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MECHANICAL VS INTRINSIC COMPONENTS IN THE IMPROVEMENT OF BRACHIAL ARTERIAL COMPLIANCE

COMPARISON OF THE EFFECTS OF ATENOLOL VERSUS RAMIPRIL IN HYPERTENSIVE PATIENTS

RICARDO L. ARMENTANO[1], SEBASTIAN GRAF[1], AGUSTIN J. RAMIREZ[2], JORGE D. ESPINOSA[2], LAURA BRANDANI[2], HUGO BAGLIVO[2], RAMIRO SÁNCHEZ[2]

[1]*Proyecto Dinámica del Sistema Arterial, Universidad Favaloro;* [2]*Sección Hipertensión Arterial, Instituto de Cardiología y Cirugía Cardiovascular, Fundación Favaloro, Buenos Aires*

Abstract The aim of this study was to compare the mechanical and intrinsic effects of an angiotensin converting enzyme inhibitor, vs a β-blocker, on brachial arterial compliance. In a double blind study, 34 essential hypertensive patients were treated for 3 months with either ramipril 2.5-5.0 mg daily (n=17, age 57±7y, 11 males) or atenolol 50-100 mg daily (n=17, age 53±8y, 11 males). Blood pressure (BP), brachial artery diameter (D), brachial-radial pulse wave velocity (PWV) and effective compliance (C_{eff}), were measured before and at the end of the study. Isobaric evaluation (C_{iso}) was performed in the entire population studied at an average mean BP of 110 mmHg. Ramipril significantly reduced BP from 155±16/94±6 mmHg to 140±15/85±7 mmHg (p<0.001) without affecting heart rate (HR; 74±10 vs. 75±12 bpm). In addition, it significantly improved both PWV (18%; p<0.001) and arterial compliance (45%; p<0.001), from which 35% was related to a pressure independent effect (p<0.01). Atenolol also induced a reduction in both BP (159±17/96±10 to 133±13/81±8 mmHg; p<0.001) and HR (76±10 to 57±7 bpm; p<0.001). In a similar way, PWV (11%; p<0.05) and C_{eff} (30%; p<0.05) were significantly improved without significant change in C_{iso}. This suggests that blood pressure reduction was responsible for compliance improvement. In conclusion, it is suggested that atenolol induces only hemodynamic changes, mediated mainly by BP reduction. In contrast, the improved brachial buffering function observed after ramipril involves not only hemodynamic changes, but also changes mediated by other mechanisms, such as modification of wall structures.

Key words: hypertension, ramipril, atenolol , isobaric compliance, brachial artery

Resumen ***Componentes mecánicos vs intrínsecos en la mejoría de la compliance braquio-arterial. Comparación de los efectos del atenolol vs el ramipril en pacientes hipertensos***

El objetivo de este trabajo fue comparar los efectos mecánicos e intrínsecos sobre la compliance de la arteria braquial, entre un inhibidor de la enzima de conversión de la angiotensina vs un betabloqueante. Es un estudio doble ciego, con 34 pacientes hipertensos esenciales tratados en forma randomizada durante 3 meses con ramipril 2.5-5.0 mg/día (n=17, edad 57±7 a, 11 masc) o atenolol 50-100 mg/día (n=17, edad 53±8 a, 11 masc). La presión arterial (PA), el diámetro braquial (D), la velocidad de la onda del pulso braquial-radial (VOP) y la compliance efectiva (C_{ef}) fueron medidos al comienzo y al finalizar el estudio. Se realizó un estudio isobárico (C_{iso}) en toda la población estudiada, a una PA media de 110 mmHg. El ramipril redujo la PA (155±16/94±6 mmHg a 140±15/85±7 mmHg; p<0.001) sin afectar la frecuencia cardíaca (FC; 74±10 vs. 75±12 lpm), disminuyó la VOP un 18% (p<0.001) y aumentó la C_{ef} un 45% (p<0.001), de la cual un 35% fue atribuida a un efecto independiente de la presión (p<0.01). El atenolol, indujo una reducción de la PA (159±17/96±10 a 133±13/81±8 mmHg; p<0.001) y FC (76±10 a 57±7 lpm; p<0.001), disminuyó la VOP un 11% (p<0.05) y aumentó la C_{ef} un 30% (p<0.05), sin cambios significativos en C_{iso}. En conclusión, se sugiere que el atenolol induce solamente cambios hemodinámicos, mediados principalmente por la PA. Por el contrario, la mejora observada luego del ramipril, involucra no solamente cambios hemodinámicos sino también cambios mediados por otros mecanismos, tales como modificación de la estructura parietal.

