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Heart valve viscoelastic properties — a pilot study

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Abstract

The effects of cryopreservation on the biological tissue mechanics are still largely unknown. Generalized Maxwell model was applied to characterize quantitatively the viscoelastic behavior of sheep mitral heart valve tissue. Three different groups of specimens are supposed to be tested: fresh tissue specimens (control group), cryopreserved allografts from tissue bank and allografts already used as tissue replacements taken from the animals approximately one year after the surgery. Specific aim of this study is to determine whether or not the treatment used for storage in tissue bank influences significantly the mechanical properties and behavior of the tissue. At the moment, only the first group of specimens was examined. The methodology presented in this paper proved suitable to complete the study.

Keywords: allograft heart valves, mitral valve, heart valve banking, mechanical properties of cusp tissue, cusp tissue rheology

1. Introduction

Cardiovascular diseases represent the main cause of morbidity and premature mortality in the European Union. Coronary artery disease, valvular heart disease, stroke and rheumatic heart disease, etc. account for approximately 40% of deaths in European population and cost the European Union's economy € 169 billion in 2003 [2].

Several types of heart valve disease may be recognized, e.g. mitral valve prolapse, mitral stenosis, mitral regurgitation, etc. Possible treatment involves the use of drugs (none of the drugs prescribed for valve disorders are curative; their major function is above all to reduce the severity of the symptoms and to prevent complications), balloon valvuloplasty, surgical repair and, when the damage to the valve is severe enough to be potentially life threatening, valve replacement surgery [5]. Replacement surgery represents often the last option and surgical repair is preferred where possible. However, in the case of serious valves damage, the original tissue must be replaced.

After half century of history, cardiac valves surgery became routine in developed countries. From the very beginning mechanical and biological heart valve substitutes were designed, investigated and developed in parallel. Biological valve prostheses were simultaneously perfected

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in two lines – the commercial interest was focused mainly into the xenograft heart valve substitute construction, while lot of scientific interest was paid to clinical use of allograft heart valves on smaller cohorts of patients. Currently about 49% of patients requiring heart valve replacement receive mechanical valve substitute and about 49% have their valves replaced by xenograft. Only 2% of diseased valves are being replaced by allografts. Nevertheless, none of these types represent the ideal valve substitute. Mechanical valve prostheses are durable, but thrombogenic, e.g. patients need anticoagulation therapy (with its complications) for the rest of the life. To the contrary, biological valve substitutes are not thrombogenic, the anticoagulation therapy is not necessary, but the tissue degeneration remains the main reason for structural valve deterioration. Even allografts tends to structural valve deterioration as well, they are offering some advantages in infective terrain – bacterial endocarditis.

