Arterial wall mechanics as a function of heart rate: role of vascular smooth muscle

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Abstract. Vascular wall viscoelasticity can be evaluated using a first-order lumped model. This model consists of a spring with elastic constant $E$ and a dashpot with viscous constant $\eta$. More importantly, this viscoelastic model can be fitted in-vivo measuring arterial pressure and diameter. The aim of this work is to analyze the influence of heart rate over $E$ and $\eta$. In two anesthetized sheep, diameter in thoracic aorta and intravascular pressure has been registered. The right atrium was connected to a programmable stimulator through a pair of pace-maker wires to produce changes in stimulation heart rate (HR) from 80 to 160 bpm. Additionally, local activation of vascular smooth muscle was induced with phenylephrine. After converting pressure and diameter signals into stress and strain respectively, $E$ and $\eta$ were calculated in control state and during muscle activation. The elastic modulus $E$ did not present significant changes with heart rate. The viscous modulus $\eta$ decreased 49% with a two-fold acceleration in heart rate from 80 to 160 bpm. However, the product $\eta \times$ HR remained stable. The viscous modulus $\eta$ increased 39% with smooth muscle activation. No significant pressure changes were registered during the experiment. The contractile action of vascular smooth muscle could contribute to increasing arterial wall viscosity. The decrease of $\eta$ when HR increased might be related to smooth muscle relaxation mediated by endothelium activity, which was stimulated by flow increase. We conclude that HR can modulate arterial wall viscoelasticity through endothelium-dependent mechanisms.

1. Introduction
The mechanical properties of the aortic wall are of great importance and play a preponderant role in the regulation of parietal tension and deformation [1]. Previous studies have suggested a viscoelastic behaviour of the arterial wall, using an elastic (collagen and elastin fibres mainly) [2] and a viscous element (smooth muscle) [3].

Several theoretical models have been used to characterize mechanical properties of the arterial wall. In general, the vascular wall can be described using a simplified model of two parameters that describes the elastic and viscous behaviours of the stress-strain relation. If the wall were completely composed of elastin, the stress-strain (or pressure-diameter) relation would be exclusively linear. However, at great deformations, there exists a greater recruitment of collagen fibres, which gives the stress-strain relation a non-linear characteristic [2]. In these conditions, all the stored energy in the wall would then be restored. On the other hand, together with this phenomenon, there also coexists a viscous dissipation of energy in every beat, evidenced in stress-strain loops as hysteresis [3].
A more complete model considers vascular smooth muscle as a contractile element (CE) in series with another elastic element which, combined with elastin and collagen, composes the total elastic modulus of the wall [4]. This model suggests that smooth muscle would present viscosity due to the cells that compose it, and to another component that would depend on the degree of its activation. This activation degree could modulate, in the same way, the total elasticity of the wall.

The frequency dependence of the arterial wall can be analyzed by means of the complex modulus. However, this modulus uses Fourier decomposition of the signals from stress and strain, assuming linearity. This complex modulus shows certain independency at high frequencies.

It is known that within the main components of the arterial wall (elastin, collagen and smooth muscle), the only one that presents a frequency dependence is smooth muscle. Its activation is susceptible to the velocity of change in elongation and shortening [3], [5], [6]. There are other experimental evidences that suggest that the wall can be sensitized by the exposition to pulse pressure and shear stresses due to flow [7]-[9]. This could indicate that, as a consequence of an increase of heart rate, a modulation of the degree of smooth muscle activation could exist, consequently changing the viscous modulus of the vascular wall.

The objective of the present work is to analyze the dependence of the mechanic parameters of the arterial wall with heart rate using a first order simple model with elastic and viscous moduli.

2. Materials and methods

2.1. Modelling

Figure 1 shows the complete model of the arterial wall [4]. The PEC corresponds to the elastic component composed by elastin and collagen fibres. As can be seen, the elastin fibres are constantly submitted to all levels of deformation, whereas the collagen fibres are gradually “recruited” as the strain degree increases. The CE is conditioned to smooth muscle activity, in series with the SEC. In this way, we define two branches: the passive branch (corresponding to the left branch in figure 1) and the active branch (corresponding to the right branch in figure 1).