Palabras clave: hipertensión, ramipril, atenolol , compliance isobárica, arteria braquial

Reduction of arterial compliance is a well-known alteration observed in large arteries of hypertensive subjects. It is considered to be one of the major determinants of the pulse pressure increase thus favoring, the development of left ventricular hypertrophy[1], which is known to be the substrate for cardiac failure, cardiac arrhythmia, myocardial infarction and sudden death.

The effect of different antihypertensive drugs on arterial function has been previously reported[2]. Chen-Huan et al[3] found that arterial stiffness was significantly lower under ACEI (angiotensin converting enzyme inhibitor) administration than under beta blockade, despite similar decrease in blood pressure. Notwithstanding, the

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Postal address: Dr. Ricardo Armentano, Universidad Favaloro, Av. Belgrano 1723, 1093 Buenos Aires, Argentina
Fax: (54-11) 4384-0782 e-mail: armen@favaloro.edu.ar

reported effects of betablockers on arterial compliance are somehow controversial. Some authors have suggested an impairment of compliance secondary to α adrenergic mediated vasoconstriction[4], while others have provided evidence that heart rate reduction could be the substrate for the arterial compliance improvement[5].

It is known that blood pressure increase stretches and dilates arteries and reduces distensibility[6]. This is explained by the fact that, for the same arterial segment, compliance is a nonlinear function of blood pressure[7]. Therefore, any method used to address this basic question must compare subjects with and without elevated blood pressure, at the same level of pressure, thus enabling to evaluate whether the decrease in arterial compliance is a mechanical consequence of high blood pressure or an intrinsic effect of hypertension on the arterial wall.

The aim of the present study was to discriminate the participation of mechanical versus intrinsic components in the brachial arterial compliance improvement induced either by ramipril, an ACEI, or atenolol, a β adrenoceptor antagonist, in mild to moderate essential hypertensive patients.

Material and Methods

Subjects. Thirty-four mild to moderate essential hypertensive patients were included in this study, after they provided a written informed consent. Subjects were recruited from the Hypertension Section of the Institute of Cardiology and Cardiovascular Surgery of the Favaloro Foundation. They were included if their office blood pressure values ranged between 179-140/109-90 mmHg measured with a mercury sphygmomanometer (mean of three measurements in the sitting position, Korotkoff phase V sound) as stated by the American Heart Association[8].

History and physical examination, screening biochemical testing, renal echography, and isotopic radiorenographic studies excluded secondary forms of hypertension. Renal function was normal in all patients (serum creatinine: 0.8 to 1.2 mg %). No subject received oral contraceptives or estrogen before or during the study.

Patients with obesity (BMI: >30 Kg/m^2), coronary or valvular heart diseases and chronic medical illnesses such as diabetes mellitus, thyroid disorders, hepatic or renal diseases or alcoholism were excluded from the study. In all subjects, the presence of mitral or aortic diseases was ruled-out through Doppler echocardiography.

Antihypertensive therapy was discontinued 4 weeks before starting the study. During this period, the patients received placebo. After that, they were randomized to ramipril (2.5 mg/day, group R) or atenolol (50 mg/day, group A). If after 30 days with either treatment the diastolic blood pressure (DBP) values were above 90 mmHg, the dose taken was doubled (ramipril to 5.0 mg/day or atenolol to 100 mg/day). The patients received this drug schedule until the end of the study (3 months).