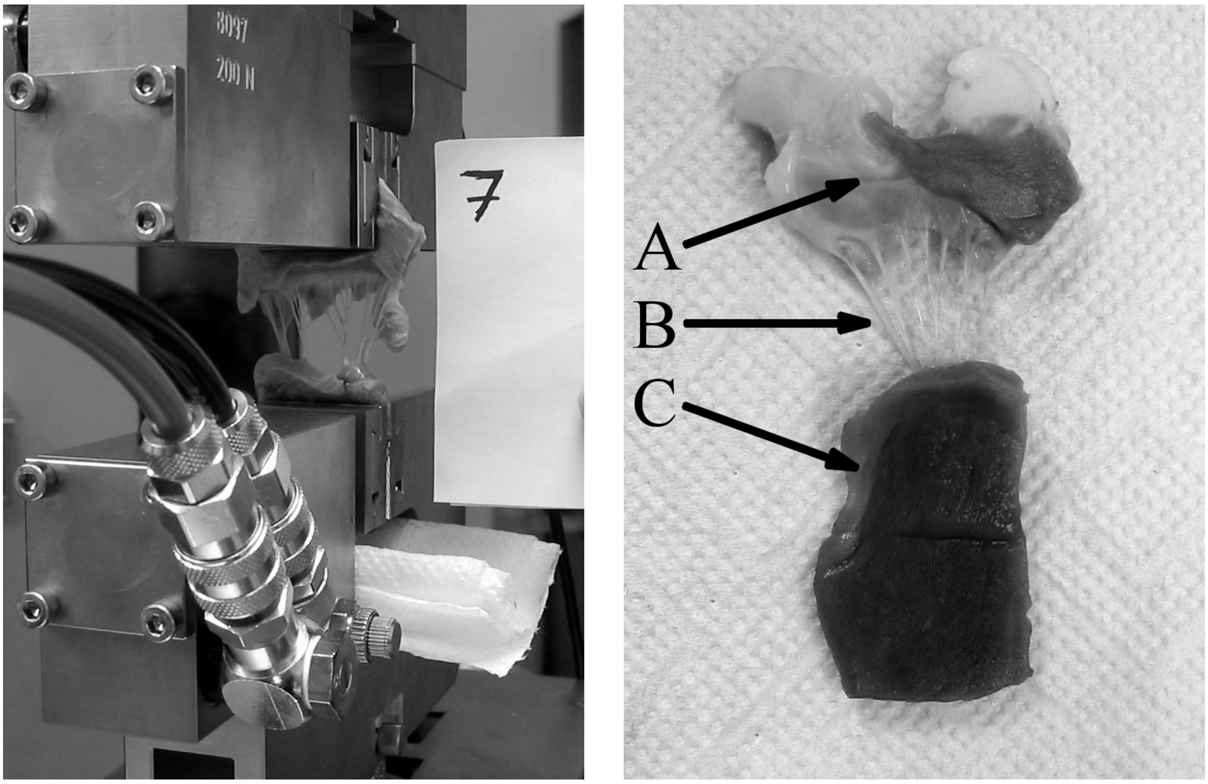
Currently, human donors valves are more frequently preserved in the tissue banks within the frame of transplant programs for their later use. Heart valve tissue may be stored in a tissue transplant bank up to five years. The tissue is specially processed and kept at very low temperature. However, the effects of cryopreservation on the tissue mechanics are still largely unknown. Thus, a question arises whether such a treatment influences significantly the mechanical behavior and properties of the tissue, and how much eventually. Cryopreserved aortic allografts were tested mechanically and the results were compared to those of the porcine xenografts and fresh tissue in [4]. No significant difference was observed between the allograft and the fresh tissues. The xenograft material, however, was less extensible than the other two and it showed significantly lower rates of stress relaxation as well.

The aim of this study was to introduce the methodology and experimental setup that would allow to determine whether there exists, from a mechanical point of view, a significant difference among the fresh mitral heart valve tissue, cryopreserved mitral heart valves stored in a tissue bank and cryopreserved mitral heart valves already used for replacement and taken away from the animals approximately one year after the surgery. Usual method for describing viscoelasticity of various materials is the application of mechanical models assembling elastic and viscous elements, see [3]. Important feature of this approach is that the models' governing differential equations can easily be found, at least in linear case. Based on the similar time–dependent behavior of these models and that of the tissue under consideration, generalized Maxwell model was chosen in this study. The model exhibits the viscoelastic phenomena of stress–relaxation and creep.

The paper is organized as follows: Section 2 describes in detail the material and method used in this study. Experimental setup is presented and loading protocol is defined. Theory of generalized Maxwell models is briefly described and the leading relations are derived that describe the stress–relaxation behavior of these models. Section 3 introduces the materials parameters' identification procedure and its error estimates. Viscoelastic moduli are identified applying a curve fitting method, the accuracy of the fitting is examined and the results are shown in this section. Section 4 discusses the results and the appropriateness of the methodology used in this study. Finally, Section 5 gives a brief concluding statement.

2. Material and method

Stepwise stress–relaxation measurements were made on samples from sheep. There are $N = 18$ samples of fresh tissue in the control group. Similar loading protocol with stepwise stretches was reported e.g. by [3]. Zwick Roell Z050 traction machine equipped with pneumatic grips and 200 N loading cell was used for material testing. The specimens were fixed between



(a) Heart valve tissue sample between the pneumatic grips of the 200 N loading cell of the experimental apparatus Zwick Roell Z050.

