Echocardiography on Prehypertension and Stage I Hypertension

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Abstract

Background: Prehypertension and stage I hypertension are associated with left ventricular (LV) remodeling. In this study, we compared echocardiographic parameters of preclinical hypertensive target organ damage in individuals with prehypertension and stage I hypertension selected from the same population.

Methods: We compared baseline echocardiogram measurements of participants included in the PREVER study with prehypertension (PREVER-prevention; n=106) or stage I hypertension (PREVER-treatment; n=128). Sex-specific differences in echocardiographic parameters were also investigated.

Results: Mean systolic and diastolic BP were significantly higher in the stage I hypertension group (141.0/90.4 mmHg) than in the prehypertension group (129.3/81.5 mmHg, P<0,001 for both). Mean age was 55 years old (30 to 70), with an almost equal number of men and women, of which 80% were white and 7% had diabetes. Most parameters of LV mass, LA size and diastolic function were similar between the prehypertension and stage I hypertension groups. Hypertensive individuals had larger LA diameter and posterior wall thickness, and lower lateral e' velocities, even after adjustment for age, sex and body mass index. Sex-specific analysis showed higher LV mass in stage I hypertension compared to prehypertension only in women (141.1 ± 34.1 g vs. 126.1 ± 29.1 g, P<0.05).

Conclusions: In middle-aged individuals with low cardiovascular risk, differences in echocardiographic parameters related to target organ damage are likely subtle between prehypertension and stage I hypertension, although women with stage I hypertension had significantly higher LV mass, which may indicate sex-specific adaptive response to blood pressure in earlier stages of hypertension.

Keywords: Prehypertension; Hypertrophy, Left Ventricular; Cardiac Volume.

Introduction

According to the Eighth Joint National Committee (JNC 8) guidelines on hypertension,[1] prehypertension is defined as SBP ranging from 120 to 139 mmHg and/or DBP from 80 to 89 mmHg, without the use of any antihypertensive medication.[1] Prevalence of prehypertension among adults is approximately 30%, and is markedly higher among men than women (39 and 23%, respectively).[2]

Prehypertension independently elevates the risk of cardiovascular disease.[3,4] In addition, the presence of hypertensive target organ damage in patients with high blood pressure increases the risk for cardiovascular disease.[1] Blood pressure (BP) in high-normal range is associated with long-term consequences on left ventricular (LV) structure and function.[5] Also, increased LV mass predicts progression of prehypertension to hypertension, regardless of baseline BP,[6-8] with the probability of developing hypertension in 4 years being increased by 39% for each 7.9 g/m^2 in LV mass index.[8]

Echocardiography is an important tool to evaluate hypertensive target organ damage, providing a better estimate of patients' cardiovascular risk and prognosis.[9,10] It is a sensitive and accessible imaging method which detects parameters that are known to correlate independently with cardiovascular events, such as alterations in LV mass, LV geometric pattern, left atrial (LA) size and LV diastolic function.[10-14]

LV mass was similar in patients with masked hypertension and prehypertension,[15] and was higher in middle-aged individuals with prehypertension and few cardiovascular risk factors than in individuals with optimal BP.[16] In young adults with high prevalence of obesity and diabetes mellitus[17] and in older population of men and women,[18] prehypertension was associated with higher LV remodeling and impaired diastolic function than in individuals with optimal BP. There are few studies comparing left ventricular parameters in individuals with prehypertension and hypertension stage I.[17,18] Also, whether there are sex-specific differences in cardiac remodeling in prehypertensive individuals is not so well studied.

The purpose of this study is to investigate the pattern of echocardiographic parameters of preclinical hypertensive

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Artigo recebido em 20/08/2018; revisado em 10/10/2018; aceito em 28/11/2019

DOI: 10.5935/2318-8219.20190020

target organ damage (LV mass, LA size and diastolic function) in low cardiovascular risk middle-aged men and women with prehypertension, and compare it with individuals presenting stage I hypertension.

