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Original Article

Measuring and Modeling the Viscoelastic Properties of the Human Saphenous Vein Using the Pressure–Diameter Test

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ABSTRACT

Coronary artery bypass graft surgery is a customary therapy for vascular-related diseases, with many thousands of such a surgical modality reported annually. In this surgery, the saphenous vein, internal mammary artery, or radial artery is grafted in order to replace the coronary arteries. Using a device designed in our own laboratory, we primarily sought to find a suitable model representing the mechanical behavior of the human saphenous vein wall and then to assess its mechanical properties. The most important feature of this device is its ability to simulate the physiological conditions that exist inside the human body. We obtained 2 samples from the saphenous opening and the medial epicondyle in patients with hypertension. After performing measurements at frequencies near to the heart beat frequency and finding the loss and storage moduli for each frequency, we found that—in the scanned frequency range—the Kelvin model was the best approach to evaluating the viscoelastic behavior of the vessels. Our findings also indicated that the elasticity and damping coefficients could be deemed equal along the length of the saphenous vein. Accordingly, we would advise that heart surgeons not consider the changes in the mechanical properties along the length of the saphenous vein at the time of transplantation. ***(Iranian Heart Journal 2016; 17(3):27-35)***

Keywords: Mechanical behavior ■ Pressure–diameter test ■ Viscoelastic modeling ■ Soft tissue■ Saphenous vein

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Atherosclerosis is a progressive and gradual disease and is deemed the most important health problem around the globe. The disease occurs due to the thickening of the coronary arteries. Annually, in excess of 900 thousand deaths occur due to cardiovascular diseases in the United States. About three-quarters of these deaths are related to coronary artery diseases.[1] In Iran, cardiovascular diseases, particularly coronary artery diseases, have been introduced as the 1st and the most common cause of death in all ages and in both sexes.[2] These diseases of the cardiovascular system are caused by damage to arterial epithelial cells, which form the innermost layer of vessels in the vicinity of the blood flow.

All blood vessels comprise different components such as smooth muscles, elastins, collagens, fibroblasts, and ground substances.[3] Veins are structurally similar to arteries but they have thinner walls, less elastic intermediate layers, and thicker collagen external layers.[4] In vessels with large diameters, the mechanical properties are essentially provided by the unique viscoelastic properties of each component.

Where hypertension is the primary disease of the middle layer of vessels (the tunica media), atherosclerosis is the primary disease of the inner layer (the tunica intima).[5] In fact, the latter constitutes the most frequent vascular disorder overall. The risk factors for atherosclerosis include hyperlipidemia, smoking, diabetes mellitus, genetic predisposition, social stress, sedentary lifestyle, and hypertension.[6] Specifically, atherosclerotic plaques tend to occur at locations with a complex geometry (e.g., along the outer section of a bifurcation), most commonly in abdominal aortas, iliac arteries, coronary arteries, femoral arteries, popliteal arteries, carotid arteries, and cerebral arteries (Fig. 1).

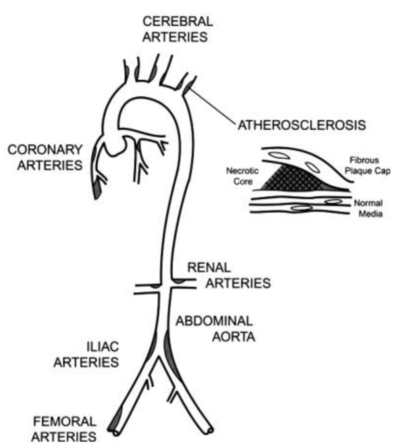

Figure 1. Some preferential locations of atherosclerosis in blood vessels

Two different therapeutic methods, namely stenting and coronary artery bypass graft surgery (CABG), are usually considered for atherosclerosis.[7] Given the riskiness of these methods, however, they are drawn upon only in urgent cases of atherosclerosis, when the drug therapy has failed. CABG is a common treatment for vascular diseases and is done by replacing the blocked coronary artery with a saphenous vein, or an internal mammary artery, or a radial artery.[8] This surgical modality is performed with the use of autologous grafts thousands of times annually the world over. There has, therefore, been considerable incentive—not least among biomechanical and biomaterial engineers—to study the mechanical properties of the vessel wall. Indeed, biomechanical engineers can present the best part of the vessel for graft to the surgeon by measuring the mechanical properties of the replaced arteries in bypass graft and comparing them with the mechanical properties of the coronary artery. Biomaterial engineers work on the construction of artificial blood vessels and prostheses; one of their major fields of interest is to design and produce materials that would match the mechanical behavior of blood vessel walls.