(b) Valve tissue sample after the experiment. Part of anterior leaflet of mitral valve (A) with its chordae tendineae (B) and part of papillary muscle (C).

Fig. 1. Two pictures of the experimental setup.

the grips of the apparatus with a free length corresponding to the specimens' dimensions, see Fig. 1. The samples were stretched in steps of 1 millimeter every 5 minutes and the loading protocol consisted in six loading cycles. The time elapsed from the beginning of the step was chosen to reach (approximately) the steady–state. The stress–relaxation curves were recorded. Since the specimens' geometrical form was very complicated and irregular that would cause the difficulties in assessment of geometrical characteristics, e.g. cross–section area, the mechanical behavior was studied in terms of forces and elongation rather than in terms of stresses and strains.

Five element generalized Maxwell model was used in this study for the description of the stress–relaxation behavior of the tissue. A simple Maxwell body includes a viscous element (η) and an elastic element (E_S) connected in series. Generalized Maxwell models consist of some simple Maxwell bodies coupled in parallel. In addition, an elastic element (E_P) may be connected in parallel to them. In this respect, five element generalized Maxwell model consists of two Maxwell bodies coupled in parallel with an elastic element connected in parallel to them.

Assuming the linearity of each parallel branch of the model for one step of stretching, the total force is the sum of the forces induced in the parallel branches of a generalized model:

$$F(t) = F_P + \sum_{i=1}^{n} F_i(t), \tag{1}$$

where $n = 2$ is the number of Maxwell bodies and $F_P = eE_P$ is the force of the parallel elastic element, e represents the stretch and E_P the parallel elastic modulus. Since the stretch of each loading step is instantaneous in the relaxation experiments, $de/dt = 0$ and the governing differential equation for each Maxwell body reduces to:

$$\dot{F}_i(t) + \tau_i^{-1} F_i(t) = 0, \quad i = 1, 2, \tag{2}$$

where the superimposed dot denotes the usual time derivative, the time constant $\tau_i = \eta_i / E_i$ represent the corresponding relaxation time for one step of stretching and η_i and E_i denote the viscous and elastic modulus of i–th Maxwell body, respectively. Taking into account the initial condition $F_i(0) = eE_i$, the solution for the force function for one step of stretching can easily be obtained as:

$$F_i(t) = eE_i \exp(-t/\tau_i), \quad i = 1, 2, \tag{3}$$

where t is the time elapsed from the beginning of the loading step. The solution for generalized Maxwell model with n Maxwell bodies with parallel elastic element (E_P) attached to them may be expressed as:

$$F(t) = eE_P + \sum_{i=1}^{n} eE_i \exp\left(-t/\tau_i\right). \tag{4}$$

Equation (4) is the final force–time relation with material parameters E_P, E_1, E_2, η_1 and η_2 to be identified.

3. Results

The above equations describe a single step of stretching at constant values of the parameters E_P, E_1, E_2, η_1 and η_2. Their values are different for each relaxation step. To identify these parameters, a direct exponential fitting to the experimental data was performed using statistical software R. The fitting process was the Gauss–Newton algorithm based on the nonlinear least–squares method.

A set of material parameters was determined for each stretching step for each specimen of the tested group. Residual standard error and correlation coefficient were computed to estimate the error of fitting. Mean value and standard deviation of all mechanical parameters and error estimates were then computed for each loading cycle, see Fig. 2 and Fig. 3. The result of the identification are summarized in Tab. 1 that presents the mean values and standard deviations of the identified parameters. Tab. 2 shows the mean value of the correlation coefficient R that represents the accuracy of the fitting process in each loading cycle. Note that the correlation coefficient R is defined as:

$$\mathrm{R} = \frac{\sum[F(t_j) - \bar{F}(t_j)][F_m(t_j) - \bar{F}_m(t_j)]}{\sqrt{\sum[F(t_j) - \bar{F}(t_j)]^2 \sum[F_m(t_j) - \bar{F}_m(t_j)]^2}}, \tag{5}$$

where t_j denotes the discretized time vector, i.e. the time instants corresponding to data acquisition of the experimental apparatus, $F(t_j)$ stands for the theoretical (fitted) values of force in