Measurements. Studies were performed in a temperature-controlled laboratory (21-23°C). The subjects were previously informed about the study and instructed to be relaxed in the supine position with the right arm supported at mid-thoracic level and the hand relaxed and opened. After a 15 minutes resting period the study was started.

Systolic (SBP) and diastolic (DBP) blood pressure were measured in the right arm with a Dinamap 801 device (Critikon, Tampa, Fl. USA) calibrated against a mercury sphygmomanometer. The blood pressure value herein reported was the mean value resulting from five readings obtained every minute during the brachial artery diameter measurement. Mean arterial pressure (MAP) was calculated as follows: MAP=DBP + [(SBP - DBP)/3].

The brachial artery internal lumen diameter was determined by echography *(Hewlett Packard Sono 1500, Andover, Mass, USA)* with a 7.5 MHz mechanical transducer. The sound beam was perpendicularly adjusted to the far arterial wall surface. All the measurements were made in the end-systolic period, identified by EKG, during which the artery is at maximal dilatation. The reproducibility of these measurements was tested by repeated readings (n=24) in 6 normotensive and 8 hypertensive subjects and the overall variation coefficient (VC) was 3.92±3.17%.

Pulse wave velocity (PWV) in the brachial-radial arteries was calculated as the ratio of the distance between the two measurement points and the time interval separating the feet of the two pulse waves, measured with two tonometers (Millar Instruments, Houston, USA) that were held over the skin in the most prominent parts of the brachial and radial artery. By this way, an accurate pressure waveform can be digitized. A special software, developed in our laboratory, allowed the on-line recording of the peripheral waveform, which was assessed visually on a monitor. This ensured that the best possible recording was obtained and that artifacts resulting from movement were minimized. The software uses the second derivative algorithm in order to locate the onset of the pressure wave and includes measurement in at least ten pair of pulses.

Brachial artery compliance was calculated by means of the formula derived from the Bramwell-Hill equation[1, 9], as follows:

$$PWV = \sqrt{\frac{dP}{dD} \cdot \frac{D}{2 \cdot \delta}} \quad (1)$$

and then defining diametrical effective arterial compliance as, $C_{eff} = \frac{dD}{dP}$, evaluated at the mean prevailing pressure

$$C_{eff} = \frac{1334 \cdot D_m}{2 \cdot \delta \cdot PWV^2} \quad (2)$$

Where δ is the blood density, PWV is the pulse wave velocity and D_m is the mean brachial artery diameter[10].

Assessment of the brachial compliance-pressure curves. In order to estimate the mechanical pressure dependence of the brachial artery compliance, we used a non-linear model for representing the diameter-pressure relationship in the brachial artery. By using this previously validated model[10], the diameter-pressure curve was obtained during changes in distending pressure, according to the following formula:

$$D = D_m + Ceff \cdot P_m \cdot \ln \frac{P}{P_m} \quad (3)$$

where D_m is the measured mean brachial artery diameter, P_m the measured prevailing mean blood pressure and C_{eff} the compliance measured at P_m, according to Equation 2.

The local arterial compliance-pressure curve was then deduced as the first derivative function of the diameter-pressure curve (dD/dP), according to the equation:

$$C(p) = \frac{C_{eff} \cdot P_m}{P} \quad (4)$$

Using this formula, we can draw the modeled compliance-pressure curve (Figure 1) over a wide range of pressures (75-150 mmHg).

Isobaric compliance (C_{iso}) was then computed by using equation 4, with $P = P_i$, where P_i represents the isobaric

