Acta of Bioengineering and Biomechanics
Vol. 21, No. 3, 2019

Original paper
DOI: 10.5277/ABB-01305-2019-04

Mechanical guidelines on the properties of human healthy arteries in the design and fabrication of vascular grafts: experimental tests and quasi-linear viscoelastic model

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Purpose: Knowledge of mechanical behavior of healthy human arteries as the guidelines to target properties of vascular grafts deserves special attention. There is a lack of mathematical model to characterize mechanical behavior of biomaterial while many mathematical models to reflect mechanics of human arteries have been proposed. The objective of this paper was set to measure mechanical properties of healthy human arteries including Common Carotid Artery (CCA), Abdominal Aorta Artery (AAA), Subclavian Artery (SA), Common Iliac Artery (CIA) and Right and Left Iliac Artery (RIA and LIA) and compare them to those of commercial ePTFE and Dacron®. *Methods*: Series of stress relaxation and strain to failure tests vere performed on all samples. The experimental data was utilized to develop quasi-linear viscoelastic (QLV) model of both natural and artificial arteries. *Results:* ePTFE is the stiffest sample, while the CCA is the most compliant one among all. RIA and CIA are more viscous than the other natural arteries, while AA and CCA are less viscous. The proposed model demonstrated an accurate fit to the experimental results, a proof of its ability to model both nonlinear elasticity and viscoelasticity of the human arteries and commercial ones. *Conclusions:* ePTFE and Dacron® are much stiffer than human arteries that may lead to the disruption of blood hemodynamic and may not be biomechanically feasible as a replacement.

Key words: *elasticity, constitutive model, human artery, artificial artery, quasi-linear viscoelasticity*

1. Introduction

One cannot deny the many benefits that vascular grafts have brought to humans in serving as artificial replacements for damaged blood vessels. However, the issue of which of their biomechanical properties improve the patency rate is still a matter of debate.

Similar to all soft tissues, arteries show very low stress at low strains, called the toe region, which is caused by blood pressure [4]. By increasing the blood pressure, the biomechanical behavior of arteries could reach the linear stress–strain section. Moreover, a different mechanical response in the circumferential and longitudinal direction has been reported for arteries [28]. Studies on human arteries have revealed that healthy arteries are incompressible, anisotropic, nonlinear, and viscoelastic. Moreover, mechanically, they are highly dependent on location and physiological function. In addition, the viscoelastic nature of human arteries which means the dependence of arterial strain on its history of stress, when subjected to biological pressure range, causes a delayed response to pressure changes. This phenomenon has an important role in arterial deformation [27]. Generally, smaller arteries are more viscous than large ones due to the large content of smooth muscle cells [24]. Compliance (radial extensibility of an artery or graft under physio-

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Received: January 20th, 2019
Accepted for publication: June 17th, 2019

logical pressure) and viscoelastic mismatches between the graft and host artery especially at the anastomotic line can lead to the disruption of wall shear stress tensor as well as blood flow patterns and, subsequently, the occurrence of intimal hyperplasia (IH), which is the main reason of graft failure [12]. Lowering compliance and viscoelastic mismatches will reduce the generation of IH, and consequently improve patency rates [17].

To lower these mismatches, Young's modulus in the physiologic range (slope of stress–strain curve equivalent to 80–120 mmHg) and stress relaxation (in strain level of 30% of initial length) of vascular grafts must be close as much as possible to those of healthy human blood vessels. So, to find a guideline for substituting natural blood arteries, both stress–strain curves, especially Young's modulus in the physiologic range, as well as viscoelastic properties should be considered. Thus, it seems imperial to have knowledge on the mechanical properties, structure and function of healthy human blood vessels, which have been rather widely reported in previous studies, especially those arteries that are exposed to a disease such as coronary artery disease, peripheral arterial disease, cerebrovascular disease, renal artery stenosis and aortic aneurysm [5], [9].

