Age, Gender and Hypertension-Related Remodeling Influences Left Ventricular Torsion Assessed by Tagged Cardiac Magnetic Resonance in Asymptomatic Individuals: The Multi-Ethnic Study of Atherosclerosis

Running title: Yoneyama et al.; Age and hypertension remodeling and torsion

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Abstract:

Background—The aim of the present study was to evaluate how torsion is influenced by left ventricular (LV) remodeling associated with age, gender and hypertension in a large community-based population.

Methods and Results—Myocardial shortening and torsion were assessed by tagged cardiac magnetic resonance (CMR) in 1478 participants without clinically apparent cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA). Torsion was defined as the difference between apical and basal rotation, divided by slice distance. In multivariable linear regression models, older age was associated with lower stroke volume (-3.6 ml/decade, p<0.001) and higher LV mass –to-volume ratio (0.03 g/ml/decade, p<0.001) along with lower circumferential shortening (-0.17%/decade, p<0.05). Torsion, however, was greater at older ages (0.14 °/decade, p<0.001) and in women (0.37°/cm vs. men, p<0.001). Hypertensive participants had higher LV mass and LV mass-to-volume ratio (15.5g and 0.07 g/ml, respectively, p<0.001 for both). Circumferential shortening was lower in hypertensive (-0.42%, p<0.01), whereas torsion was higher after adjustment for age and gender (0.17°/cm, p<0.05).

Conclusions—Older age is associated with lower LV volumes and greater relative wall thickness, and accompanied by lower circumferential myocardial shortening, whereas torsion is greater with older age. Hypertensive individuals have greater LV volumes and relative wall thickness and lower circumferential shortening. Torsion, however, is greater in hypertension independent of age and gender. Torsion may therefore represent a compensatory mechanism to maintain an adequate stroke volume and cardiac output in the face of progressively reduced LV volumes and myocardial shortening associated with hypertension and aging.

Key words: aging; cardiac magnetic resonance imaging; hypertension; remodeling; torsion
Introduction

Epidemiologic studies report that 40-50% of patients with heart failure have preserved ejection fraction (EF),¹,² and the prevalence of heart failure with preserved ejection fraction increases with age, especially in women.² Hypertension increases with age and represents one of the most important risk factors for heart failure, and increases wall thickness in response to elevated blood pressure (BP) as a compensatory mechanism to minimize wall stress.³ However, alterations of left ventricular (LV) structure and function associated with hypertension, independent of aging and gender are not entirely understood. These observations suggest that LV function changes with age and gender and hypertension may predispose to heart failure.

LV systolic deformation is a complex 3-dimensional phenomenon characterized by circumferential and longitudinal shortening, radial thickening as well as ventricular torque, for the purpose of ejecting blood from the left ventricle into the aorta under pressure. Critical to enabling LV systolic deformation, the orientation of myofibers changes smoothly across the LV wall from a left-handed helix in the subepicardium, circumferential orientation in the mid wall, to a right-handed helix in the subendocardium.⁴⁻⁶ During ejection, the subendocardial and subepicardial layers shorten simultaneously resulting in rotation of the apex and base in counterclockwise and clockwise directions respectively, when viewed from the apex.⁷ LV systolic torsion limits myocardial energy consumption and minimizes transmural fiber stress gradients and oxygen demand, resulting in a more efficient LV contraction.⁴,⁸⁻¹⁰ During isovolumic relaxation, torsional unfolding occurs and contributes to diastolic suction and reduction of LV pressure.⁵,⁷ Thus, torsion and unfolding are considered to be important indicators of cardiac performance, and LV hypertrophy and fibrosis associated with hypertension could result in significant alterations of LV torque. It has previously been suggested that higher
LV systolic wringing motion is found in the elderly, however, study sample sizes were small. Therefore, torsion has not been previously evaluated in a large cohort study. Also, the assessment of torsional deformation by echocardiography is methodologically challenging, because the distance between the basal and the apical short-axis slices is difficult to assess accurately by echocardiography.

