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Full Title

The relationship between left ventricular wall thickness, myocardial shortening and ejection fraction in hypertensive heart disease: insights from cardiac magnetic resonance.

Running heading

LVH independently augments EF in hypertension

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Abstract

Hypertensive heart disease is often associated with a preserved left ventricular ejection fraction despite impaired myocardial shortening. We investigated this paradox in 55 hypertensive patients (52±13 years, 58% male) and 32 age- and sex-matched normotensive control subjects (49±11 years, 56% male) who underwent cardiac magnetic resonance at 1.5T. Long-axis shortening (R=0.62), midwall fractional shortening (R=0.68) and radial strain (R=0.48) all reduced (p<0.001) as end-diastolic wall thickness increased. However, absolute wall thickening (defined as end-systolic minus end-diastolic wall thickness) was maintained, despite the reduced myocardial shortening. Absolute wall thickening correlated with ejection fraction (R=0.70, p<0.0001). In multiple linear regression analysis, increasing wall thickness by 1mm independently increased ejection fraction by 3.43 percentage points (adjusted β-coefficient: 3.43 [2.60–4.26], p<0.0001). Increasing end-diastolic wall thickness augments ejection fraction through preservation of absolute wall thickening. Left ventricular ejection fraction should not be used in hypertensive heart disease without correction for degree of hypertrophy.

Text

Introduction

In systemic hypertension, left ventricular hypertrophy (LVH) may occur in the face of increased afterload (1). The development of hypertensive LVH is pathological and is an independent predictor for sudden cardiac death(2), ventricular arrhythmias(3), coronary artery disease(4) and heart failure(5), which is often in the context of a normal left ventricular ejection fraction (LVEF). The hypertrophied hypertensive myocardium is associated with reduced long-axis shortening (LS), yet the left ventricular ejection fraction (LVEF), which is a traditional marker of LV systolic function, remains in the normal range(6), leading some to believe that hypertensive heart disease is a diastolic disorder. The apparent paradox of global myocardial systolic long-axis dysfunction but normal LVEF has previously been explained by a "compensatory increase in short-axis shortening"(7). However, observational data does not support this hypothesis; for example, there are abnormalities of both midwall and longitudinal fractional shortening in hypertensive hypertrophic left ventricular disease(8)(9)(10).

An alternative theoretical explanation argues that an increase in end-diastolic left ventricular wall thickness (EDWT) leads to increased end-systolic left ventricular wall thickness (ESWT) and a correspondingly augmented absolute wall thickening (AWT), where AWT is the difference between ESWT and EDWT. Assuming no significant change in the external diameter of the left ventricle during systole(11), the resultant absolute displacement of the endocardial border could be normal and therefore LVEF maintained. This concept has been demonstrated by mathematical modeling of

concentric LVH (12)(13). Such mathematical modeling controls for, and therefore removes, the potential impact of other variables such as body surface area, heart rate, blood pressure, ventricular-arterial coupling, peripheral vascular resistance and abnormalities in left ventricular relaxation.

We sought to accurately determine the biophysical relationship between EDWT, longitudinal and midwall myocardial shortening, AWT and LVEF in a human hypertensive cohort using cardiac magnetic resonance (CMR) since it is the gold-standard for non-invasively assessing left ventricular (LV) mass and volume(14). A detailed assessment of the relationship between these variables will aid better understanding of the pathophysiology of hypertensive heart disease and may have important implications for refining our understanding of the mechanisms of heart failure with normal ejection fraction (HFNEF), with implications for its treatment.

Materials and Methods

Study subjects

Fifty-five hypertensive subjects (age: 52 ± 13 years, gender: 58% male, office SBP: 174 ± 29mmHg, office DBP: 98 ± 16mmHg) were recruited from the Bristol Heart Institute tertiary hypertension clinic between 2011 and 2013. Baseline demographic and clinical characteristics were recorded. In order to investigate hypertensive LVH, exclusion criteria consisted of clinical or CMR evidence of any concomitant myocardial pathology that may confound the hypertrophic response (e.g. previous

myocardial infarction, moderate-severe valvular heart disease, dilated cardiomyopathy, suspected athlete's heart, hypertrophic or infiltrative cardiomyopathy).