The mechanical properties of human blood vessels such as tensile strength, ultimate strain and Young's modulus have been reported by several investigators. However, different methods of data extraction have led to a wide range of results for a particular vessel such as the human saphenous vein, making it hard to use it as basic mechanical information in designing and fabricating synthetic vascular grafts [7], [22]. Nevertheless, the mechanical properties of vascular grafts (ePTFE, Dacron®, polyurethane, etc.), such as dynamic compliance and viscoelastic behaviors such as relaxation, creep, cyclic, and strain rate dependency, while being more important than static properties, have not been completely addressed and require greater attention [7], [11].

Vascular grafts with diameters larger than 6 mm, which are commercially produced from expanded polytetrafluoroethylene (ePTFE) or polyethylene therphtalate (PET, Dacron®) and different construction patterns (woven, knitted and braided) have earned good success. However, vascular grafts with medium and small diameters have not achieved considerable success due to the risk of IH and graft thrombosis, the main clinical issues of graft failure [23]. In most cases, commercial vascular grafts demonstrate lower strain and a relatively higher linear stress response than that of human arteries at similar levels of strain (stiffer or less compliant) [21]. Several investigations have focused on the mechanical properties of different commercial vascular grafts such as ePTFE, Dacron® and tissue-engineered ones as replacements of injured vessels, but their dynamic properties, such as viscoelastic behavior, deserve to be more specifically investigated.

In addition, very few types of vascular grafts as well as tissue-engineered ones have been characterized by a constitutive model to capture their mechanical behavior, while many mathematical models have been proposed for natural vessels. Strain energy density function-based models [15], structure-based models [8], linear and nonlinear viscoelastic models [8], [16], as well as quasi-linear viscoelastic (QLV) models [2], [5] have been widely used to characterize the mechanical behavior of natural arteries and veins. In 1972, Fung proposed the QLV theory by considering both nonlinear elasticity and history dependency of materials' viscoelasticity. Since then, it has been frequently used to model the viscoelastic behavior of soft tissues. Also, this theory is based on a step change in strain level, something which is not possible to achieve in reality [6]. To overcome this limitation, in recent years, Abramovitch and Woo proposed a novel (or modified) QLV model by including the ramping phase of the experiment [1].

Furthermore, a proper constitutive model for the mechanical properties of healthy human arteries plays an essential role in many procedures, such as improvement of diagnostics procedures, optimizing the design of vascular grafts, investigating age-related changes in the arterial system, examination of diseases and other investigations.

Given the lack of proper comprehensive mechanical guidelines on the properties of natural healthy human arteries in the design and fabrication of vascular grafts and also the constitutive model for vascular grafts, the goal of this study was divided into three main parts:

1. to measure the mechanical properties of healthy human arteries, such as the CCA, AAA, LIA, RIA, CIA and SA to develop guidelines to target the properties of vascular grafts with a focus on viscoelastic properties by performing a series of stress relaxation tests at different strain levels as well as stress–strain tests;
2. to determine the mechanical properties of commercial ePTFE and Dacron® with the same protocol of human arteries, and;
3. to propose a comprehensive QLV model to be used in finite element modeling and analysis of healthy natural arteries and commercial ones.

2. Materials and methods

Sample preparation

The healthy CCA, AAA, LIA, RIA, CIA and SA were removed from 3 individuals with permission from donors under the ethical rules of the 2013 Declaration of Helsinki (Seventh edition). All the extracted samples were kept in normal saline and refrigerated until the tests were begun. Samples were tested within 12 hours. The mean ± standard deviation (SD) radius and thickness of different human arteries, commercial ePTFE and Dacron® were measured precisely using a micrometer having a resolution of 0.005 mm 0.05% (Mitutoyo Corporation), reported in Table 1. Natural samples were sprayed with saline solution to prevent drying of the tissue during the experiment.

