

Dynamic responsiveness of the vascular bed as a regulatory mechanism in vasomotor control

Mair Zamir,^{1,2,3} Katelyn Norton,¹ Arlene Fleischhauer,¹ Maria F. Frances,¹ Ruma Goswami,¹ Charlotte W. Usselman,¹ Robert P. Nolan,⁵ and J. Kevin Shoemaker^{1,4}

¹Neurovascular Research Laboratory, School of Kinesiology, ²Department of Applied Mathematics, ³Department of Medical Biophysics, and ⁴Department of Physiology and Pharmacology, The University of Western Ontario, London, Ontario, N6A 3K7, Canada

⁵Behavioural Cardiology Research Unit, University Health Network, Toronto, Ontario, M5G 2M9, Canada

The dynamics of blood supply to a vascular bed depend on lumped mechanical properties of that bed, namely the compliance (C), resistance (R), viscoelasticity (K), and inertance (L). While the study of regulatory mechanisms has so far placed the emphasis largely on R , it is not known how the remaining properties contribute collectively to the play of dynamics in vasomotor control. To examine this question and to establish some benchmark values of these properties, simultaneous measurements of pressure and flow waveforms in the vascular bed of the forearm were obtained from three groups: young healthy individuals, older hypertensives with controlled blood pressure, and older hypertensives with uncontrolled blood pressure. The values of R and C were found to vary within a wide range in each of the three groups to the extent that neither R nor C could be used independently as an indicator of health or age of the subjects tested. However, higher level dynamic properties of the bed, such as the time constants and damping index, which depend on combinations of C , K , and L , and which may reflect measures of the dynamic responsiveness or “sluggishness” of the system, were found to be maintained over a wide range of pulse pressures. These findings support a hypothesis that the pulsatile dynamics of blood supply to a vascular bed are adapted to the individual baseline values of R and C in different subjects with the effect of optimizing the level of dynamic responsiveness to changes in pressure or flow, and that this dynamic property of the vascular bed may be a protected and/or regulated property.

INTRODUCTION

Neurovascular control of blood supply to a vascular bed has, for many years, been thought of primarily as a control of vascular resistance, mediated by a change of vessel diameters at the arteriolar level of the vascular bed (Burton, 1965; Guyton, 1971; Lawry, 1977; Ross, 1978; Fox, 1993; Brooks et al., 1996). In more recent years it has been recognized that, in addition to vessel diameter, vessel compliance is an important mechanical property of the vascular bed that may also play a role in the regulatory process (Strand, 1983; Rowell, 1993; Berne and Levy, 2001; Germann and Stansfield, 2005; Zamir et al., 2007). In the same way that a change in the diameter of blood vessels affects the resistance of the vascular bed in steady flow, a change in the compliance of blood vessels affects the impedance of the vascular bed in pulsatile flow. The result in both cases is a change in the rate of blood supply to that bed. Because of the pulsatile nature of blood flow, however, a change in the compliance of a vascular bed affects not only the rate of blood supply to that bed, but also, and perhaps more importantly, it affects the dynamics of blood supply to that bed.

It is known that the dynamics of pulsatile blood flow through a vascular bed are influenced by four basic mechanical properties of that bed: resistance (R) due to viscous drag at the vessel wall, compliance (C) and viscoelasticity (K) due to viscoelastic resistance to stretch of the vessel wall, and inertance (L) due to inertia of the blood and vessel wall (Zamir, 2005). Broadly speaking, the steady (or mean) component of pulsatile flow depends on R , whereas the oscillatory component depends on C , K , and L . However, because of wave reflections and the dependence of the wave speed on vessel diameter as well as on vessel compliance, the steady and oscillatory components of pulsatile flow are not entirely independent of each other (Milnor, 1989; Nichols and O'Rourke, 1998; Zamir, 2005). Therefore, the dynamics of pulsatile blood flow as a whole are influenced by the oscillatory part of the flow, and it is in this sense that the compliance, viscous, and inertial properties of a vascular bed affect blood supply to that bed.

From a purely mechanical perspective, the dynamics of an oscillatory CKL system are well understood and

Correspondence to M. Zamir: zamir@uwo.ca

Abbreviations used in this paper: BMI, body mass index; C , compliance; CBP, controlled blood pressure; K , viscoelasticity; L , inertance; R , resistance; UBP, uncontrolled blood pressure.

