Left atrial strain in patients with arterial hypertension

Early effects of arterial hypertension: left atrial deformation analysis by two-dimensional speckle tracking echocardiography

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Abstract

Background: Arterial hypertension (HTN) causes left ventricular (LV) cavity dysfunction even if ejection function (EF) remains preserved. Recent studies have shown that diastolic dysfunction and left atrial (LA) dilatation are also associated with myocardial dysfunction. The aim of the present study was to explore the nature of LA longitudinal function disturbances in hypertensive patients with normal LV and LA structure and conventional function parameters.

Methods: Methods: Peak atrial longitudinal strain (PALS) was evaluated in 78 patients with systemic HTN and preserved EF (≥ 55%) divided in 41 patients with diastolic dysfunction but no hypertrophy (group HTNdd), and 37 patients with no diastolic dysfunction or hypertrophy (group eHTN). Results were compared with those from 38 age- and gender-matched healthy controls.

Results: Indexed LA area and indexed LA volume were within the normal range and not different between the two patient groups and controls. eHTN group had reduced global PALS ($p < 0.001$) and four-and two-chamber average PALS ($p < 0.001$ for both). Similar abnormalities were seen in HTNdd group but to a worse degree ($P < 0.01$ for both). LV EF was not different between the eHTN and HTNdd groups compared to controls. LV E/e' ratio was the strongest predictor of reduced global PALS in both eHTN and HTNdd groups.

Conclusion: Asymptomatic untreated HTN patients with preserved LVEF and normal diastolic function have compromised LA strain despite normal cavity size, consistent with preclinical LA myocardial dysfunction.

Key words: arterial hypertension, echocardiography, atrial strain, speckle tracking

Introduction

Arterial hypertension (HTN) is one of the common diseases associated with the increased incidence of heart failure [1, 2] and is one of the independent risk factors for atrial fibrillation (AF) [3, 4] through perpetual structural and functional changes in the left atrium (LA) [5]. Hypertensive cardiopathy starts in the left ventricle (LV) [6] while ejection fraction (EF) is still maintained [7]. Subsequently, progressive deterioration of diastolic and systolic function occur as a reflection of long term afterload, despite not easily detected by conventional echocardiographic methods [8, 9]. Speckle tracking echocardiography (STE) is a novel non-Doppler-based technique for objective quantification of myocardial deformation which reflects intrinsic myocardial function [10-12]. Recent developments allowed STE to quantify longitudinal LA myocardial deformation dynamics, confering new insight into LA function analysis [13-16]. However, our knowledge on the use of STE in early detection of LA dysfunction in patients with systemic hypertension remains limited.

We sought in this study to explore LA longitudinal function by STE in patients with early HTN who do not have any evidence for structural or functional cardiac abnormaliuties by conventional echocardiographic techniques.

Methods

Study population: We studied 78 patients (age 59.6 ± 6.2 years, 44 men) with systemic HTN according to the current criteria set by the European Society of Hypertension and European Society of Cardiology recommendations [17] who were referred to the Echo Laboratory of Le Scotte Hospital, University of Siena for a diagnostic examination between January 2009 and September 2011. Patients were < 70 years of age, had newly diagnosed, not pharmacologically treated HTN, were in New York Heart Association class I, but had no ECG evidence for LV hypertrophy.

The patient cohort was classified into 2 groups; 41 with evidence for LV diastolic dysfunction (group HTNdd), and the remaining 37 with no diastolic dysfunction (group eHTN). No patient had evidence of secondary hypertension based on extensive clinical and laboratory examinations; more than mild valve disease; overt coronary artery disease (defined by at least one of the following: history of effort angina, acute coronary syndrome or revascularization procedures; positive exercise stress test; segmental wall motion abnormalities); hypertrophic cardiomyopathy; AF or other major arrhythmias; previous pacemaker implantation, heart transplantation or inadequate acoustic windows. In addition, all patients had

preserved LV systolic function (EF ≥ 55%) and normal LA size (indexed LA volume <28 ml/m2). Thirty-eight age-matched healthy normotensive subjects, with no history of cardiovascular disease served as controls, non of whom had abnormal findings at physical examination, electrocardiogram or baseline echocardiography or took cardiac medications. All patients and controls gave a written informed consent to participate in the study, which was approved by the local ethics commitee. The research project was in compliance with the declaration of Helsinki.

