



# Medium to Long Term Follow-Up of Treated Hypertensive Mediated Heart Disease

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## Abstract

**Introduction** Hypertensive mediated heart disease is the consequence of anatomical and functional changes in cardiovascular system. The benefits on left ventricular (LV) diastolic impairment and remodeling of hypertension treatment are well established.

**Aim** To evaluate LV structure, systolic and diastolic function of treated hypertensive patients on a medium to long term follow-up.

**Methods** Prospectively observational cohort study. Hypertensive patients over 18 years, ultrasound evaluation of LV structure and diastolic and systolic function, follow-up at least once a year. Diastolic function assessed following recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

**Results** 285 patients, mean follow up of  $1731 \pm 952$  days. Sample mean age  $56.3 \pm 12.5$  years, 166 patients (58.3%) were males. Baseline blood pressure  $147.8 \pm 19/86.8 \pm 11$  mm Hg, 5 years blood pressure  $134.4 \pm 15.7/79 \pm 9$  mm Hg ( $p < 0.005$  SBP and  $p < 0.01$  DBP). Baseline fixed dose combinations 115 patients (40.4%), follow-up 53.1% ( $p < 0.05$ ). LV remodeling was detected in 88 patients (30.9%) vs. 30.1% at 5 years ( $p = \text{NS}$ ). The frequency of an E/e' ratio  $> 14$  was reduced from 38 patients (13.3%) to 3.6% ( $p < 0.001$ ), e' septal velocity  $< 7$  cm/sec or e' lateral velocity  $< 10$  cm/sec was reduced from 38.6% (110 patients) to 19.3% ( $p < 0.001$ ). Baseline normal diastolic function was detected in 85.6% (244 patients) and 94% at the end of the follow-up ( $p < 0.02$ ).

**Conclusions** In this observational cohort followed by a mean of 5 years, the main benefit of hypertension treatment was the prevention or regression of diastolic dysfunction.

**Keywords** Hypertension · Treatment · Left ventricular hypertrophy · Diastolic dysfunction · Tissue Doppler

## 1 Introduction

Hypertensive mediated heart disease is the consequence of anatomical and functional changes in the cardiovascular system and is characterized by left ventricular hypertrophy (LVH), left atrial enlargement, left ventricular diastolic dysfunction, subtle or evident systolic dysfunction, and neurohumoral hyperactivity. All of these are predisposing factors to atrial fibrillation or flutter, heart failure, coronary artery disease and sudden cardiac death [1].

An analysis performed on a 4 years follow-up of 2604 individuals of the Framingham Heart Study suggested that the dynamic changes in LV geometric pattern over time are common in the community. Subjects with normal geometry developed concentric remodeling in 19.45% of the cases and LVH in 12%. Furthermore, patients with LVH regressed to normal geometry in 41.85% of the cases while remained with some degree of LVH in 43.9%. Higher BP, greater BMI, older age and male sex were the main clinical correlates of an adverse change in LV geometry [2].

A sample in which 68% of the participants had CAD, 87% hypertension and 45% diabetes was evaluated to identify the relationship between LV diastolic impairment and remodeling to treatment. Receiving at least one of the 5 typical classes of drugs designed for hypertension treatment was considered an adequate therapy. Treated patients had lower

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LV end diastolic pressure, wall stress, pressure/volume ratio and mass/volume ratio, without differences in systolic blood pressure and LV mass index. CAD in hypertensive patients did not significantly affect LV structural, hemodynamic or mechanical characteristics, while diabetes did not reach statistical significance; nonetheless, there was a trend towards increased LV mass/volume ratio and LV mass index and decreased LV wall stress and Tau constant [3].

In a pooled pairwise comparisons of 53 publications that included 7684 patients the effect of the 5 major drug classes showed a great correlation between percent changes from baseline to end of treatment in LV mass and systolic BP. The changes in RWT were caused by changes in percentage in LV mass/LV mass index and of SBP. A significant decrease in LV mass with all classes of drugs and with combination treatment was observed, with a mean percent decrease of LV mass or LVMI of 5.45%. The treatment's duration was not considered in the model although all the studies included lasted at least 6 months [4].

The aim of the present study is to evaluate LV structure, systolic and diastolic function of a cohort of hypertensive treated patients on a middle to long term follow-up.

## 2 Methods

This is a prospectively observational cohort study with the sample conducted at the Cardiology Institute of the Sanatorio Británico de Rosario, Argentina. The study has been carried out in accordance with the Code of Ethics of the World Medical Association for experiments involving humans. The inclusion criteria were as follows: (1) essential hypertensive patients over 18 years of age of both sexes at their first consultation, (2) 2D and M Mode echocardiography, mitral Doppler and tissue Doppler of sufficient quality to perform the calculation of the LV mass and evaluate LV diastolic and systolic function, (3) follow-up at least once a year. The exclusion criteria in this study lists: (1) clinical cardiovascular disease that could impact on the development of left ventricular hypertrophy or ventricular dysfunction, such as aortic or mitral valve disease, myocardial or pericardial disease, congenital heart disease, renal insufficiency, morbid obesity or thyroid disease; (2) prior clinical diagnosis of heart failure syndrome or an ejection fraction lower than 54%; (3) medical history of ischemic heart disease or prior diagnosis of coronary artery disease, (4) rhythm disturbances like right or left bundle branch block, atrio-ventricular block, pre-excitation syndrome, or supraventricular arrhythmias; (5) neoplasms or any oncologic previous treatment.