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have been fully resolved mathematically (Kreyszig, 1983; Zamir, 2005). In particular, it has been found that with different combinations of values of the parameters C , K , and L , the system exhibits different modes of behavior that reflect the extent to which the system is overdamped or underdamped. We believe that this issue is highly relevant in the physiological system because it represents a measure of the dynamic responsiveness of a vascular bed to a change in flow or pressure under the oscillatory conditions of pulsatile flow. It also offers a context in which to assess any change in this responsiveness after acute or chronic changes in the mechanical properties of the system as embodied in the values of R , C , K , and L .

The vasomotor control mechanisms of blood supply affecting the steady component of the flow, and mediated by vascular bed resistance, have been widely studied and are reasonably well understood (Burton, 1965; Guyton, 1971; Lawry, 1977; Ross, 1978; Fox, 1993; Brooks et al., 1996). However, the same is not true of the mechanisms affecting the oscillatory component of the flow, which may be influenced by vascular bed C , K , and L . Here, we focus on the question of how these lumped properties of the vascular bed affect the blood supply to that bed, with the aim of determining the role played by the dynamics of the system in the control and regulation of this supply. To examine this question and to establish some benchmark values of these properties, we tested three groups of human subjects of diverse age and health status.

MATERIALS AND METHODS

Subjects

57 individuals participated in this study. The participants, described in detail in Table I, were grouped as young and healthy individuals ($n = 11$) and diagnosed hypertensive patients. The pharmacologic profile of the patient group was as follows: α blockade (2%), angiotensin-converting enzyme inhibitors (22%), calcium channel blockade (18%), diuretic (28%), antihyperlipidemic agents (16%), β blockade (4%), angiotensin receptor blockade (30%), and anticoagulants (5%). 15 of these patients had fasting glucose levels that were 6 mM or higher. All participants provided signed consent to the study that had been approved by the Human Subjects Research Ethics Board at The University of Western Ontario. Subsequently, the patients were grouped based on whether or not their blood pressure was ($n = 19$) or was not ($n = 27$) under control through their clinical treatments. This selection was made to provide a wide range of values for blood pressure and blood flow.

Experimental design

For the patients, blood samples were obtained from the antecubital fossa with the participant in the seated position after a 12-h fast to assess markers of metabolic and inflammatory status (see Table I). Blood samples were not obtained from the young participants as they were judged to be healthy based on their responses to a health questionnaire. Subsequently, all vascular measurements were made with the participant in the supine position after 20 min of rest. Blood pressure was measured continuously for 10 min from the middle finger of the right hand using the volume

TABLE I
Participant characteristics

	Young	Patient
Age (years)	25 $\pm$ 4	60 $\pm$ 8
Age range	21–35	48–73
Height (m)	1.80 $\pm$ 0.08	1.69 $\pm$ 0.09
Weight (kg)	78 $\pm$ 13	83 $\pm$ 21
BMI (U)	24 $\pm$ 3	29 $\pm$ 7
SBP (mm HG)	126 $\pm$ 14	144 $\pm$ 18
DBP (mm HG)	74 $\pm$ 10	76 $\pm$ 9
MAP (mm HG)	93 $\pm$ 11	100 $\pm$ 11
Glucose (mmol/L)		5.85 $\pm$ 0.76
HDL (mmol/L)		1.54 $\pm$ 0.42
LDL (mmol/L)		3.29 $\pm$ 0.78
Total cholesterol (mmol/L)		5.39 $\pm$ 0.92
Triglycerides (mmol/L)		1.29 $\pm$ 0.60
hsCRP (mg/L)		2.83 $\pm$ 3.90
hsCRP Range (mg/L)		0.3–18.6

Values are mean $\pm$ SD. Blood samples were not assessed for the young group as their clinical status was not in question. Normal ranges: glucose, 3.6–6.0 mmol/L; HDL, (male) $\geq$ 1.0 mmol/L and (female) $\geq$ 1.3 mmol/L; LDL, $<$ 2.6 mmol/L; total cholesterol, $<$ 5.2 mmol/L; triglycerides, $<$ 2.3 mmol/L; hsCRP, 1.0–1.3 mg/L. There were 8 males and 3 females in the young group and 21 males and 24 females in the patient group. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; hsCRP, high sensitivity C-reactive protein.

clamp technique (Finometer; Finapres Medical Systems BV). These values were validated with sphygmomanometer measurements. The Finometer system provides an analogue signal for the blood pressure waveform recorded at the finger and at the brachial artery. The brachial artery pressure waveform is calculated from the finger pressure waveform by a transfer function built into the Finometer software (Bos et al., 1996). The accuracy of the calculated shape of the resulting blood pressure waveform at the brachial site has been confirmed in our laboratory across a range of maneuvers using handheld tonometry (Zamir et al., 2007).