Methods

Study design

The PREVER study is a multicenter randomized controlled trial (RCT), designed to evaluate the management of prehypertension (PREVER-prevention) and stage I hypertension (PREVER-treatment). Population, methods and results of the PREVER study are described in detail elsewhere.[19,20] The participants were screened through advertising, campaigns of BP measuring in hospitals, squares and shopping malls in 21 clinical centers across 10 Brazilian states. They were invited to clinical and BP assessment in the study clinics and allocated to the PREVER-prevention or PREVER-treatment trial according their BP classification. An automatic electronic device Microlife BP 3BTO-A, licensed for fabrication by Micromed Biotecnologia Ltda (Brasília, Brazil), was used to measure BP and an average of two readings at each study visit was used to estimate the level of BP. The study was approved by each study center institutional review board and written informed consent was obtained from all participants.

An echocardiographic investigation was performed at a single center of PREVER-treatment and PREVER-prevention studies. All participants from the Hospital de Clínicas de Porto Alegre (HCPA) center were invited to participate in the ancillary echocardiographic study, where the transthoracic echocardiography was performed at baseline and after 18 months of treatment. Baseline tests were used for this analysis.

Population

All eligible participants of the PREVER study, aged 30-70, were submitted to a pre-enrollment lifestyle intervention phase. Those whose BP remained between 120-139/80-89 mmHg (PREVER-prevention study) or ≥140/90 mmHg (PREVER-treatment study) after 3 months of lifestyle intervention were enrolled in the RCT. Participants of the PREVER-prevention study were randomly assigned to a chlortalidone/amiloride 12.5/2.5 mg combination pill or to placebo, and the ones of the PREVER-treatment study were randomly assigned to a chlortalidone/amiloride 12.5/2.5 mg combination pill or to losartan 50 mg, with a follow-up of 18 months. Exclusion criteria included, in addition to the clinical trial criteria, baseline echocardiographic examination with image quality unsuitable for reading.

Echocardiographic study

All echocardiographic examinations were performed using the same equipment (Envisor C HD or HD 11, Philips, USA) with a standard multifrequency sectorial transducer by two trained cardiologists blinded to clinical trial information and treatment allocation. Images were acquired following a standardized protocol. Cine loops and static images of 3 consecutive beats were recorded of standard 2D, M-mode, Doppler and tissue Doppler echocardiographic views and were digitally recorded for central reading.

Echocardiographic studies were blindly read by a single physician using a dedicated workstation (Image Arena version 4 – TomTec, Germany). Measurements were performed in accordance with international society guidelines.[21] LV mass was calculated using the corrected American Society of Echocardiography method (LV mass = 0.8 x [1.04 x (IVST + LVDD + PWT)^3 – LVDD^3] + 0.6) and was indexed for body surface area (LV mass index – LVMI). LV hypertrophy was considered if LVMI was >115 g/m^2 for men and >95 g/m^2 for women. RWT was calculated as (2 x PWT)/LVDD, and increased RWT was defined when >0.42, from which geometric patterns (normal, concentric remodeling, concentric hypertrophy and eccentric hypertrophy) were derived.[21]

LV ejection fraction was calculated using the Teicholz formula from the parasternal long-axis view. LA volume was measured at ventricular systole, just before mitral valve opening, and calculated from apical 4- and 2-chamber views using biplane method of disks. LA diameter was measured at the end of LV systole, between the leading edge of the posterior aortic wall and the leading edge of the LA posterior wall. LV diastolic function was evaluated with transmitral pulsed Doppler (peak E velocity, peak A velocity, E/A ratio and deceleration time) and mitral annulus tissue Doppler velocity (early diastolic velocity – e', late diastolic velocity – a'). Normal diastolic function was defined as: medial e' ≥7 cm/s, lateral e' ≥10 cm/s and LA volume index <34 ml/m^2, in the absence of pulmonary hypertension.[22]

Statistical methods

Comparisons between groups were assessed by independent-samples t-tests for continuous variables and Chi squared test for categorical variables, and also stratified by sex. Multivariate analysis was performed for adjustment of echocardiographic outcomes to age and body mass index. Intraobserver reproducibility was evaluated in 20 randomly chosen studies using intraclass correlation coefficient; it varied between 0.99 and 0.67, with lower reproducibility for the posterior wall thickness measurement, and was similar to previous studies.[23-25] Data analysis was performed with PASW Statistics 18. Data are expressed as mean ± SD or number (percentage). P<0.05 was considered statistically significant.