Average office systolic (SBP) and diastolic blood pressures (DBP) were acquired in all subjects after seated rest from both arms, assessed using standard automated sphygmomanometry with an appropriately-sized cuff(15). Standard 24-hour ambulatory blood pressure monitoring (ABPM) was also performed(16).

A cohort of 32 age- and sex-matched normotensive control subjects (age: 49 ± 11 years, gender 56% male, office SBP: 126 ± 12mmHg, office DBP: 77 ± 10mmHg) healthy volunteers free from cardiovascular disease, with normal blood pressure and ECG, and on no regular medication, were used as an age- and sex-matched control group.

The study complied with the Declaration of Helsinki. The local research ethics committee confirmed that this study conformed to the governance arrangements for research ethics committees. Subjects provided written consent for their CMR images to be used for research.

CMR protocol

All CMR studies were performed at 1.5T (Avanto, Siemens, Erlangen, Germany) using a spine coil, a body array coil and retrospective electrograph (ECG) triggering by

specialist CMR technicians. Steady-state free precession (SSFP) end-expiratory breath-hold cines were acquired in the standard 4-chamber, 2-chamber and 3-chamber cardiac long-axis planes and in the LV short-axis from the atrioventricular ring to the apex. Representative CMR parameters were as follows: repetition time (TR) 40.05ms, echo time (TE) 1.13ms, slice thickness 8mm, no interslice gap, field of view 260 x 320mm, flip angle 75°, in-plane voxel size 2 x 2mm.

CMR analysis

All CMR analysis was performed by a single CMR reader, with > 4 years of CMR experience, using cvi42 software (Circle Cardiovascular Imaging Solutions Incorporated, Calgary, Canada). LV volumes, LVEF and LV mass were estimated using established clinical methods as described previously[17]. Mass to volume ratio (M/V) was calculated as previously described[18]. This data was acquired blinded to the myocardial fractional shortening measurements, and vice versa. Changes in lengths in the longitudinal and radial directions of the myocardium between end-diastole and end-systole have recently been demonstrated to represent a simple technique to quantify myocardial strain relative to both in vivo myocardial tagging and validated finite element computation modeling techniques[19]. Consequently, we used a 6-point mitral annular plane systolic excursion indexed to the LV end-diastolic length as a measure of global long-axis shortening as described previously[17]. EDWT and ESWT were measured in the middle of each of the basal and mid LV myocardial segments on the long-axis cines with measurements performed perpendicular to the LV wall. Measurements of the thickness of the apical segments

were prone to partial volume averaging, particularly at end-systole, due to the conical configuration of the LV and therefore were not included in the analysis. EDWT has previously been demonstrated to have better levels of inter and intra-observer agreement when measured from long-axis compared to short axis cines[20]. Furthermore, it was easier to take into account the effect of through-plane motion of the mitral valve during systole using long-axis cines compared to the short-axis cines using mitral valve plane tracking software (cvi42, Circle Cardiovascular Imaging Solutions Incorporated, Calgary, Canada). Papillary muscles and trabeculae were excluded from wall thickness measurements. Relative wall thickness was defined as EDWT indexed to left end-diastolic diameter. AWT was defined as the absolute difference between ESWT and EDWT. Radial strain was defined as the percentage increase in wall thickness (i.e. engineering strain or relative wall thickening). LV internal diameters at end-diastole (LVIDd) and at end-systole (LVIDs) were measured at the LV basal and mid levels from the long-axis cines. All measurements were repeated twice and the mean value used for subsequent analysis. Midwall circumferential fractional shortening (mFS) was estimated using the following established equation, which has been described previously[10]:

$$mFS\ (\%) = ((LVIDd + EDWT) - (LVIDs + H)) / (LVIDd + EDWT)\ x\ 100$$

Where:

$$H = ((LVIDd + EDWT)^3 - (LVIDd)^3 + (LVIDs)^3)^{1/3} - LVIDs$$

Statistical analysis

Statistical analysis was generated using the Real Statistics Resource Pack software (Release 3.2.1) and using SPSS v.21 (Armonk, NY, USA: IBM Corp). Categorical variables were analyzed using Fisher's exact tests. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using unpaired Student's T tests or one-way analysis of variance with Bonferroni post-hoc correction for between groups comparisons, as appropriate. Multiple linear regression analysis was performed to investigate independent determinates of EDWT, LAS and mFS on LVEF. The impact of multi-collinearity was excluded by acceptable values in variance inflation factor tests. Reproducibility was assessed by intra-class correlation coefficient (ICC) (two-way mixed, absolute agreement, average measures). The intra-observer intra-class correlation coefficient for EDWT was 0.962 (95% confidence interval: 0.956–0.968), for ESWT was 0.966 (0.959–0.971), LV end diastolic length was 0.987 (0.984–0.989) and for LV end systolic length was 0.990 (0.987–0.992). Statistical significant was set at two-tailed $p<0.05$.