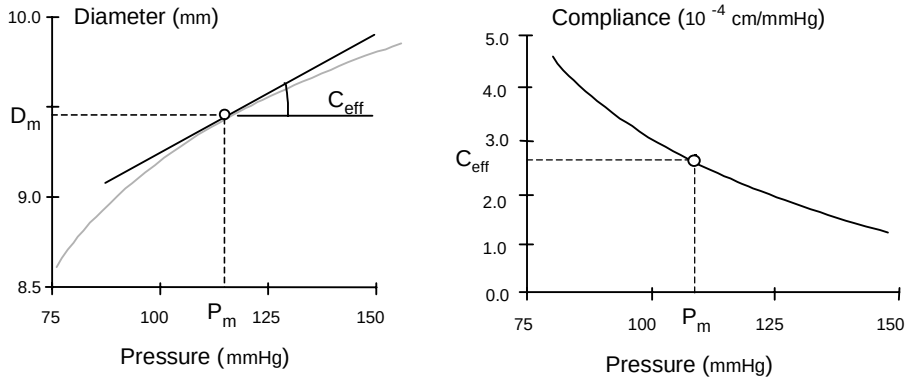

Fig. 1.– Left panel: Diagram of the arterial pressure-diameter relationship. The modeled pressure-diameter curve using a logarithmic model over a wide range of pressures (75-150 mm Hg) is depicted. The logarithmic curve was mathematically defined by only two parameters: a measured point of the curve and the slope of the curve at that point. The point of the curve was the (D_m, P_m) point of measurement, with D_m being the measured mean brachial artery diameter and P_m the measured prevailing mean blood pressure. The slope of the curve at this point was the compliance (C_{eff}) measured at the prevailing mean pressure, derived from the Bramwell-Hill equation. Right panel: Modeled compliance pressure curve and effective compliance measured at the prevailing mean pressure.

pressure. The isobaric pressure was calculated as the average MAP value of the two groups studied (mean pretreatment + mean antihypertensive treatment pressure)/2. The P_i value obtained and used in this study was 110 mmHg.

Echocardiographic measurements

Left ventricular two-dimensional and M-mode echocardiograms were obtained with a Hewlett-Packard Sonos 1500 (Hewlett-Packard, Andover, Massachusetts) connected to a probe phased array 2.0-2.5 MHz. Left ventricular wall thickness and left ventricular internal dimensions were determined according to the criteria of the American Society of Echocardiography (ASE)[11]. Left ventricular mass (LVM) was calculated by the equation approved in the Penn Convention[12, 13].

$$LVM = 1.04\left[(LVEDD + IVST + LVPWT)^3 - LVEDD^3\right] - 13.6 \quad (7)$$

Where LVEDD is left ventricular end-diastolic diameter, IVST is interventricular septum thickness and LVPWT is left ventricular posterior wall thickness.

Left ventricular mass index (LVMI) was calculated as the relationship between LVM and body area.

Statistical analysis. All data are reported as mean ± SD. Arterial parameters and clinical characteristics before and after ramipril and atenolol were analyzed using repeated measures one-way analysis of variance (ANOVA). The presence of significant differences was assessed using a Student Newman-Keuls post-hoc test. Differences in absolute changes between ramipril and atenolol groups were assessed by using an unpaired t-test.

The compliance-pressure curve was analyzed in each patient by measuring the area under the curve (AUC) within a pressure range of 75-150 mm Hg. The AUC of the pre-treatment condition was then compared with that corresponding to the treatment condition by using a paired t-test[14]. AUC is a more powerful statistical tool than C_{iso} for comparing two curves and detecting a significant shift of one compliance-pressure curve, since it takes into account the whole section of the compliance-pressure curve and not only one point[15]. Values of $p<0.05$ were considered statistically significant[14].

The Ethic and Research Committee of the Institute of Cardiology and Cardiovascular Surgery of the Favaloro Foundation approved the protocol.

Results

Nine out of 17 patients (53%) in group R complained of adverse effects (mild cough in 3, moderate cough in 1, mild fatigue in 2, mild headache in 1, sexual impotence in 1 and mild skin rash in 1). Eight out of 17 patients (47%) in group A had any of the following symptoms: mild fatigue (1), sexual impotence (1), mild skin rash (1), tachicardia (2), mild bronchospasm (1), nightmares (1) and mild dizziness (1). No patient was withdrawn from the study. The mean daily dose was 3.79 mg for ramipril and 67.65 mg for atenolol.

No significant differences in age (group R: 57±7 years; group A: 53±8 years), body mass index (group R: 27±2 kg/m^2; group A: 26±3 kg/m^2) and gender (group R: 11 males; group A: 11 males) were found. Similarly, at baseline, all measured and calculated hemodynamic arterial parameters did not show significant differences between pretreated groups (Table 1).

