Aims Left atrial (LA) enlargement is related to left ventricular (LV) remodelling and diastolic dysfunction (DD), reflecting cardiac target organ damage. The aim of this study was to investigate the relation of one-dimensional (1D) and volume derived indexes of LA enlargement with abnormal segmental relaxation in hypertensive patients.

Methods and results We evaluated 90 hypertensive patients and 50 non-hypertensive volunteers with normal ejection fraction (EF). Global DD was evaluated based on conventional indexes (E/A, deceleration time, LV isovolumic relaxation time), and segmental early and late diastolic strain rates (SR) were recorded from 18 LV segments. The number of segments with abnormal relaxation (SR_e/SR_a < 1.1) was represented as segmental DD. LA size was evaluated based on 1D left atrial dimension (LAD) and left atrial volume (LAV), and indexed by body surface area (BSA) and height. The hypertensive patients had higher segmental DD (9.5 ± 4.2 vs. 5.2 ± 3.2, P < 0.05) and appeared to have higher 1D and volume-derived indexes of LA size compared to the controls. Individuals with global DD had more deteriorated segmental relaxation and higher LA size compared with those without global DD. When participants were separated according to normal, mildly dilated, and moderately to severely dilated LA size, there was progressive deterioration of segmental DD, mean Ea, and filling pressures, along with the progression of LA enlargement. Volume-derived indexes, LAV/BSA, LAV/height, and LAV, appeared to have better correlations with segmental DD, as well as with linearly changed parameters of DD (Mean Ea, E/Ea), LV remodelling (LVMI, relative wall thickness), age, and systolic blood pressure (SBP), compared to the respective 1D-based (LAD) LA indexes. LAV/BSA was proved to be an independent predictor of segmental DD (β: 0.23, R²: 0.48), along with LVMI, SBP and age, irrespective of gender.

Conclusion LA size constitutes a morphological expression of abnormal segmental relaxation, with volume-derived indexes of LA enlargement, exhibiting higher correlation with segmental DD compared to the respective 1D indexes, and LAV/BSA to be an independent predictor of segmental DD in hypertensive heart disease.

Keywords Left atrium; Diastolic dysfunction; Strain rate

Introduction Systemic hypertension is regarded as one of the most important preventable causes of premature morbidity and mortality in developed and developing countries,1 and a major contributor to the pathogenesis of a large proportion of heart failure cases in a population-based sample.2 Cardiac remodelling, the major pathophysiological result of increased blood pressure, affects both ventricular and atrial components and is manifested clinically as changes in the size, shape, and function of the heart.3,4 Left atrial (LA) remodelling has been documented as an important predictor of cardiovascular events,5 which is independently related to stroke and death,6 as well as to systolic and diastolic heart failure.7 Furthermore, it is also well recognized that particularly in systemic hypertension, LA enlargement is related to left ventricular (LV) hypertrophy and diastolic abnormalities, reflecting cardiac target organ damage and underlying subclinical cardiovascular disease.3,8–10

Novel echocardiographic techniques, such as strain (S) and strain rate (SR), have evolved recently and have conferred new insight into myocardial deformation and LV mechanics.11
As a result, although the association of global diastolic dysfunction (DD) with LA enlargement has been well described, little is known about the relation of LA remodelling with regional segmental relaxation evaluated by SR echocardiography. Altered segmental relaxation is regarded as a better method for detecting early changes in diastolic function, since it is evident before global indexes of DD become informative. Therefore, the aim of the present study is to investigate the relation of one-dimensional (1D) and volume-derived indexes of LA enlargement with the novel index of abnormal segmental relaxation, evaluated by strain techniques.

Methods

Study subjects

The study population consisted of 90 consecutive patients with essential hypertension, who met the inclusion criteria, recruited from the Hypertension Outpatient Clinic as well as the Echocardiography Department, and 50 non-hypertensive volunteers as control. Individuals were excluded from the study, if they were not in sinus rhythm, or if they had a history of coronary artery disease, regional wall motion abnormalities, mitral or aortic stenosis, congenital disease, cardiomyopathy, mitral or aortic regurgitation, pericardial disease, or cor pulmonale. Participants who also had more than three of their LV segments suboptimal for SR analysis were originally excluded from the study. All patients had a history of hypertension for more than 1 year and were currently under medical treatment. The control group consisted of volunteers who were normotensive, according to their BP measurements and medical records. The control group was set as a standard for all the recordings.

Assessment of global diastolic dysfunction

All subjects had normal EF and were evaluated for global DD based on known conventional echocardiographic criteria [using E/A, deceleration time (DT), LV isovolumic relaxation time (IVRT), pulmonary veins S, D, and A flow velocities], along with tissue Doppler parameters (E/Ea).