Standard echocardiography: All echocardiographic examinations were performed according to the recommendations of the American and European Society of Echocardiography [18, 19]. Echocardiographic studies were performed using a high-quality echocardiograph (Vivid 7, GE Medical System, Horten, Norway), equipped with an adult 1.5 - 4.3 MHz phased array transducer, and one lead ECG was continuosly displayed. Subjects were studied while in the left lateral recumbent position. LV internal diameters at end-systole and end-diastole (LV ESD and LV EDD, respectively) were measured from the left parasternal cross-sectional recording of the minor axis. Likewise interventricular septum and posterior wall thickness (IVST and PWT, respectively), were measured at end-diastole from the same M-mode recording. LV EF was calculated from the apical views using the biplane modified Simpson method. LV mass (LVM, in grams) was calculated using the Penn formula [20].

LVM = 1.04 [(LVIDd + PWTd + IVSTd)3 – LVIDd] – 13.6 g,

where LVIDd is LV end-diastolic internal diameter; PWTd, diastolic posterior wall thickness; and IVSTd, diastolic interventricular septal thickness. To determine LV hypertrophy LVM was subsequently indexed to body surface area (BSA) [18, 21, 22]. Relative diastolic wall thickness (RWT) was also determined as twice the posterior wall thickness divided by LV end-diastolic diameter, which was used to confirm the presence of LV hypertrophy [18].

LV longitudinal function: LV longitudinal function was studied using pulsed Tissue Doppler imaging, with the sample volume placed at the lateral angle of the mitral annulus from the apical 4-chamber view [23]. Peak systolic (s'), early diastolic (e'), and late diastolic (a') annular velocities were obtained. e' and the derived e'/a' ratio were used to assess LV diastolic relaxation [24]. Mitral annular plane systolic excursion (MAPSE) was meaured using the standard M-mode technique with the cursor placed at the lateral angle of the annulus from the apical 4-chamber view, using the zoom function [25-27].

LV longitudinal myocardial function: LV myocardial function was studied using STE from the apical long axis, 4- and 2-chamber views, during a brief breath hold and with a stable ECG recording. The frame rate was set between 60 and 80 frames per second. Three consecutive heart cycles were recorded and averaged. Peak LV longitudinal strain from the apical views was defined as the peak negative value on the strain curve during the entire cardiac cycle. LV cavity was traced manually from the innermost endocardial edge at end-systole, and the software automatically defined the longitudinal strain throughout the cardiac cycle. The time interval between the R wave and aortic valve closure was measured and used as a time reference. The automated algorithm provided the longitudinal peak systolic strain (LPSS) value for each LV segment from a 17-segment model polar plot, and the average value of LPSS for each apical view [28].

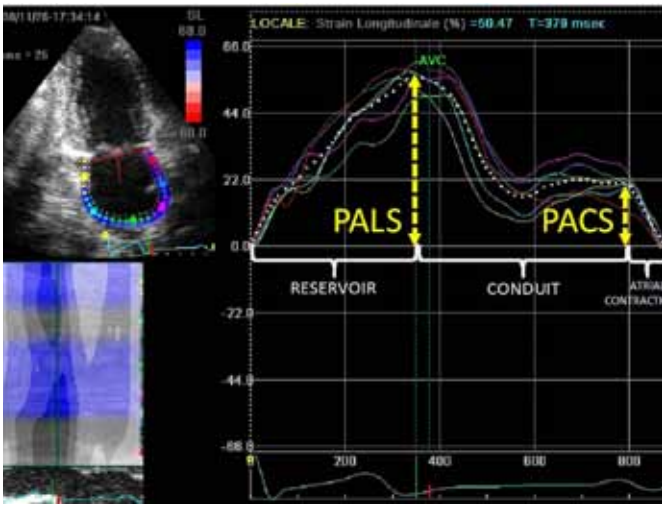

Figure 1. Measurement of peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS).

