INTRODUCTION
Collagenous soft tissues, such as skin, ligaments, and heart valves, have long been shown to exhibit viscoelastic behavior. To model this behavior, an appropriate constitutive relationship is chosen, such as the quasilinear viscoelastic (QLV) theory of Fung [1], and its associated material parameters determined by curve-fitting with appropriate test data. Accurate estimation of material parameters is critical for developing models and for quantifying differences between normal, diseased, or industrially processed tissues.

Because of the strong nonlinearity of the QLV constitutive equation, parameter estimation remains a challenge. To simplify the estimation procedure, the nonlinear elastic and viscoelastic responses of the material are typically assumed to be independent, and the appropriate functions are fit separately to the loading and relaxation phases of a uniaxial test. To satisfy the conditions for independence, an instantaneous step displacement should be applied to the tissue. This is impossible to achieve in practice since real-world stress relaxation experiments are limited to ramp displacements. Although some researchers have accounted for the ramp displacement, and demonstrated improvements in the accuracy of the estimated QLV parameters [2,3], these methods have all required additional assumptions or extrapolations which may affect their accuracy.

The goal of this study was to develop a robust method for directly fitting the QLV constitutive model to the stress-time data from the entire ramp-and-hold test, without requiring any additional assumptions, extrapolations, or idealizations of the ramp displacement. To accomplish this, an adaptive grid refinement (AGR) global optimization algorithm was used. The AGR global optimization algorithm, unlike gradient-based minimization approaches, is derivative-free and does not require search vectors or gradients of the objective function [4]. Another advantage of the AGR method is that it does not require initial guesses for parameters, only upper and lower bounds. We hypothesized that material constants obtained using this direct-fit method would better represent the experimental stress relaxation data for heart valve cusp material, and better predict the response of the material to a subsequent cyclic test. To test these hypotheses, parameters estimated by the AGR direct fit method were compared with those obtained by separate fits of the loading and relaxation data sets. Parameters estimated by both methods were then used to predict a subsequent cyclic test.

METHODS
We used an alternate form of the QLV constitutive equation. Assuming a zero initial stress state, continuous elastic and reduced relaxation functions in $0 \leq t < \infty$, and the constraint $G(0) = 1$, the constitutive relationship can be written as

$$T(t) = T^e[\lambda(t)] + \int_0^t T^r[\lambda(t - \tau)] \frac{dG(\tau)}{d\tau} d\tau,$$

where $t$ is time, $\lambda(t)$ is the time dependent stretch, $T^e[\lambda]$ is the elastic response, and $G(\tau)$ is a “box spectrum” reduced relaxation function. The partial derivative of this function is

$$\frac{dG(\tau)}{d\tau} = \frac{C}{\tau} \left( e^{-\tau/\tau_1} - e^{-\tau/\tau_2} \right),$$

with the parameters $C$, $\tau_1$, and $\tau_2$ to be evaluated from experimental data. Taking the partial derivative eliminates the exponential integral functions that normally appear in the reduced relaxation function. This is advantageous for stability and speed of numerical evaluation. For the nonlinear elastic response, we chose the power law function

$$T^e(\lambda) = A(\lambda - 1)^n,$$

because it fit our data better than a single exponential function.

Uniaxial stress-relaxation tests were performed on 5 aortic valve cusp specimens harvested from porcine hearts obtained fresh from the abattoir. Circumferentially oriented rectangular strips of 5 mm width were dissected from the central region of each cusp using a steel cutting block. All specimens were approximately 1 mm thick, and were tested at a ramp displacement rate of 10 mm/s. Prior to testing, each specimen was preconditioned for 25 cycles, then stretched and held for 300 seconds. After 300 seconds, there was little or no detectable change in relaxation rate, although relaxation continued...
very slowly. For one specimen, a subsequent cyclic test was performed.

The AGR global optimization algorithm (Global Optimization, Loehle Enterprises, Naperville, IL) was programmed in Mathematica™ (Wolfram Research Incorporated, Champagne, IL). A least squares objection function

\[ L_{\text{error}} = \sqrt{\sum (T_{\text{model}} - T_{\text{data}})^2} \]

and solution space were defined by specifying upper and lower bounds for each parameter. This domain was divided into regular intervals (initial grid of 10), and the objective function evaluated at each grid point. A small percentage of these solutions with the lowest error were retained as specified by a user supplied “contraction” value (1%). Each retained solution was then surrounded by a new grid of points spaced at 1/3 the distance of the initial grid, and a new set of solutions computed. Contraction was again applied, and the process was repeated until only one (optimal) solution remained. Parameters were also separately estimated by dividing the stress relaxation data into loading and relaxation phases (stress-stretch data for loading, and normalized stress-time data for relaxation). Nonlinear elastic parameters and viscoelastic parameters were separately estimated using the same AGR method as above for each data set. For both the direct-fit and separate fit methods, means and standard deviations for each parameter were computed and compared using analysis of variance with a significance level of \( p < 0.05 \).

RESULTS

For all heart valve specimens, the reduction in stress was between 25 and 30% of the peak stress after 300 seconds of relaxation. The rate of relaxation was very high initially (2 to 4 MPa/s during the first 0.2 seconds), and became more gradual over time. Stress relaxation computed with parameters estimated by the direct-fit method was nearly indistinguishable from the raw data (Fig. 1, solid line). Stress relaxation computed with parameters estimated from separate fits of the loading and relaxation data always underestimated the true stress relaxation (Fig. 1, dashed line).

Cyclic stress predicted with parameters estimated by the direct-fit method more closely represented the experimental data (Fig. 2). Predictions using these parameters overestimated the peak stress by only 3%, whereas predictions using separately estimated parameters overestimated peak stress by 8%. The least squares error for all 10 cycles (using equation 4) was 0.003 for the direct-fit method, and 0.016 for the separate fit method.

All three viscoelastic parameters \( C \), \( \tau_1 \), and \( \tau_2 \) were found to be significantly different between the two methods (\( p < 0.05 \), \( n = 5 \)), whereas the nonlinear elastic parameters \( A \) and \( B \) were not (Table 1). The \( C \) parameter was significantly higher (approximately 30%) when estimated using the direct-fit method, while the viscoelastic time constants \( \tau_1 \) and \( \tau_2 \) were both significantly lower.

DISCUSSION

The results supported our hypothesis that the direct-fit parameter estimates would better represent the true stress-strain behavior of the tissue. The direct-fit method uses the actual stretch history of the ramp loading of the experiment, rather than an idealized representation. The direct-fit method also eliminates extrapolation or other assumptions regarding the experimental stretch history. In fact, any stretch history can be used. Accuracy of the estimated parameters will depend on whether a particular experimental stretch history contains sufficient data to provide sensitivity for each parameter.

Our separately estimated parameters agree well with those of Sauren [5], the only other reported QLV parameters known to us for tensile loading of heart valve tissues. Our direct-fit parameter estimates, however, indicate faster initial viscoelastic response and a shorter long-term response than previously reported. This rapid initial response improved predictions of the cyclic response, since the model could respond faster to the peaks in the sawtooth waveform.

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REFERENCES