Smart Damping Modulation of Carotid Wall Energetics in Human Hypertension
Effects of Angiotensin-Converting Enzyme Inhibition

Ricardo L. Armentano, Juan G. Barra, Daniel Bia Santana, Franco M. Pessana, Sebastian Graf, Damian Craiem, Laura M. Brandani, Hugo P. Baglivo, Ramiro A. Sanchez

Abstract—Damping is the conversion of mechanical energy of a structure into thermal energy, and it is related to the material viscous behavior. To evaluate the role of damping in the common carotid artery (CCA) wall in human hypertension and the possible improvement of angiotensin-converting enzyme (ACE) inhibition, we used noninvasive CCA pressure (tonometry) and diameter (B-mode echography) waveforms in normotensive subjects (NT group; n=12) and in hypertensive patients (HT group; n=22) single-blind randomized into HT–placebo (n=10) or HT-treated (ramipril, 5 to 10 mg/d during 3 months; n=12). Vascular smooth muscle (VSM) null tonus condition was achieved from in vitro pressure and diameter waveforms (Konigsberg microtransducer and sonomicrometry) measured in explanted human CCA (n=14). Arterial wall dynamics was described by viscous (η), inertial (M), and compliance (C) parameters, mean circumferential wall stress, viscous energy dissipation (W_η), peak strain energy (W_p), damping ratio (ξ=W_η/W_p), and modeling isobaric indexes C_{iso} and W_{iso}. The lack of VSM tonus isobarically increased wall stress and reduced η, C_{iso} and damping (P<0.01). Wall stress, η, and W_η were greater in HT than in NT (P<0.015) and arrived near normal in HT-treated (P<0.032 respect to HT), with no changes in HT–placebo. Whereas C_{iso} increased in HT-treated (P<0.01) approaching the NT level, ξ did not vary among groups. During hypertension, because of the W_η increase, the arterial wall reacts increasing W_η to maintain ξ. ACE inhibition modulates VSM activation and vessel wall remodeling, significantly improving wall energetics and wall stress. This protective vascular action reduces extra load to the heart and maintains enhanced arterial wall damping. (Hypertension. 2006;47:384-390.)

Key Words: carotid arteries ■ muscle, smooth, vascular ■ compliance ■ viscosity

Arteries are essentially viscoelastic tubes, and their main functions are to act as conduits and to buffer flow pulsation imposed by the contracting heart.1 Purely elastic materials permit all the stored energy to be restored during the unloading phase. However, arteries are not purely elastic (ie, they exhibit marked viscous behavior). Damping is the conversion of mechanical energy of a structure into thermal energy, and it is related to the material viscous behavior.2 Arterial wall viscosity, mainly related to vascular smooth muscle (VSM), is a source of energy dissipation, considering viscosity as an energy-dissipating phenomenon during mechanical transduction.1,3–5 Thus, whereas part of the energy stored by the arterial wall during elastic distension, namely peak strain energy, is fully restored, the remaining part of the energy corresponding mainly to the viscous deformation is dissipated within the arterial wall.3,6,7

Previously, we found that the viscos modulus followed the VSM activation level.6,8 A larger viscos modulus indicates a greater expenditure of energy in the pulsatile vessel expansion with each heartbeat. We also demonstrated that VSM activation by phenylephrine or renovascular hypertension in dogs and sheep increases arterial wall viscosity showing wall viscosity as intrinsic evaluator of VSM status.6,7,9 Similarly, in hypertensive (HT) patients, we reported an increase in arterial wall viscosity.10 The aortic energy loss and the wall stiffness have been found to be increased in HT compared with normotensive (NT) patients; these properties improved in both groups after administration of a calcium antagonist.11

Vibrations from high-frequency harmonic components produce structure injuries. The aim of damping is reducing accelerating oscillations.2 We suggest that VSM cells, as smart dampers, exert a protective effect against high-frequency stretching, adjusting energy dissipation. During physiological and pathological situations, VSM and its viscous damping could play an important role modulating
arterial stretching, which is ultimately responsible for wall mechanics. According to its type, the reaction is referred to as pressure-dependent myogenic response,12 flow-dependent response mediated by endothelium,13 or vascular remodeling.14 These adaptive mechanisms are claimed to maintain circumferential wall stress,15 or wall strain,16 within a normal and uniform level.