Blood flow velocity was measured in the right brachial artery continuously during a 5-min interval using Doppler ultrasound (4.7 MHz; GE System Five; GE Healthcare) with the digital quadrature signal being translated into an analogue of the instantaneous mean velocity sampled at 200 Hz. A two-dimensional image of the brachial artery (10 MHz; B-Mode ultrasound; GE System Five; GE Healthcare) was made to provide a measure of vessel diameter from the average of three measures made near the site of velocity measurement. The blood pressure and blood velocity waveforms were sampled at 200 Hz, and the electrocardiogram was sampled at 1,000 Hz using a computer-based data acquisition and analysis system (PowerLab; ADInstruments). Subsequently, pulsatile blood flow rate was calculated as the product of brachial artery cross-sectional area and the instantaneously recorded mean blood velocity.

Data analysis

The value of vascular R in a vascular bed is determined from simultaneous measurements of mean pressure and mean flow at the point of entry to that bed. In the same way, the values of C , K , and L in a vascular bed can be determined from simultaneous measurements of the oscillatory components of pressure and flow at the point of entry to that bed. Thus, all the mechanical properties of the vascular bed can be obtained from pulsatile pressure

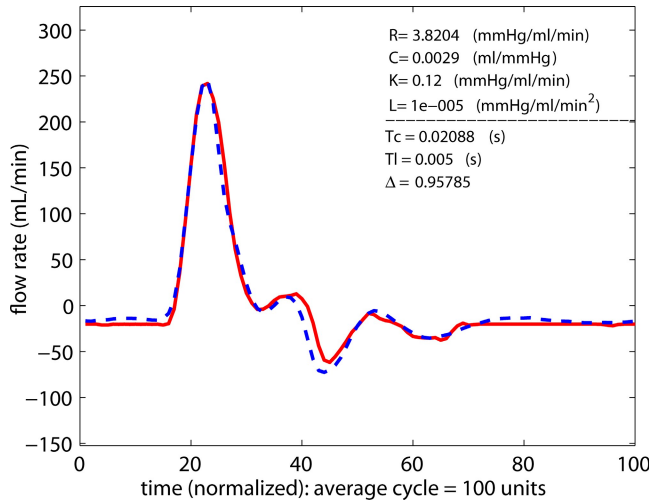


Figure 1. Measured (solid) and calculated (dashed) flow waveform. Values of C , K , and L shown are those that produced the best agreement between the two waveforms and were thus deemed to be values of the corresponding lumped properties of the vascular bed.

and flow waveforms at the point of entry to that bed because these waveforms contain both the mean (steady) and the oscillatory components of the flow.

The calculations of C , K , and L were based on a modified Windkessel model of the vascular bed in which C , K , and L are in series with each other and in parallel with R (Zamir et al., 2007). The measured pressure waveform is used to calculate a flow waveform based on this model, and the calculated waveform is compared with the measured flow waveform. The values of C , K , and L are then deemed to be those that produce the best agreement between the measured and calculated waveforms as illustrated in Fig. 1.

The free dynamics of the flow rate q in a CKL system in series are governed by the second-order differential equation (Kreyszig, 1983),

$$t_L \frac{d^2 q}{dt^2} + \frac{dq}{dt} + \frac{1}{t_C} q = 0, \quad (1)$$

where t_L, t_C are inertial and capacitive time constants, respectively, defined by

$$\begin{aligned} t_L &= L / K \\ t_C &= CK. \end{aligned} \quad (2)$$

The solution of Eq. 1 is given by

$$q(t) = A \exp(\alpha_1 t) + B \exp(\alpha_2 t), \quad (3)$$

where “exp” is the exponential function, and

$$\alpha_{1,2} = \frac{-1 \pm \sqrt{1 - (4t_L / t_C)}}{2t_L}. \quad (4)$$

This solution exhibits three different modes of behavior of $q(t)$ depending on the value of the nondimensional parameter,

$$\Delta = 4t_L / t_C, \quad (5)$$

which we shall refer to as the “damping index.”