Tagged cardiac magnetic resonance (CMR) provides accurate information on the slice distance and is commonly used as the gold standard method for cardiac deformation assessment. Since the rotation gradient has been reported to be nearly linear from the LV base to apex, torsion can therefore be accurately expressed as twist normalized by slice distance. The aim of the present study was to evaluate how torsion is influenced by LV remodeling associated with age, gender and hypertension in a large community-based multi-ethnic population.

Methods

Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective study designed to evaluate mechanisms that underlie development and progression of subclinical cardiovascular diseases among asymptomatic individuals in the general population. Details of the MESA study design have been previously described. In brief, between July 2000 and August 2002, 6,814 men and women who identified themselves as Caucasian, African-American, Hispanic, or Chinese and were 45 to 84 years old and free of clinically apparent cardiovascular disease were recruited. CMR was performed in 5004 participants as a part of the baseline examination. In this ancillary study, 1773 consecutive participants underwent tagged CMR studies at enrollment in six centers.
(Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California). The participants for the tagged CMR study were randomly selected. Of these, results of 295 (16.6%) participants were excluded due to technical issues; poor quality or missing slice acquisition either at the basal or apical level. A total of 1478 participants were thus enrolled in the study. All participants gave informed consent for the study protocol, which was approved by the institutional review boards of all MESA field centers as well as the CMR reading center.

MRI Protocol

Baseline CMR images were acquired using 1.5T MR scanners: Signa LX or CVi (GE Medical Systems, Waukesha, WI, USA), Symphony or Sonata (Siemens Medical Systems, Erlangen, Germany). After acquisition of standard scout images, two- and four-chamber cine MR images were acquired using steady state free precession imaging sequences. Short-axis cine images were then obtained with retrospective gating with a temporal resolution of ≤ 50 ms, from above the mitral valve plane to the LV apex. Three tagged short-axis slices (base to apex) were obtained with an image plane distance of 5-8mm. Parallel striped tags were prescribed in two orthogonal orientations (0° and 90°) using ECG-triggered fast gradient echo sequence with spatial modulation of magnetization. Parameters for tagged images were field of view, 40 cm; slice thickness, 8 to 10 mm; repetition time, 6 ms; echo time, 3.0 ms; flip angle, 10° to 12°; matrix 205x128 with Siemens scanner and 128x64 with GE scanners; temporal resolution, 20 to 41 ms; and tag spacing, 7 mm. The detailed protocol for the tagged CMR studies is previously described.6

MRI data analysis

LV end-systolic volume (LVESV) and end-diastolic volume (LVEDV), stroke volume (SV), LV
mass and LVEF were measured using commercially available software (MASS 4.2, MEDIS, Leiden, The Netherlands), as previously described. In short, the endocardial and epicardial myocardial borders were contoured using a semi-automated method. The difference between the epicardial and endocardial areas for all slices was multiplied by slice thickness and section gap and then multiplied by the specific myocardial density (1.04 g/ml) to determine LV mass. LV mass index (LVMI) was defined as LV mass divided by height to the power of 1.7. Mass-to-volume (M/V) ratio was calculated as LV mass divided by LVEDV. LV length at end diastole was calculated as the average distance from epicardial apex to the mitral valve insertion measured from the 2 and 4 chamber views. LV sphericity index at end diastole was calculated as the percentage of the LVEDV relative to the volume of a calculated sphere with the LV length. Higher index represents a more spherical shape of the ventricle.