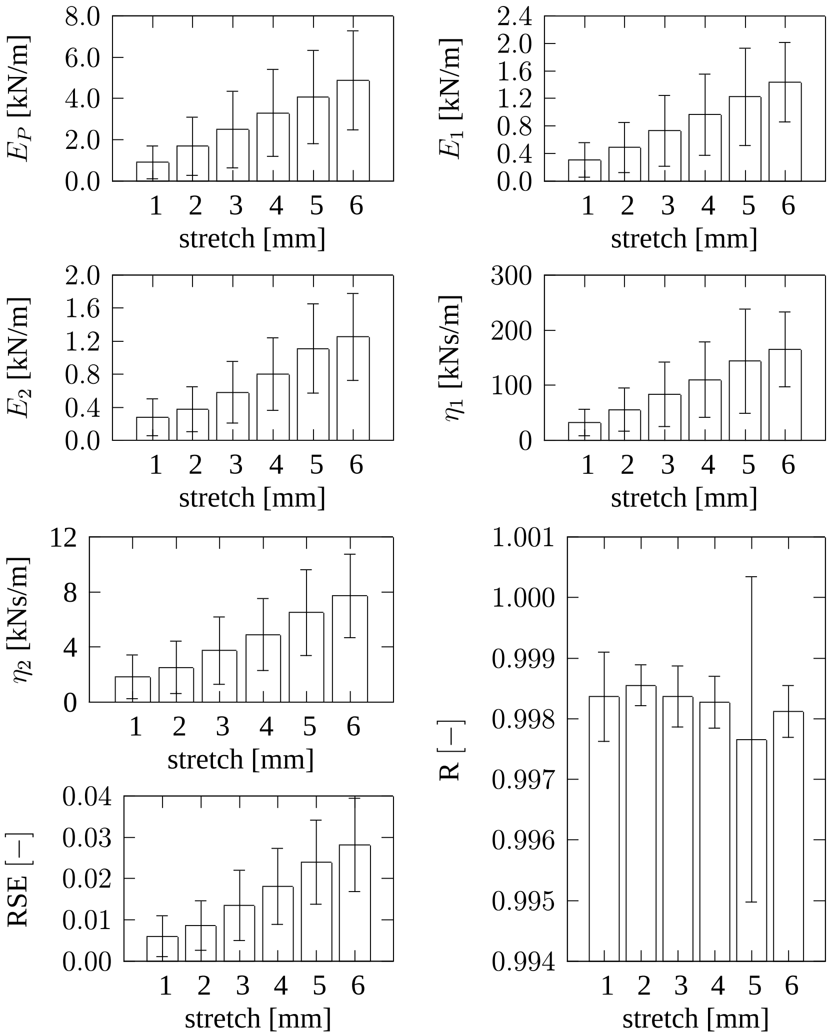


Fig. 2. Mean values and standard deviations of the material parameters and error estimates of the fitting process plotted versus stretch corresponding to loading cycles. Elastic material parameters E_P, E_1 and E_2 are expressed in kN/m and viscous material parameters η_1 and η_2 are expressed in kNs/m. RSE denotes the Residual Standard Error and R denotes the correlation coefficient. Both these quantities are dimensionless and they represent the accuracy of the fitting process.

stretch (mm)	E_P (kN/m)	E_1 (kN/m)	η_1 (kNs/m)	E_2 (kN/m)	η_2 (kNs/m)
1	0.92±0.80	0.31±0.25	32.20±23.78	0.28±0.22	1.84±1.60
2	1.69±1.40	0.49±0.36	55.84±38.89	0.38±0.27	2.53±1.90
3	2.50±1.86	0.73±0.51	83.40±58.61	0.58±0.37	3.75±2.46
4	3.29±2.11	0.97±0.59	109.93±68.63	0.80±0.44	4.91±2.61
5	4.07±2.25	1.23±0.71	143.95±94.84	1.11±0.54	6.50±3.12
6	4.89±2.40	1.44±0.58	165.31±67.61	1.25±0.53	7.72±3.04

Tab. 1. This table presents mean values ± standard deviations of the material parameters identified in each loading cycle that corresponds to applied stretch.