Table 1. Outer radius and thickness of human arteries, ePTFE and Dacron®

Artery/Graft	Outer Radius [mm]	Thickness [mm]
AAA	9.31 ± 1.48	2.18 ± 0.71
CIA	6.01 ± 1.09	2.12 ± 0.84
RIA	4.24 ± 0.48	1.78 ± 0.29
LIA	4.02 ± 0.17	1.61 ± 0.33
CCA	4.69 ± 0.73	1.48 ± 0.37
SA	5.77 ± 1.44	1.67 ± 0.52
ePTFE woven	11 ± 0.01	0.4 ± 0.01
Dacron® (woven)	5 ± 0.01	0.7 ± 0.01

Test procedure

All tension tests were performed by a universal tension test device (SANTAM Corporation-STM-1) equipped with a 250 N load cell with an accuracy of ±0.01 N. Preconditioning of the blood vessels is an important step in mechanical tests, so, based on earlier studies, the conditioning of the tissue can be fully reached after about 10 cycles, when the hysteresis is diminished [5]. Therefore, the preconditioning of samples was performed by applying a preload of 0.05 N for ten cycles. The strain rate of 1%/min was employed to carry out the tension tests and to obtain the strain–strain curves. Furthermore, to obtain the viscoelastic behaviors of human arteries, commercial ePTFE and Dacron®, a series of stress–relaxation tests at strain levels (depending on the failure strain of the samples) of 10, 20, 30, 40 and 50% was conducted at a strain rate of 1%/min and holding time of 5 minutes, following the application of preconditioning cyclic loads. A minimum of three samples was taken from each individual arteries and commercial ones and only the results of samples ruptured away from the grips were taken into consideration.

QLV theory

QLV is a simplified nonlinear viscoelastic model in which the viscoelastic section is divided into time and strain-dependent components, proposed to express hyperelasticity as well as the nonlinear relaxation behavior of the arterial walls. According to the QLV model proposed by Fung, the stress relaxation behavior of arteries is expressed as [6]:

$$\sigma(t) = G(t) * \sigma^e(\varepsilon) \tag{1}$$

where $\sigma^e(\varepsilon)$ is the stress corresponding to an instantaneous strain and $G(t)$ is the reduced relaxation function representing the stress of the arteries normalized by the stress after the initial ramp strain. Also, ε and t are the strain and time, respectively. According to the Boltzman superposition principle, the stress at time t is expressed as:

$$\sigma(t) = \int_{-\infty}^{t} \frac{G(t-\tau)(\partial\sigma^e(\varepsilon))}{\partial\varepsilon} \frac{\partial\varepsilon}{\partial\tau} \partial\tau \tag{2}$$

The decaying exponential equation was chosen to describe the reduced relaxation behavior of human arteries and commercial vascular graft [25], [26]:

$$G(t) = ae^{-t/\tau_1} + ce^{-t/\tau_2} + ge^{-t/\tau_3} \tag{3}$$

The reduced relaxation function (Eq. (3)) has the form of the generalized Maxwell model ($n = 3$). In this model, the time parameters τ_1, τ_2 and τ_3 represent the relaxation times of the sample over the short, medium and long terms, respectively. The relaxation time constant is the ratio of the spring constant to coefficient of viscosity in each branch, i.e., $\tau_1 = a/\eta_1$, $\tau_2 = c/\eta_2$ and $\tau_3 = g/\eta_3$. Also, a, c and g are spring constants in the generalized Maxwell model, representing elastic behavior of the arteries. Likewise, η_1, η_2 and η_3 are the coefficients of viscosity in the generalized Maxwell model, representing viscous properties of the arteries.

On the other hand, the instantaneous nonlinear elastic response of arteries can be described by an exponential approximation relation, as follows:

$$\sigma^e(\varepsilon) = A(e^{B\varepsilon} - 1) \quad A \text{ and } B \geq 0 \tag{4}$$

where A is a linear factor having the same dimension as stress, and B is a dimensionless parameter showing the nonlinearity of elastic response. To apply the QLV theory to develop a model for the stress relaxation test, the procedure has two parts. The first part is a linear increase in strain with a constant rate of γ at a time period of $0 \le t \le t_0$, i.e., $\frac{\partial \varepsilon}{\partial \tau} = \gamma$ (Ramp). The second part is for the time of $t \ge t_0$ where the strain is held constant, i.e., $\frac{\partial \varepsilon}{\partial \tau} = 0$ (Hold).