The mechanical properties of the vessel wall depend on the mechanical role of the passive components (i.e., elastin and collagen fibers) and the active components (i.e., smooth muscle cells in the vessel). These components determine the elastic, viscous, and inertial properties of vessels. The inertial effect is negligible due to the quasi-static assumption of changes and slight accelerations.[9] However, elastin and collagen fibers create the elastic properties of a healthy vessel. The modulus of the elasticity of the vessel wall comes from the modulus of the elasticity of elastin fibers and the modulus of the elasticity of collagen fibers.[10] The viscous properties of vessels are due to the smooth muscle of the vascular tissue.[11]

In the literature, there are 3 methods for determining the mechanical properties of blood vessels: the tensile test method,[12] which does not comply with the physiological conditions of vessels in the body; *in-vivo* method,[13] which only determines the modulus of elasticity; and pressure–diameter method,[14] which is the most appropriate and the most useful method. In the pressure–diameter test, the exerted pressure in blood vessels is used. In this test, the inflation (or the diameter) of the tested sample vessel is measured and the pressure is recorded simultaneously. Then, the mechanical properties of the vessel are extracted using the ratio between pressure and diameter at any point and the time delay between these 2 signals. Using this method for the human saphenous vein in patients with hypertension and normotensive subjects with coronary artery disease, Milesi et al.[15] demonstrated that the vessels of the hypertensive patients was stiffer than the vessels of the normotensive subjects. Bia et al.[16-18] designed a simulator and conducted the pressure–diameter test to examine the dynamic properties of the vessel wall. The authors drew upon the Kelvin model and performed the test on 3 types of samples—namely arteries, veins, and artificial prostheses—and found that the elastic modulus obtained from the arteries was smaller than that of the veins and the artificial prostheses. Additionally, they reported that while the damping coefficient of the veins was greater than that of the arteries, the damping coefficient of the artificial prostheses was lower than that of the arteries. In their investigations, the pressure was obtained by means of indirect testing and using empirical relationships. However, in our study, in addition to the direct measurement of pressure and the elimination of errors caused by empirical relationships, the main innovation is the frequency change of the pressure throughout the test. This frequency change in the physiological range helps select the best model for the dynamic behavior of blood vessels.

METHODS

To obtain the mechanical properties of the vessel wall tissue, we designed a device (the pressure–diameter test device) to test blood vessels (Fig. 2). The sample was installed between 2 tubes (by means of silk suture ligatures), such that one of them was fixed, while the other one could be moved to and be fixed at different locations. Inflation was designed to replicate the pulsatility of the physiological environment. The air pressure was monitored by 2 pressure transducers, located on both sides of the rigid cannula. There being a small difference between the measured pressure and the actual pressure inside the center of the specimen, 2 pressure transducers were used in the device, and the pressure within the central length of the sample was obtained using the average of both sensors. Given the maximum matching between the system of this device and the physiological circulatory system, it provides a reliable and appropriate environment to achieve the mechanical properties of blood vessels in operating conditions. Through the application of pressure in a swinging manner and use of a closed-loop control system in the liquid with physiological properties, the pressure inside the sample and the diameter were recorded simultaneously by PC.

According to Figure 2, at point A, there was a mechanism whereby the vessel could be stretched manually. This stretch rate (2%) was provided for pre-conditioning. The measurement of the pre-conditioning was done with a ruler mounted on the wall. The liquid temperature of the container surrounding the vessel was also adjustable; it was set at a constant 37^{o}C. According to the physiological range, the frequency of the applied pressure was adjustable from 0.1 to 10 Hz by a computer program. The data acquisition frequency was adjusted at 50 Hz.