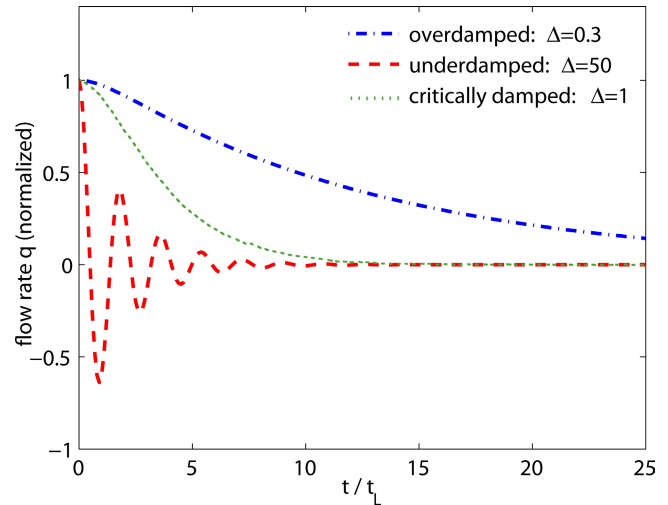


Figure 2. The three dynamic modes of the CKL system. Flow rate (normalized) is increased from a baseline of 0 to 1.0 and then allowed to return to that baseline. Values of the damping index Δ on which the three curves are based are shown in the legend.

When $\Delta > 1$, the behavior of $q(t)$ is oscillatory and is known as an “underdamped” mode of behavior, whereas when $\Delta < 1$, the behavior is non-oscillatory and is referred to as “overdamped.” When $\Delta = 1$, the behavior is referred to as “critically damped” in the sense that it is neither overdamped nor underdamped, as illustrated in Fig. 2. These modes of behavior are usually discussed in the context of a mechanical spring–dashpot–mass system in which C is a measure of the strength of the spring, K is a measure of friction within the system, and L is a measure of the mass (Kreyszig, 1983). In “free dynamics,” the mass is pulled so as to stretch the spring and then let go, allowing the spring to return to its neutral length. The mode of this return to neutral depends on the value of Δ as illustrated in Fig. 2. The equivalent scenario in the physiological system is a change in pressure or flow that will disturb the prevailing oscillatory state of the system (Zamir, 2005). The way in which the system responds to this change and ultimately returns to a stable oscillatory state will depend on the value of Δ .

Because the mechanical properties C , K , and L are involved in the dynamics of blood supply to a vascular bed, it is reasonable to ask if the dynamics of the system are overdamped or underdamped, or more generally, under what range of values of the damping index does the physiological system operate? Our study is devoted specifically to this question, which has not been previously addressed.

RESULTS

Interobserver reproducibility

Because the mechanical properties of the vascular bed are determined by using a model to fit a calculated flow wave to a measured flow wave (Fig. 1), there is concern that decisions regarding the quality of fit will differ between observers. Therefore, we tested the reproducibility of these values as obtained by two different observers in 29 patients. Based on Pearson coefficients, there was strong correlation in the values of R ($y = 1x - 4.1$; $r^2 = 0.99$; $P < 0.0001$), C ($y = 0.99x + 4.89$; $r^2 = 0.99$; $P < 0.001$),

TABLE II

Difference between average values of mechanical properties of the vascular beds in the Young and Patient groups

	Young	CBP patient	UBP patient	Difference young vs. averaged patient
R (mm HG/ml/min)	6.0 ± 4.0	4.35 ± 2.96	3.63 ± 1.37	-35%
C (ml/mm HG)	$4.0 \times 10^{-3} \pm 2.0 \times 10^{-3}$	$5.7 \times 10^{-3} \pm 3.5 \times 10^{-3}$	$4.1 \times 10^{-3} \pm 1.8 \times 10^{-3}$	+20%
K (mm HG/ml/min)	$6.5 \times 10^{-2} \pm 4.0 \times 10^{-2}$	$11.9 \times 10^{-2} \pm 7.1 \times 10^{-2a}$	$13.2 \times 10^{-2} \pm 8.8 \times 10^{-2a}$	+95%
L (mm HG/ml/min ²)	$1.4 \times 10^{-5} \pm 1.0 \times 10^{-5}$	$2.0 \times 10^{-5} \pm 3.0 \times 10^{-5}$	$2.0 \times 10^{-5} \pm 2.0 \times 10^{-5}$	+42%

Values are mean $\pm$ SD. Averaged patient value is based on the combined CBP and UBP groups.