For the diagnosis of hypertension the 2018 European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension criteria was applied [5]. Office blood pressure was measured

with a digital sphygmomanometer (OMRON model HEM-705CPINT), and the average of three consecutive measurements 1 minute apart after 5 minutes in the sitting position is reported. The echocardiography studies were performed with an Esaote MyLab 7 ultrasound scanner provided by harmonic capability with a 2.5 MHz phase array multifrequency transducer and standardized protocol and conducting a tissue Doppler study by DP. The intraobserver variability was previously tested and the concordance was acceptable [6].

The left ventricular mass was assessed by the method of Devereux and indexed by height<sup>2</sup>, and left ventricular hypertrophy was considered when its value was greater than 95 g/m<sup>2</sup> in women and 115 g/m<sup>2</sup> in men [7–9]. Diastolic function was assessed by conventional Doppler of the mitral valve orifice corrected by age and tissue Doppler of the interventricular septum and lateral wall at the mitral annulus level in the apical 4 chamber conventional view, and diastolic dysfunction was diagnosed following the recommendations for the evaluation of left ventricular diastolic function by Echocardiography from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [10].

Systolic function was assessed by the rate of systolic excursion (s' wave) of the interventricular septum at the mitral annulus level in cm/sec with tissue Doppler. End diastolic volume (EDV), end systolic volume (ESV), and ejection fraction (EjF) were assessed by the modified Simpson biplane method.

The 10-year ASCVD risk was evaluated by the 2013 ACC/AHA Guideline of the Assessment of Cardiovascular Risk [11].

### 2.1 Statistical Analysis

Continuous variables are reported as means with their standard deviations for normally distributed variables or median (interquartile range) for non-normally distributed variables, and discrete variables as absolute values and percentages. For normally distributed variables the analysis was performed using unpaired one-way ANOVA. For non-normally distributed variables Kruskal–Wallis test was used. Differences in proportions were evaluated by Chi-square test. Pearson correlation coefficient between blood pressure and ultrasonography variables was evaluated. A 2-tail p value < 0.05 was considered statistically significant.

## 3 Results

A total of 285 consecutive patients were included in the cohort, with a mean follow-up of 1731 ± 952 days. The mean age of the sample was 56.3 ± 12.5 years and 166 patients

(58.3%) were males. The time evolution of hypertension was  $8.3 \pm 9.3$  years. The 10-year ASCVD risk of the sample was  $13.5 \pm 13.1\%$  while the 10-year risk for a sample like this one with optimal risk factor levels must have been  $4.9 \pm 5.3\%$ . Eighty five patients (29.9%) were of borderline CV risk, 44 patients (15.4%) of low CV risk, 87 patients (30.5%) of moderate CV risk and 69 patients (24.2%) of high CV risk. Nineteen patients (6.7%) were diabetics; 89 patients (31.2%) had dyslipidemia, 41 patients (14.4%) were smokers and 108 patients (37.9%) were former smokers. The baseline blood pressure was  $147.8 \pm 19/86.8 \pm 11$  mm Hg, while at the end of the follow-up the blood pressure was  $134.4 \pm 15.7/79 \pm 9$  mm Hg ( $p < 0.005$  SBP and  $p < 0.01$  DBP) (Fig. 1). The baseline heart rate was  $71.8 \pm 12.4$  beats/min and at the end of follow-up it was  $67.1 \pm 10.7$  beats/min ( $p = \text{NS}$ ). The percentage of patients whose blood pressure did not reach the goals was 46.7 at baseline; 33.6 at 1 year; 36 at 2 years; 30.1 at 3 years; 42.3% at 4 years; and 30.1 at 5 years of follow-up ( $p < 0.005$ ).

One hundred sixty nine patients (59.3%) were receiving RAS blockade at baseline which was increased to 68.9% at the end of follow up ( $p = \text{NS}$ ); 73 patients (25.6%) were treated with calcium channel blockers which rose to 42.2% at five years ( $p < 0.01$ ); thiazide or thiazide like diuretics at baseline were indicated in 70 patients (25.6%) which was increased to 32.5% ( $p = \text{NS}$ ), on the other hand, beta blockers treatment was slightly reduced from 23.2% (66 patients)

to 22.9% ( $p = \text{NS}$ ). At baseline 40.4% (115 patients) were receiving fixed-dose combinations which increased during follow up to 53.1% ( $p < 0.05$ ) (Fig. 2).