Results

From the 1,385 participants of the PREVER study, the 398 participants from Hospital de Clínicas de Porto Alegre center were invited to participate in the echocardiographic evaluation, 247 of them were willing to participate, and 234 of these fulfilled the inclusion criteria; there were 106 individuals with prehypertension and 128 with stage I hypertension. (Figure 1)

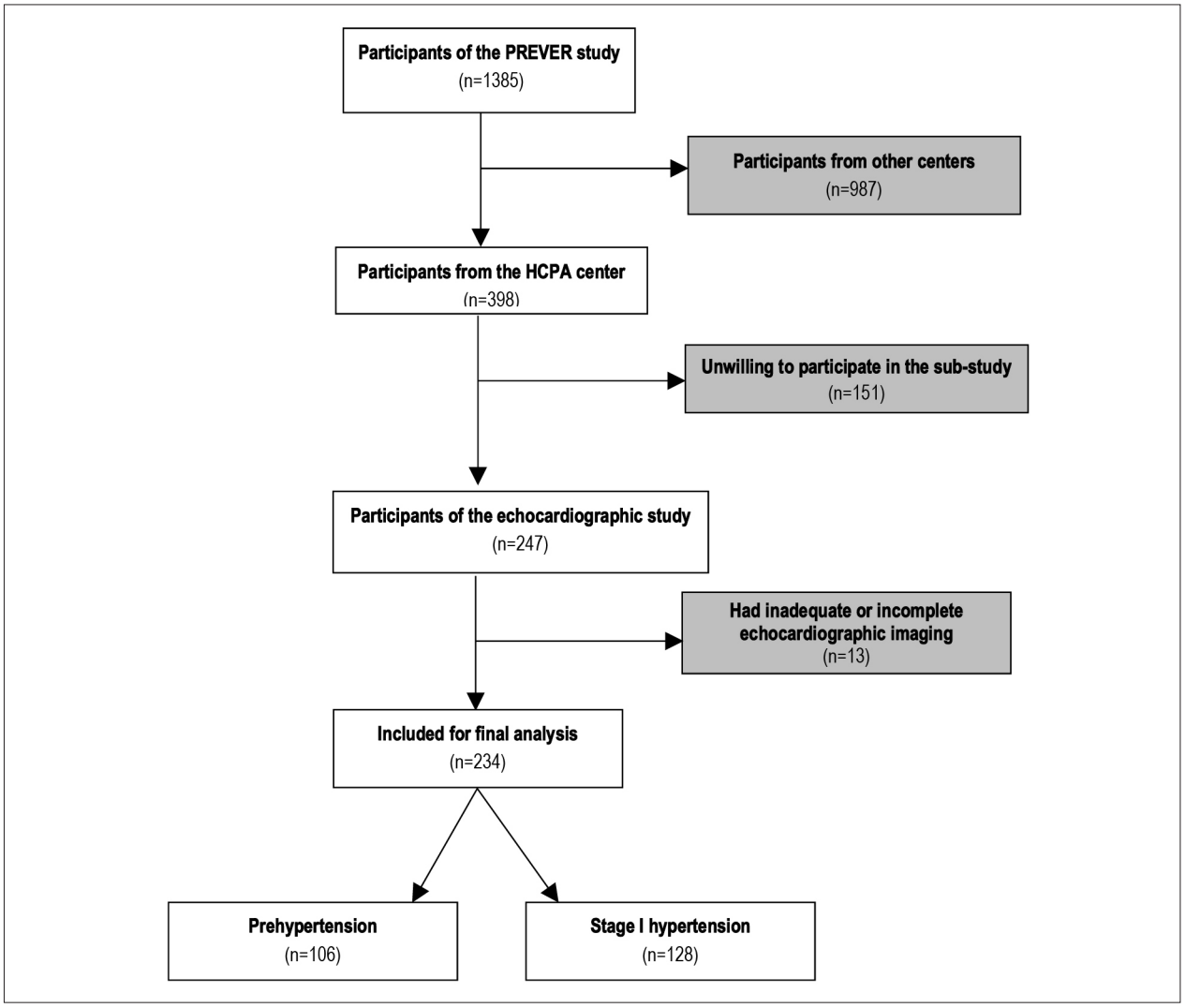

Figure 1 – *Study flow diagram.*

Distribution of clinical characteristics was similar between groups (Table 1), with the exception of systolic and diastolic BP, which were higher in stage I hypertension group (141.0 ± 7.0 / 90.4 ± 5.8 mmHg) than in prehypertension group (129.3 ± 5.1/81.5 ± 5.4 mmHg, P<0.001 for both). The mean age of the study sample was 55 years, with an almost equal number of men and women, and most participants (80%) were white.

Comparison of echocardiographic parameters of cardiac structure and function between groups is shown in Table 2. Most parameters of LV mass, LA size and diastolic function were similar between the prehypertension and stage I hypertension groups. Participants with stage I hypertension had a significantly higher LA diameter, LV diastolic diameter, LV mass, posterior wall thickness, and smaller lateral e'. The proportion of individuals with normal LV diastolic function was similar between prehypertension and hypertension (62.3% vs. 54.7%, P=0.24, respectively). After multivariate adjustment for age, sex and body mass index, only LA diameter, posterior wall thickness and lateral e' remained different between groups.