^aSignificantly different from Young ($P < 0.05$; non-paired t tests, Bonferroni corrected).

and K ($y = 0.92x + 0.011$; $r^2 = 0.89$; $P < 0.001$), but less so in the values of L ($y = 0.57x + 1.01$; $r^2 = 0.28$; $P < 0.01$). These results were expected because the main focus of the model is on fitting the systolic peak flow, which is dominated by the compliance C , whereas K and L play diminished roles. The value of R is in fact independent of the observer because it is determined by the measured mean flow and mean pressure.

Test-retest reproducibility

The stability of this approach to reflect vascular mechanical properties was also tested in six patients in whom clinical and anthropometric status had not changed in two sessions separated by a period of 4 mo. Based on Pearson coefficients, there was strong correlation in the values of body mass index (BMI) ($y = 1.0x - 0.32$; $r^2 = 0.99$; $P < 0.0001$), systolic blood pressure ($y = 1.33x - 54$; $r^2 = 0.87$; $P < 0.01$), R ($y = 0.96x + 0.43$; $r^2 = 0.82$; $P < 0.01$), and compliance C ($y = 0.85x + 0.0003$; $r^2 = 0.98$; $P < 0.0001$).

R , C , K , and L

The averaged values of R , C , K , and L across the experimental groups are shown in Table II. The values of R , C , and L were similar across groups. However, compared with the young group, K was 95% higher in both the controlled blood pressure (CBP) and uncontrolled blood pressure (UBP) groups ($P < 0.05$). Values of R and C were found to vary within a wide range in each of the three groups and with a distinct inverse relationship between the two properties (Fig. 3). When viewed in terms of sex difference, there was a clear bias toward high-resistance low-compliance for females and low-resistance high-compliance for males.

Time constants and damping index

The time constants characterizing the dynamics of blood flow within a vascular bed, t_L , t_C , as defined in Eq. 2, are shown in Fig. 4. In contrast to Fig. 2, where R and C varied within a wide range and with a distinct relationship between them, the time constants are seen here to be confined to a smaller range with no apparent relationship between them. However, when the data in Fig. 4 are viewed in the context of the damping index Δ , it is seen

that the scatter of the data points is actually contained within the range $0.1 < \Delta < 10$, with an average at approximately $\Delta = 2.5$.