![Figure 1. Schematic representation of a Kelvin model. SEC: series elastic component. PEC: parallel elastic component. CE: contractile element.](image)

For the present work, this model is reduced into a Voigt model of two elements, whose constitutive equation is the following:

\[ \sigma = E \cdot \varepsilon + \eta \cdot \frac{d \varepsilon}{dt} \]  

(1)

where \( \sigma \) is the stress, \( E \) elastic modulus, \( \varepsilon \) the strain and \( \eta \) the viscous modulus.
2.2. Surgical Instrumentation

The experiments were done in two adult (castrate male) Corrediale-Romey Marsh sheep of approximately 62 kg and 3 years of age (Estancia San Julián, Gualeguay, Entre Ríos, Argentina) in total agreement with the established norms by the Comité Institucional para el Cuidado y Uso de los Animales (Universidad Favaloro, NIH-PHS Nro. A5556-1) and the Guide for the Care and Use of Laboratory Animals published by the U.S. National Research Council (National Academy Press, Washington, D.C. 1996).

Under pre-medication with acepromazine maleate (0.2 mg/kg IM) general anaesthesia was induced with sodium thiopental (20 mg/kg IV), and maintained with halothane (1.5-2% in pure oxygen at 2.5 L/min) under assisted mechanic ventilation (Neu movent 910, TECME SA, Córdoba, Argentina). Ventilation was controlled during all the experiment using positive pressure at a frequency of 12 cycles per minute and a tidal volume of 15 mL/kg, and adjusting to maintain a CO₂ of 25-30 mmHg (Siemens-Elema capnograph E336E, Sweden). Heart rate and blood oxygen saturation were continually monitored with a pulse oxymeter (Novametrix, model 5154, Medical System Inc, Wallingford, Connecticut).

After a thoracotomy was done in the forth left intercostal space, a pair of ultrasonic transducers (2 mm, 5 MHz) was implanted in the middle third of the descendent thoracic aorta for measuring the external aortic diameter. Through canalization of the femoral artery, a 6 French pressure microtransducer (Gaeltec Ltd, UK) was introduced which, after verifying by palpation that its endovascular position was corresponded with the diameter transducers, was fixed in the exterior. The instrumentation also included a pair of pace-maker electrodes sutured to the wall of the right atrium.

2.3. Data collection

The transit time of the ultrasonic signal (wave velocity of 1580 m/s) of the aortic diameter was converted into distance using a sonomicrometer (Triton Technology Inc., model 120) and monitored with oscilloscope (Tektronix TDS 210) for confirming its optimum quality. The aortic pressure and diameter signals were sampled at 4 KHz in a computer (PC Pentium II) equipped with a multichannel analogical-digital converter of 12-bits (LabPC 1200, National Instruments, Austin, Texas, USA) using a specific software developed in the Department of Electronics of Universidad Favaloro.

2.4. Experimental protocol

Twenty minutes after instrumentation, the following manoeuvres were recorded:

a) Heart rate changes: after registering a basal heart rate (87 beats/minute), excitation frequency was induced with a programmable electrostimulator (Medtronic Inc, model 5325, Minneapolis; USA) for values of 80, 100, 120, 140, 150 y 160 beats/minute. The pacing in each selected frequency lasted 30 seconds, with a same resting period.

b) Vascular smooth muscle local stimulation: at basal heart rate, phenylephrine solution (10 mg/mL) was externally dropped over the aortic wall of the studied segment (a total of 1 mL was administered in approximately 10 seconds).

2.5. Data processing

Pressure and diameter signals were converted into stress and strain, respectively, as was previously described [3]. The value of $E$ of equation (1) was calculated by lineal adjustment of the elastic points of the loop. For viscosity calculus, the elastic stress was subtracted from the total stress, and the value of the viscous modulus ($\eta$) was adjusted in a linear regression with the strain's first derivative.

3. Results

The analyzed loops correspond to a short registering period during which the ventilator was held still (not turning for 10 seconds) to avoid undesired haemodynamic changes. Figure 2 shows a series of six consecutive loops that do not present differences between beats.
As it can be noted in figure 3, the elastic modulus turned out to be independent from heart rate ($R^2=0.05$, $p=NS$). On the other hand, the wall viscosity modulus $\eta$ showed to decrease with heart rate ($R^2=0.9421$, $p<0.0001$) to an approximate rate of 48.8% per octave (figure 4). Figure 5 shows the product of the viscosity modulus $\eta$ times the heart rate expressed in radians per second. This product resulted stable with the frequency.