It is well known that HT wall thickening is one of the main compensatory mechanisms to preserve circumferential wall stress,14,15,17 Moreover, arterial wall viscosity is associated with higher intima-media thickness (IMT), suggesting that intima-media thickening might be related to the VSM alterations found in hypertension.18

Alternatively, there is evidence that in HT patients, treatment with an angiotensin-converting enzyme (ACEI) inhibitor (ACEI) has beneficial effects on arterial function.17,19–22 In a previous study, we found that atenolol and ramipril improved arterial compliance, whereas only ramipril produces this effect independently of blood pressure reduction, supporting the idea that an ACEI might have specific effects on wall viscoelasticity.23

The aim of this study was to evaluate wall energetics and the damping induced by VSM in the human common carotid artery (CCA) in NT, HT, and ACEI-treated HT patients, and in explanted human CCA segments (null tonic).

Materials and Methods

The study included: (1) in vitro pressure and diameter measurements in human CCA segments from multiorGAN donors, and (2) noninvasive pressure and diameter measurements in patients.

In Vitro Study

Tissue procurements agree with the guides of the transplant program of the Instituto Nacional de Donación y Trasplante de Células, Tejidos y Órganos de Uruguay, and conform to ethical and safety concerns for therapeutic use, including written consent.24 CCA were procured from 7 donors (23 to 45 years of age; mean 29.6) in brain death condition. The CCA segments (5 to 8 cm in length) were washed with saline solution and stored at 4°C. Warm ischemia was maintained in all cases for 4 days. Each CCA segment (n=14) was nontraumatically mounted on a specifically designed cannulae of the flow circuit loop (in vitro system) and immersed and perfused with oxygenated Tyrode solution (37°C; pH 7.4).25 Pressure was measured with a solid-state microtransducer (Königsberg Instruments) laterally placed in the proximal cannula. Arterial diameter was measured with a pair of ultrasonic gauges (5 MHz; 2-mm diameter) sutured to the adventitia at 5 to 8 mm from the pressure microtransducer. A sonomicrometer (Triton Technology) converted the transit time (1500 m/s) into distance. Once placed in the organ chamber, the segments were allowed to equilibrate for 1.5 minutes under a steady-state flow (150 mL/min), mean pressure (~83 mm Hg), and stretching rate (70 cycles/min). Pressure and diameter signals of 10 to 20 consecutive cycles were sampled every 5 ms. Pressure and pump rate levels were chosen to be similar to those observed in NT patients.

In Vivo Noninvasive Study

Twelve NT subjects (50±4 years of age; 6 males; body mass index [BMI] 25±1 kg/m²) and 22 patients with mild to moderate essential hypertension (HT group; blood systolic/diastolic pressure 140 to 179/90 to 109 mm Hg) were included in the study. After a washout period of 4 weeks, they were randomly distributed into an HT-treated group (n=12; 51±3 years of age; 6 males; BMI 27±1 kg/m²) receiving the ACEI ramipril as antihypertensive treatment (5 to 10 mg/d during 3 months) and an HT–placebo group (n=10; 50±4 years; 5 males; BMI 27±1 kg/m²). All individuals gave informed consent for the study.

Echographic studies were performed with a real-time B-mode ultrasound imager (ATL HDI 5000).18 The left CCA was examined with a 7.5-MHz probe, 3 cm proximal to the vessel bifurcation. A fixed image at end-diastole and a sequence of images were acquired to determine IMT and instantaneous CCA diameter waveform, respectively.18 These procedures involved automatic detection of the anterior and posterior wall interfaces (Iotec System) validated previously against the sonomicrometry.26

CCA pressure waveforms were recorded every 1 ms by tonometry (Millar Instruments Inc.) at the same point of the diameter measurement.14 Similarly, tonometric waveforms were registered at level of the brachial artery, which was calibrated using the respective systolic and diastolic values assessed by sphygmomanometer. The mean and diastolic values of brachial signal was used to calibrate the CCA waveform.10–27 We assumed that mean pressure does not change in large conduit arteries and that diastolic pressure (as opposed to systolic pressure) does not substantially differ between the brachial and the CCA.28

A surface ECG was acquired and stored together with the diameter and pressure signals. The pressure and diameter waveforms were identified according to the QRS complex of the ECG.