LV diastolic function: Pulsed-wave Doppler velocities of LV filling were recorded from the apical 4-chamber view, by placing the sample volume at the level of the tips of the mitral valve leaflets and the centre of the forward LV filling jet. Early (E) and late (A) diastolic LV filling velocities were measured and E/A ratio was calculated. E/A ratio [29] and E wave deceleration time were used as standard indeces of LV diastolic function [19] and raised E/e' was taken as a a marker of raised filling pressures [30].
LA structure and function: LA area and volume were measured using the biplane method of disks (modified Simpson's rule), in the apical 4- and 2-chamber view at end-systole (maximum LA size), and a mean value of area and volume were obtained and indexed to BSA [18]. LA myocardial function was studied using STE from the apical 4- and 2-chamber views of the conventional 2D grey scale images during a brief breath hold and with a stable ECG recording [31]. Care was taken to obtain true apical images using standard anatomical landmarks to avoid foreshortening the LA, therefore allowing a clear delineation of the atrial endocardial border. We also avoided inclusion of the LA appendage in the apical 2-chamber view in order to minimize its potential effect on LA strain measurements. As previously described [10], LA endocardial border was manually traced in both the 4- and 2-chamber views, thus delineating a region of interest (ROI), consisting of 6 segments. After the segmental tracking quality analysis and manual adjustment of the ROI, the longitudinal strain curves were generated by the software for each atrial segment (**Figure 1**). Peak atrial longitudinal strain (PALS), measured at the end of the reservoir phase, was calculated by averaging values observed in all LA segments (global PALS), and by separately averaging values observed in the 4- and 2-chamber views. Likewise, peak atrial contraction strain (PACS), obtained during LA systole, was measured as the average of all 12 segments (global PACS) and by separately averaging values from the two apical views (4- and 2-chamber PACS). Inadequately tracked segments were automatically excluded from the analysis, by the software, and the final strain values represented the remaining segments. Three consecutive heart cycles were recorded and averaged, using a frame rate of 60-80 frames/second. Analysis of the acquired data was made off-line using a single experienced and independent echocardiographer, not directly involved in the image acquisition or patient's management, using a commercially available semi-automated 2D strain software (EchoPac, GE, USA).

Blood pressure and heart rate measurements: Blood pressure (BP) (average of three measurements spaced by 2 minutes, using a cuff sphygmomanometer) was recorded at the end of the echocardiographic examination, after few minutes rest in a quiet room [17]. Heart rate (HR) was measured (for 60 seconds) in the sitting position, after the second BP measurement [17].

Reproducibility: Among a total of 1392 LA segments, the software was able to track 1307 (93.9 %) segments. To assess reproducibility of global PALS, 15 HTN patients were randomly selected. Bland-Altman analysis was performed on the repeated measurements made a week later by the same and a second independent observer to evaluate the intra- and interobserver agreement, respectively. Bland-Altman analysis demonstrated good intra- and interobserver agreement, with small bias not significantly different from zero. Mean differences ± 2 standard deviations were 0.5 ± 2.3% and 0.7 ± 3.7%, for intra- and interobserver agreement, respectively. Intra- and interobserver coefficient of variation of global PALS were 3.1%, and 3.2%, respectively.

Statistical Analysis

Data are shown as mean ± SD. A P value <0.05 was considered statistically significant. Analyses were performed using the SPSS (Statistical Package for the Social Sciences, Chicago, Illinois) software Release 11.5. Pearson's correlation coefficients were calculated to assess the relationships between continuous variables. Multiple regression analysis was performed to identify independent determinants of STE measures of LA function. Between group comparisons of continuos variables were performed using analysis of variance (ANOVA), followed by Scheffé post hoc pairwise comparison test. The independent determinants of reduced global PALS in the eHTN and HTNdd patients were explored using stepwise multivariate regression analysis.

Results

Characteristics of eHTN and HTNdd groups vs. controls

The characteristics of the study population are listed in **Table 1**. No significant difference was observed between groups with regards to age, sex, heart rate, height, weight and BSA. Systolic, diastolic and mean BP were significantly higher in both eHTN and HTNdd groups compared to controls ($p < 0.001$ for both) (inclusion criterion).

Left ventricular structure and function (Table 2)

LV EF, EDV and ESV were not different between patient's groups and controls. LV EDD was larger in the HTNdd group compared to controls ($p < 0.001$). LV mass and indexed mass were significantly higher in the two patient's groups ($p < 0.001$ for all), Septal and posterior wall thickness were higher in the two patients groups ($p < 0.001$ for all) but RWT was higher only in eHTN group ($p < 0.001$). Global LV LS was not different between the two patient groups. HTNdd group had reduced lateral LV systolic long axis amplitude of motion and systolic velocity ($p < 0.001$ for both). Similar abnormalities were seen in eHTN group but to less degree (p = ns). HTNdd patients had reduced e' compared to controls ($p < 0.001$), resulting in raised E/e' ($p < 0.001$). E/A was not different in the eHTN but reduced in the HTNdd group ($p < 0.001$) compared to controls.