Results

Demographics

The demographic and baseline clinical data for hypertensive subjects and normotensive controls are documented in **Table 1**. The study sample was stratified into tertiles by EDWT. There were significantly more female subjects with EDWT < 9mm compared to both EDWT 9 -11m and EDWT > 11mm respectively, $P < 0.05$. No other demographics differences were demonstrated across the study population.

There were no statistically significant differences in the anti-hypertensive medication regimens between the hypertensive cohorts. There were step-wise increases in both M/V and RWT with increasing EDWT, consistent with increasing concentric LVH with increasing EDWT in our sample of patients. EDWT correlated with office SBP (R = 0.43, P < 0.001) and office DBP (R = 0.32, P < 0.005) but did not correlated with ABPM SBP (R = 0.24, P = 0.12), ABPM SBP (R = 0.18, P = 0.27) or ABPM MAP (R = 0.18, P = 0.27).

Impact of increasing EDWT on mFS, LS and RS

There was a strong positive significant correlation between mFS and LAS (R=0.73, p<0.001) (**Figure 1A**). Both mFS (R=0.84, p<0.001) and LAS (R=0.64, p<0.001) correlated significantly with RS (**Figure 1B and 1C**). EDWT correlated with mFS (R=0.68, p<0.001) (**Figure 2A**), LAS (R=0.62, p<0.001) (**Figure 2B**) and RS (R=-0.48, p<0.001)(**Figure 2C**). The hypertensive cohort with EDWT >11mm had significantly lower LAS and mFS compared to hypertensives with EDWT 9 – 11mm, hypertensives with EDWT <9mm and normotensive controls, on pairwise comparisons with Bonferroni adjustment (**Table 2**).

Impact of increasing EDWT on ESWT and AWT

As EDWT increased, there was an increase in end-systolic wall thickness (R=0.92, p<0.001) (**Figure 3A**) but and an increase AWT (R= 0.43, p<0.005) (**Figure 3B**). There

were significant increases in AWT from all hypertensive subgroups compared to normotensive controls (**Table 2**) and there was significant increases in AWT from hypertensive subjects with EDWT 9 – 11m and EDWT > 11m compared to EDWT < 9mm respectively (**Table 2**).

Impact of increasing EDWT and AWT on LVEF

Despite reduction in mFS, LAS and RS with increasing EDWT, there was a borderline significant weak correlation between EDWT and LVEF (R=0.26, p=0.05) (**Figure 3C**). Absolute wall thickening correlated significantly with LVEF (R=0.70, p<0.0001) (**Figure 3D**).

Impact of increasing EDWT on indexed EDV, indexed ESV and indexed SV

Increasing EDWT negatively correlated with both indexed EDV (R=-0.37, p<0.05) and indexed ESV (R=-0.30, p<0.05). However, the reduction in both indexed EDV and indexed ESV with increasing EDWT resulted in no significant difference in the indexed stroke volume (R=-0.081, p=0.55).

Multiple linear regression analysis

Regression analysis was performed using variables that have a biophysically plausible and direct influence on LVEF. LVEF was set as the dependent variable and EDWT, LAS and mFS as independent variables. All variables were continuous. EDWT, LAS and

mFS were all independently and positively correlated with LVEF (**Table 3**). Essentially, a 1 mm increase in EDWT would independently account for an increase in the LVEF by an absolute value of 3.43%. The increase in EDWT compensates for the independent reduction in LVEF by an absolute value of 2.01% and 1.05% for a 1.00% absolute reduction in LAS and mFS by respectively.

Discussion

Our study investigated the impact of EDWT on LVEF in hypertensive heart disease using segmental engineering strain measurements derived from CMR, the gold-standard non-invasive cardiac imaging modality for LV wall thickness and function, in a sample of 55 hypertensive and 32 normotensive subjects.