The baseline LVMI was  $87.3 \pm 20.4$  grs/m<sup>2</sup> and  $89.3 \pm 19.7$  grs/m<sup>2</sup> at the end of the follow ( $p = \text{NS}$ ); and some type of LV remodeling was detected in 30.9% (88 patients) vs. 30.1% at 5 years ( $p = \text{NS}$ ). The mean E/e' ratio showed a reduction from  $10.2 \pm 3.5$  to  $9.2 \pm 2.5$  ( $p = \text{NS}$ ) and the frequency of an E/e' ratio  $> 14$  was reduced from 13.3% (38 patients) to 3.6% ( $p < 0.001$ ). At the same time, the frequency of an e' septal velocity  $< 7$  cm/sec or an e' lateral velocity  $< 10$  cm/sec was reduced from 38.6% (110 patients) to 19.3% ( $p < 0.001$ ). No differences were detected regarding left atrium volume or parasternal long axis left atrium diameter during the follow-up. Normal diastolic function was detected in 244 patients (85.6%), indeterminate in 35 patients (12.3%), and diastolic dysfunction in 6 patients (2.1%), the figures were 94%, 4.8% and 1.2%, respectively, at the end of the follow-up period ( $p < 0.02$ ). The mean baseline septal tissue s' wave velocity was  $7.4 \pm 1.5$  cm/sec which increased to  $8.1 \pm 1.4$  cm/sec at 5 years ( $p = \text{NS}$ ) (Table 1, Fig. 3). The Pearson correlation coefficient between systolic blood pressure during follow-up and mean tissue Doppler septal e' wave was  $-0.3088$  ( $p < 0.005$ ), mean E/e' ratio 0.39658 ( $p < 0.005$ ), mean tissue Doppler septal s' wave  $-0.476$  ( $p < 0.005$ ); while for diastolic blood pressure was 0.242477 ( $p < 0.025$ ), 0.3160062 ( $p < 0.005$ ), and

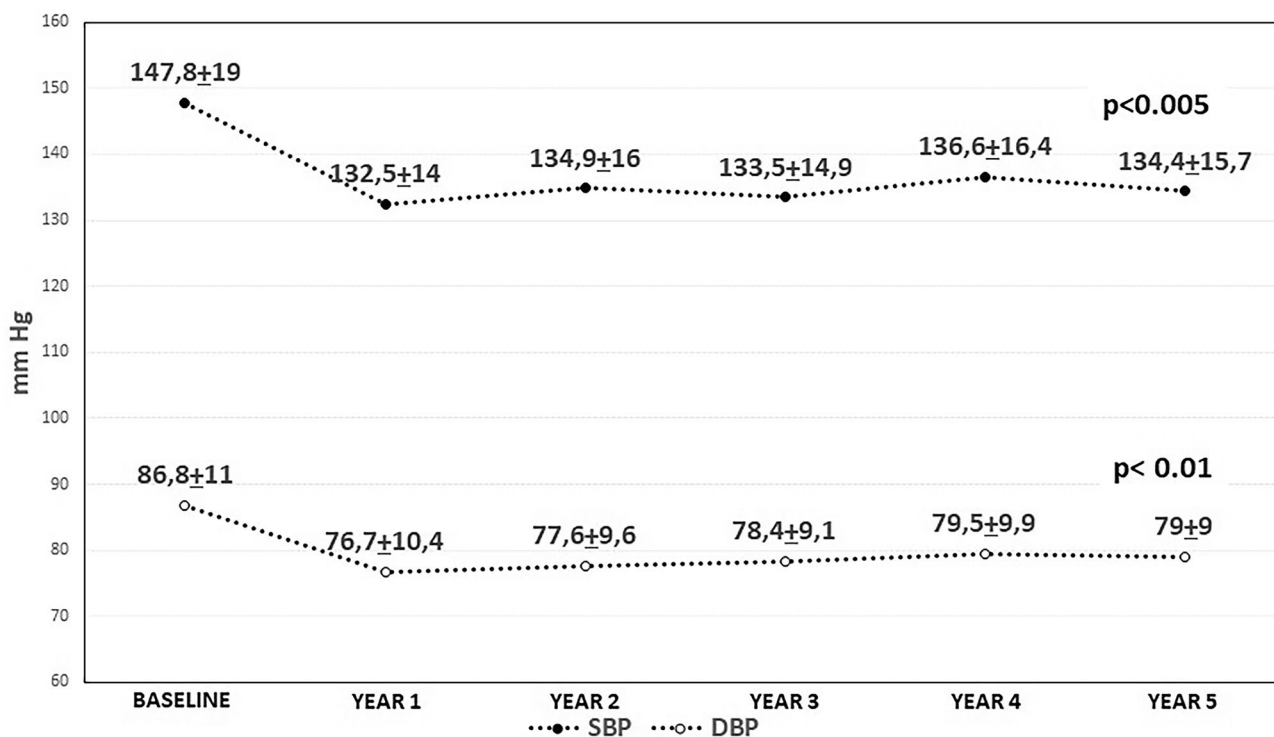
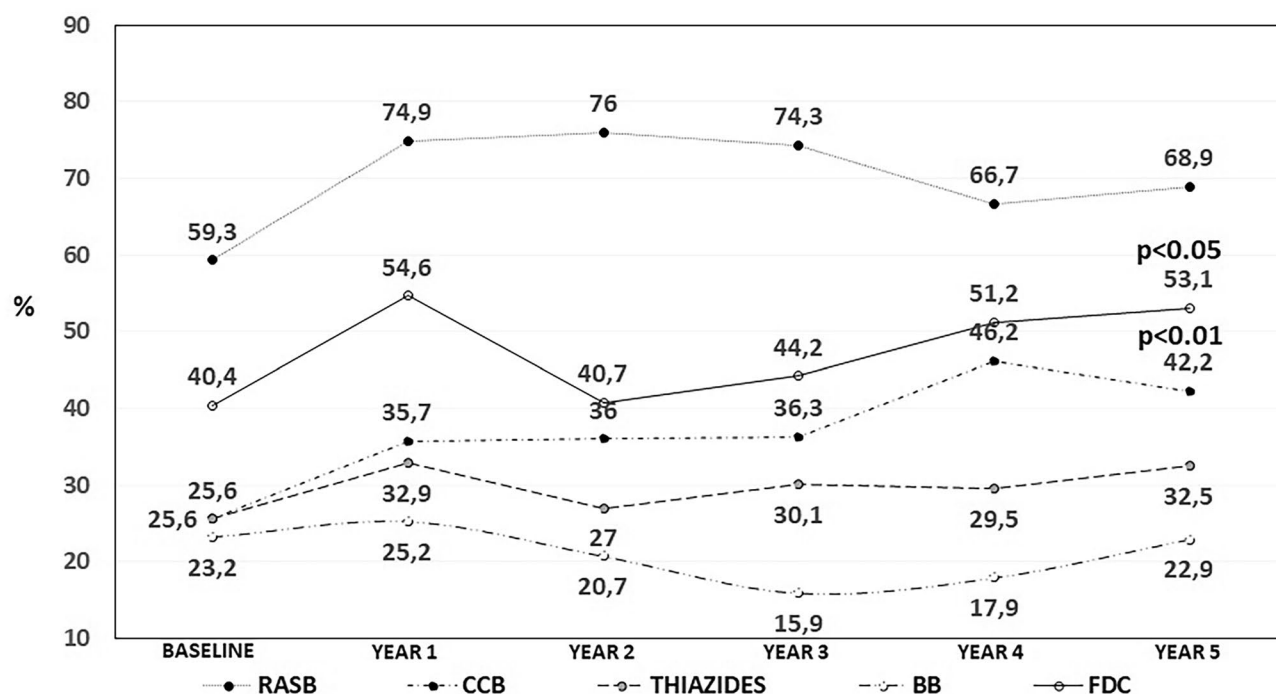