The capillaries were protected from possible damage, when being transferred from the hospital to the laboratory, by storage in a container at 4^{o}C. This is commonly mentioned in the literature for the protection of the properties of organs. Vessel removal and the mechanical test lasted about 1.5 hours. We measured all excessive textures (e.g., the fat) in the removed vessels and the surroundings of the vessels before the test so as to measure the diameter with a scaled band.

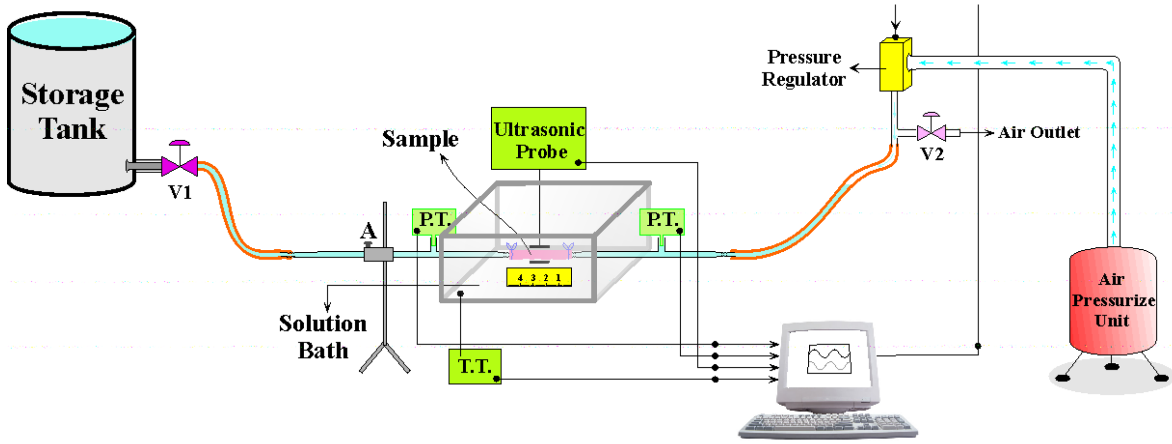

Figure 2. Schematic depiction of the experimental set-up designed for monitoring the pressure–diameter variations of blood vessels.

From 10 patients with hypertension, 2 samples were taken from the saphenous opening (in the thigh area) and the medial epicondyle (in the knee area) and sent to the laboratory. Some information about the patients is presented in Table 1. At the time of removing the saphenous vein, the whole vein from thigh to ankle was removed. Note also that the author was provided with the parts not having been used by the surgeon. In the operating room, following vein removal, heparin was injected into the vein to flush out the blood. Additionally, the branch locations were checked for bores, and the branches were fastened with clips or surgical thread, if needed.

Table 1. Characteristics of the studied cases

Sex	Age (y)	Weight (kg)	Average Blood Pressure (mm Hg)
Male: 6 Female: 4	55.8±6.7	79.2±19.3	**15.7/9.5**

In this experiment, for each sample, frequencies with periods of 0.3, 0.4, 0.5, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0 seconds and frequency ranges of 0.5–3.3 Hz or 30–200 bpm were applied. Thereafter, according to the reference,[14] E*, E_1, and E_2 were calculated using the following equations:

$$E^* = \frac{\sigma_{max}}{\varepsilon_{max}} \qquad \sigma = 2P\frac{(R_i * R_e)^2}{R_e^2 - R_i^2} \times \frac{1}{R^2}$$

$$\varepsilon = \Delta R / R_o$$

In these equations, P was pressure, R_i was the internal radius of the vessel, R_e was the external radius of the vessel, and R was the average radius ($\frac{R_i + R_e}{2}$). The storage (E_1) and loss (E_2) moduli were obtained using the following equations:

$$E_1 = E^* \cos \Delta\theta \qquad E_2 = E^* \sin \Delta\theta$$

RESULTS

For 10 pairs of saphenous veins, obtained from the subjects' thighs and knees, the diameter–pressure test was carried out using a diastolic pressure of 89 mm Hg or a systolic pressure of 158 mm Hg. The test was repeated for each sample at 11 different frequencies. To avoid the effect of waste tensions resulting from the last loadings, we did not apply the data of 5 sways at the beginning of the test. The samples were obtained from the saphenous veins of 48 men, hospitalized in Shahid Modares Hospital to undergo CABG.
Figure 3 illustrates 4 states and demonstrates the pressure–diameter diagram in which the hysteresis loop is depicted. This diagram proves the existence of damping elements and the fitness of the viscoelastic model for modeling the behavior of the saphenous vein. It clearly shows that the energy loss level increased with the applied frequency. The loading and unloading stages of the dynamic test are also marked in the diagram.

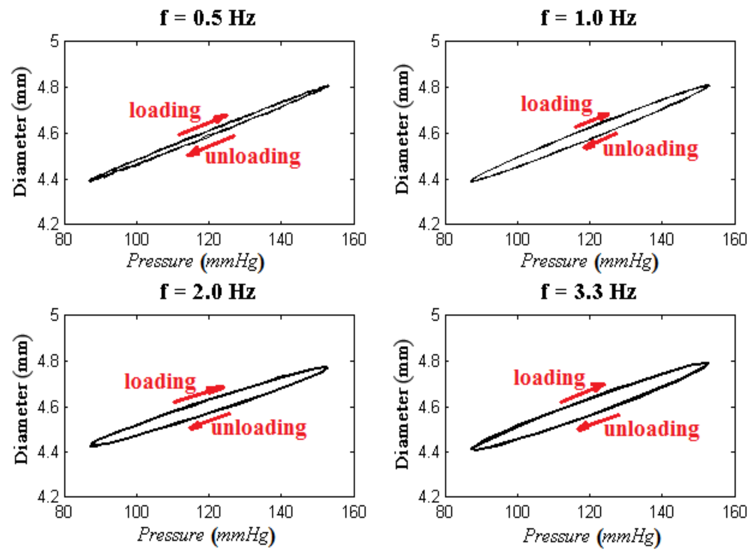

Figure 3. Pressure–diameter hysteresis cycles, measured at different frequencies for a sample.

Figure 4 presents the diagram of the storage and loss moduli with respect to the frequency changes for the sample taken from the thigh area. While the storage modulus (E_1) remained almost constant at 1101.4±66.8 mPa along the frequency changes, the loss modulus increased approximately linearly (R^2=0.87). The Kelvin viscoelastic model was represented by a purely viscous damper and a purely elastic spring connected in parallel. The constancy of E_1 and the direct proportional change of E_2 due to the frequencies applied were necessary and sufficient conditions for the confirmation of the suitability of the Kelvin model for a viscoelastic material.[19] The slope of the fitted line, which played the role of the damping coefficient, η, in the Kelvin viscoelastic model, was 4.13 mPa·s. Figure 5 reveals that as regards the saphenous vein obtained from the same subject's knee, the SD for E_1=1029.8 mPa was 6.7% and η was 8.04 mPa·s.

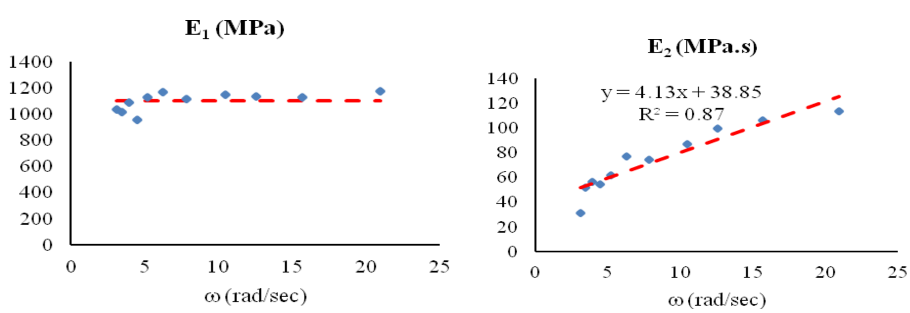

Figure 4. Variations in the storage and loss moduli with respect to frequency for a saphenous opening sample.