The pathophysiology of LVH and its functional consequences are incompletely understood. However, the concept that left ventricular (LV) wall geometry affects the LVEF is longstanding(21). De Dumesnil et al. proposed that wall thickening is the direct reflection of shortening that occurs in the circumferential and longitudinal directions(22). Subsequent work by Rademakers et al. demonstrated the importance of cross-fibre shortening in determining wall thickening in a canine model using tagged cardiovascular magnetic resonance (CMR)(23). More recently, the notion that LV geometry impacts on its ejection fraction has been reaffirmed by an echocardiographic study by Aurigemma et al.(24), which showed that elderly subjects with high relative wall thickness maintained their LVEF despite depressed

midwall fractional shortening. Palmon et al. demonstrated that both longitudinal and circumferential shortening were reduced in hypertensive subjects with LVH and a normal ejection fraction, using tagging CMR(25). Furthermore, Vinch et al. demonstrated significantly lower midwall fractional shortening (mFS) in patients with hypertensive heart disease compared to normal controls, despite unchanged mean endocardial shortening and ejection fraction(26). Similar findings were demonstrated by Koh and colleagues(27). More recently, Mizuguchi and colleagues showed reduced longitudinal, circumferential and radial strain in hypertensive patients with concentric hypertrophy in an echocardiographic study(6).

It is therefore clear that LVH is associated with abnormalities of both midwall and longitudinal fractional shortening. However, the reason why LVEF, a traditional marker of LV systolic function, usually remains in the normal range despite these abnormalities is unclear. A theoretical explanation argues that an increase in end-diastolic left ventricular wall thickness (EDWT) leads to increased end-systolic left ventricular wall thickness (ESWT) and a correspondingly augmented absolute wall thickening (AWT), where AWT is the difference between ESWT and EDWT. Assuming no significant change in the external diameter of the left ventricle during systole(11), the resultant absolute displacement of the endocardial border could be normal and therefore maintain LVEF. This concept has been demonstrated by mathematical modeling of concentric LVH (12). Furthermore, in an trans-esophageal echocardiographic study of 15 patients with hypertension, Frielingsdorf et al. demonstrated that absolute and fractional wall thickening was inversely related to

EDWT, but did not investigate the relationship between these variables and LVEF(28).

Our findings that increasing EDWT was accompanied by reduced myocardial longitudinal and circumferential shortening are consistent with the existing literature. However, we additionally demonstrate, for the first time, the independent and significant relationships between both longitudinal and circumferential shortening and EDWT on LVEF using multiple linear regression analysis. Whilst an increase in EDWT independently results in a significant increase in LVEF, it is associated with a reduction in LAS, mFS and RS, which in turn, significantly and independently lowers LVEF.

The importance of AWT

In spite of the worsening strain abnormalities with increasing EDWT in our cohort, both LVEF and indexed SV remained in the normal range for all EDWT values. Our results offer further insights to help explain this apparent paradox. As EDWT increased, we also demonstrated a corresponding increase in wall thickness at end-systole. As a result, there was a maintained absolute wall thickening over the range of end diastolic wall thicknesses investigated. Consequently, the absolute endocardial displacement remained normal with increased EDWT, despite reduced myocardial shortening. The maintenance of AWT with increasing EDWT is not due to compensatory radial thickening because there is a concomitant reduction in radial strain. We provide evidence that the preservation of AWT, and therefore LVEF, is secondary to the degree of LVH defined by EDWT. Of note, the influence of a given

amount of AWT in smaller left ventricles will have a greater impact on LVEF. Our study provides *in vivo* validation of this mechanism described in mathematical modeling experiments of concentric LVH(12). In summary, a ventricle with normal EDWT, normal LAS and normal mFS will result in similar AWT as a ventricle with concentric LVH, reduced LAS, mFS and RS. The AWT is an important determinant of the LVEF and indexed SV in both these hypothetical scenarios. Our results show how there can be important abnormalities of systolic function, defined by reduced myocardial shortening, and yet a normal LVEF and hence explain why LVEF is a poor marker of systolic dysfunction in the context of LVH.