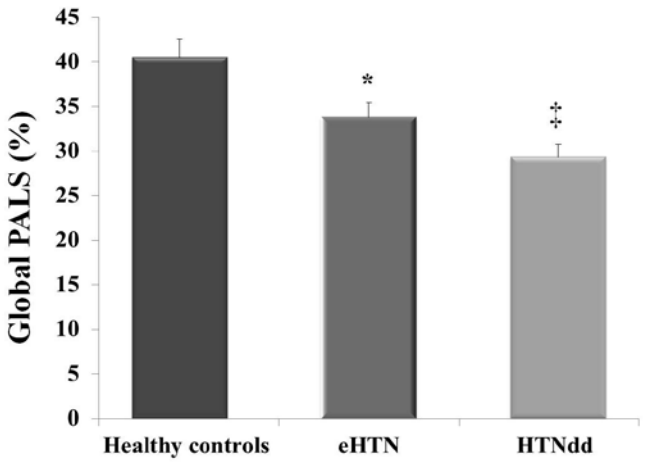

Figure 2. Comparison of global peak atrial longitudinal strain (PALS) among controls and hypertensive patients. *p< 0.001 vs. healthy controls by the Scheff´ pairwise comparison test. ‡p < 0.01 vs. eHTN by the Scheff´ pairwise comparison test. eHTN, patients with hypertension, evidence of diastolic dysfunction but no hypertrophy; HTNdd, patients with early hypertension no diastolic dysfunction and no hypertrophy.

Left atrial structure and function

Indexed LA area and indexed LA volume were not different from controls. Global and 4- and 2-chamber PALS was reduced in eHTN and HTNdd ($p < 0.001$ for all) but to a worse degree in the latter group ($P < 0.01$ for both), figure 2. Only eHTN group had reduced global PACS ($p < 0.001$).

Predictors of reduced global PALS in eHTN and HTNdd groups

Univariate analysis of 4-chamber PALS and global PALS in all hypertensive patients is shown in **figure 3**.
Global and 4-chamber PALS correlated negatively with E/e' ($p <0.0001$), age ($p <0.0005$) and LVMI ($p <0.005$) and positively with s' ($p<0.01$) and MAPSE ($p <0.0005$). The multivariate regression analysis identified E/e' ratio (ß = -0.501, $p <0.0001$) and LA indexed volume (ß = -0.251, $p <0.0001$) as the only independent predictors of reduced global PALS in the eHTN group (overall model R2 = 0.58, $P <0.0001$). E/e' ratio was the principal determinant, accounting for 51.1% of the total variability explained by the model. Likewise, E/e' ratio (ß = -0.620, $p <0.0001$), LA indexed volume (ß = -0.312, $p <0.0001$) and MAPSE (ß = 0.203, $p <0.0001$) independently predicted the reduced global PALS in the HTNdd group (overall model R2 = 0.69, $P <0.0001$). E/e' ratio was the strongest predictor, accounting for 59.6% of the total variability explained by the model.

Discussion

Findings: Our analysis shows three sets of findings:

a) HTNdd patients had reduced global PALS despite normal LA size and normal LV EF but compromised lateral wall systolic and diastolic function, in comparison with age- and gender-matched controls;

b) global PALS was reduced also in patients with normal diastolic function (**Figure 2**);

c) E/e' ratio was the strongest predictor of reduced global PALS in eHTN and HTNdd patients.

Table 1. Demographics of the study population.

Variable	Healthy controls (n= 38)	eHTN (n= 37)	HTNdd (n= 41)
HR (beats/min)	67±12	74±11	75±12
Age (years)	60.2±5.3	59.3±8.8	62.3±7.3
Male (%)	63	64	65
Height (cm)	165±10.2	168±11.2	164±10.2
Weight (Kg)	66±19.5	79.8±20.1	71.2±18.3
BMI (Kg/m2)	26.0±4.1	28.1±3.8	27.6±3.6
Systolic BP (mm Hg)	114.6±9.4	148.7±9.2*	148.6±11.9*
Diastolic BP (mm Hg)	74.3±6.4	92.3±6.9*	91.2±6.4*
Mean BP (mm Hg)	90.9±7.1	114.5±7.3*	116.7±8.1*

Data are presented as mean ± standard deviation.
eHTN, patients with hypertension, evidence of diastolic dysfunction but no hypertrophy; HTNdd, patients with early hypertension no diastolic dysfunction and no hypertrophy; HR, Heart rate; BMI, body mass index; NYHA, New York Heart Association.
Blood pressure (BP) was measured ar the end of the echocardiographic examination.
* $p < 0.001$ for patients vs healthy controls.