Blood pressure values were significantly reduced by ramipril: 9.7% ($p<0.01$) for SBP, 9.6% ($p<0.001$) for DBP and 7.8% ($p<0.01$) for MBP (See table 1). Atenolol treated patients showed a significant reduction in BP, 16.3% ($p<0.001$) for SBP, 15.6% ($p<0.001$) for DBP and 16.1% ($p<0.001$) for MBP. Significant differences were observed in SBP, DBP and MBP absolute changes between ramipril and atenolol groups ($p<0.05$).

Heart rate did not change with ramipril but showed a significant decrease after atenolol (25%, $p<0.001$). (Table 1).

Brachial-radial pulse wave velocity was improved by 18% with ramipril ($p<0.001$) whereas atenolol decreased it by 11% ($p<0.05$).

LVMI decreased significantly in both groups (group R: 16%, $p<0.001$; group A: 11% $p<0.01$).

TABLE 1.– Measured and calculated hemodynamic arterial parameters before (Baseline) and after treatment (3 Months) with ramipril and atenolol

	Ramipril Group (n = 17)		Atenolol Group (n = 17)	
	Baseline	3 Months	Baseline	3 Months
Measured Parameters				
SBP (mm Hg)	155 ± 16	140 ± 15*	159 ± 17	133 ± 13§
DBP (mm Hg)	94 ± 6	85 ± 7§	96 ± 10	81 ± 8§
HR (beats/min)	74 ± 10	75 ± 12	76 ± 10	57 ± 7§
D_m (cm)	0.41 ± 0.06	0.41 ± 0.07	0.42 ± 0.07	0.41 ± 0.06
Calculated Parameters				
MBP (mm Hg)	115 ± 10	106 ± 9*	118 ± 9	99 ± 9§
PWV (m/s)	11.6 ± 1.7	9.5 ± 1.1§	11.7 ± 1.3	10.4 ± 1.8†
C_{eff} (10^{-4} cm/mm Hg)	2.0 ± 0.4	2.9 ± 0.8§	2.0 ± 0.5	2.6 ± 0.9†
C_{iso} (10^{-4} cm/mm Hg)	2.1 ± 0.4	2.8 ± 0.8*	2.1 ± 0.6	2.3 ± 0.8
LVMI (g/m^2)	117 ± 29	98 ± 26§	116 ± 28	103 ± 26*

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, D_m: mean arterial diameter, MBP: mean blood pressure, PWV: pulse wave velocity, C_{eff}: effective brachial compliance, C_{iso}: isobaric brachial compliance, LVMI: left ventricular mass index.
**p<0.01, †p<0.05, §p<0.001, baseline vs treatment;*

Intrinsic versus mechanical pressure effects in brachial artery compliance

Ramipril improved C_{eff} by 45% and C_{iso} by 35%. The improvement in arterial compliance corresponding to a decrease in mechanical stretching was only 10% of the total increase (Table 1). In contrast, atenolol increased C_{eff} by 30% without changes in C_{iso}, i.e. the improvement in the buffering function was mediated mainly by the decrease in blood pressure (Figure 2). No significant differences in the absolute change of C_{eff} between ramipril and atenolol groups were found. However, absolute changes in C_{iso} were higher (p<0.05) under ramipril administration (Figure 2).

Figure 3 shows the mean compliance-pressure curves before and after treatment with ramipril (left panel) and before and after treatment with atenolol (right panel), where the isobaric comparison of the compliance-pressure relationship over a wide range of pressures can be assessed. Significant differences were found over the entire operative range of pressures (75-150 mmHg) between baseline and ramipril-treated groups (p<0.001, AUC). However, the comparison between baseline and post-treatment values under atenolol did not show any significant differences.