By substituting the strain history into the QLV model, the stress response for both parts of $0 \le t \le t_0$ and $t \ge t_0$ is expressed as:

$$\sigma(0 \le t \le t_0) = \int_0^t [ae^{\frac{-(t-\tau)}{\tau_1}} + ce^{\frac{-(t-\tau)}{\tau_2}} + ge^{\frac{-(t-\tau)}{\tau_3}}]ABe^{B\gamma\tau}\partial\tau \quad (5)$$

(ramp)

$$\sigma(t > t_0) = \int_0^{t_0} [ae^{\frac{-(t-\tau)}{\tau_1}} + ce^{\frac{-(t-\tau)}{\tau_2}} + ge^{\frac{-(t-\tau)}{\tau_3}}]ABe^{B\gamma\tau}\partial\tau \quad (6)$$

(hold)

Parameter estimation

The unknown parameters of the proposed model for human arteries and the commercial grafts were obtained by fitting the model to the experimental data. For this purpose and to minimize the error between the experimental data and the model, the error function of χ has been described. The function of χ that is the sum of squares difference between the results obtained from the experiments ($\sigma_i^{\exp}(t_i)$) and the QLV model ($\sigma_i^{(\text{QLVmodel})}(t_i)$) for both ramp and constant strain parts, is expressed by the following equation [20]:

$$\chi(A \cdot B \cdot a \cdot \tau_1 \cdot c \cdot \tau_2 \cdot g \cdot \tau_3) = \sum_{t_i=0}^{t_o}[\sigma_i^{\exp}(t_i) - \sigma_i^{\text{QLV model}}(t_i)]^2 + \sum_{t_i=t_o}^{t^\infty}[\sigma_i^{\exp}(t_i) - \sigma_i^{\text{QLV model}}(t_i)]^2. \quad (7)$$

The nonlinear optimization function fmincon of Matlab software (R2014 a) was used to minimize the function χ, expressing the quality of the model that fits the experimental data.

3. Results

The stress–strain curves of different healthy human arteries, as well as commercial ePTFE and Dacron® at a strain rate of 1%/min, are demonstrated in Fig. 1. Also, the physiologic pressure range (80 to 120 mmHg) of natural human arteries is depicted in the same figure [9]. By exploring Figure 1 and the elasticity of all samples, the results reveal that ePTFE is the stiffest sample with E_P of 14.23±0.29 MPa, while the human CCA is the most compliant one among all. The Young's modulus of Dacron® with E_P of 10.7 ± 0.18 MPa is close to that of ePTFE but still much stiffer than natural human arteries. The maximum ultimate stress of 2.7 ± 0.53 MPa and ultimate strain of 70 ± 6.3% were obtained for the CCA; in the physiologic range, it's Young's modulus was 1.24 ± 0.22 MPa, which is the lowest Young's modulus among all arteries. Among the samples, the CIA had the lowest ultimate stress of about 1.08 ± 0.34 MPa.