We also performed a sex-specific analysis (Table 3). LA diameter was larger in both men and women with stage I hypertension. Only in women LV mass and LV mass index were higher in stage I hypertension (141.1 ± 34.1 g and 79.2 ± 16.0 g/m^2) than in women with prehypertension (126.1 ± 29.1 g and 73.4 ± 15.6 g/m^2, P=0.05 and 0.04, respectively). After adjustment for age and body mass index, men with stage I hypertension had a smaller lateral e'. Other parameters of LA size, relative wall thickness and diastolic function were similar between prehypertensive and hypertensive men and women.

LV geometric patterns analysis (Table 4) showed a similar prevalence of normal geometry, concentric LV remodeling, concentric LV hypertrophy and eccentric LV hypertrophy between groups, with similar distribution in men and women

Table 1 - Sample clinical characteristics.

Characteristic	Pre-hypertension (n=106)	Hypertension (n=128)	*P*
Sex (male)	50 (47.2)	71 (55.5)	0.24
Age (years)	55.6 ± 8.9	54.4 ± 7.8	0.29
Skin color (white)	83 (78.3)	105 (82.0)	0.51
Education (years)	11.5 ± 3.8	11.2 ± 3.9	0.58
BSA (m²)	1.83 ± 0.19	1.87 ± 0.17	0.07
BMI (kg/m²)	27.6 ± 4.0	28.4 ± 4.4	0.14
SBP (mmHg)	129.3 ± 5.1	141.0 ± 7.0	<0.001
DBP (mmHg)	81.5 ± 5.4	90.4 ± 5.8	<0.001
Total cholesterol (mg/dl)	193.7 ± 34.8	194.3 ± 35.3	0.90
HDL cholesterol (mg/dl)	49.6 ± 12.6	49.8 ± 13.1	0.90
LDL cholesterol (mg/dl)	120.4 ± 31.9	116.5 ± 30.9	0.34
Creatinine (mg/dl)	0.83 ± 0.18	0.84 ± 0.18	0.46
Diabetes	5 (4.7)	12 (9.4)	0.21
Smoking*	49 (46.2)	68 (53.1)	0.36
Alcoholic beverage consumption*	100 (94.3)	111 (86.7)	0.08
Heart rate (bpm)	70 ± 12	72 ± 11	0.17

** Current or past. BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are expressed as mean ± SD or as number (percentage).*

Table 2 - Echocardiographic parameters of cardiac structure and function.