**Rotation and Myocardial Strain Analysis**

Rotation and circumferential shortening were assessed in short axis tagged slices using HARP software (Harmonic Phase, Diagnosoft, Palo Alto, CA). Endocardial and epicardial contours were manually traced on the image corresponding to the remaining cardiac phases automatically. Tagged images and rotation, twist and torsion curves were assessed as illustrated in Figure 1A. Rotation (°) was defined for each short axis slice as average angular displacement in the LV midwall layer. During a normal systole, the basal rotates in a clockwise, and the apex in a counterclockwise direction when viewed from the LV apex. Normal apical rotation is by definition positive; twist (°) was calculated as the net difference between apical and basal rotation angle for each frame during the cardiac cycle using MATLAB® (The MathWorks, Natick, MA, USA). To normalize twist for slice distance, torsion (°/cm) was calculated by dividing peak systolic twist by the inter-slice distance h (cm). The distance h was calculated as...
the sum of one image plane thickness and the gap between planes. Circumferential shortening was represented by the absolute peak strain value and determined and averaged from 4 LV segments (anterior, lateral, inferior, and septal) from the LV midwall layer on the mid-ventricular slice. Positive numbers represent more shortening. The ratio between torsion and stroke volume (T/SV) was calculated to estimate the effect of torsion compensation with LV volume change, as showed by the slope during systole in torsion-volume loop as described by Notomi et al.\textsuperscript{25} Higher ratio represents higher torsion or compensation for lower SV. Torsion-to-circumferential shortening (T/CS) ratio was calculated to estimate the slope of the relation between torsion and circumferential strain during the ejection period, as described by Lumerns et al.\textsuperscript{26} This ratio describes subendocardial function, and dysfunction causes the ratio to increase.\textsuperscript{27}

**Risk factor measures**

Standardized questionnaires were used to obtain information about smoking history and medication usage, and for history of high BP, high cholesterol, and diabetes. Smoking was defined as current, former, or never. Participant’s height and weight were measured, and resting BP was measured 3 times with participants in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, GE Healthcare, Waukesha, Wisconsin). The average of the last 2 measurements was used. Pulse pressure was calculated as systolic BP minus diastolic BP. Total cholesterol and glucose levels were measured from blood samples obtained after a 12-h fast. Diabetes was defined as fasting glucose $\geq$126 mg/dl or use of hypoglycemic medication or insulin. Hypertension was classified according to the Seventh Report of the Joint National Committee on the Detection, Evaluation, and treatment of High Blood Pressure.\textsuperscript{28} Glomerular filtration rate (GFR) was estimated as previously described.\textsuperscript{29}

**Statistical analysis**
Summary statistics were presented using mean ± standard deviation for continuous variables, and percents for categorical variables. The nonparametric Wilcoxon-type trend tests for ordered groups were used to test the trends of continuously measured clinical characteristics, risk factors and CMR parameters across four age categories (44-54, 55-64, 65-74, and 75-84 years), and the chi-squares tests were used to evaluate the differences across the same age categories for categorical variables. The Wilcoxon rank-sum test was used to test the different distributions of torsion levels between man and woman.

Multivariable linear regression models were used to evaluate the effects of age, gender and hypertension on the CMR measurements. Specifically, different CMR measurements, such as LVESV, LVEDV, among others, were used as dependent variables and the potential covariates include age, gender, ethnicity, heart rate, smoking, systolic BP, total-cholesterol, glucose, GFR, and the use of medication to control hypertension, lipidemia or diabetes, among others. For regression models with torsion and circumferential shortening as dependent variables, LVEDV was included as a covariate in addition to the covariates used for other CMR measurements. In order to evaluate the relationship between LV measurements and gradations of BPs, the regression models included the same covariate adjustments with systolic BP excluded.

Standardized values were defined by dividing the differences between the observed values and the sample means by the corresponding standard deviations. Nonparametric regression estimates for the unknown curves were computed using LOWESS smoothing method and the local linear smoothing method. The Epanechnikov kernel and bandwidth=8 were used for the local linear smoothing method. Statistical analyses were performed using the STATA statistical software package (Version 11. College Station, Tex). A two-sided p-value <0.05 was considered statistically significant.
Results

The participants mean age was 65.0±9.7 years and 46.4% were women in the MESA baseline examination. Baseline characteristics according to age categories are displayed in Table 1. Systolic and pulse pressure were greater with increased age. Hypertension was more common among older participants. Of the total population, 14% were diabetic, 48% were hypertensive, and 48% had none of these conditions.

Torsion by age category and gender

The change in rotation from base to apex was approximately linear (Figure 1C) and the median distance from the basal to the apical slice was 3.0 cm (inter quartile range 3.0cm, 3.01cm). Overall, torsion was 3.9±1.3 °/cm and differed significantly between women and men (4.2±1.3 °/cm vs. 3.5±1.1 °/cm, P<0.001). Torsion was found to differ by gender in all age categories (Figure 2).