Hypertensive remodelling

Left ventricular remodeling is postulated to be a constructive adaptive physiological response to result in a normalization of stroke volume(29). We have demonstrated that the indexed EDV and indexed ESV reduce with increasing EDWT but indexed SV remains within the normal range as EDWT increases, consistent with previous mathematical modeling(30). This lends weight to the hypothesis that hypertensive LVH occurs concurrently or before the abnormality causing contractile dysfunction(30). In the context of hypertension, reduced contractility of the hypertrophied myocardium is postulated to occur, at least in animal models, as a consequence of production of different myosin heavy chain isoforms mediated by changes in expression of myocardial contractile and metabolic proteins through secondary messenger cell signaling pathways such as phosphoinositides and proto-oncogenes(31).

Implications for heart failure with preserved ejection fraction (HFpEF)

Our findings may have important implications for understanding the pathophysiology of HFpEF. The term HFpEF describes patients with a left ventricular ejection fraction (LVEF) >45-50% but clinical features of heart failure(7). HFpEF is a common disease, affecting approximately 50% of patients with heart failure(32). Myocardial shortening abnormalities are common in HFpEF(33) and patients often have hypertension and concentric LVH(34). As AWT compensates for myocardial shortening impairment in hypertensive heart disease with normal LVEF and normal indexed SV, it is perplexing why some patients develop clinical symptoms of heart failure in the context of hypertensive heart disease. This is best explained by the blunted cardiovascular response to exercise with failure to augment SV and cardiac index on exertion(35) and reduced contractile reserve(36).

Left ventricular mass is an important determinant of risk in hypertensive heart disease with differing risk dependent on the remodeling pattern(37). We have shown the detailed biophysical relationships between EDWT and myocardial shortening, LVEF and ventricular volumes. We suggest that geometric patterns seen in hypertension may be explained by the combination of wall thickness and myocardial shortening. A combination of both EDWT and myocardial shortening may give incremental prognostic information over the traditional marker of LVEF alone.

Limitations

The study population size was modest. However, our correlations with AWT and our multiple linear regression results were highly significant suggestive sample size was

adequate. The latter is likely related to the improved accuracy and reproducibility of CMR compared to echocardiography, which affords a marked reduction in sample size for the same statistical power(38). Our study was limited to hypertensive subjects attending a tertiary hypertension clinic. Most subjects are likely to have moderate to severe hypertension, which may preclude extrapolation beyond this particular cohort. However, the study was primarily designed to assess the interaction of EDWT on LVEF and not the impact of severity of hypertension. Nonetheless, there were no significant differences in office systolic or diastolic blood pressure across the subgroups with EDWT <9mm, 9 – 11mm and >11mm respectively (Table 1). Furthermore, modeling data would suggest that only a mild increase in EDWT (e.g. > 12mm) is necessary to significantly increase LVEF(12)(39). Obesity can affect LV remodeling and hypertrophy(40) and whilst obesity was common in our sample, there were not significant differences in mean BMI across the subjects (Table 1).

Engineer's strain was calculated directly by measuring LAS and RS manually. Similar techniques quantifying changes in myocardial length and thickness at end-diastole and end-systole have been validated against myocardial tagging and finite element models(19). However, we elected to calculate mFS using a widely used and previously validated equation(10) because there is a large circumferential strain gradient (approximately 3-36%) across the wall of the myocardium, with the subendocardial myocardium being displaced more than the epicardial myocardium(41), consequently the midwall myocytes cannot be easily tracked through the cardiac cycle as their position relative to the endocardial and epicardial

borders changes continually during LV contraction. As a result, tracking-derived values for circumferential strain may not be representative of mFS. Nevertheless, it should be noted that the equation used to estimate mFS makes assumptions about left ventricular geometry, as it presumes the external and internal contours are ellipsoidal in systole and diastole. However, there are currently no alternative validated methods. In addition, assumptions are made in the calculations that there is no loss in myocardial muscle volume during contraction even though there is likely to be a small reduction in volume as a result of vascular compression. Finally, through-plane motion was visually taken into account using our method but this phenomenon may degrade the accuracy of strain values generated from strain software in the short axis. Our relatively simple wall thickness measuring method, but using a gold-standard imaging technique, was reproducible. Further work is required to confirm whether similar techniques can be applied to other settings, potentially opening the possibility to explore pre-existing large cardiac imaging databases.