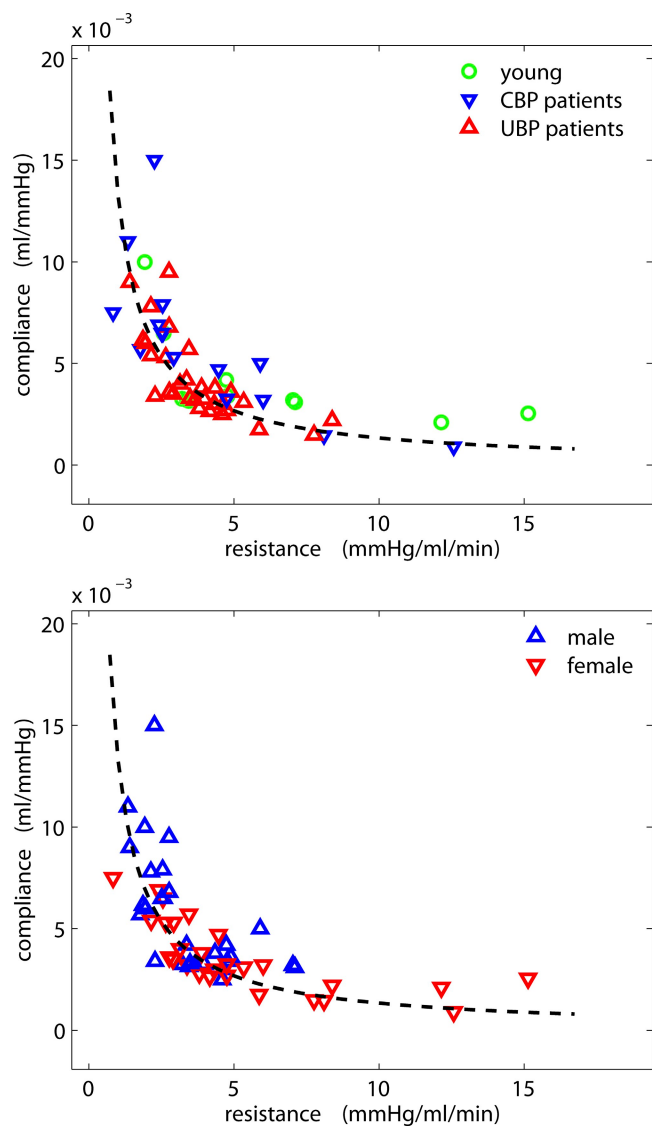


Figure 3. Values of the resistance R and compliance C as determined in the three groups of subjects, showing a wide spectrum ranging from high-resistance low-compliance at one end to low-resistance high-compliance at the other. Data points are associated with group (top) and sex (bottom).

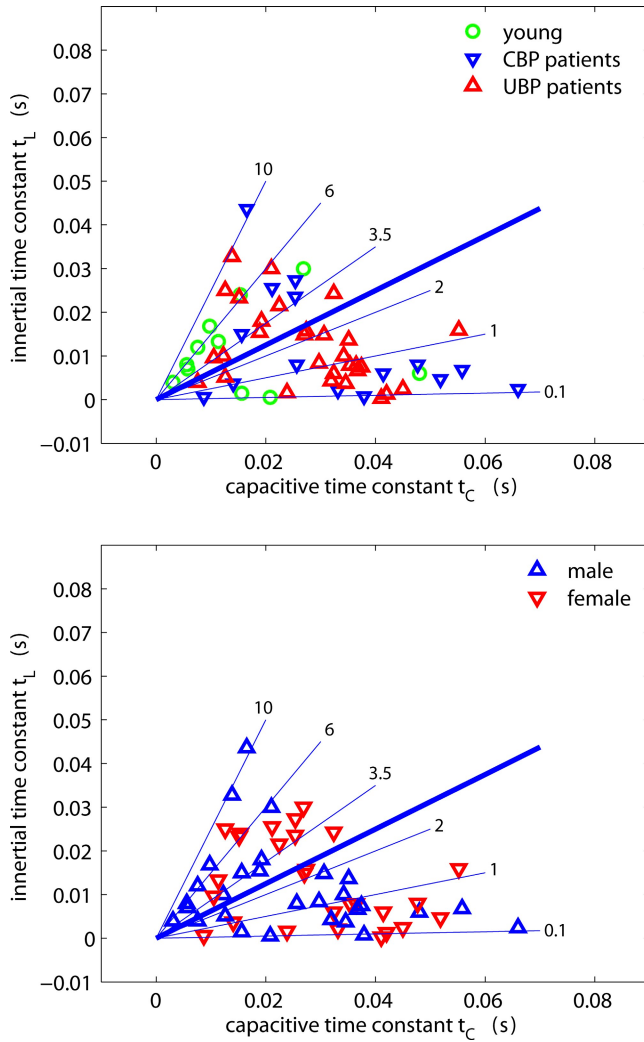


Figure 4. Inertial and capacitive time constants as measured in the three groups of subjects, showing no relation between them, in contrast with the relation between R and C observed in Fig. 3. When viewed in the context of the damping index $\Delta (=4t_L/t_C)$, however, the scatter of the data points is seen to be contained in the range of $0.1 < \Delta < 10$ (thin lines), with an average at approximately $\Delta = 2.5$ (heavy line). Data points are associated with group (top) and sex (bottom).

In Fig. 5, values of the damping index Δ in the three groups of subjects were plotted against the corresponding values of pulse pressure, the latter being another important dynamic property of the system that was also found to vary widely across the three groups (from a low of 30 mm HG to a high of over 100 mm HG). The results show that an average value of $\Delta \approx 2.5$ was actually maintained across the wide range of pulse pressures. Using this value in the framework of Fig. 2, the results are shown in Fig. 6, where it is seen that this average value of Δ corresponds to a dynamic behavior very close to that of critical damping ($\Delta = 1$).

An important observation in these three figures is that the sex bias seen in Fig. 3 is entirely absent in Figs. 4 and 5.