LV structure and function with age, gender and hypertension

Associations of LV structure and function with age, gender and hypertension in multivariable linear regression models are displayed in Table 2. Older age was associated with lower LVESV, LVEDV, SV and higher M/V ratio (-2.9, -6.5, -3.6ml/decade and 0.03g/ml respectively, all p<0.001). Circumferential shortening also was significantly lower with older age (-0.17%/decade, p<0.05) and torsion was greater with older age (0.14°/cm/decade p<0.001) after adjusting for traditional risk factors. But the association of torsion with age was no longer significant after adjustment for LVEDV in addition to traditional risk factors. The torsion/stroke volume ratio (T/SV), which can be interpreted as torsion compensation for lower SV, and the torsion/circumferential shortening ratio (T/CS ), interpreted as torsion relative to myocardial dysfunction, were significantly higher with older age.
LVESV and LVEDV were lower in women (-6.4 ml and -4.3 ml vs. men, respectively, both p<0.05) but SV did not differ between genders. The LV sphericity index as well as circumferential shortening were higher in women (3.3% and 1.05% vs. men, respectively, both p<0.001). Also, torsion was greater in women (0.37°/cm vs. men, p<0.001) and the gender differences remained highly significant after adjustment for LVEDV. There was significantly more torsion compensation (T/SV ratio) with lower SV in women (3.7°/cm*L vs. men, p<0.05) but no differences in myocardial dysfunction (T/CS ratio) were documented.

Hypertensive participants had higher LV mass and M/V ratio (15.5g and 0.07 g/ml, respectively both p<0.001). Circumferential shortening was lower in hypertensive MESA participants (-0.42%, p<0.01), whereas torsion was higher (0.17°/cm, p<0.05) compared to participants without hypertension. In hypertensive participants, greater myocardial dysfunction expressed by a greater T/CS ratio was observed, but there was no increase in the T/SV ratio.

The relation of LV structure and function with gradations of BPs is shown in Table 3. Higher systolic BP was associated with greater LVEDV (1.6ml/10mmHg, p<0.001) and higher LVM (3.2g/10mmHg, P<0.001). Torsion correlated positively with systolic BP (0.06°/cm/10mmHg, p<0.05) as well as pulse pressure (0.11 °/cm/10mmHg, p<0.05) but no correlation was found with diastolic BP. Also the associations of LV remodeling and torsion with increasing BP are displayed in Figure 3. The correlations between torsion and LV measurements are shown in Figure 4 and the influence of hypertension on torsion and age-related remodeling is displayed in Figure 5.

Reproducibility of LV torsion

To assess inter/ intra observer variability, 30 cases were randomly selected and then independently analyzed by 2 different observers. Inter/ intra-observer class correlation
coefficient was 0.94 (95%CI, 0.86-1.03) and 0.91 (95% confident interval; CI, 0.81-1.01), respectively.

**Discussion**

Torsion is directly related to myocardial fiber orientation, structure and function, and assessment of torsion has been introduced as an important component of LV mechanical behavior. The aim of the present study was to evaluate how LV remodeling associated with age, gender and hypertension influences LV torsion in a large community-based population. In the present study we demonstrate that 1) torsion is higher with increased age and in women; 2) torsion is associated with lower LV volumes and circumferential strain; 3) and that hypertension increases torsion independently of age and gender. Below, we first discuss the effects of age and gender on cardiac remodeling as a necessary pre-requisite for a full understanding of the influence of hypertension on LV mechanical behavior.