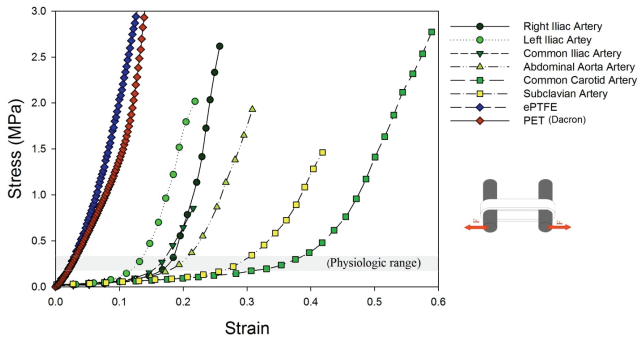

Fig. 1. Strain to failure curves of human arteries, ePTFE and Dacron®

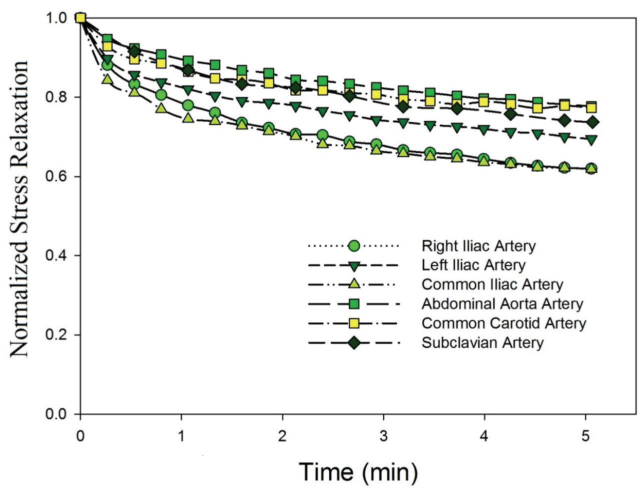

Fig. 2. Normalized stress relaxation–time response of human arteries

The normalized stress relaxation–time curves of all human arteries at a strain level of 30% are illustrated in Fig. 2. According to Figure 2, RIA and CIA are the most viscoelastic arteries among others, where the amount of stress relaxation is 40 ± 3.7% in 5 minutes, while AAA and CCA are the less viscous ones with a stress relaxation level of only about 20%.

The Young's modulus of human blood vessels, commercial ePTFE and Dacron® in the physiologic range (80–120 mmHg) was determined, and compared to those reported in the literature, as presented in Table 2. Since Young's modulus of the samples in the physiologic range has not been reported directly in previous studies, these values were extracted by measuring the slope of the reported stress–strain curves in the physiologic range. To find a guideline for substituting natural blood arteries, both stress–strain curves, especially Young's modulus in the physiologic range, as well as viscoelastic properties should be considered. According to Figs. 2 and 3, the stress relaxation ranges of commercial grafts and human arteries are in good agreement with each other, which, as mentioned in the introduction section, is a very important property.

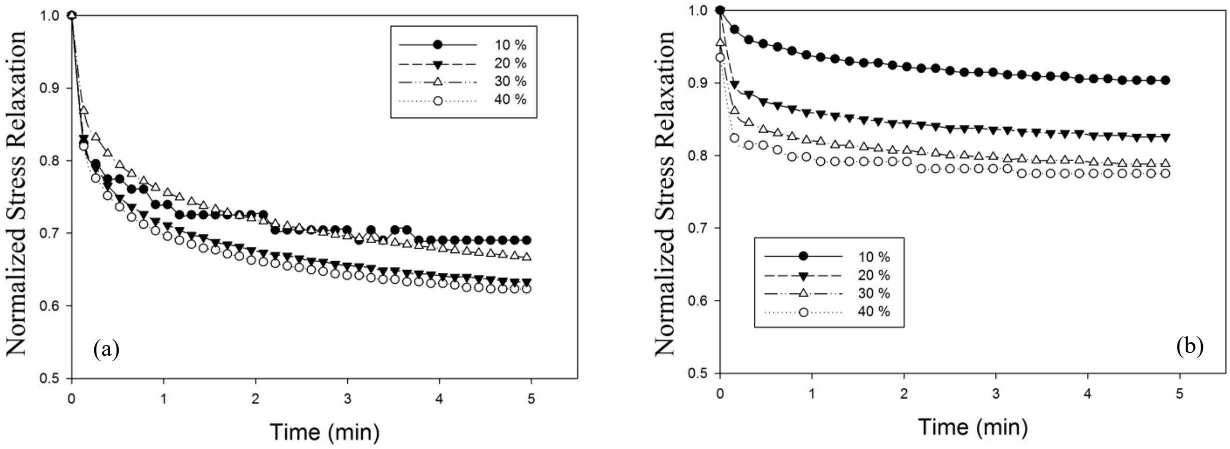

Fig. 3. Normalized stress relaxation-time response of (a) commercial ePTFE and (b) Dacron® at four different strain levels of 10, 20, 30 and 40%

Figures 3a and 3b present the normalized stress relaxation-time curves of ePTFE and Dacron® at strain levels of 10, 20, 30 and 40%, respectively. According to Fig. 3a, ePTFE demonstrates more viscous behavior than Dacron®; the amount of stress relaxation in ePTFE is about 31 to 38%, while for Dacron® it is about 8–22% (Fig. 3b).