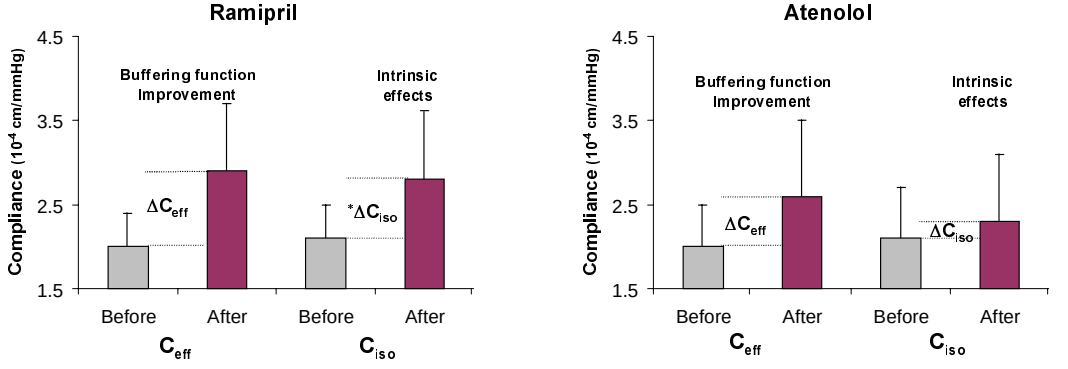

Fig. 2.- Intrinsic effects of the buffering function improvement with ramipril (Left Panel) and atenolol (Right Panel). ΔC_{eff}: Absolute change in C_{eff} before and after treatment; ΔC_{iso}: Absolute change in C_{iso} before and after treatment. *p<0.05: ΔC_{iso}-ramipril vs ΔC_{iso}-atenolol

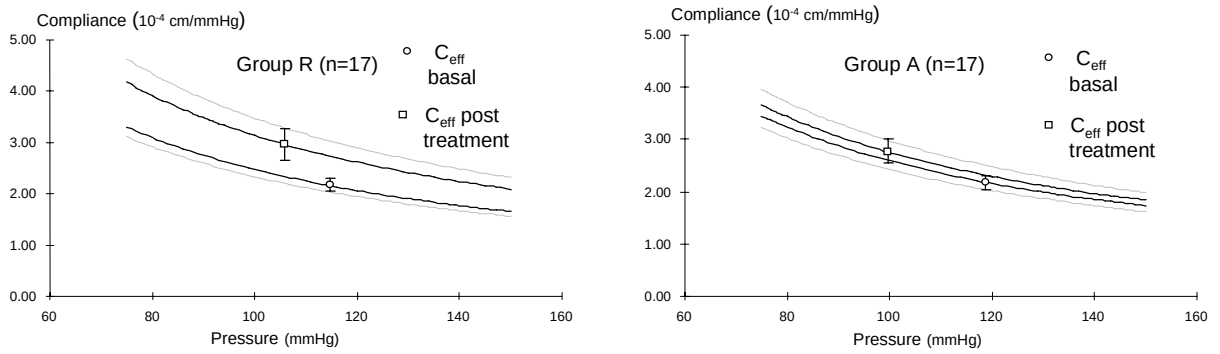

Fig. 3.– Compliance-pressure curves before and after treatment with ramipril (Group R) and before and after treatment with atenolol (Group A). Both graphs show the mean compliance-pressure curves (solid lines) and their respective Standard error of mean (SEM, thin dotted lines). Ramipril administration shifted the compliance-pressure curves upwards ($p<0.001$, AUC paired t-test).

Discussion

The aim of this study was to discriminate, in mild to moderate hypertensive patients, the mechanical and intrinsic effects of ramipril and atenolol on arterial compliance of the brachial arterial wall.

We used a noninvasive modeling method for estimating the mechanical pressure dependence of diameter and compliance. This allowed us to compare the brachial arterial compliance without the mechanical influence of pressure, by obtaining isobaric values. Only three variables (mean diameter, mean pressure and effective compliance) were needed to define this model[10]. In a previous study[16], it was shown that the use of a more sophisticated methodology, on the basis of noninvasive recordings of pressure and diameter pulses with tonometric and echotracking devices, allowed the determination of the pressure-diameter hysteresis loop. This approach permitted the discrimination of the purely elastic and viscous components of the arterial wall. In the same work, we showed that the purely elastic pressure-diameter relationship can be modeled by a logarithmic function containing the mean pressure diameter point. The present approach uses the mean pressure diameter operating point and the slope at this same point, which defines one and only one logarithmic function. Our «one point» methodology appears satisfactory to characterize the elastic behavior of the arterial wall avoiding any sophisticated methodology.