Parameter	Pre-hypertension (n=106)	Hypertension (n=128)	P*	P**
LAD (mm)	34.6 ± 4.2	36.5 ± 4.2	0.001	0.002
LAV (ml)	47.5 ± 11.5	50.2 ± 13.7	0.10	0.27
LAVI (ml/m2)	25.8 ± 5.8	26.8 ± 7.2	0.27	0.28
LVDD (mm)	43.6 ± 4.5	45.1 ± 4.8	0.01	0.08
LVSD (mm)	26.1 ± 4.0	26.9 ± 3.9	0.13	0.32
LVEF Teichholz (%)	70.6 ± 7.7	70.6 ± 7.4	0.99	0.92
LVM (g)	145.8 ± 34.5	156.6 ± 39.2	0.03	0.12
LVMI (g/m²)	79.3 ± 15.4	83.0 ± 17.0	0.08	0.15
IVST (mm)	10.2 ± 1.4	10.0 ± 1.2	0.29	0.08
PWT (mm)	9.6 ± 1.2	10.0 ± 1.1	0.01	0.04
RWT	0.44 ± 0.06	0.45 ± 0.06	0.80	0.76
LV stroke volume (ml)	72.3 ± 20.0	74.3 ± 16.0	0.42	0.99
Cardiac index (l/m²)	2.6 ± 1.0	2.8 ± 0.6	0.08	0.08
Lateral e' (cm/s)	14 ± 3	13 ± 3	0.05	0.01
Medial e' (cm/s)	9 ± 2	9 ± 2	0.33	0.19
Lateral E/e' ratio	6.1 ± 7.1	5.7 ± 1.5	0.61	0.33
Medial E/e' ratio	8.1 ± 2.1	8.4 ± 2.2	0.35	0.24
Mitral E/A ratio	1.0 ± 0.2	1.0 ± 0.3	0.76	0.80
DTE (ms)	225 ± 45	229 ± 46	0.51	0.71

** Unadjusted. ** Adjusted for sex, age and body mass index. LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; IVST, interventricular septum thickness; PWT, posterior wall thickness; RWT, relative wall thickness; LV, left ventricle; DTE, deceleration time of E wave. Data are expressed as mean ± SD or as number (percentage).*

(data not shown). When dichotomized for the presence of normal or abnormal LV geometry, the prevalence of abnormal LV geometry was also similar between groups (70% for prehypertension, 68.5% for stage I hypertension, P=0.80).

Discussion

This study shows that most echocardiographic parameters of preclinical hypertensive target organ damage are similar among individuals with prehypertension and stage I hypertension. This finding suggests that there are few differences between prehypertension and individuals diagnosed with high blood pressure.

There are few studies comparing echocardiographic parameters in patients with prehypertension and hypertension,[16-18] but they investigated individuals in different age and clinical conditions. The Strong Heart Study compared the cardiac structure and function of American Indians (adolescents and young adults) with a high prevalence of obesity and diabetes in different groups according to BP (optimal BP, prehypertension and hypertension);[17] in this population, there was a progressive increase in LV mass and a lower prevalence of normal LV geometry according to the rise of BP, but the difference between groups was less evident when prehypertension and hypertension were compared. In a sample of middle-aged individuals,[16] there was no difference in LV mass between prehypertension and stage I hypertension (215 g and 218 g, respectively, P=0.94), even with higher differences of systolic BP between prehypertensive (122 mmHg) and hypertensive individuals (151 mmHg). The ARIC study[18] compared echocardiographic abnormalities in elderly participants with optimal, prehypertensive and hypertensive stages, and they were progressively more frequent from optimal BP to true hypertension. Our findings concerning the comparison between prehypertension and hypertension extend the ARIC observation to younger individuals. Although alterations in BP have a pathophysiological continuum, there is evidence that an increase in LV may be a predictor of hypertension, and not only a consequence of it.[8]

We had a higher prevalence of LV concentric remodeling than previous studies[26] possibly for two reasons: our measurements were made using second harmonic 2D images instead of M-mode images, and we used 0.42 as cut-off for RWT, according to recent guidelines for chamber quantification[21] – while most previous studies used higher cut-offs (>=0.44 or <= 0.45).

Interestingly, we found that LV mass was higher in stage I hypertension compared to prehypertension only in women. A difference of 12 mmHg in SBP and 9 mmHg in DPB between groups had an impact on LV mass in women, and as far as we know, this is the first time that this is shown in this population. Cardiac structure is known to be different between men and women, since left ventricular chamber size and mass are 15-40% lower in women even after adjustment for body size.[27] Moreover, the consequences of pressure overload and systolic hypertension differs between sexes. Rohde et al. reported that women responded to chronic pressure overload with a disproportionally greater

Table 3 - Echocardiographic parameters of cardiac structure and function by sex.