Table 2. Young's modulus in the physiologic pressure obtained in current study and previous studies

	Young's modulus in the physiologic pressure [MPa]		
Artery/Graft	Pietrabiss [18]	Kamenskiy [9]	Current paper
Femoral	1.39	–	–
AAA	1.28	1.55	2.16 ± 0.31
Thoracic	1.17	1.15	–
CIA	0.89	1.39	2.27 ± 0.38
CCA	–	0.82	1.24 ± 0.18
SA	–	1.21	1.76 ± 0.22
Renal	–	0.96	–
RIA	–	–	3.12 ± 0.29
LIA	–	–	3.46 ± 0.36
ePTFE knitted	4.39	–	–
ePTFE woven	8.33	–	14.23 ± 0.29
PET knitted	6.42	–	–
Dacron® (woven)	6.25	–	10.7 ± 0.18

To fit the QLV model to the experimental data, stress relaxation tests were performed to all samples by stretching them at a strain rate of 1%/min with up to 1 MPa stress, and then holding in the stretched position for 5 min. The optimum QLV model parameters obtained from the nonlinear elastic response of arteries as well as the reduced relaxation function have been reported in Table 3 by minimizing the error function mentioned in the parameter estimation section. The experimental results for all arteries were compared to the results of the QLV model to validate the accuracy of the model, as demonstrated in Fig. 4. The difference between the stress results of the proposed QLV model and that of the experimental data was less than 6%. It should be noted that the relaxation responses of human arteries as well as artificial vascular grafts did not reach an asymptotic line within 5 minutes. Also, as presented in Table 3, the optimum

Table 3. QLV model parameters for different arteries and commercial vascular grafts

Artery/Graft	QLV Parameters								
	$\sigma^e(\varepsilon) = A(e^{B\varepsilon} - 1)$			$G(t) = ae^{-t/\tau_1} + ce^{-t/\tau_2} + ge^{-t/\tau_3}$					
	A	B		a	τ_1 [s]	c	τ_2 [s]	g	τ_3 [s]
CIA	1.51E-1	13.04		0.092	0.11	0.0047	21.28	0.015	1123.60
CCA	0.64E-1	5.31		0.038	0.27	0.0096	12.50	0.0721	2173.91
SA	0.74E-1	8.15		0.021	0.17	0.0132	22.22	0.0096	1639.34
RIA	0.23E-1	15.56		0.115	0.21	0.0154	40.00	0.047	1298.70
LIA	1.16E-1	13.77		0.1723	0.07	0.00582	21.28	0.028	1333.33
AAA	2.84E-1	10.31		0.066	0.40	0.0064	17.24	0.0062	1149.43
ePTFE woven	3.04	40.241		0.092	0.11	0.00472	20.83	0.016	1098.90
Dacron® (woven)	2.51	17.761		0.0082	0.12	0.0105	12.35	0.056	1219.51