Fig. 1 Follow-up mean ± SD systolic and diastolic blood pressure. SBP systolic blood pressure, DBP diastolic blood pressure



**Fig. 2** Treatment assigned during follow-up. *RASB* renin-angiotensin-aldosterone blockade, *CCB* calcium channel blockade, *BB* beta blockers, *FDC* fixed-dose combinations

**Table 1** Echocardiographic parameters during follow-up

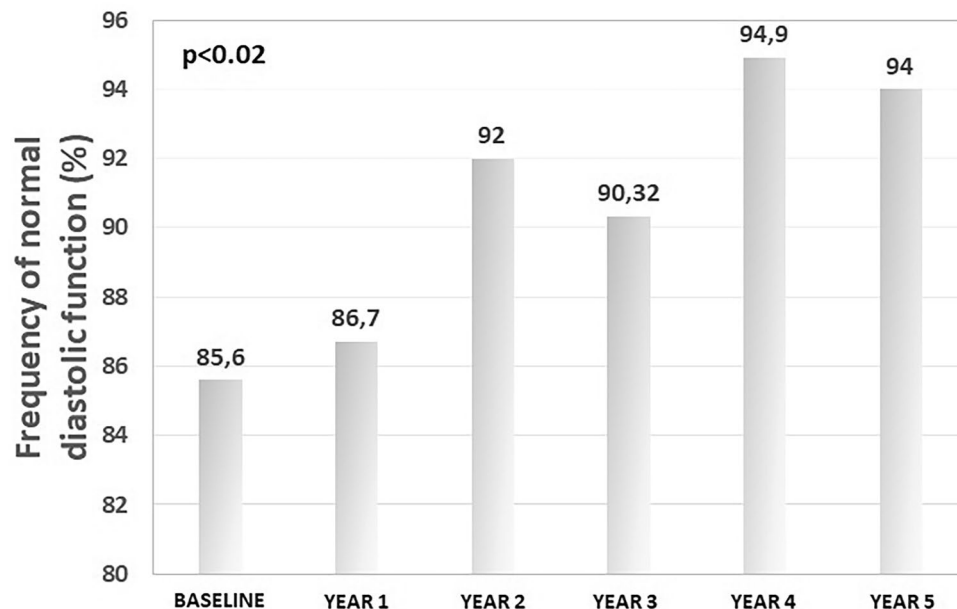
	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
N	285	143	150	113	78	83
Mean tissue Doppler septal e' wave (cm/sec) (SD)	7.9±2.4	7.8±2.1	8.1±2.1	8.2±2.1	8.1±1.9	8.1±1.9
Mean E/e' ratio (SD)	10.2±3.5	10.3±3.4	9.6±3	9.2±2.4	9.1±2.2	9.2±2.5
Frequency E/e' ratio > 14 (n-%)	38–13.3	15–10.5	11–7.3	4–3.5	1–1.3	3–3.6
Frequency septal e' < 7 or lateral e' < 10 (n-%)	110–38.6	52–36.4	40–26.7	29–25.7	12–15.4	16–19.3
Frequency of left atrium dilation (n-%)	31–10.9	19–13.3	11–7.3	16–14.2	15–19.2	9–10.8
Mean paraesternal long axis left atrium diameter (cm)	3.55±0.4	3.56±0.4	3.46±0.4	3.49±0.4	3.55±0.5	3.53±0.4
Normal diastolic function (n-%)	244–85.6	124–86.7	138–92	102–90.3	74–94.9	77–94
Indetermined diastolic function (n-%)	35–12.3	16–11.2	11–7.33	10–8.8	4–5.1	4–4.8
Diastolic dysfunction (n-%)	6–2.1	3–2.1	1–0.67	1–0.9	0–0	1–1.2
Mean tissue Doppler septal s' wave (cm/sec) (SD)	7.4±1.5	7.6±1.7	7.7±1.4	7.9±1.7	8.3±1.4	8.1±1.4
Mean LVMI (grs/m <sup>2</sup> ) (SD)	87.3±20.4	85.5±11.1	84.6±20.9	86.3±19.7	86.7±19.1	89.3±19.7
Frequency of LVH (n-%)	60–21.1	28–19.6	27–18.0	31–27.4	17–21.8	21–25.3
LVH or diastolic dysfunction (n-%)	65–22.8	30–21	28–18.7	32–28.3	17–21.8	21–25.3
Frequency of concentric remodeling (n-%)	28–9.8	10–7.0	5–3.3	3–2.7	0–0	4–4.8
Any remodeling (n-%)	88–30.9	38–26.6	32–21.3	34–30.1	17–21.8	25–30.1
Mean ejection fraction (%) (SD)	66.8±10.1	68.5±11.2	65.7±11.5	66.6±10.7	65.2±11.4	63.1±7.7

LVMI left ventricular mass index, LVH left ventricular hypertrophy

–0.407519 ( $p < 0.005$ ), respectively. The mean difference during follow-up was for SBP  $-6.2 \pm 22$  mm Hg, DBP  $-1.2 \pm 15$  mm Hg; pulse pressure  $-4.7 \pm 16$  mm Hg; tissue e' wave  $0.3 \pm 2$  cm/sec; mean E/e' ratio  $-0.67 \pm 2.5$ ; tissue

s' wave  $0.7 \pm 1.5$  cm/sec; LVMI  $-4 \pm 24$  grs/m<sup>2</sup>, and paraesternal long axis left atrium diameter  $-0.6 \pm 4$  mm. The correlation coefficient between pulse pressure difference during follow-up and mean E/e' ratio difference was 1.8704

**Figure 3** Frequency of normal diastolic function during follow-up



( $p < 0.05$ ). No other change in ultrasonography structural and functional parameters were related to follow-up hemodynamic variables. No differences were detected regarding ultrasonography parameters between patients on target or uncontrolled blood pressure during the follow-up (Table 2).

#### 4 Discussion

The analysis of a 5 years' follow-up cohort of 285 hypertensive treated patients showed that a sustained reduction of BP around 13/7 mm Hg had benefits on diastolic function parameters and reduced the frequency of diastolic dysfunction. On the other hand, structural abnormalities like LV remodeling, increased LV mass index or atrium dilation did not show any improvement, but they did not get worse during follow-up. Therefore, an adequate control of BP plays a key role in the reversal of hypertension mediated heart disease. Arguably, the increase in the amount of drugs received by the patients and the use of fixed-dose combinations explained that better BP control in this cohort.