In light of the limitations, our calculations should only be considered as improved approximations and, in our view, the trends observed and concepts described are likely to be valid and are concordant with recent modeling studies(42).

Clinical implications

Hypertensive heart disease is often associated with a normal ejection fraction with the supposition that ventricular systolic function is also normal. We, however, have

shown that myocardial shortening and strain gradually decrease as wall thickness increases despite a maintained ejection fraction. We have shown that the absolute wall thickening is a major determinant of ejection fraction and that, in turn, absolute wall thickening is determined by both myocardial shortening and wall thickness. Myocardial shortening (and therefore function) and radial strain are reduced in the presence of left ventricular hypertrophy and normal ejection fraction. There is no compensatory increase in radial function that normalizes the ejection fraction when long-axis shortening is abnormal as previously thought. The ejection fraction is a poor measure of systolic function particularly in the setting of hypertrophic ventricles. Our findings have important clinical, physiological and prognostic implications.

Conclusion

Our study quantified, for the first time, the relationships between left ventricular myocardial shortening (longitudinal shortening, midwall fractional shortening and radial strain), end-diastolic wall thickness, absolute wall thickening, and ejection fraction. Our analyses provide additional novel insights into the mechanism by which hypertensive patients can have significant contractile dysfunction and a normal ejection fraction. We confirm previous work showing reduced long-axis shortening and midwall fractional shortening in the setting of a normal LVEF and indexed stroke volume. We demonstrate for the first time, using multiple linear regression analysis, that LAS, mFS and EDWT are each significantly and independently correlated with

LVEF. As EDWT increases, AWT is maintained which preserves LVEF and indexed SV despite falls in both long-axis and midwall fractional shortening. The maintenance of AWT is simply a result of increased EDWT and decreased myocardial fractional shortening.

Importantly, LVEF and the term systolic function are *not* synonymous and LVEF should not be used as an accurate index of LV function in the presence of LVH, without correction for the degree of LV end-diastolic wall thickness.

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Figure legends

Figure 1: Scatter graphs for hypertensive subjects and normotensive controls: A) showing the relationship of midwall fractional shortening to long-axis shortening, B) showing the relationship of radial strain to midwall fractional shortening and C) showing the relationship of radial strain to long-axis shortening.

Figure 2: Scatter graphs for hypertensive subjects and normotensive controls: A) showing the relationship of midwall fractional shortening to mean end-diastolic wall thickness, B) showing the relationship of long-axis shortening to mean end-diastolic wall thickness and C) showing the relationship of radial strain to mean end-diastolic wall thickness.

Figure 3: Scatter graphs for hypertensive and normotensive controls: A) showing the relationship of EDWT to ESWT, B) showing the relationship of EDWT to AWT, C) showing the relationship of EDWT to LVEF and D) showing the relationship of AWT to LVEF.

Tables

Table 1. Demographics and baseline clinical characteristics of hypertensive subjects and normotensive controls.

Table 2: Left ventricular volumetric, myocardial thickness and myocardial shortening data for hypertensive subjects and normotensive controls.

Table 3. Multiple linear regression analysis assessing the independent effects of end-diastolic wall thickness, long-axis shortening and midwall fractional shortening on LV ejection fraction.

Table 1: Demographics and baseline clinical characteristics of hypertensive subjects and normotensive controls.

	Controls (n = 32)	EDWT < 9 mm (n = 16)	EDWT 9 – 11 mm (n = 21)	EDWT >11 mm (n = 18)	P-value
Demographics					
Age (years)	49 ± 11	47 ± 15	55 ± 10	52 ± 11	= 0.112
Gender (% male)	56	13	76	78	< 0.001*
BMI (kg/m^2)	26 ± 5	29 ± 4	30 ± 4	32 ± 5	< 0.001†
Blood pressure					
Office SBP (mmHg)	126 ± 12	174 ± 27	172 ± 30	176 ± 32	< 0.001‡
Office DBP (mmHg)	77 ± 10	97 ± 16	100 ± 17	98 ± 17	< 0.001‡
ABPM SBP (mmHg)	…	154 ± 28	150 ± 12	168 ± 23	= 0.087
ABPM DBP (mmHg)	…	89 ± 18	90 ± 9	97 ± 13	= 0.309
ABPM MAP (mmHg)	…	108 ± 21	105 ± 10	115 ± 13	= 0.192
Anti-HTN medication					
No. anti-HTN medications	…	3 ± 2	4 ± 2	4 ± 2	= 0.266
ACEi (%)	…	38	71	39	= 0.057
ARB (%)	…	25	33	61	= 0.074
Calcium channel blocker (%)	…	44	62	61	= 0.496
Thiazide diuretic (%)	…	44	43	28	= 0.555
Loop diuretic (%)	…	13	5	17	= 0.494
K+ sparing diuretic (%)	…	75	86	72	= 0.856
Beta-blocker (%)	…	44	38	44	= 0.923