Data Analysis

In vitro and noninvasive pressure and diameter waveforms were interpolated in time to obtain the same number of data points allowing calculation of the averaged cardiac cycle. Then, a third-order linear autoregressive with exogenous input model was used to fit the data, obtaining the compliance (C), viscous (η), and inertial (M) parameters.6,8

Isobaric compliance (Ciso) was calculated as reported previously,5,10 using 110 mm Hg as isobaric pressure (average mean arterial pressure before and after ACEI treatment).

Systolic, mean, and diastolic circumferential stresses (Lamé’s equation) were calculated as 0.1334 (P · Rm)/IMT, where P and Rm are the systolic, mean, or diastolic values of pressure and midwall radius, respectively. Rm was calculated as (Ri−Rf)/2, being Ri and Rf the external and internal radii, respectively. Systolic, mean, and diastolic stresses were calculated as Rm/R0, where R0 is a reference value of midwall radius for an unstressed situation extrapolated at 25 mm Hg in each noninvasive measurement. Each CCA R0 in vitro was determined experimentally at 25 mm Hg.29 Because artery wall volume does not change in vivo, assuming incompressibility of the wall,29 CCA mass was considered a more appropriate variable than IMT to examine vascular remodeling.30 Thus, CCA mass, expressed as mass per length (L) unit, was calculated as ∂L/(∂L−∂L), assuming a wall density (ρ) of 1.066 g/cm³.

A system in which the damping force is proportional to the velocity of stretching is said to present viscous damping. The viscous energy dissipation (Wv) in such a system during a quarter-cycle was computed as:11 Wv=ωη · A/r, where ω is angular frequency [2π heart rate], η represents the loss modulus of the complex elastic modulus,1 and A is pulsatile cross-sectional area.

The peak strain energy (Wp) stored in the wall during a quarter-cycle that will be recovered without loss during unloading is:2 Wp=−2A/r·C. Thus, the isobaric calculus of the peak strain energy could be modeled by: Wp=−2A/r·C. A quantitative measure of damping is achieved by the equivalent viscous damping ratio (ξ): ξ=Wp/Wp, defined as the ratio of energy dissipated per cycle in a given arterial segment to the peak strain energy stored in the same segment.

Statistical Analysis

The inherent effect of VSM, comparing in vitro (null tonus) versus NT (normal tonus) data, and the effect of hypertension, comparing NT versus HT data, were assessed using unpaired t tests. The effects of treatments (ACEI inhibition or placebo) in HT patients were established by paired t tests. When multiple comparisons were needed, ANOVA followed by Bonferroni correction were performed. Differences were considered significant for P<0.05. Calculu
Effects of VSM Tone
The effect of vasomotor tone was studied under virtually mean isobaric conditions between NT and in vitro experiments (Table 1). The presence of VSM tone in NT subjects reduced circumferential wall stress (33%; \(P=0.001\)) and caused arterial wall compliance (44%; \(P=0.035\)) and viscosity (130%; \(P=0.003\)) increases. Carotid energetics (Table 2) showed higher dissipation (61% \(P=0.082\)) and lower strain energy (55%; \(P=0.004\)) improving damping ratio \(\xi\) (286%; \(P=0.0003\)).

Effects of Arterial Hypertension
Hypertension increased pressure, diameter, IMT, circumferential wall stress (37%; \(P=0.004\)), and CCA wall mass (37%; \(P=0.007\)), shifting arterial pressure–diameter relationship to the upper right side (Table 1; Figure). Compliance diminished (46%; \(P=0.0004\)), and viscosity increased (82%; \(P=0.0001\)) with hypertension. Simultaneously, energy dissipation increased 75% with respect to the NT values (\(P=0.013\)) to compensate the higher peak strain energy (70% \(P=0.007\)), thus maintaining constancy of the damping parameter \(\xi\) (Table 2). Isobaric analysis showed that changes in compliance are totally independent of the pressure levels imposed by the disease.