**Age and torsion**

It has been reported that LV twist is higher during infancy compared to adulthood.\textsuperscript{14} Torsion indexed to LV length, however, decreases until early adulthood because the LV elongates.\textsuperscript{14} Several smaller studies have suggested higher LV systolic wringing motion in older volunteers, as quantified by the twist magnitude measured by 2D-speckle tracking echocardiography,\textsuperscript{12} circumferential to longitudinal shear angles measured by 3D-tagged CMR,\textsuperscript{30, 31} as well as torsion indexed to LV length using Doppler tissue imaging.\textsuperscript{14} In the present study we demonstrate that torsion is higher with increased age, and we found that this was related to a gradual increment in apical rather than basal rotation in a community based population of individuals aged 45-84 years and without history of cardiovascular diseases. Ageing has been previously associated with
concentric remodeling, subendocardial dysfunction, and reduced elasticity of restoring forces of the LV, with consequent impaired LV recoil and untwist. The increase in peak systolic torsion appears to parallel age related progressive decline in subendocardial function suggesting that reduced subendocardial function could result in less endocardial opposition to the dominant epicardium, and thus enhanced torsion. Beyar et al, using a theoretical mathematical model of LV mechanics, reported a shortening gradient across the LV wall with greater shortening in the subendocardium relative to the subepicardial myocardial layers when torsion was not considered in the model. In that analysis, the introduction of torsion reduced the need for endocardial myofiber shortening, with consequent reduction in myocardial energy demand and oxygen consumption. The data suggest that torsion enables efficient LV systolic function without the need to augment endocardial shortening. In our study, the greater torsion seen in older participants could reflect a mechanism to compensate for lower myocardial shortening in order to maintain LVEF and SV. In this regard, according to the lever-arm theory, a greater radius difference between the endocardium and the epicardium (i.e. secondary to greater wall thickness relative to cavity radius) would result in increased torsion, because helical contraction of subendocardial and subepicardial muscle layers would counteract one another.

With increasing age, LV volumes become smaller and the M/V ratio is greater with enhanced radius difference between endo- and epicardium, leading to enhanced torsion. However, in the present study, torsion was not positively correlated with M/V ratio, suggesting that reduction of myocardial shortening rather than the pure effect of the lever-arm theory is responsible for the age related increase in torsion. Indeed, previous studies from our group have reported that myofiber shortening is progressively lower in MESA participants with increased LV mass/volume ratio due to the deleterious effects of concentric remodeling on myocardial...
contraction.\textsuperscript{33}

**Gender differences in LV torsion**

In the present study, torsion and circumferential shortening were higher in women compared to men. Several studies have shown that women have higher LVEF\textsuperscript{20,40} and greater systolic elastance than men reflecting greater myocardial contractility.\textsuperscript{34} In the normal ventricle, the helical fiber orientation enables systolic fiber rearrangement, and during contraction, the subendocardial fibers are sheared toward the LV cavity, thus enhancing LV wall thickening.\textsuperscript{4,7} During LV ejection, LV twist has been shown to be linearly and negatively related to LV volume.\textsuperscript{41} In the present study, we demonstrate that peak torsion is negatively related to both end-systolic and end-diastolic LV volumes. Hearts with smaller ventricles exhibit greater torsion, suggesting that increased torsion is required to maintain an adequate cardiac output in smaller hearts. On the other hand, fiber orientation is dependent on LV shape.\textsuperscript{42} In the present study, more spherical hearts were found in women compared to men before and after controlling for age, race, body size and traditional risk factors. A more spherical LV shape entails a more horizontal orientation of fiber angles, thus favoring torsion. Finally, another potential mechanism for gender differences in LV architecture and function was proposed by Redfield et al who reported that arterial stiffening was more pronounced with higher age and more in women than in men.\textsuperscript{34} Differences in arterial function might also underlie the observed gender differences in torsion shown in this study. However, further assessment is needed to evaluate such potential mechanisms for the observed gender differences in torsion.