* EDWT < 9mm vs all other subgroups

† Controls vs EDWT 9 – 11mm and EDWT > 11mm, respectively

‡ Control vs all other subgroups

EDWT = end-diastolic wall thickness, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ABPM = 24-hour ambulatory blood pressure monitor, MAP = mean arterial pressure, anti-HTN = anti-hypertensive, ACEi = Angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker

Table 2: Left ventricular volumetric, myocardial thickness and myocardial shortening data for hypertensive subjects and normotensive controls.

	Controls (n = 32)	EDWT < 9 mm (n = 16)	EDWT 9 – 11 mm (n = 21)	EDWT >11 mm (n = 18)	P-value
LV volumetrics					
LV-EF (%)	64 ± 7	64 ± 6	67 ± 8	67 ± 11	= 0.422
Indexed EDV (ml/m^2)	77 ± 18	90 ± 11	83 ± 17	81 ± 17	= 0.109
Indexed ESV (ml/m^2)	29 ± 11	32 ± 8	28 ± 12	27 ± 11	= 0.586
Indexed SV (ml/m^2)	48 ± 12	56 ± 5	55 ± 10	55 ± 13	= 0.146
Myocardial mass & thickness					
Indexed LV mass (g/m^2)	58 ± 11	81 ± 20	88 ± 11	118 ± 16	< 0.001* †
RWT (mm/ml)	0.09 ± 0.02	0.11 ± 0.02	0.13 ± 0.03	0.14 ± 0.03	< 0.01‡ §
M/V (g/ml)	0.76 ± 0.13	0.91 ± 0.14	1.08 ± 0.20	1.45 ± 0.27	< 0.05¶ Δ
AWT (mm)	4.4 ± 0.9	5.4 ± 1.4	6.5 ± 1.2	6.8 ± 1.3	< 0.05* **
Myocardial shortening					
Long-axis shortening (-%)	16 ± 2	13 ± 3	11 ± 2	8 ± 2	< 0.005‡ †
Radial strain (%)	62 ± 15	68 ± 15	65 ± 12	52 ± 12	< 0.05††
mFS (-%)	18 ± 2	20 ± 2	18 ± 3	15 ± 3	< 0.001†

* Control vs all other subgroups

† EDWT > 11mm vs all other subgroups

‡ Controls vs EDWT 9 – 11mm and EDWT > 11mm, respectively

§ EDWT > 11mm vs EDWT < 9mm

¶ EDWT > 11mm vs all other subgroups

Δ EDWT 9 – 11mm vs all other subgroups

** EDWT < 9mm vs all other subgroups

†† EDWT > 11mm vs EDWT 9 – 11mm and EDWT < 9mm, respectively

EDWT = end-diastolic wall thickness, LV-EF = left ventricular ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume, LV = left ventricular, RWT = relative wall thickness, M/V = mass to volume ratio, AWT = absolute wall thickening, mFS = midwall fractional shortening

Table 3. Multiple linear regression analysis

Variable	Univariate coefficient of regression (95% CI)	p-value	Multivariate coefficient of regression (95% CI)	p-value
EDWT	0.91 (-0.01 – 1.82)	0.051	3.43 (2.60 – 4.26)	< 0.0001
LAS	0.86 (0.06 – 1.66)	0.035	2.01 (1.29 – 2.74)	< 0.0001
mFS	0.906 (0.23 – 1.59)	< 0.01	1.05 (0.26 – 1.84)	< 0.01

CI = confidence interval, EDWT = end-diastolic wall thickness, LAS = long-axis fractional shortening mFS = mid-wall fractional shortneing