The main therapeutic target in old adult hypertensive patients should be to prevent major cardiovascular events, but in young hypertensive subjects, like the present sample in which the mean age was a little more than 50 years old, the focus should be to prevent the development of hypertensive mediated organ damage [12]. In a population-based cohort of participants enrolled in the Olmsted County Heart Function Study the prevalence of diastolic dysfunction increased from 23.8% to 39.2% after 4 years of follow-up. And during 6.3 years of additional follow-up heart failure developed in 2.6% of those patients whose diastolic function

normalized or remained normal, in 7.8% of patients who remained or progressed to mild diastolic dysfunction, and 12.2% in patients that remained or progressed to severe dysfunction. Diastolic dysfunction was associated to incident heart failure even after adjustment of age, hypertension, diabetes or coronary artery disease [13]. The profile of heart failure among Framingham study participants had dramatically changed in the last decades, the frequency of heart failure with preserved ejection fraction (LVEF  $\geq 50\%$ ) grew 41% from 1985 to 1994 and 56% from 2005 to 2014. At the same time, heart failure with reduced ejection fraction (LVEF  $< 40\%$ ) decreased from 44 to 31%. The authors speculate that poor cardiovascular risk factors control is the main reason for these epidemiologic observations [14]. Recently, a consensus recommendation from the Heart Failure Association of the European Society of Cardiology proposed a stepwise diagnostic process for heart failure with preserved ejection fraction that includes a pre-test assessment, a second step that requires a comprehensive echocardiography and a natriuretic peptide score, and in cases of diagnostic uncertainty a third step with echocardiographic or invasive hemodynamic exercise stress tests, and one final step is to establish the possible etiology of the heart failure. The diagnosis is based on functional, morphological and biomarker major and minor criteria that include septal or lateral  $e'$  wave, average  $E/e'$  ratio, tricuspid regurgitation velocity, left atrial volume index, left ventricular mass index, global longitudinal strain, and NT-proBNP or BNP. So this recommendation requires the presence of ultrasound diastolic dysfunction or reduced LV longitudinal contractility, and abnormal cardiac biomarkers to confirm the diagnosis of heart failure with preserved ejection fraction [15]. With this

**Table 2** Echocardiographic parameters during follow-up in patients on target or uncontrolled blood pressure

BP at target	Baseline		Year 1		Year 2		Year 3		Year 4		Year 5	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
N	152	133	95	48	96	54	79	34	45	33	58	25
Mean tissue Doppler septal e' wave (cm/sec) (SD)	7.9±2.4	7.9±2.5	7.6±2	8.1±2.3	8.2±2.3	8.1±2	8.1±2.1	8.2±2.3	8.5±2.1	8±1.6	8±1.9	8.4±2
Mean E/e' ratio (SD)	10±3.3	10.4±3.7	10±2.7	11.1±4.5	9.5±1.8	9.8±3.2	8.9±2.4	9.7±2.2	8.7±1.9	9.6±2.5	9.3±2.3	9±3
Frequency E/e' ratio > 14 (n-%)	20-13.2	18-13.5	4-4.2	11-22.9	7-7.3	4-7.4	2-2.5	2-5.9	0-0	1-3.0	1-1.7	2-8.0
Frequency septal e' < 7 or lateral e' < 10 (n-%)	54-35.5	56-42.1	37-38.9	15-31.3	31-32.3	9-16.7	19-24.1	10-29.4	6-13.3	6-18.2	13-22.4	3-12.0
Frequency of left atrium dilation (n-%)	13-8.6	18-13.5	13-13.7	6-12.5	3-3.1	8-14.8	9-11.4	7-20.6	8-17.8	7-21.2	7-12.1	2-8.0
Mean paraaesternal long axis left atrium diameter (cm)	3.53±0.4	3.57±0.4	3.57±0.5	3.54±0.4	3.46±0.4	3.44±0.5	3.46±0.4	3.54±0.5	3.6±0.5	3.54±0.5	3.54±0.4	3.53±0.4
Normal diastolic function (n-%)	132-86.8	112-84.2	85-89.5	39-81.3	89-92.7	49-90.7	74-93.7	28-82.4	42-93.3	32-97	54-93.1	23-92
Indeterminate diastolic function (n-%)	19-12.5	16-12.0	8-8.4	8-16.7	7-7.3	4-7.4	4-5.1	6-17.6	3-6.7	1-3.0	3-5.2	1-4.0
Diastolic dysfunction (n-%)	1-0.7	5-3.8	2-2.1	1-2.0	0-0	1-1.9	1-1.3	0-0	0-0	0-0	0-0	1-4.0
Mean tissue Doppler septal s' wave (cm/sec) (SD)	7.3±1.4	7.6±1.6	7.4±1.3	8±2.4	7.6±1.3	7.7±1.6	7.8±1.6	7.9±1.9	8.7±1.4	7.8±1.3	8.1±1.2	8.2±1.8
Mean LVMI (grs/m <sup>2</sup> ) (SD)	86.9±20	87.8±21.1	84.8±11.1	86.8±11.4	83±21.4	87.8±20	84.2±17.4	90.1±24.1	85.5±16.7	88.5±21.8	86.6±18.1	95±12.5
Frequency of LVH (n-%)	36-23.7	24-18	20-21.1	8-16.7	16-16.7	11-20.4	23-29.1	8-23.5	10-22.2	7-21.2	13-22.4	8-32.0
LVH or diastolic dysfunction (n-%)	37-24.3	28-21.1	21-22.1	9-18.8	16-16.7	12-22.2	24-30.4	8-23.5	10-22.2	7-21.2	13-22.4	8-32.0
Frequency of concentric remodeling (n-%)	14-9.2	14-10.5	7-7.4	3-6.3	1-1.0	4-7.4	3-3.8	0-0	0-0	0-0	2-3.4	2-8.0
Any remodeling (n-%)	51-33.6	38-28.6	27-28.4	11-22.9	17-17.7	15-27.8	26-32.9	8-23.5	10-22.2	7-21.2	15-25.9	10-40.0
Mean ejection fraction (%) (SD)	66.9±10	66.7±10.2	67.1±11.3	71.3±10.4	66.2±17.8	65.1±11.3	67.1±11.3	66.6±9.4	65.2±13.1	66.1±10	63.4±7.8	62±7.4