Three-Month Follow-Up
ACE inhibition decreased systolic pressure, diameter, circumferential wall stress, and CCA wall mass, shifting the arterial pressure–diameter relationship to the left (Table 1; Figure). Ramipril had a strongly geometric effect on CCA wall, independently from its peripheral action, evidenced by the increase in the relative change of pulsatile diameter (31%; \(P=0.025\)), \(C_{iso}\) (23%; \(P=0.030\)), and \(W_{S(80)}\) (26%; \(P=0.045\)) changing the slope of the stress–strain relationship (Figure). Compliance (+36%; \(P=0.010\)), wall viscosity (−27%; \(P=0.008\)), dissipation (−36%; \(P=0.018\)) and strain energy (−33%; \(P=0.022\)) changed with ACEI treatment, maintaining enhanced \(\xi\) (Table 2). After 3 months, no significant changes were observed in HT patients enrolled in the placebo subgroup (Figure).

Discussion
A complete characterization of carotid wall energetics in human hypertension was achieved comparing NT subjects and HT patients with ACEI or placebo treatment. In the conduit circulation, whereas pressure rises rapidly during systole, diameter increases slower. As a result, the \(x\)-\(y\) composition between pressure and diameter exhibits a hysteresis loop.\(^6,10,11\) This particular behavior is not attributable to nonlinear properties of the wall but to energy dissipation.\(^32\) We postulate that this apparent disadvantage could positively contribute to the damping exerted by the arterial wall.

Analysis of the pressure–diameter relationship provides a valuable insight into carotid mechanics. First, changes in...
and is attributable to the viscosity of the arterial wall. The amount of energy dissipated related to strain energy supplied by the heart (minus sign in the $W_r$ formulae) is a measure of the wall damping level and provides information about arterial wall protection.

To the best of our knowledge, this work is the first to demonstrate the constancy of wall damping among different in vivo conditions, maintaining enhanced arterial wall protection, and obviously, paying the corresponding energy dissipation “costs.”

The lack of VSM tonus (in vitro) reduced arterial wall viscosity, isotonic compliance, and damping, suggesting that these are dependent on the integrity of the neurohumoral system. Arterial wall viscosity, the stress–strain relationship, and energy dissipation were worse in the HT group than in the NT group and remained normal in HT-treated, whereas no changes were observed in the HT-placebo group. These results are coincident with those reported by Stefanadis et al, in which before and after bolus administration of the calcium antagonist diltiazem, aortic elastic properties were improved and energy loss was reduced in NT and HT subjects.11 In the referred work, energy dissipation, measured from the area of the pressure–diameter hysteresis loop, was close to 2 J/m², increasing by 72% in hypertension. In HT patients, the concomitant increase of both arterial wall viscosity caused a noticeably augmentation of energy dissipation, which may be related to local protection of each functional unit. The modifications of the arterial system observed during hypertension might be related to the prevailing high pressure, to the arterial wall structural changes attributable to hypertension, or by a combination of both. Local alterations of compliance ($C$ and $C_{n0}$) provoke pulse pressure augmentation with concomitant increase in peak strain energy. In the pressure waveform, this hyperpulsatility is manifest by a higher systolic level and by a steeper slope at its onset.11 The pulsatile work (proportional to the $W_p$ of the left ventricle is increased. The hyperpulsatility also increases the harmonic content in the dynamics of the arterial wall. The interplay