**Hypertension and torsion**

In the present study, we demonstrated that hypertensive heart has higher LV mass and M/V ratio, and that hypertension is an independent predictor of increased torsion. In pressure overload
hypertrophy, increasing systolic wall stress leads to an increasing LV wall thickness as a compensatory mechanism to minimize wall stress. This pattern of concentric remodeling might enhance torsion because of the greater radius difference between the endocardium and the epicardium as proposed by the lever-arm theory as we discussed previously (see “age and torsion” section above). We also found that hypertensive individuals had a higher torsion to shortening (T/CS) ratio without differences in the torsion to stroke volume (T/SV) ratio. This suggests that enhanced torsion is not caused by reduced LV volumes, and that the mechanisms of increased torsion associated with hypertension may thus be at least in part different from that seen in association with aging alone. In hypertension, reduced circumferential shortening would also be expected to reduce torsion. A possible explanation is the increased afterload associated with hypertension. It has been reported that chronic afterload augmentation leads to increased torsion but reduced circumferential shortening in patients with aortic stenosis. The apparent contradiction involving increased torsion despite reduced circumferential shortening may be explained by increased endocardial myocardial oxygen consumption, as demonstrated in patients with increased arterial stiffening. Since the oblique fiber structure of the endocardium and epicardium are oriented in different directions, reduced subendocardial function may alter the balance between the opposing rotational forces and thus result in enhanced torsion. This may in fact represent a compensatory mechanism to maintain cardiac function in the face of increased afterload and/or vascular stiffness. Torsion has been found to be lower with increasing extent of transmural ischemia and/or infarction. Consequently, increased torsion in hypertensive hypertrophy can function as an early indicator of systolic myocardial dysfunction likely to be predominantly at the subendocardial level. However, as myocardial dysfunction progresses to involve the entire transmural extent of the LV wall,
torsion decreases, as documented in advanced decompensated hypertrophic cardiac disease.

Limitations

Approximately 17% of participants were excluded due to technical issues related to data acquisition and analysis. Even though tagged CMR is currently the reference method for assessment of LV deformation, the limitations of CMR and tagging will benefit from further technical development.

The median distance from the apical to basal slice was only 3 cm. Thus, the slices were relatively close to each other which may lead to underestimation of torsion. Therefore, our measurements of apical rotation may have slightly underestimated true apical rotation. We did not assess longitudinal strain and the spatial resolution of the tagging sequences used is also limited. Despite these technical limitations, this is still the largest myocardial MRI tagging study performed so far, allowing for unique investigation of cardiac mechanics at the population level.

Conclusions

Torsion assessed by tagged CMR is greater with hypertension, older age and in women compared to men in a large cohort of individuals without evidence of prior cardiovascular disease. Age is associated with lower LV volumes and greater relative wall thickness, and accompanied by lower circumferential myocardial shortening, whereas torsion increases with older age. The smaller LV volumes with greater contraction in women drive the greater torsion.

Hypertension is associated with greater LV volumes and relative wall thickness as well as with lower circumferential shortening. Torsion, however, is greater in hypertensive individuals independent of age and gender. Torsion may therefore represent a compensatory mechanism that maintains an adequate stroke volume and cardiac output in the face of progressively reduced LV volumes and myocardial shortening associated with ageing and/or hypertension.
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Conflict of Interest Disclosures: O.G. received support from the Fulbright Foundation, the Norwegian Medical Association and the Norwegian Research Council.

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**Table 1.** Baseline characteristics according to age categories.