LVMI left ventricular mass index, LVH left ventricular hypertrophy



background, the results of the present observational cohort support the notion that achievement of blood pressure targets in hypertensive patients may improve diastolic function or reduce the progression to diastolic dysfunction which might delay or prevent the onset of heart failure.

Using speckle-tracking echocardiography, a sample of 135 hypertensive patients treated with anti-hypertensive medications for more than one year and 54 normotensive controls were non-invasively examined for LV systolic and diastolic function. Patients were divided into groups according to the presence of LVH and heart failure, and heart failure patients were divided in two groups: preserved ejection fraction ( $EF \geq 50\%$ ) and reduced ejection fraction ( $EF < 50\%$ ). Hypertensive patients with LVH had a significant deterioration of systolic and diastolic properties compared to normotensive controls, in addition, pulmonary capillary wedge pressure estimated using kinetics-tracking index was higher in hypertensive patients with LVH than in those without LVH, and further elevated in patients with HFpEF regardless of similar ejection fraction. No differences were detected in LV longitudinal strain between HFrEF and HFpEF. The estimated pulmonary capillary wedge pressure and  $E/e'$  ratio showed a relation with heart failure in all subjects and in the hypertensive group [16]. Similarly, the sample of the present study kept between normal ranges the ejection fraction during the whole follow-up, and beyond the technical difficulties and limitations to get a reliable  $s'$  wave, it remained stable with a non-significant velocity increase from 7.5 to 8.1 cm/sec from baseline to the end of follow-up. The baseline frequency of an  $E/e'$  ratio  $>14$  was 13.3%, of a septal  $e' < 7$  or lateral  $e' < 10$  was 38.6%, and the frequency of normal diastolic function 85.6%, and at the end of follow-up the figures were 3.6; 19.3 and 94%, respectively. According to the results, the main benefit of hypertension treatment in this study seems to be the prevention or regression of diastolic dysfunction.

The EMPEROR-Preserved trial included patients with heart failure and preserved ejection fraction. Ninety percent of the sample had hypertension, 49% diabetes, 35% history of coronary artery disease and 29% history of myocardial infarction. This highlights the relevance of cardiovascular risk factors and chronic ischemic syndromes in the pathogenesis of this phenotype of heart failure. The mean baseline ejection fraction was 54%, while the frequency of LV hypertrophy was just 10%, the  $E/e'$  ratio  $> 13$  was 13%, and any left atrium size/volume increase was 82% [17]. These ultrasound data (the baseline ejection fraction was 66.8%, more than 10% higher than in EMPEROR-Preserved, and the frequency of LA dilation was just 10%) clearly established a specific and different profile of patients from the present study which can nevertheless explain the transition from hypertensive mediated heart damage to heart failure with preserved ejection fraction. The frequency of

LV hypertrophy and  $E/e'$  ratio  $> 14$  was quite similar in both studies. LA remodeling could explain that 35% of the patients randomized to the trial had atrial fibrillation/flutter at screening, one of the most frequent triggers of heart failure while in the present study atrial arrhythmias were an exclusion criteria.

This study identified diastolic dysfunction according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging which required the presence of at least three of four abnormal variables: the annular  $e'$  velocity at septal and lateral level, the average  $E/e'$  ratio, the left atrium maximum volume index, and the peak tricuspid regurgitation velocity [10]. The ASE/EACVI guidelines and standards authors recommend that due to the several hemodynamic factors that affect each signal, some measurements may fall in the normal range despite the presence of diastolic dysfunction, therefore, a frame integrating all the variables is the best approach to achieve an adequate diagnosis. The patient's sample of the study consists mostly of middle age adults, without heart failure, with an ejection fraction over 54% and without atrial arrhythmias. Thus, patients are probably going through early stages of diastolic dysfunction, where left ventricular end diastolic pressure is the only abnormality, left atrial pressure remain normal or near-normal, and left ventricle stiffness and myocardial relaxation are not extensively affected. This data allow for a speculative explanation about the discrepancy between changes in diastolic parameters and changes in left atrial dimensions.