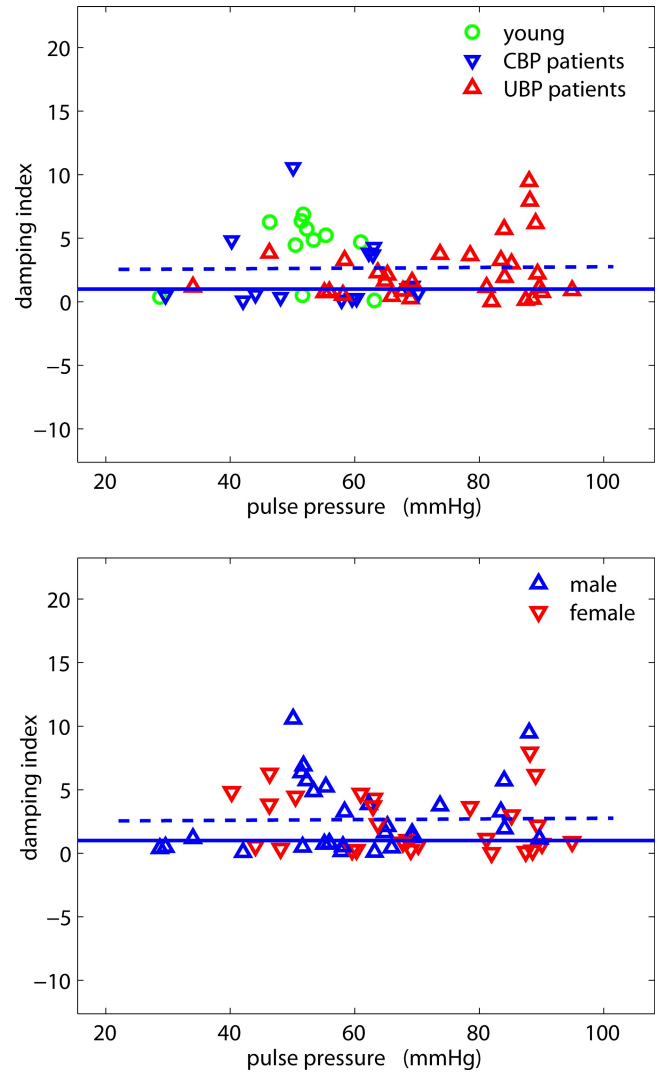


Figure 5. Damping index in the three groups of subjects over the wide range of pulse pressures in these subjects. Not only is a mean value of Δ (dashed line) seen to be maintained over the wide range of pulse pressure, but this value is also remarkably close to that of critical damping (solid line). Data points are associated with group (top) and sex (bottom).

DISCUSSION

The main result of this study is that the mechanics of a vascular bed, here being that of the forearm, cannot be characterized by vascular resistance alone but must include compliance as another distinct property. Furthermore, because of the wide variability in R and C among different individuals, neither R nor C in itself can be used as an independent indicator of the status of that vascular bed in a way that predicts the health or age of the subjects tested. In other words, the results suggest that the mechanical properties of a vascular bed are not universal properties across different individuals. Our search for benchmark values for R and C , therefore, leads to the conclusion that there are no benchmark

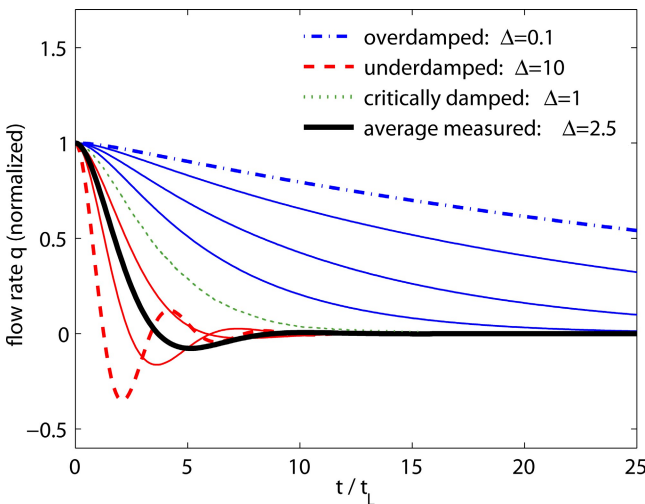


Figure 6. Dynamic responsiveness of the CKL system based on the average value of Δ (≈ 2.5) measured in the three groups of subjects and placed in the framework of Fig. 2. Thin lines represent intermediate values between those given in the legend.

values for R and C at a group or population level, but there are baseline values that are specific to individuals with a great deal of variability between individuals. The results are then remarkable in the sense that despite this variability in the values of R and C , the value of the damping index Δ was maintained close to the critically damped value, supporting a hypothesis that the mechanical responsiveness of the vascular bed may be a protected and/or regulated property.