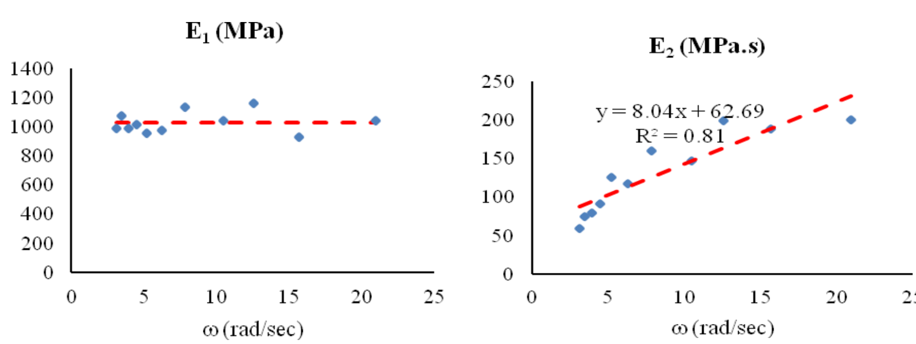

Figure 5. Variations in the storage and loss moduli due to frequency for a sample taken from the knee area.

Showing the pressure–diameter test results for a sample pair of saphenous veins in the thigh and knee areas, we verified the viscoelastic behavior, fitness of the Kelvin viscoelastic model for this sample, and linearity of the material behavior. Table 2 presents the results for the 10 tested pairs of saphenous veins. Table 3 shows the means and SDs of the properties the saphenous veins, obtained from the thigh and knee areas. According to this table, the average of η was 15.16 mPa·s in the thigh area and 14.58 mPa·s in the knee area. Similarly, the elastic coefficient, E, was about 722.44 mPa for the thigh area and 638.44 mPa for the knee area. Finally, the mean of η/E was 0.021 mPa for the thigh are and 0.022 mPa for the knee area. In terms of these means, the η and E values were higher for the thigh.

Table 2. Obtained properties for 10 pairs of saphenous veins

Sample Number	Saphenous Opening (Thigh)			Medial Epicondyle (Knee)		
	E (mPa)	η (mPa·s)	η/E (s)	E (mPa)	η (mPa·s)	η/E (s)
1	477.4	16.2	0.034	421.9	13.1	0.031
2	369.8	10.4	0.028	303.3	7.7	0.025
3	1416.1	35.3	0.025	1063.7	29.2	0.027
4	275.8	5.5	0.020	265.3	4.6	0.017
5	1101.4	4.1	0.004	1029.8	8.0	0.008
6	440.7	9.8	0.022	425.8	6.2	0.015
7	579.5	8.3	0.014	527.9	11.9	0.023
8	789.9	17.5	0.022	741.3	22.1	0.030
9	668.1	15.1	0.023	628.3	15.8	0.025
10	1105.7	29.4	0.027	977.1	27.2	0.028

Table 3. Summary of the results for the saphenous veins in the knee and thigh areas

	Property	Average	SD	Minimum	Maximum
Saphenous opening (thigh)	η	15.16	10.16	4.10	35.30
	E	722.4	374.6	275.8	1416.1
	η/E	0.021	0.008	0.004	0.034
Medial epicondyle (knee)	η	14.58	8.82	4.60	29.20
	E	638.4	301.0	265.3	1063.7
	η/E	0.022	0.007	0.008	0.031

Table 3 shows that the η and E means were lower for the knee than for the thigh. Additionally, η/E was higher for the knee than for the thigh. To statically study the significance of these differences, we employed the independent *t*-test (Table 4). A comparison of η, E, and η/E showed no significant differences between thigh and knee vis-à-vis these indices ($P>0.05$). The results, presented in Table 4, show that these differences did not constitute statistical significance.