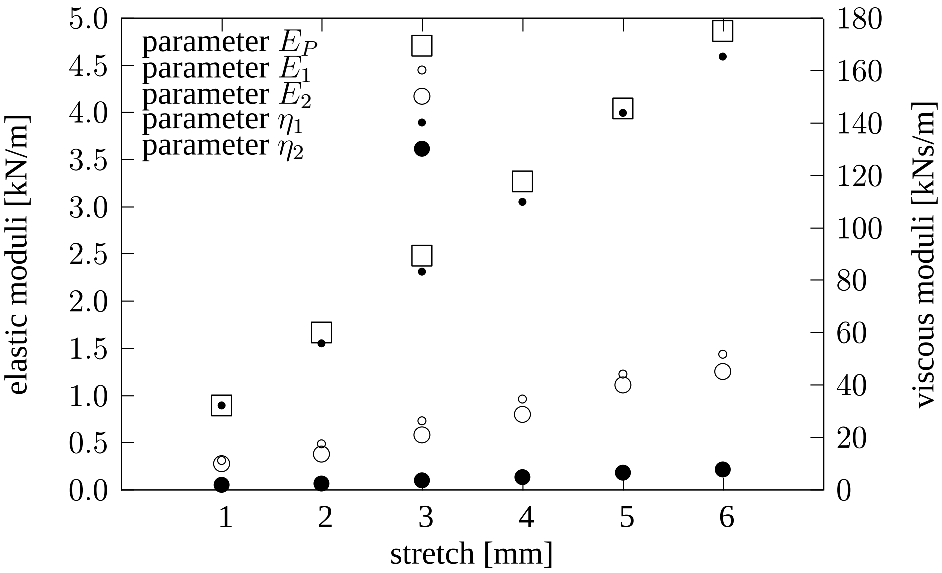


Fig. 3. Mean values of the material parameters plotted versus stretch corresponding to loading cycles. Elastic material parameters E_P, E_1 and E_2 are expressed in kN/m and viscous material parameters η_1 and η_2 are expressed in kNs/m.

cycle	(−)	1	2	3	4	5	6
R	(−)	0.99836	0.99855	0.99837	0.99827	0.99766	0.99812

Tab. 2. Mean value of the correlation coefficient R that represents the accuracy of the fitting process in each loading cycle corresponding to applied stretch.

time t_j, $F_m(t_j)$ denotes the measured (experimental) value of force in time t_j and the superimposed bar $^-$ denotes the mean value of the respective quantity. The closer R is to 1, the higher is the accuracy of the fitting process.

The data records were examined globally as well. Since the sampling frequency is set up internally by the experimental apparatus, the number of degrees of freedom is slightly different for each sample. Thus, the time–force relations were "normalized" from around 2800 degrees of freedom to exactly 1200 degrees of freedom using the cubic spline interpolation. Again, mean value and standard deviation were computed from the time–force data records for the control group. Finally, the theoretical time–force relation corresponding to the selected Maxwell model was reconstructed using the mean values of measured material parameters. This relation was confronted with the mean measured force–time relation as shown on the Fig. 4.