Data interpretation: The findings of this study show clear evidence for LA structural and functional disturbances in patients with HTN irrespective of the degree of underlying ventricular diastolic dysfunction. The two patients groups, we studied, showed all consequences of increased LV afterload in the form of global and segmental hypertrophy, increased mass index and relative wall thickness, irrespective of ECG changes. In addition, the group of patients with diastolic dysfunction had clear evidence for subendocardial abnormalities affecting the lateral wall amplitude of motion and systolic and diastolic velocities. The additional LV long axis abnormalities were the extra predictor of the compromised LA myocardial dysfunction in this group. Despite these differences the two patients groups shared signs of raised LA pressure shown by E/e' as the main predictor of LA reduced myocardial strain. Of note, E/A ratio did not discriminate between patients groups.

Our findings support previous works which showed that in patients with HTN LV lengthening rate (velocity) is compromised and atrial systolic activity is exaggerated, as a compensatory mechanism [32-34]. Such increased atrial force must be related to some intracavitary changes in the absence of LA outlet pathology [35]. HTN represents a chronic state of left heart afterload which is known to cause increased LV wall stress and consequently subendocardial ischaemia [36-38]. This pathophysiology was clearly the case in the HTNdd group but not with the eHTN group. However, the fact that the two groups of patients had similar compromise of LA strain suggests an additional mechanism. E/e' as the main predictor of reduced LA strain suggests a potential increase in reflected waves with their effect on LA wall stress and hence the compromised strain. This level of rise in LA pressure might be subclinical and unnoticed by the conventional Doppler echocardiographic techniques but of clinical relevance since it affected LA structure and function [39]. We have previously shown that long standing

Table 2. Echocardiographic characteristics of the study population.

	Healthy controls (n= 38)	eHTN (n= 37)	HTNdd (n= 41)
LV EF (%)	59.1±7.3	57.5±5.6	57.4±6.0
LV EDD (mm)	45.1±5.3	47.7±5.5	49.4±5.6*
LV ESD (mm)	28.1±4.5	30.1±4.5	28.2±4.0
LV EDV (ml)	83.3±7.9	87.3±13.2	80.3±9.2
LV ESV (ml)	36.7±6.2	38.1±5.6	32.3±6.1
IVST (mm)	9.2±2.0	10.9±2.0*	11.3±2.1*
PWT (mm)	8.6±2.1	10.3±2.3*	10.2±2.0*
Relative wall thickness	0.38±0.05	0.42±0.07*	0.41±0.05
indexed LV mass (g/ m2)	95.6±26.3	102.3±19.1*	103.0±18.2*
LA area (cm2)	15.3±4.0	15.4±4.9	16.3±4.8
Indexed LA area (cm2/m2)	8.6±4.2	8.7±4.8	9.1±4.6
LA volume (ml)	42.9±4.7	42.9±5.3	44.5±5.4
Indexed LA volume (ml/m2)	24.1±4.9	24.7±5.8	24.9±5.2
Global LV LS (%)	-16.7±2.5	-16.2±3.6	-17.2±3.5
Global PALS (%)	40.5±5.2	33.8±6.5*	29.3±5.5†
Four-chamber PALS average (%)	39.2±5.1	31.9±6.7*	27.4±5.7†
Two-chamber PALS average (%)	41.5±5.7	35.3±6.9*	31.6±5.6†
Global PACS (%)	16.5±3.0	18.4±4.0*	14.8±4.2
Four-chamber PACS average (%)	15.4±3.1	17.5±3.9	13.7±4.0
Two-chamber PACS average (%)	17.1±3.2	19.3±4.1	15.6±4.3
LV filling variables			
E/A ratio	1.19±0.41	1.14±0.2	0.81±0.27*
Longitudinal function			
s' (cm/s)	9.27±2.32	8.22±1.94	8.0±2.59*
e' (cm/s)	12.4±4.6	11.25±3.14	9.69±3.35*
a' (cm/s)	10.06±3.1	10.76±3.28	12.31±3.58*
E/e' ratio	6.61±3.32	7.08±3.45	8.92±2.71*
MAPSE (mm)	14.3±2.6	13.9±2.0	13.1±2.1*