### TABLE 2. Biomechanical Parameters Used to Evaluate the Carotid Energetics in NT Subjects and in Patients With Mild to Moderate Essential Hypertension Before and After Treatment With Ramipril (HT-Treated)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NT (n=12)</th>
<th>HT (n=12)</th>
<th>HT-Treated (n=12)</th>
<th>In Vitro (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance ($10^{-3}$ m/kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective</td>
<td>8.46±0.88</td>
<td>4.57±0.33†</td>
<td>6.23±0.52*§</td>
<td>5.87±0.69*</td>
</tr>
<tr>
<td>Isobaric</td>
<td>6.29±0.62</td>
<td>4.66±0.34*</td>
<td>5.72±0.38§</td>
<td>4.53±0.53*</td>
</tr>
<tr>
<td>$\gamma$ (kPa · s/m)</td>
<td>962±124</td>
<td>1748±107†</td>
<td>1280±131§</td>
<td>418±73†</td>
</tr>
<tr>
<td>$M$ (kPa · s²/m)</td>
<td>4.50±1.25</td>
<td>7.69±1.21*</td>
<td>3.18±0.52§</td>
<td>0.24±0.02†</td>
</tr>
<tr>
<td>$W_p$ (J/m²)</td>
<td>9.21±1.85</td>
<td>16.14±2.07*</td>
<td>10.27±1.33§</td>
<td>5.73±0.62</td>
</tr>
<tr>
<td>$W_{st}$ (J/m²)</td>
<td>35.9±4.8</td>
<td>60.9±7.4</td>
<td>40.7±4.8</td>
<td>79.8±11.8†</td>
</tr>
<tr>
<td>$W_{is}$ (J/m²)</td>
<td>47.4±5.7</td>
<td>58.7±6.7</td>
<td>43.4±4.7</td>
<td>103.2±15.9†</td>
</tr>
<tr>
<td>Damping (%)</td>
<td>0.27±0.04</td>
<td>0.28±0.03</td>
<td>0.25±0.02</td>
<td>0.07±0.01†</td>
</tr>
</tbody>
</table>

The same parameters assessed in vitro from postmortem CCA specimens are also reported.

$\gamma$ and $M$ indicate viscous and inertial parameters, respectively; $W_p$, beat-to-beat energy dissipation; $W_{st}$, peak–strain energy; $W_{is}$, isobaric peak–strain energy.

Values are expressed as mean±SEM. *P<0.05 and †P<0.01, respect to NT group; ‡P<0.05 and §P<0.01, HT-treated vs HT.
between $W_0$ and $W_0$ could help to preserve the arterial wall avoiding mechanical degradation.

Our experimental setup manages pressure waveforms by controlling mean and diastolic values, with the aim of maintaining mean flow constant. This permits to mimic in vitro the purely elastic parameters observed in vivo, whereas viscous and inertial behaviors are determined by the dynamic conditions of the system, bounding the bias in hysteresis loop and therefore in the quantification of wall energy dissipation. Nevertheless, in the in vivo condition, pulse pressure did not appear to be relevant in determining energy dissipation, as was suggested in a study performed in anesthetized rats in which within an in vivo pulse pressure range similar to that reported in our work, the energy dissipation remained almost unchanged. Actually, the in vitro group represents a comparator group used to discriminate the purely relaxation effect attributable to null tonus.

Peak strain energy is, in essence, the energy involved in the known pulse pressure deleterious effects on the arterial wall. Compensatory increase in energy loss, possibly related to pulse diameter, maintains the same ratio (damping) implying modifications of the intrinsic mechanical properties of the carotid wall. The fact that wall damping remains constant, despite different pressure levels, suggests that the arterial wall reacts increasing dissipation to prevent the deleterious effects of high-frequency harmonic components present in the pressure waveform. These results also suggest that VSM could modulate energy dissipation.

After ACEI treatment, wall viscosity and cross-sectional area were reduced resulting in a dramatical decrease of $W_0$. ACEI provoked pressure lowering, and the arterial wall reacted by decreasing energy dissipation maintaining it close to NT values. This suggests that ACEI can diminish energy dissipation (maintaining local protection), decreasing additional load to the heart.

The improvement in $C_{ps}$ and $W_{(slw)}$ by ramipril in HT patients was related to local intrinsic arterial changes, in agreement with a previous study reporting a differential effect of ramipril with respect to another agent (atenolol) despite similar pressure reduction.

Recent results show that ramipril reduces large artery stiffness independently from the mean arterial pressure reduction, increasing the elastin to collagen ratio. Other ACEI-based treatments, such as quinapril, reduce diastolic diameter with increase in relative pulsatile changes in diameter. The values reported for relative pulsatile diameter changes are practically indistinguishable from ours. Analyzing their pressure and diameter data, we obtain the same pattern of action shown in the Figure (ie, a shifting pressure–diameter relationship shifted downward and to the left, and with a lower slope). In addition, enalapril reduces carotid hypertrophy by a reduction in carotid pulse pressure decreasing internal diameter, arterial mass, circumferential wall stress, and significant increase in distensibility.