4. Discussion

Actual configuration of the experimental apparatus does not allow to immerse the specimen in any liquid media, e.g. physiological solution. Thus, in order to prevent dehydration of the specimen the total testing time was reduced, and so, there is no preconditioning phase in the testing protocol. The role of preconditioning is discutable although it has been shown that the preconditioned state of the porcine aortic valve material is a function of the deformation history that has occurred before the preconditioning cycles and that preconditioning without an adequate rest period between tests increases predictive errors [1]. However, this study was focused

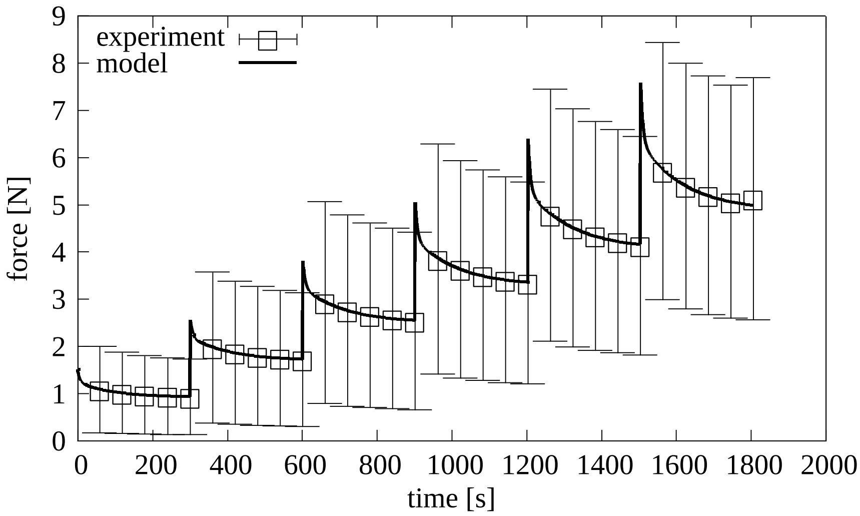


Fig. 4. Force–time response to loading protocol as predicted by the Maxwell model using the mean values of material parameters compared to mean experimental force–time dependency with standard deviation shown. Only few experimental data points are shown on the graph for lucidity.

on relatively regular samples of aortic cusps while this paper deals with rather complex geometrical structure of the mitral valve apparatus. Skipping the preconditioning phase is therefore an adequate approach since the aim of the study is to find and select a criterion that would allow to consider the importance of differences in mechanical behavior of the three groups of specimens regardless of the physical meaning of such a criterion and, thus, prior sample's deformation.

Tab. 2 shows that the model fits appropriately to the measured data. Note that a preliminary study revealed insufficiency of the three element model yet single exponential function cannot render the experimental data. Small perturbation of the correlation coefficient value appears in the 5th loading cycle. It may be attributed to numerical instability of the algorithm, inappropriate choice of the initial parameters' guess and/or to some error in the input data. However, it does not seem to influence the identified values of the materials' parameters; at least, no similar perturbation is manifested in the identified data. Moreover, this perturbation is of the order 10^{-3} and the correlation coefficient's value still exceeds 0.99 being a very satisfactory results.

General tendency of the increasing value of the identified parameters as functions of the applied stretch is apparent on Fig. 2. Fig. 3 shows a nearly linear dependence of the identified parameters on the applied stretch. Almost equal slopes of the E_1 and E_2 elastic moduli linear dependencies is apparent while there is a significant difference between the slopes of the viscous moduli functions. Yet this was not the objective of this work, linear dependence of the material parameters on the stretch must be prove, even though it is usually a common feature of many materials under a small loading. Note that the parameter E_P represent the sample's rigidity (spring constant) in the equilibrium state, i.e. at the end of each loading cycle. It may not be practically related to the usual Young modulus since the cross-section area of a sample is not well defined; see the sample's complex geometry on Fig. 1(b).

The variance of the identified values lies within the range expected for a soft biological tissue. It is with no doubt influenced by a relatively small number of specimens, $N = 18$. However, this study is considered as preliminary and its main aim is to introduce a methodology of comparison of different groups of samples so that the number of samples to be tested will increase.

5. Conclusion

Five element Maxwell model seems to be simple yet adequate tool for description of the heart valve tissue rheology. Even for a relatively small number of tested specimen the fitting process gave satisfactory results. On the contrary, three element Maxwell model did not render the measured data based on the chosen loading protocol. The method introduced here proved to be suitable to determine the tissue's rheology. It allows to compare quantitatively mechanical properties of different tissue samples and to analyse variance of parameters that characterize the tissue mechanics.

Acknowledgments

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