The diagnosis of global DD was based on the following criteria: E/A < 1 and DT > 50 ms, E/A > 0.5 and DT > 150 ms, E/A > 1.5 and DT > 90 ms, E/A > 2.5 and/or IVRT > 105 ms, and/or pulmonary S/D > 1.5 or S/A > 50 ms, and/or pulmonary E/Ea > 15.

The valsalva manoeuvre, pulmonary venous’ recordings, and annular Tissue Doppler tracings were also used for diagnosis of pseudo normal type II DD.

The study was approved by the Local Research Ethics Committee and an informed consent was given by all participants.

Echocardiography

All the participants were studied by using standard two-dimensional (2D) and Doppler echocardiography, with Toshiba Apio model SSA-770A.

Parasternal and apical projections were obtained according to the recommendations of the American Society of Echocardiography (ASE). LV ejection fraction (EF) was derived using Simpson’s modified biplane method. LV mass was estimated with the area-length formula as described in detail in the ASE document on LV quantification. LV mass index was then calculated using the formula: LVmass/BSA, where BSA is the body surface area. Relative wall thickness (RWT) was estimated according to the formula: RWT = 2 × posterior wall thickness/LVEDD, where LVEDD is the left ventricular end-diastolic diameter.

Pulsed-wave Doppler of mitral inflow was performed in the apical four-chamber view, with the sample volume placed at the level of the mitral valve tips. Peak velocities of E and A waves and their ratio E/A, DT, and IVRT were measured.

Pulsed-wave tissue Doppler recordings from the septal and lateral sites were also recorded from the apical four-chamber view. A pulsed sample volume of 5 mm was placed over the mitral annulus, and the average of three consecutive cardiac cycles of peak diastolic velocities during early filling (Ea) was measured. Mean Ea was estimated averaging the septal and lateral values. LV filling pressures were estimated by calculating the E/Ea mean ratio.

Pulse pressure was estimated by the formula: pulse pressure = SBP − DBP. Mean arterial pressure was estimated by the formula: mean arterial pressure = diastolic blood pressure + 1/3 (SBP − DBP).

Left atrial size

The LAD was measured at the base of the heart in the parasternal short-axis view at the level of the aortic valve according to the recommendations of ASE developed in conjunction with the European Association of Echocardiography.

Measurement of LAV was conducted with the biplane method of disks (modified Simpson’s rule) using apical four-chamber (A4C) and apical two-chamber (A2C) views at ventricular end-systole according to the same above-mentioned recommendations. LAD and LAV were subsequently indexed by BSA and height.

Tissue Doppler image samples acquisition for strain rate analysis

Tissue Doppler images of cine-loops of three cardiac cycles from the lateral, septal, anterior, inferior, anteroseptal, and posterior wall from the apical four-, three-, and two-chamber views were acquired separately at end-expiratory apnoea and stored digitally. To optimize the tissue velocity signals, the 2D image was optimized to obtain a clear differentiation between the myocardium and the blood pool. We used the narrowest image sector angle (30°), possible to achieve the maximum Doppler frame rate, typically >150 frames/s. The recorded wall was positioned in the centre of the sector, so that the direction of motion interrogated was as near as possible parallel to the direction of the insonating beam, giving an insonation angle <15° in all the recordings in order to avoid underestimation of values due to angle dependency. The insonation frequency was set at 2.8 MHz. Filter harmonic imaging was set as a standard for all the recordings.

Strain rate off-line analysis

Analysis of SR parameters was performed off-line using the incorporated USTQ-770A program of the Toshiba Apio System. One sample volume region of interest (ROI) was placed at the basal part of each LV segment (in an 18-segment model), so that there was no migration beyond the limits of the selected myocardium. An automatic ROI-tracking mode was activated in order to ensure that the measurements reflected the motion of a myocardial tissue segment throughout the cardiac cycle. We used a 6 mm × 9 mm oval ROI for longitudinal measurements.

Early and late diastolic SR parameters SRe and SRa of basal, mid, and apical segments were recorded separately from each LV wall in the longitudinal direction. SRe/SRa < 1.1 was regarded an index of altered segmental relaxation-segmental DD as previously described (Figure 1). The total number of segments with altered segmental relaxation was calculated for all the participants and presented as segmental DD.

Statistical analysis

Data were analysed using SPSS 12 software (SPSS, Chicago, IL, USA). Continuous variables expressed as mean ± standard deviation were compared using Student’s t-test for independent groups. When the
assumptions to use the Student’s t-test were not satisfied, comparison between groups was performed using the Mann–Whitney U-test. Pearson’s correlation was used to evaluate bivariate linear relations. Multiple linear regression analysis was used to assess the influence of selected variables (LAV/BSA, LVMi, SBP, age, gender) on segmental DD applying an enter method. A P-value of <0.05 for a two-tailed test was considered significant.