## 5 Limitations

First, the study reported was carried out in a single center, which means that demographic characteristics, therapeutic interventions and ultrasound data not necessarily are representative of what happens in medical practice in different settings. Second, although the patients sample was obtained consecutively, some type of bias selection cannot be excluded, neither can some degree of bias be ruled-out in the follow-up since some patients may have delayed or suspended their consultations due to non-related disease variables like COVID-19 pandemic or lockdown. Third, the evaluation of systolic function was performed by measuring ejection fraction by 2D modified Simpson method and tissue Doppler  $s'$  wave, but it is well known that global longitudinal strain obtained by speckle tracking is a better way to detect subtle alterations in LV contractility. Finally, the sample of patients in this cohort was selected on the basis of strict inclusion and exclusion criteria: subjects in primary prevention without previous or current diagnosis of heart failure and echocardiographic ejection fraction over 54%, which does not necessarily represent the universe of hypertensive

patients, and therefore, the information obtained cannot be extrapolated to other clinical scenarios.

## 6 Conclusions

The present cohort of 285 patients on primary prevention at moderate CV risk followed for a mean of 5 years showed that small reductions in blood pressure can prevent or reverse diastolic dysfunction. However, regression of structural damage, like LV hypertrophy, LV remodeling or LA dilation was not feasible. Although controlled clinical trials have proven that by using antihypertensive treatment small but statistically significant reductions in LVMI are shown, the present study indicates that this is not necessarily reproducible outside of research. Still, these results should have an impact on routine care practice and early diagnosis and appropriate treatment initiation is the best way to prevent hypertensive mediate heart damage.

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## Declarations

**Conflict of interest** The authors of the original research entitled “Medium to long term follow-up of treated hypertensive mediated heart disease” declare no conflict of interest.

## References

- Okwuosa TM, Soliman EZ, Lopez F, Williams KA, Alonso A, Ferdinand KC. Left ventricular hypertrophy and cardiovascular disease risk prediction and reclassification in blacks and whites: the Atherosclerosis Risk in Communities Study. *Am Heart J*. 2015;169:155–61.
- Lieb W, Gona P, Larson MG, Aragam J, Zile MR, Cheng S, Benjamin EJ, Vasan RS. The natural history of left ventricular geometry in the community. Clinical correlates and prognostic significance of change in LV geometric pattern. *Am Coll Cardiol Imaging*. 2014;7:870–8.
- Sharifov OF, Denney TS Jr, Prabhu SD, Lloyd SG, Gupta H. Impact of medical therapy for cardiovascular disease on left ventricular diastolic properties and remodeling. *IJC Heart Vasc*. 2019;23:100365.
- Salveti M, Paini A, Bertacchini F, Stassaldi D, Aggiusti C, Rosei CA, Bassetti D, Agabiti-Rosei E, Muiesan ML. Changes in left ventricular geometry during antihypertensive treatment. *Pharmacol Res*. 2018;134:193–9.
- Williams B, Mancia G, Spiering W, Agabiti-Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESH/ESC guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2018;36:1953–2041.
- Piskorz D, Bongarzone L, Citta L, Citta N, Citta P, Keller L, Tommasi A. Association of systolic dysfunction with left ventricular hypertrophy and diastolic dysfunction in hypertensive patients. *Rev Fac Cien Med Univ Nac Cordoba*. 2014;71:158–64.
- Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–8.
- Devereux RB, Pini R, Aurigemma GP, Roman MJ. Measurement of left ventricular mass: methodology and expertise. *J Hypertens*. 1997;15:801–9.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W, American Society of Echocardiography’s Nomenclature and Standards Committee, Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee, American Heart Association, European Association of Echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7:79–108.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
- Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D’Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O’Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2014;129:S49–73.
- Piskorz D. Hypertensive mediated organ damage and hypertension management. How to assess beneficial effects of anti-hypertensive treatments? *High Blood Press Cardiovasc Prev*. 2020;27:9–17.
- Kane J, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC Jr, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306:856–63.
- Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, Aragam J, Benjamin EJ, Larson MG. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. *JACC Cardiovasc Imaging*. 2018;11:1–11.
- Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelman F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melonovsky V, Morris DA, Nagel E, Peske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–317.
- Minatoguchi S, Kawasaki M, Tanaka R, Yoshizane T, Ono K, Saeki M, Nagaya M, Sato H, Nishigaki K, Noda T, Zile MR, Minatoguchi S. Evaluation of systolic and diastolic properties of hypertensive heart failure using speckle-tracking echocardiography with high volume rates. *Heart Vessels*. 2017;32:1202–13.



17. Anker SD, Butler J, Filippatos G, Shahzeb Khan M, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi D, Chopra V, Chuquiure E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JE, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Seronde MF, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, for the EMPEROR-Preserved Trial Committees and Investigators. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. *Eur J Heart Fail.* 2020;22:2383–92.