The brachial effective compliance was computed by means of a formula derived from the Bramwell-Hill equation[1,9], and evaluated at the mean prevailing pressure of each subject. This approach requires an accurate evaluation of the PWV. Therefore, PWV was obtained by using an automatic computer software developed in our laboratory, based on the second derivative algorithm that identifies the onset of the pressure wave[17]. This point is considered to be relatively free of wave reflections.

Our results show that ramipril improved the effective compliance by 45%, where 10% was assigned to mechanical pressure effects and 35% was attributed to modifications of the arterial wall structure. In contrast, atenolol improved the buffering function by 30% but failed to induce any significant change in the structure of the arterial wall, despite greater reduction in blood pressure. To extend the isobaric comparison to a wide blood pressure range (75-150 mmHg), we compared the area under the curve (AUC) of each patient before and after treatment, thus taking into account the whole section of the compliance-pressure curve, rather than only one point[15]. By this way, it was confirmed that only ACEI administration improved the intrinsic components of the artery buffering function.

Although both drugs induced a decrease in the brachial PWV, the atenolol-induced antihypertensive effect was greater than that induced by ramipril. In this way, there is a large body of evidence about the beneficial effects of the treatment with an ACE-inhibitor on arterial function[18, 19, 20, 21, 22] or structure[23] in hypertensive patients when compared with those treated with a beta-blocker. In our case, both drugs improved effective compliance and pulse wave velocity. In addition, when it was evaluated either by isobaric analysis or by the area under the curve, compliance was exclusively improved by ramipril. This further supports the idea that ACEI might have specific effects on the blood vessel wall characteristics presumably independent of the efficacy in reducing blood pressure. Our results are in agreement with those from Mayet et al[18] showing an intima media thickness reduction with ramipril, possibly related to reduced hypertrophy of vascular smooth muscle cells.

On the other hand, heart rate was significantly reduced only in patients with atenolol. In this regard, the inverse influence of heart rate on arterial distensibility, with greater effects on elastic than on muscular arteries, was previously demonstrated in an animal study[5]. This may occur because the arterial wall is essentially viscoelastic and, as a result of an increase in the stretching rate, the wall becomes stiffer. By this way, atenolol, due to the negative chronotropic effect[21], might influence the brachial

arterial compliance through a spurious effect on viscoelasticity. Moreover, it was also demonstrated that the heart rate-dependent reduction in arterial distensibility and compliance is not similar in all arteries, involving large elastic arteries to a greater extent than arteries with a predominant muscle structure[5].

On the other hand, both treatments were able to reduce left ventricular mass index as previously observed by other authors[4, 24]. In this sense, Agabiti-Rosei et al[25] found, in a multicentric study, that ramipril reduced LVM by 4.5% at 3 months and 14% at 6 months of treatment, whereas with atenolol the reduction of LVM was only of 4% at 3 and 6 months. In this regard, it is known that ACEI reverses structural alterations in the heart and vessels faster than other antihypertensive drugs. Thus, the greater improvement found with ramipril could be related to the well known pharmacological properties of the drug along with the reduction of blood pressure[26].

In conclusion, ramipril, an ACE-inhibitor with high lipophilic activity, improves brachial buffering function by decreasing arterial wall stiffness independently of blood pressure reduction and heart rate. This could be related to intrinsic modifications of the wall vessel structure. Thus, the effect of antihypertensive agents on large artery properties may depend on the drug family and the dose used, the blood pressure decrease, the duration of treatment and the vascular territory. The distinctive effects of antihypertensive drugs on arterial wall properties may be relevant for the prevention and management of arterial diseases.

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