Results

Characteristics of the study population

General echocardiographic and demographical characteristics of the study groups are shown in Table 1. Males slightly outnumbered females, particularly in the control group. Hypertensive patients had higher WT, LVMi, and RWT compared with control. Hypertensive patients were also slightly more obese (higher BMI) and had higher SBP, MAP, and PP compared with the control group, although they were under medical treatment. The majority of the patients were taking angiotensin-converting enzyme (ACE)-inhibitors (68%), with Ca-blockers (41%), β-blockers (33%), and diuretics (25%) following in descending order.

Diastolic dysfunction

All the participants with global DD had ≥2 indexes of conventional echocardiography (E/A, DT, IVRT, pulmonary S/D), suggestive of that diagnosis. Grade I DD was found in 61% of the hypertensive patients, whereas 6% had grade II DD. Hypertensive patients had more segments with abnormal relaxation pattern, higher DT and IVRT, lower E/A ratio, as well as lower mean Ea, and higher filling pressures (E/Ea) compared with the control group (Table 1).

Left atrial size in the control and the hypertensive group

The values of different LA size indexes of the control and the hypertensive group, as a whole and according to gender, are shown in Table 2. Hypertensive patients appeared to have higher 1D and volume-derived indexes of LA size compared with the controls, with the mean value of LAV/BSA falling within the mildly abnormal range.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General and echocardiographic characteristics of the study groups</th>
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<tr>
<td></td>
<td>Control (n = 50)</td>
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<tr>
<td>Age (years)</td>
<td>48.5 ± 8.6</td>
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<tr>
<td>Male (%)</td>
<td>60</td>
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<td>WT (mm)</td>
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<tr>
<td>Height (m)</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
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</tbody>
</table>

*P < 0.05: hypertensive vs. control.

Left atrial size and altered segmental relaxation

When participants were separated according to normal, mildly dilated, and moderately to severely dilated LA size (LAV/BSA ≤28, 29–33, and ≥34 mL/m², respectively), there was progressive deterioration of segmental DD,
mean Ea, and filling pressures, along with the progression of LA enlargement (Table 3, Figures 2 and 3).

**Left atrial size, segmental diastolic dysfunction, and global diastolic dysfunction**

When all the participants were divided according to normal or abnormal global diastolic function, it revealed that those with normal LA had more deteriorated segmental relaxation (segmental DD) and higher LA size (LAV/BSA) (Table 4).

**Left atrial size and univariate correlations**

Univariate correlations of the indexes of LA size are shown in Table 5. When compared LAD vs. LAV, LAD/BSA vs. LAV/BSA, and LAD/Height vs. LAV/Height, the volume-derived indexes appeared to have better correlations with segmental DD, as well as with linearly changed parameters of DD (mean Ea, E/Ea), LV remodelling (LVMi, RWT), age, SBP, and PP, compared to the respective 1D-based LA indexes.

**Left atrial size and independent predictors**

LA size, as expressed by LAV/BSA, was proved to be an independent predictor of segmental DD, along with LV hypertrophy (LVMi), SBP, and age, irrespective of gender (Table 6).

**Discussion**

According to our findings, LA size is increased with the progression of abnormal segmental relaxation in hypertensive heart disease. Volume-derived indexes of LA enlargement correlate better with segmental DD, as well as with other echocardiographic parameters of DD (mean Ea, filling pressures E/Ea) and LV remodelling (LVMi, RWT), than the respective 1D-based indexes of LA size. Finally, LAV/BSA proved to be an independent predictor of segmental DD, along with LV hypertrophy, SBP and age, irrespective of gender.

**Atrial remodelling and diastolic dysfunction**

In subjects with DD without primary atrial pathology or congenital heart or mitral valve disease, increased LA volume usually reflects elevated LV ventricular filling pressures.22 This is also supported by our study, given the significant correlation of LAV/BSA with E/Ea (Table 5) and the progressive increase of LA size with the progressive elevation of LV filling pressures, as appear in Table 3. During ventricular diastole, the left atrium is exposed to LV pressures; so with increased LV stiffness or non-compliance, as happens in DD, LA pressure rises to maintain adequate LV filling. Increased LA pressure, in turn, elevates atrial wall tension, which leads to chamber dilatation and stretching of the atrial myocardium.21 Thus, LA volume increases with the progression of the severity of DD,12,22 a fact that is also demonstrated in our study (Figure 2). As DD progresses over time, the structural changes of the LA may also express the chronicity of exposure to abnormal filling pressures22,23 and provide predictive information beyond that of the grade of diastolic dysfunction.24