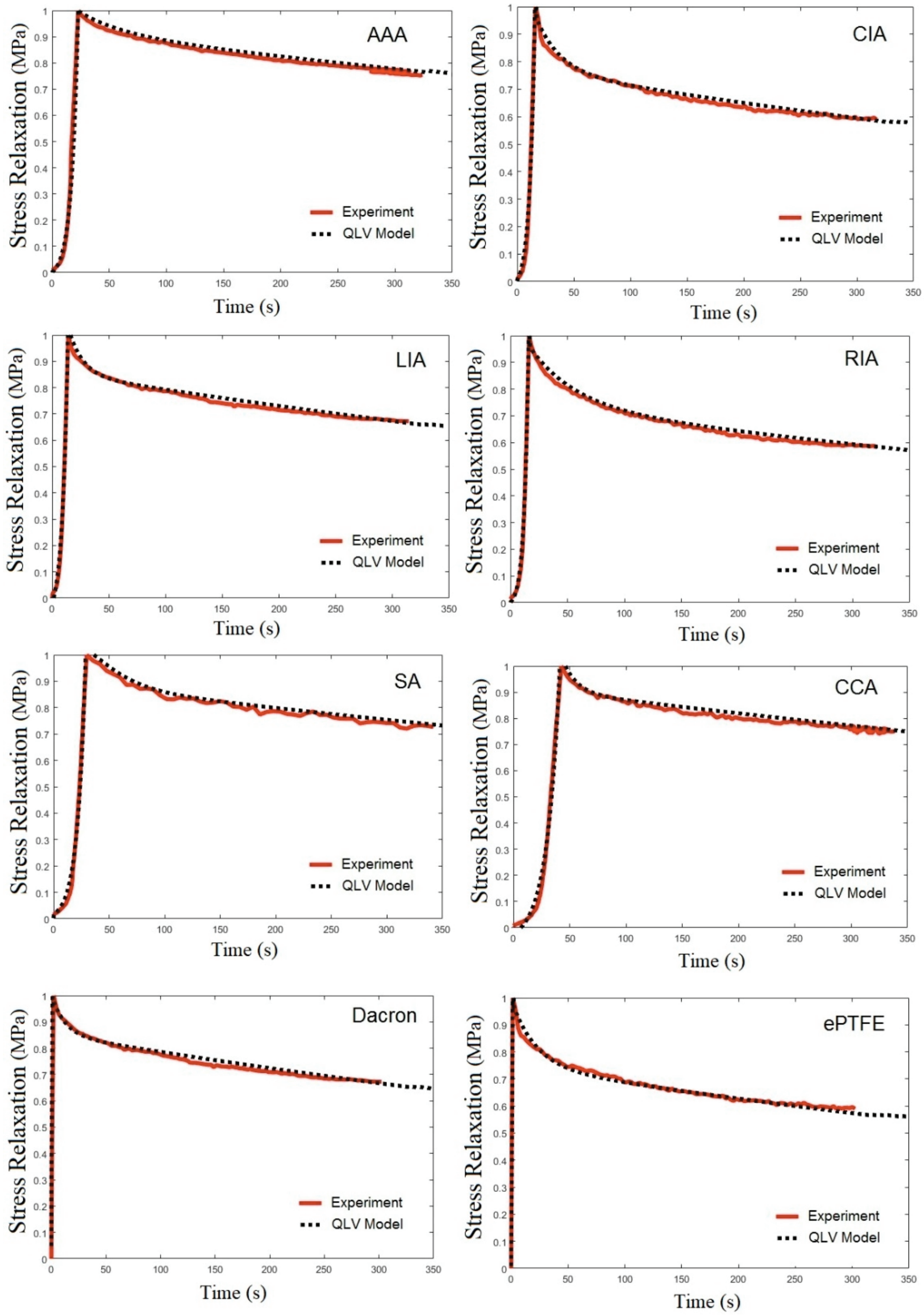

Fig. 4. Experimental results for all arteries as well as the results of QLV model (strain rate at ramp section is 1%/min)

elastic response parameters of A and B were different for each artery due to the obvious variability in the toe region and linear section of the stress–strain curve of human arteries (Fig. 1).

4. Discussion

The nonlinear elastic response and viscoelastic characteristics of healthy human arteries as well as commercial Dacron® and ePTFE were measured and compared together. In brief, a series of uniaxial tensile and relaxation tests were performed on all natural and commercial samples. Results revealed that the lowest and highest ultimate stress among natural arteries are related to the CIA and CCA, respectively. The Young's modulus of tissues in the physiologic range should be taken into account as an important parameter in the design and fabrication of vascular grafts. Therefore, Young's modulus of natural arteries was determined in the physiologic range to be approximately 1.2–3.4 MPa, while the mechanical testing results of commercial ePTFE and Dacron® indicated a much stiffer behavior (up to 11 times stiffer) than that of human arteries, suggesting that the commercially available vascular grafts may not be a proper replacement biomechanically. It should be noted that the high stiffness of commercial Dacron® and ePTFE could lead to the disruption of wall shear stress tensor and blood flow patterns and, subsequently, the occurrence of IH which has been reported to be the main reason of poor long term patency and graft failure [12], [14].

