A at cycle 2</td>
<td>0.75 ± 0.005</td>
<td>2.66 ± 0.4</td>
<td>0.085 ± 0.002</td>
</tr>
<tr>
<td>Series C at cycle 2</td>
<td>0.74 ± 0.005</td>
<td>2.64 ± 0.4</td>
<td>0.079 ± 0.002</td>
</tr>
<tr>
<td>Series A at cycle 4</td>
<td>0.72 ± 0.012</td>
<td>2.6 ± 0.2</td>
<td>0.089 ± 0.002</td>
</tr>
<tr>
<td>Series C at cycle 4</td>
<td>0.68 ± 0.012</td>
<td>2.6 ± 0.2</td>
<td>0.089 ± 0.002</td>
</tr>
<tr>
<td>Series A at cycle 6</td>
<td>0.68 ± 0.015</td>
<td>2.65 ± 0.1</td>
<td>0.095 ± 0.001</td>
</tr>
<tr>
<td>Series C at cycle 6</td>
<td>0.64 ± 0.005</td>
<td>2.57 ± 0.1</td>
<td>0.095 ± 0.001</td>
</tr>
<tr>
<td>Porcine aortic root</td>
<td>0.83 ± 0.04</td>
<td>4.79 ± 0.92</td>
<td>0.12 ± 0.02</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The nonlinear shape of the stress–strain curve of PVA hydrogel after controlled freeze/thaw cycling is unique when compared to most engineering materials, for which the stress–strain relationship is typically linear in the elastic region. The stress–strain relationship of PVA is remarkably similar to that of soft tissues such as porcine aortic root and arteries.$^{23-27}$ The authors, to their knowledge, are the first to
report a material that can exhibit the same nonlinear tensile stress–strain relationship as the porcine aortic root.

The reasons for the nonlinear shape of the stress–strain curve of arteries was examined by Roach and Burton\textsuperscript{25} and Sherebrin et al.\textsuperscript{26} They selectively removed collagen and elastin, and concluded that the initial low stiffness region of tension-length curve was mainly contributed by elastin, whereas collagen played the dominant role for the high-stiffness portion.

From the microstructure point of view, there are three different regions within the PVA hydrogel: crystalline, amorphous, and water. Uncoiling and reorganizing of the polymer chain in PVA hydrogel under loading contributes to the nonlinear tensile properties but this subject requires further study in order to understand the interaction among the different regions.

The ability to modify the tensile property of the PVA material by varying the number of freeze/thaw cycles and thaw rate is an unusual characteristic. Increased cycles of freeze/thaw result in a stiffer material because of the mechanism of crystallite formation and liquid–liquid phase separation. The fact that a slower thawing rate resulted in stiffer material can be explained by the increasing time of reorganizing the polymer chains and expelling water from PVA. A loss of water was noted with increased freeze/thaw cycles. On the other hand, the thawing rate also affects the size and number of the crystalline regions. Holding time produces no difference on the tensile properties of PVA, because the above-mentioned process has been completed during the thawing process from $-20$ to $20$ °C.

The stress-relaxation studies quantified the time-dependent stress decay behavior of this viscoelastic material. As shown in Figure 8, there was good agreement between Eq. (2) and the experimental data. Conventional fitting of relaxation data has previously utilized a linear logarithmic function of stress remaining versus time relationship.\textsuperscript{27,28} This usually results in a linear fit with one slope, but two or more straight linear fits with distinctly different slopes have also been reported.\textsuperscript{29} There was no particular justification for this approach to the treatment of relaxation data, and the present three-term exponential approach minimized numerical post-

![Figure 7. The four-part injection mold.](image)

![Figure 8. Comparison of stress-relaxation properties of PVA Series A at 2, 4, and 6 freeze/thaw cycles and the porcine aortic root.](image)
processing of the raw data, thereby expressing the physical phenomena more directly. In the case of soft tissue such as bovine pericardium, the choice of this equation was based on reasoning that the principle components of pericardial tissue are collagen, elastin, and ground substance. Of these, collagen and elastin are the two main load-bearing components, and each of these components has different tensile and relaxation properties. It has been postulated that Eq. (2) may provide a fit common to all shear relaxation data for materials that have similar structural components. It is tempting to assign physical meaning to these parameters in terms of PVA components—that \( k_1 \) and \( k_2 \) represent, respectively, the relaxation rate constant of crystalline and amorphous regions in PVA hydrogel, that the proportion of crystalline and amorphous regions are represented by \( \alpha \) and \( \beta \) in Eq. (2) and that freeze/thaw cycles may affect only one of the structural components. However, it is premature to make such a distinction. For such a model to be accurately defined, further independent structural characterization of PVA must be done.

The injection mold used to fabricate a stent is easy to assemble and open, which ensures that the PVA stent will not be damaged. Warming the mold and PVA solution during filling ensures that the entire cavity is filled with PVA solution.

The bioprosthesis heart-valve stent prototype fabricated with the use of PVA hydrogel is expandable, and therefore can move in conformity with the movement of the aortic root. This should result in reduced blood-flow impedance and reduced abnormal stress on the heart valve cusps, thus providing a more durable bioprothetic heart valve.

A potential problem for the use of a polymer based heart-valve stent is deformation due to polymer creep. Past studies have identified this as a potential problem. Cyclic loading test has been initiated to assess the long-term mechanical stability of the PVA hydrogel subsequent experiments will determine its creep properties.

Current results show that the tensile properties of PVA can be modified to cover a wide range, from the elasticity of human skin to the human aorta. Our preliminary results of cyclic loading of PVA hydrogel and biocompatibility testing provide support for applications in the medical field. PVA hydrogel is not only suitable for application as a bioprothetic heart valve stent, but also for other soft-tissue applications. These applications include grafts, catheters, artificial skin, and artificial organs.

In conclusion, the freeze/thaw process produces very consistent changes in the mechanical properties of PVA hydrogel. Different holding times of 1 or 6 h at −20 °C do not change the tensile properties of the PVA hydrogel. Slower thawing rate of 0.2 °C/min versus 1 °C/min resulted in higher elastic modulus of the PVA hydrogel. A family of tensile properties of PVA hydrogel can be obtained by varying the number of freeze/thaw cycles and thawing rate. The tensile properties of PVA hydrogel can be modified by freeze/thaw cycling to closely match the porcine aortic root in the physiological range. PVA hydrogel at freeze/thaw cycle 4 has adequate stress-relaxation behavior compared to that of porcine aortic root. A prototype of an expandable artificial heart valve stent was successfully fabricated by the use of an injection molding method.

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REFERENCES

18. Ratner BD, Hoffman AS. Synthetic hydrogels for biomedical applications. In Andrade JD, editor, Hydrogels for medical and...