In another work, the change in diameter showed a tendency to increase in response to the calcium antagonist nifedipine, whereas, in agreement with our present results, diameter decreased in response to ACEI treatment. To distinguish direct from pressure-related effects of treatment, we re-examined the results of the referred work, in which a 3-month nifedipine treatment produced a similar arterial pressure reduction ($\pm 16$ mm Hg) as in the present ramipril group ($\pm 17$ mm Hg). In that study, the change in the position of the pressure–diameter relationship between the HT state and the state after nifedipine treatment is the same as the one observed in the present study between NT and in vitro situations. The nifedipine-induced vasodilatation counteracts the decrease in viscosity maintaining arterial wall energy dissipation unchanged. In contrast, ACEI may have accounted for the arterial wall remodeling.

The hyperactivity, hyperplasia, or hypertrophy found in established HT patients could have the role of maintaining the same wall damping as NT despite higher levels of arterial pressure, coincident with findings in vitro from studies showing the great influence of pulsatility on phenotype and growth of VSM. VSM modulates its degree of activation or vessel wall remodeling to prevent the deleterious high-frequency harmonic components from damaging wall constituents. Considering wall viscosity as a pressure-independent parameter of VSM status, as well as $C_{ps}$ and $W_{(slw)}$, we would be able to conclude that the different viscous behaviors (and energy dissipation) found in HT and HT-treated are determined by intrinsic changes in the arterial wall. The present results are supported by those from other studies reporting that ramipril reduces hypertrophy of VSM cells, and increases deposition of elastin while reducing collagen and also confirm previous works from us in which a strong relationship between IMT and viscosity, as well as IMT and inertia, was demonstrated.

There is a large body of evidence about the beneficial effects of ACEI treatment on arterial function or structure in HT patients. ACEI might have effects on blood vessel wall independently of the efficacy in reducing blood pressure. This effect seems to be related to the inhibition of tissue and circulating angiotensin II and to potentiation of bradykinin, resulting in decreased proliferation and migration of VSM cells, decreased oxidative stress, increased endothelial NO formation, and restored elastin-to-collagen ratio, leading to improved endothelial and vascular buffering function. Presumably, the effect is not specific to ACE inhibition but to VSM modulation, independent of how it is achieved. In rats, changes in vascular wall mechanics and elastin-to-collagen ratio are modulated differentially by angiotensin II receptors.

Our study remarks that arterial wall viscosity is indicative of the level of VSM tone, increasing during hypertension and decreasing with ACEI treatment. VSM cells, as smart damping devices, modulate energy dissipation. This apparent disadvantage could positively contribute to maintain the cushioning exerted by the arterial wall in transferring pressure to stretching. VSM alterations found in established HT patients could have the role of maintaining damping, thus modulating beat-to-beat energy dissipation despite the higher levels of arterial pressure present in the circulation but producing an additional load to the heart. The improvement in wall energy dissipation induced by the modulation of compliance, wall stress, and viscosity to maintain wall protection,
avoiding extra load to the heart in the ramipril-treated group, could be partially related to the ACE inhibition.

Perspectives

In recent years, considerable attention has been paid to research and development of structural control devices, with particular emphasis on alleviation of wind and seismic oscillations on building and bridges. Because of their low power requirements and full safety, smart-damping strategies appear quite attractive.45 We suggest that smooth muscle cells, as smart dampers, exert a protective effect against high-frequency stretching, adjusting energy dissipation. Recent studies demonstrated that high-frequency vibrations could affect the arterial wall,46 causing lesions in endothelial cells and increasing vasoconstriction concomitant with increased vibrations, such as occurs in the hands of workers operating vibrating tools.47 These hemodynamic changes take place in a frequency range easily accounted within the range of observable during the rapid upstroke of the pressure wave-form in HT patients. The elements and theory developed in the present study should be of interest for the early detection and follow-up of arterial wall modifications. Moreover, specifically in the case of hypertension treatment, the most relevant finding of our study would be that the lowering in energy dissipation is not a phenomenon purely linked to VSM tone, and that the vascular remodeling of the smooth muscle plays a valuable role in “smart” damping strategies. However, these observations should be confirmed by larger studies.

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