Data are presented as mean ± standard deviation.
LA, left atrial; LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; IVST, interventricular septum thicknesses; PWT, posterior wall thicknesses; LS, longitudinal strain; PALS, peak atrial longitudinal strain; PACS, peak atrial contraction strain; E, early diastolic peak flow velocity; A, late diastolic peak flow velocity; s', peak systolic mitral annulus velocity; e', peak early diastolic mitral annular velocity; a', peak late diastolic mitral annulus velocity; MAPSE, mitral annular plane systolic excursion.
* $p < 0.001$ for patients vs healthy controls
† $p < 0.01$ versus eHTN patients

hypertensives limited by breathlessness have significantly reduced LA myocardial strain and strain rate, which destabilises overall atrial function and make the patients subject to atrial fibrillation [38, 40, 41].

Clinical implications: the reproducible compromised LA myocardial function may guide towards optimizing hypertension treatment [42], even in the absence of clear evidence for LV dysfunction. LV diastolic dysfunction, shown by long axis amplitude and velocities should provide more accurate assessment of compromised segmental function compared with the conventionally used E/A ratio. Even in the absence of LV diastolic dysfunction LA compromised strain function should be considered as an early myocardial embarresment which needs aggressive management of HTN in order to avoid perpetual deterioration of LA function and irreversible cavity remodelling.

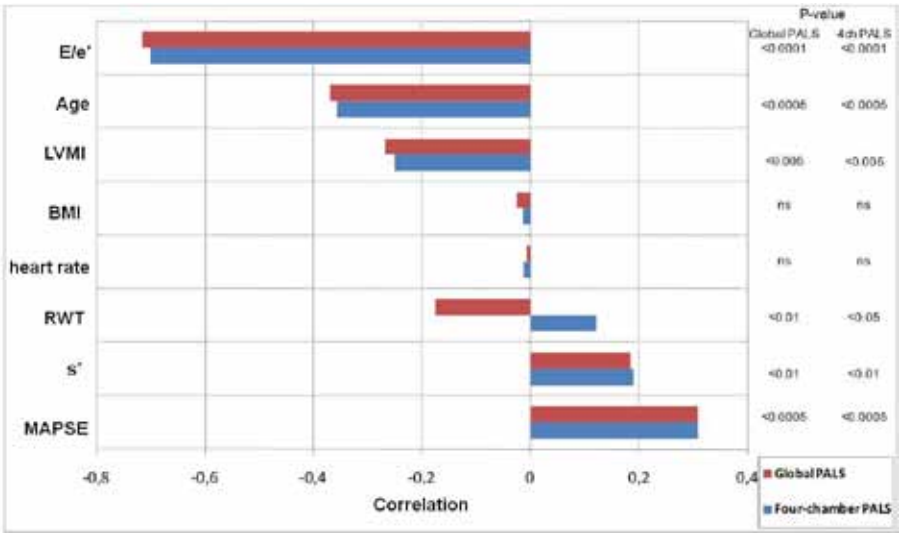

Figure 3. Linear correlations with 4-chamber peak atrial longitudinal strain (PALS) and global PALS in hypertension patients. MAPSE, mitral annular plane systolic excursion; s' peak systolic mitral annulus velocity; LVMI, left ventricular mass index; RWT, relative wall thickness; BMI, body mass index.

Limitations: We did not have any invasive measures of LA function but relied on the well validated non-invasive Doppler echocardiographic markers. Our sample volume was not large enough to warrant strong broad application but suggest a potential use of LA measurements in assessing early functional changes, the prevention of such effect by optimizing anti-hypertension treatment strategies remain to be determined.

Conclusions: Asymptomatic not pharmacologically treated hypertensive patients with preserved LVEF and normal diastolic function have early compromise of LA strain despite normal cavity size, suggesting an evidence for preclinical LA myocardial dysfunction.

Authors' Contribution

MC, ML, MS, SB and FDA were responsible for the collection of data; MC and ML drafted the manuscript; MC performed the statistical analysis; SM was responsible for the design of the study and revised the manuscript for important intellectual content. MH also revised the manuscript for important intellectualcontent; MF, FMR and SL also revised the manuscript. All authors read and approved the final manuscript.

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