The data in this study were obtained under baseline conditions and reflect the chronic state of the individual and vascular bed tested. In this context, the data suggest that the dynamics of blood flow in a particular vascular bed are adapted to the baseline values of R and C in that bed. The question then arises as to how the system responds to chronic changes in these values, such as those produced by pathology, aging, or exercise training.

The results in Fig. 3 suggest that at least a portion of the answer to this question does not lie with the isolated values of R or C because these vary widely between participants. Rather, the answer appears to involve some higher level dynamic properties of the system, namely, the time constants t_L, t_C . From a functional perspective, these findings suggest that the wide variations in the values of R and C do not translate into variability in the dynamic responsiveness of the system. More specifically, a vascular bed with higher or lower baseline values of R or C does not have correspondingly higher or lower time constants and therefore does not respond more or less “sluggishly” to changes in pressure or flow.

An overall measure of the degree of responsiveness (or “sluggishness”) of a dynamical system is the damping index (Δ). The index is based on the ratio of the two time constants and, as discussed earlier, its values are such that $\Delta = 1$ represents a state of so-called critical damping in

the sense that higher or lower values of Δ represent states of underdamping and overdamping, respectively. An average value of $\Delta \approx 2.5$ was found to be maintained over the wide range of pulse pressures in the three groups of subjects (Fig. 5), which is remarkable not only because of the existence of this average, but also because of how close its value is to the critical value of $\Delta = 1$.

These findings suggest that the dynamics of blood supply to a vascular bed are adapted to the baseline values of R and C in each individual with the effect of maintaining a certain level of responsiveness to changes in pressure or flow. Although this conclusion can be based on the group results in Figs. 3–5, the sex results in the same figures lend a strong and further support to this conclusion in that the sex bias seen in Fig. 3 is entirely absent in Figs. 4 and 5.

The mechanism by which the dynamic responsiveness of a vascular bed may be maintained is not clear. We speculate that the viscoelastic property K , which appears in the definition of the time constants t_L, t_C , may be matched to the prevailing values of R , C , and L with the effect of optimizing the level of dynamic responsiveness. We found some support for this by comparing the average mechanical properties of the young group with those of the two patient groups. The results are in Table II, showing that the largest difference between the two groups is in the value of K . Because the patient groups differed from the young group both in age and pathology, it is not possible to determine from these results if only one or both of these factors account for the difference in K .

By definition, the value of K reflects the viscoelastic property of the vessel wall, or more accurately, the proportion of viscosity to elasticity within the wall tissue. The correspondence between these mechanical properties of the wall and its histology in health and disease is not well understood. Elastin is known to provide the main elastic component within the vessel wall, but the viscous component is more elusive. Its constituency within the vessel wall is not clearly identified, yet it has been shown on theoretical grounds to play a key role in the dynamics of the wall under the conditions of pulsatile flow (Hodis and Zamir, 2008). Our modeling approach provides a noninvasive method of obtaining a measure of this important property of the arterial wall within the lumped vascular bed under investigation and of its potential role in vascular remodeling.

Although the conventional view holds that a change in vascular resistance, and possibly compliance C , are the main tools by which acute changes in pressure and flow are achieved, the results of our study relate to how the system adapts to chronic changes in vascular bed properties, as in aging or disease states, or as a result of simple variability in these properties between individuals. The results support a hypothesis that the dynamic responsiveness of a vascular bed is a protected property. This study did not examine the directionality of this

hypothesis. It may be that the viscoelastic property K of the vessel wall, because of its effect on the values of the time constants and the damping index, may be the means, or a means, by which the dynamic responsiveness is sustained. Conversely, chronic changes in K that occur in aging or disease states may be counteracted by changes in R and C with the effect of maintaining an optimal level of dynamic responsiveness.

Although the compliance C can be clearly associated with the elastin fibers within the vessel wall, the histological basis of the viscoelastic property K is not known. We suspect that it may derive from the intercellular matrix of polysaccharide and other connective tissue rather than from the better known constituents of the vessel wall, such as elastin, collagen, and smooth muscle cells.

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