	Female				Male			
	Prehypertension (n=56)	Hypertension (n=57)	P*	P**	Prehypertension (n=50)	Hypertension (n=71)	P*	P**
LAD (mm)	33.3 ± 4.0	35.3 ± 4.2	0.01	0.01	36.0 ± 4.1	37.6 ± 4.0	0.04	0.05
LAV (ml)	45.7 ± 12.4	48.1 ± 14.7	0.37	0.64	49.4 ± 10.4	51.9 ± 12.9	0.27	0.30
LAVI (ml/m2)	26.4 ± 6.0	27.0 ± 7.9	0.64	0.83	25.2 ± 5.4	26.7 ± 6.6	0.23	0.20
LVDD (mm)	42.0 ± 4.7	43.5 ± 4.6	0.08	0.15	45.4 ± 3.4	46.4 ± 4.6	0.21	0.29
LVSD (mm)	24.7 ± 3.7	25.2 ± 3.5	0.41	0.51	27.7 ± 3.7	28.2 ± 3.8	0.45	0.48
LVEF Teichholz (%)	71.8 ± 8.1	72.5 ± 6.8	0.62	0.67	69.3 ± 7.1	69.1 ± 7.6	0.89	0.80
LVM (g)	126.1 ± 29.1	141.1 ± 34.1	0.01	0.05	167.9 ± 25.5	169.0 ± 38.9	0.87	0.95
LVMI (g/m2)	73.4 ± 15.6	79.2 ± 16.0	0.05	0.04	86.0 ± 12.3	86.1 ± 17.2	0.97	0.93
IVST (mm)	9.6 ± 1.3	9.7 ± 1.1	0.81	0.89	10.3 ± 1.2	10.8 ± 1.1	0.01	0.01
PWT (mm)	9.0 ± 1.0	9.6 ± 1.0	0.002	0.001	10.2 ± 0.9	10.2 ± 1.1	0.92	0.80
RWT	0.43 ± 0.07	0.45 ± 0.06	0.32	0.26	0.45 ± 0.05	0.44 ± 0.06	0.41	0.43
LV stroke volume (ml)	64.2 ± 13.4	69.8 ± 15.4	0.06	0.13	81.5 ± 22.4	77.8 ± 15.6	0.36	0.26
Lateral e' (cm/s)	13 ± 3	13 ± 3	0.27	0.15	14 ± 3	13 ± 3	0.08	0.03
Medial e' (cm/s)	9 ± 2	8 ± 2	0.12	0.06	9 ± 2	9 ± 2	0.89	0.97
Lateral E/e' ratio	5.8 ± 1.4	6.0 ± 1.5	0.41	0.43	6.4 ± 1.5	5.5 ± 1.5	0.46	0.46
Medial E/e' ratio	8.6 ± 2.4	8.9 ± 1.9	0.53	0.64	7.5 ± 1.6	8.0 ± 2.2	0.18	0.23
Mitral E/A ratio	1.0 ± 0.2	1.0 ± 0.3	0.61	0.43	1.0 ± 0.3	1.0 ± 0.3	0.90	0.66
DTE (ms)	220 ± 44	223 ± 44	0.76	0.71	231 ± 46	234 ± 48	0.73	0.41

** Unadjusted. ** Adjusted for age and body mass index. LAD, left atrial diameter; LAV, left atrial volume; LAVI, left atrial volume index; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMI, left ventricular mass index; IVST, interventricular septum thickness; PWT, posterior wall thickness; RWT, relative wall thickness; LV, left ventricle; DTE, deceleration time of E wave. Data are expressed as mean ± SD.*

Table 4 – LV geometric patterns.