**Which is the best index of left atrial enlargement?**

It is well recognized that measurement of antero-posterior 1D LA linear dimension is simple and convenient, but not a reliably accurate method to assess LA enlargement, given the fact that LA is not a symmetrically shaped three-dimensional (3D) structure.25 Furthermore, because LA enlargement may not occur in a uniform fashion, 26 1D assessment is likely to be an insensitive assessment of any change in LA size. In contrast to 1D LA assessment, LA volume by 2D or 3D echocardiography provides a more accurate and reproducible estimate of LA size, when compared with reference standards, such as magnetic resonance imaging (MRI) and cine computerized tomography.27-29 Moreover, as body size is a major determinant of LA size, indexed values may provide a standardized way to compare LA differences.30
The above observations are also supported by our study, showing that volume-derived indexes of LA enlargement had better correlations with certain clinical and echocardiographic parameters, when compared with respective 1D indexes of LA size (Table 5).

### Left atrial size, global diastolic dysfunction, and abnormal segmental relaxation

Segmental DD constitutes a novel and more sensitive index for early detection of DD compared with conventional indexes, with reasonably good reproducibility. This can be applied to age-related (control) or disease-related (HTN) DD. As also previously has been shown, segmental DD is better correlated with linearly changed indexes of DD, such as annular early diastolic velocity, than with DT, IVRT, and $E/A$. LA size appears to be significantly correlated with segmental DD, but more interestingly, to be also an independent predictor of abnormal segmental relaxation, as presented by the current study. This is a reasonable finding, as the cumulative deterioration and progression of segmental DD is related to the appearance and the severity of global DD, as expressed by conventional indexes. It must be also noted that the majority of our patients had mild DD (grade I), which is not related to pronounced LA enlargement. For that reason, the mean value of LAV/BSA in the hypertensive group as a whole, as well as in the group of participants with global DD (Table 4), ranged within the mildly abnormal level. In fact, as it is well known, some patients with mild DD (grade I) may actually have LA size still within normal range (or even upper normal), as filling pressures are not highly increased at the first stages of DD. This is also supported by our study, given the standard deviation of LAV/BSA in Table 4.

### Left atrial size, segmental diastolic dysfunction, and left ventricular hypertrophy

The role of LVH in relation to LA remodelling has previously been investigated, showing that concentric LV geometry is associated with greater LA size, and the degree of LA...
enlargement depends on LV mass. Furthermore, the close association of LVH with DD in systemic hypertension is also well known. Our study confirms the above observations, showing that LV remodelling as expressed by RWT and LVMI significantly correlates with LA enlargement (LAV/BSA) (Table 5). More interestingly, LVMI was proved to be an independent predictor of segmental DD (Table 6), supporting the close interrelation among LVH, DD, and LA remodelling.

Clinical significance

Our study provides new insight for the pathophysiology of LA enlargement in relation to a novel index of DD. This could be used in future studies or in clinical practice for monitoring of disease progression or regression. Furthermore, the reported relation of abnormal segmental relaxation with LA remodelling, both mirroring target organ damage, could be used for earlier risk stratification and decision-making in patients suffering from hypertensive heart disease, given the evidence of the earlier appearance of segmental abnormalities, compared with the information derived from conventional indexes of DD.

Limitations

Although patients with a history suggestive of coronary artery disease and/or wall motion abnormalities were originally excluded from the study, participants with silent myocardial ischaemia could not be excluded. However, microvascular and subendocardial ischaemia seem to be integral components of hypertensive heart disease, especially when accompanied by LV hypertrophy, and even with normal coronary arteries. Quantification of LV end-diastolic pressures and diagnosis of global DD were not based on invasive procedures. Nevertheless, diagnosis of DD based on Doppler measurements has been widely used by large population-based studies, and Doppler parameters have been validated against the tau index. LA volume was not measured with the gold standard of MRI or 3D echocardiography; however, the method described in our study was supported by the recommendations of the ASE, developed in conjunction with the European Association of Echocardiography for chamber quantifications. Finally, the fact that hypertensive patients were under medical treatment, taking Ca-blockers, ACE-inhibitors, and/or β-blockers, may have had some influence, directly or indirectly, on LV diastolic function, filling pressures, LV remodelling, and/or LA remodelling.

Conclusion

LA size constitutes a morphological expression of abnormal segmental relaxation, with volume-derived indexes of LA enlargement better correlating with segmental DD compared to the respective 1D indexes. LAV/BSA appears to be an independent predictor of segmental DD in hypertensive heart disease, along with LV hypertrophy, systolic blood pressure, and age.

Conflict of interest: none declared.

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