![Figure 2](image2.png)

**Figure 2.** Representative pressure-diameter loops of an anesthetized sheep registered in the descendent thoracic aorta.

![Figure 3](image3.png)

**Figure 3.** Elastic modulus ($E$) behaviour as a function of paced heart rate in an anesthetized sheep.
Finally, figure 6 depicts change in $E$ and $\eta$ for the studied segment after local activation of vascular smooth muscle with phenylephrine. The elastic modulus increased 18.3%, and the viscous modulus increased 38.6%. The arterial pressure did not show any significant change.

**Figure 6.** Effect of vascular smooth muscle activation on the elastic ($E$) and viscous ($\eta$) moduli of the arterial wall in an anesthetized sheep.
4. Discussion

The present work shows that local activation of the vascular smooth muscle in conduit arteries produces an increase of its elasticity and viscosity, even when pressure remains constant. On the other hand, the elastic modulus resulted to be independent from heart rate, whereas the viscous modulus decreased at a rate of ~50% per octave.

Vascular smooth muscle in great arteries keeps a vasomotor tone under stable conditions through a complex regulating mechanism. Whether in physiologic or pathologic situations, vascular smooth muscle plays an important role when variations of pressure and flow occur, modulating the degree of deformation and shear rate, which ultimately determine the mechanical response of the vascular wall. According to the type of response, they can be described as pressure-dependent myogenic responses [7], [9], [11] or flow-dependent endothelium mediated responses [8]. These mechanisms are described as adaptive phenomena of short term whose purpose is to maintain inside the arterial wall a circumferential stress at a normal and uniform level [12].

In this work, the local administration of phenylephrine on the studied segment produced a marked vasoconstriction and a concordant increase of the wall stress. In accordance with previous results [3], [10], [14], both elasticity and viscosity increased with activation. The former shows the increase of the arterial wall stiffness, whereas the latter suggests an increase in the ability of dissipating energy.

To analyze the frequency dependence of these moduli, the most common approach includes the use of a complex elastic modulus \( \tilde{E} \) as the quotient of the Fourier transforms of stress and strain. This technique implicitly imposes the existence of linearity between the harmonics. In arteries, the \( \tilde{E} \) has showed a marked increase from static values reaching a plateau at high frequencies [5]. Our results, calculated with real stimulus of different frequencies, are coherent with the expected ones. Using the Fourier transform of equation (1), the first order model predicts \( \tilde{E}(\omega)=E+i\eta\omega \), where \( i \) is the imaginary unit and \( \omega \) represents frequency in radians per second. The values of \( E \) resulted independent of frequency (figure 3). Despite the viscous modulus decreased significantly with frequency (figure 4), the product \( \eta\omega \) remained constant (figure 5). This assures the stability of \( \tilde{E} \) for accelerated oscillations, in accordance with the literature [3], [5], [6].

Previous works have demonstrated that \( \eta \) is sensitive to changes in the degree of smooth muscle activation [3], [10]. With the present results, we could consider the descent of \( \eta \) related to a smooth muscle relaxation. When heart rate increased, recorded pressures did not change. This suggests an increase of flow, which would increase the shear stress on the endothelial layer causing the phenomena described as vascular wall relaxation mediated by endothelium [8]. Starting with the model presented in figure 1, opposed to changes in heart rate that would lead to flow changes, the CE-SEC branch (active branch) would be modulating the viscous modulus \( \eta \) through the contractile element CE, but without altering the SEC component, while maintaining the total elastic modulus of the wall constant. However, during smooth muscle activation with phenylephrine, the SEC would be modulating the viscoelasticity of the whole set.

Our work presents certain limitations. During high frequency pacing, some beats resulted incomplete due to the short ventricular filling time. In some way, this has influenced the calculus of some parameters. However, as it can be seen on the figures, the tendencies were marked and homogeneous. Also, the relative positioning of pressure and diameter transducers had to be specially taken into account for avoiding temporal phase shifts that may influence the viscoelastic calculus. To this end, an intraluminal solid sate transducer was used that allows an exact positioning under the crystals responsible of measuring the diameter. Finally, the first-order mathematical model has limitations concerning its temporal and frequency response in a wide frequency range [5]. Nevertheless, its simplicity showed to be relevant at the time of matching results.

Future studies must be carried out; continuing the present protocol over a greater number of cases, and considering viscoelastic models with more parameters.
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