Table 4. *T*-test results to compare thigh and knee on η, E, and η/E

Property	*T* Score	*df*	*P*
η	0.136	18	0.893
E	0.553	18	0.587
η/E	-0.287	18	0.778

DISCUSSION

In the present study, 2 basic approaches were considered to be more appropriate for testing. In the related investigations,[16-18] the measurement of the flow rate was done to calculate pressure at any moment using an empirical relationship. We created a new design in the pressure–diameter test device and measured pressure directly at any moment. This approach eliminates some of the errors that the use of empirical relationships creates. Accordingly, the term "pressure–diameter" fits our system in a more realistic manner. In addition, most of the previous studies were conducted using animal vessels and there was a palpable need for research on human vessels. Furthermore, previous investigations conducted the test at a constant frequency and extracted Kelvin model coefficients without proving the appropriateness of the model for the dynamic behavior of the sample. Another question is whether it is possible to consider the approach adopted by the previous studies as the "dynamic approach" without changing the applied frequency. In the current study, all the samples were placed under loading and unloading conditions at different frequencies within the physiological range so that selection could be based on the viscoelastic model frequency according to changes in the loss and storage moduli. Then, the coefficients of the model, including stiffness and damping, were obtained.

Figure 2 shows that loss increased with a rise in frequency. This proves that the loss in the saphenous vein sample was a viscous loss. The reason is that frequency can be regarded as the representative of the term "speed". Viscous damping changes on the basis of speed and not on the basis of Coulomb damping. Each of the 4 modes illustrated in Figure 2 is the representative of the tests conducted at different frequencies. Using the equations in Section 2, we obtained the storage and loss moduli. Given that we focused on the saphenous vein, we can compare η and E based on the position of the vein (i.e., thigh or knee). It is also deserving of note that the coefficients of η and E vary between people significantly. Indeed, it is vitally important that this point be taken into consideration in research on organs and vital tissues. These variations are related to patients' features such as sex, age, smoking, weight, and physical activities. Although it is possible to arrive at such general conclusions as increased roughness among smokers or reduced tissue damping along with higher age, the hypotheses raised should be separately studied in depth in future studies.

We primarily sought to investigate the effects of the location of the saphenous vein. Our results revealed that the toughness coefficient for the knee saphenous vein was smaller than that for the thigh. Additionally, we found that $\frac{E_{\text{knee saphene}}}{E_{\text{thigh saphene}}} = 0.90 \pm 0.06$. Nevertheless, we could not confirm the hypothesis of $E_{\text{knee saphene}} < E_{\text{thigh saphene}}$ because of the high SD of $E_{\text{thigh saphene}}$ and $E_{\text{knee saphene}}$ in different people.

Krasinski et al.[20] conducted a study on the saphenous vein using the tensile stress–strain test at a frequency of 1 Hz (Table 5). Their results, despite the difference in the type of the test applied, are concordant with ours insofar as their η was almost equal to ours and their E was approximately 60% of our value. There were also some samples in which E was almost similar to the value reported in our paper.

Table 5. Values of the moduli of elasticity and damping coefficients [20]

E (mPa)	η (mPa·s)
1235±76	13.2±0.97

CONCLUSIONS

The results of the present study demonstrated that the saphenous vein walls behaved viscoelasticly. All the tests revealed that there was a loss between the applied pressure and the diameter deviations in each sample. Most importantly, the loss was directly related to the increased frequency loading. Given that loss results from viscose terms, the studied vessel walls were a viscoelastic solid. Furthermore, our results confirmed the appropriateness of the Kelvin model in explaining the dynamic behavior of the blood vessels in the study time span. As the nonlinearity of tissue behaviors in expansive areas has been proved in previous research, the research results cannot be used for the claimed areas whether for the pressure or the applied frequency. Our findings also indicated that the elasticity and dampness coefficients could be deemed equal along the length of the saphenous vein. Finally, cardiac surgeons are advised not to take into account the changes in the mechanical behavior along the length of the saphenous vein at the time of transplantation. In other words, it is not possible mechanically to demonstrate that a part of the saphenous vein is more desirable for bypass surgery.

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