LV geometric pattern	Pre-hypertension (n=106)	Hypertension (n=127)	*P*
Normal geometry	32 (30.2)	40 (31.5)	0.83
Concentric LV remodeling	67 (63.3)	75 (59.1)	0.51
Concentric LV hypertrophy	2 (1.8)	7 (5.5)	0.14
Eccentric LV hypertrophy	5 (4.7)	5 (3.9)	0.76

LV, left ventricle. Data are expressed as number (percentage).

degree of hypertrophy compared to volume.[28] In individuals with isolated hypertension, the relative odds of LV hypertrophy were 2.58 (95% CI 0.97-6.86) in men and 5.94 (3.06-11.53) in women, with an increase in LV mass at the expense of LV dilation in men and an increment in wall thickness in women.[29] There is also evidence that women may have a greater sensitivity to pressure overload and/or greater left ventricular structural plasticity in specific populations,[30] and it seems like even small BP differences may have a similar effect. The clinical consequences of LV hypertrophy are also different between sexes, with a higher risk of cardiovascular death in women than in men (HR 7.5 - 95% CI 1.6-33.8 and HR 1.3 - 95% CI 0.4-3.7, respectively) compared with individuals without LV hypertrophy.[31] This also leads to question whether prehypertension and hypertension have a different phenotypic presentation of target organ damage according to sex, and may contribute to the increased prevalence of heart failure with preserved ejection fraction (HFpEF) in women.[32]

In our study, LA volume and LA volume index were similar between groups, although hypertensive individuals had a significantly higher LA diameter than prehypertensive peers. Most previous studies do not present data of LA size when these stages of hypertension are compared; however, it is known that LA volume is more accurate to estimate real LA size, with a higher performance for the prediction of cardiovascular events.[33] Parameters of diastolic function were similar between groups, with the exception of lateral e' velocity, which was lower in hypertensive individuals (13 vs. 14 cm/s, P=0.05); however, E/e' ratio and other. This may suggest that structural changes precede detectable abnormalities in diastolic function Doppler parameters, and are consistent with recent guidelines on diastolic function evaluation, which propose a more specific and conservative approach to call the presence of mild diastolic dysfunction.[22]

In general, as recommended in JNC8, individuals with prehypertension should be treated with non-pharmacological therapies such as weight reduction, increased physical activity, sodium restriction and avoidance of alcohol excess.[1] However, there is growing evidence of benefits of pharmacological treatment of prehypertension. In the

PREVER-prevention study, the incidence of hypertension was significantly lower in the chlorthalidone/amiloride group compared to placebo. There was an interaction of treatment with sex, with an apparent greater benefit of chlorthalidone/amiloride treatment in women compared to men.[19] Since women are likely to be more sensitive to high blood pressure cardiac adaptive changes, a more accurate stratification in this population may translate into strategies for HF prevention.

Some limitations of our study should be noted. First, we did not have participants with optimal BP. Nonetheless, previous studies have shown that prehypertension is associated with higher frequency of echocardiographic abnormalities than optimal BP.[16] The characteristics of our population, originated from a single study center, mostly of middle-aged Caucasian individuals with few cardiovascular risk factors, should be taken into account to extend our findings to other populations.

In summary, in middle-aged individuals with low cardiovascular risk, differences in echocardiographic parameters related to preclinical target organ damage are likely subtle between prehypertension and stage I hypertension, although women with stage I hypertension had significantly higher LV mass, which may indicate sex-specific adaptive response to blood pressure in earlier stages of hypertension. These sex differences in LV remodeling should be explored in further studies.

Authors' contributions

Conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted: Bertoluci C, Foppa M

Conception and design of the study, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be submitted: Santos ABS, Fuchs SC e Fuchs FD.All authors have approved the final article.

Sources of Funding

This study was supported by Departamento de Ciência e Tecnologia (DECIT), Health Ministry; Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Financiadora de Estudos e Projetos (FINEP), Science and Technology Ministry; Instituto de Avaliação de Tecnologia em Saúde (IATS); and Fundação Instituto de Pesquisas Econômicas (FIPE), Hospital de Clínicas de Porto Alegre, all in Brazil. The sponsors had no participation in the design and conduct of the study, preparation and approval of the manuscript.

Potential Conflicts of Interest

All authors reported they had no conflicts of interest and financial disclosures with regard to the subject of this manuscript.

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