The stress–strain behavior of human arteries revealed high variability in the toe region and linear section of the curves, as shown in Fig. 1. Elastin fibers are responsible for elastic behavior within the biological pressure range of the arteries. When an artery is stretched further than the physiological level, collagen fibers are engaged and contribute to the elastic behavior of arteries. Furthermore, both smooth muscle cells and collagen fibers are responsible for viscous behavior of arteries. Different arteries display the various amount and orientation of collagen and elastin fibers as well as smooth muscle cells [3], [5], leading to different nonlinear elastic and viscoelastic properties.

The obtained Young's modulus of all the tested samples including the natural and commercial ones in the physiologic range in the present study were in good agreement with those of earlier studies as demonstrated in Table 2 [9], [18]. The small differences between Young's modulus of natural arteries in the physiologic range of the current study and that of previous studies, as presented in Table 2, are due to inconsistent material properties and anatomic arteries' characteristics. Furthermore, this difference could be due to the fact that the test samples used in this study were extracted from healthy arteries, while most other studies have reported the mechanical properties of diseased ones, and diseased arteries are usually stiffer than healthy ones [9]. Moreover, according to Fig. 2, RIA and CIA are more viscous than the other natural arteries, while AAA and CCA are less viscous; another finding consistent with the results of previous studies. Prior investigations have also shown that small arteries usually demonstrate more viscous behavior than large ones, due to their large amount of smooth muscle cells [24]. Generally, changes in nonlinear elastic behavior and viscoelastic properties of human arteries depend on several factors such as gender, age, diseases, smoking and lifestyle. Therefore, the difference of mechanical parameters of soft biological tissues such as human arteries from one individual to another is relatively high, leading to a higher standard deviation in the results [4], [5].

At all four strain levels tested, ePTFE clearly displayed more viscous behavior than Dacron®, as shown in Fig. 3. Furthermore, exploring the stress relaxation curves of ePTFE and Dacron® at all strain levels demonstrated that ePTFE is approximately a linear viscoelastic material while Dacron® is remarkably a nonlinear viscoelastic one. Though the amount of stress relaxation of ePTFE is closer to that of RIA and CIA, the most viscous natural arteries, its high stiffness disputes its use as a replacement.

Finally, a recently developed comprehensive [1] QLV model was utilized to predict the mechanical behavior of tissues in loading situations that may not be easily examined in reality [13]. The most important reason for using reduced relaxation function of generalized Maxwell model (n = 3) to address viscous properties of the samples, is the problem of usage of single Maxwell model that exhibits a single relaxation time, while soft biological tissues such as arteries are better modeled by many relaxation times, since their relaxation behavior over the short term differs from their relaxation behavior in the long term [10]. So, according to the proposed model, the first, second and third Maxwell model describe the relaxation behavior over the short, mid and long terms. The larger relaxation time means the less reduced relaxation that occurs.

Earlier study has demonstrated that the QLV model is a reasonable model to address mechanical behavior of soft biological tissues composed mainly of collagen fibers [19]. In accordance with the other soft tissues such as tendon, ligament and skin [1], [5], [25] and based on Fig. 4, the difference between the results of the proposed QLV model and that of the experimental data was about 6%. The predicted results matched well with the experimental data of the selected sample with high precision which proves the reliability of the proposed QLV model to capture both nonlinear elasticity and viscoelasticity of human arteries and commercial vascular grafts. It should be noted that the experimental results used in the model was selected to be in the middle range of all samples tested for each artery.

In addition, one of the most important features of the proposed QLV model was the consideration of the ramp section as well as the constant strain part, covering the whole experimental test results. Furthermore, the proposed model removes the assumption of step change in strain level in Fung's QLV model with finite strain rate. The strain rate of the ramp section of this paper was set at 1%/min, longer than other investigations that used QLV theory, which lead to improvements of the issues associated with the very fast ramp part [1].

5. Conclusions

The hyperelastic and viscoelastic properties of healthy human arteries and commercial Dacron® and ePTFE were measured, indicating that these properties are significantly different. Here, the commercial grafts demonstrated much stiffer behavior than that of human arteries, leading to the disruption of the hemodynamics of blood flow and subsequently occurrence of IH. Furthermore, the QLV constitutive models proposed for both natural and commercial arteries were able to accurately predict the experimentally measured data.

Conflicts of interest

We have no conflict of interest to declare.

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