<table>
<thead>
<tr>
<th>Age categories n=1478</th>
<th>45-54 years</th>
<th>55-64 years</th>
<th>65-74 years</th>
<th>75-84 years</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=260</td>
<td>n=355</td>
<td>n=573</td>
<td>n=290</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49.9 (2.9)</td>
<td>59.5 (2.8)</td>
<td>68.8 (2.8)</td>
<td>78.0 (2.5)</td>
<td>-</td>
</tr>
<tr>
<td>Ethnicity, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>71 (27.3)</td>
<td>104 (29.3)</td>
<td>171 (29.8)</td>
<td>93 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Chinese-American</td>
<td>24 (9.2)</td>
<td>49 (13.8)</td>
<td>94 (16.4)</td>
<td>41 (14.1)</td>
<td>0.021</td>
</tr>
<tr>
<td>African-American</td>
<td>96 (36.9)</td>
<td>94 (26.5)</td>
<td>151 (26.3)</td>
<td>68 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>69 (26.5)</td>
<td>108 (30.4)</td>
<td>157 (27.4)</td>
<td>88 (30.3)</td>
<td></td>
</tr>
<tr>
<td>Women, n(%)</td>
<td>109 (41.9)</td>
<td>182 (51.3)</td>
<td>260 (45.4)</td>
<td>135 (46.6)</td>
<td>0.126</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.2 (9.4)</td>
<td>165.9 (10.1)</td>
<td>165.3 (9.9)</td>
<td>163.7 (10.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.2 (5.0)</td>
<td>28.2 (4.8)</td>
<td>27.5 (4.6)</td>
<td>27.1 (4.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>117.7 (16.1)</td>
<td>124.2 (18.6)</td>
<td>130.5 (21.3)</td>
<td>136.5 (21.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>73.1 (9.8)</td>
<td>72.9 (10.0)</td>
<td>71.9 (10.6)</td>
<td>69.6 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>44.5 (10.4)</td>
<td>51.3 (13.7)</td>
<td>58.6 (16.8)</td>
<td>66.9 (18.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>61.9 (8.4)</td>
<td>63.8 (9.6)</td>
<td>62.3 (9.7)</td>
<td>61.8 (9.9)</td>
<td>0.180</td>
</tr>
<tr>
<td>Hypertension, n(%)</td>
<td>61 (23.5)</td>
<td>142 (40.0)</td>
<td>321 (56.0)</td>
<td>181 (62.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, n(%)</td>
<td>17 (6.5)</td>
<td>49 (13.8)</td>
<td>95 (16.6)</td>
<td>49 (17.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoker, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>124 (48.1)</td>
<td>187 (53.0)</td>
<td>287 (50.3)</td>
<td>168 (58.3)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>88 (34.1)</td>
<td>108 (30.6)</td>
<td>238 (41.7)</td>
<td>104 (36.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current</td>
<td>46 (17.8)</td>
<td>58 (16.4)</td>
<td>46 (8.1)</td>
<td>16 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>195.2 (38.5)</td>
<td>198.7 (35.3)</td>
<td>193.8 (33.9)</td>
<td>190.6 (34.6)</td>
<td>0.025</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>88.8 (14.3)</td>
<td>84.2 (17.3)</td>
<td>78.8 (17.5)</td>
<td>72.0 (17.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

 Values are means (standard deviation).
Table 2. Association of age, gender and hypertension with LV measurements

<table>
<thead>
<tr>
<th></th>
<th>Age (decade)</th>
<th>Gender (reference; women)</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV, ml</td>
<td>-2.9 (-3.8, -2.0) ‡</td>
<td>6.4 (4.1, 8.7) ‡</td>
<td>1.7 (0.02, 3.3) *</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>-6.5 (-8.1, -4.9) ‡</td>
<td>4.3 (0.2, 8.4) *</td>
<td>5.9 (3.0, 8.8) ‡</td>
</tr>
<tr>
<td>SV, ml</td>
<td>-3.6 (-4.7, -2.6) ‡</td>
<td>-1.9 (-4.6, 0.8)</td>
<td>4.2 (2.3, 6.2) ‡</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.7 (0.2, 1.1) †</td>
<td>-4.2 (-5.3, -3.1) ‡</td>
<td>0.4 (-0.4, 1.1)</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>-4.2 (-6.0, -2.4) ‡</td>
<td>22.7 (18.1, 27.3) ‡</td>
<td>15.5 (12.2, 18.8) ‡</td>
</tr>
<tr>
<td>M/V ratio, g/ml</td>
<td>0.03 (0.02, 0.05) ‡</td>
<td>0.16 (0.12, 0.20) ‡</td>
<td>0.07 (0.05, 0.10) ‡</td>
</tr>
<tr>
<td>LV sphericity index, %</td>
<td>-0.03 (-0.4, 0.3)</td>
<td>-3.3 (-4.2, -2.3) ‡</td>
<td>0.1 (-0.6, 0.7)</td>
</tr>
<tr>
<td>Circumferential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shortening, %</td>
<td>-0.17 (-0.32, -0.02)*</td>
<td>-1.05 (-1.44, 0.66) ‡</td>
<td>-0.42 (-0.70, -0.14) †</td>
</tr>
<tr>
<td>Torsion, °/cm</td>
<td>0.14 (0.07, 0.21) ‡</td>
<td>-0.37 (-0.56, -0.19) ‡</td>
<td>0.17 (0.04, 0.30) *</td>
</tr>
<tr>
<td>T/SV ratio, °/cm*L</td>
<td>4.2 (3.0, 5.4) ‡</td>
<td>-3.7 (-6.7, -0.7) *</td>
<td>-0.001 (-0.003, 0.001)</td>
</tr>
<tr>
<td>T/CS ratio, °/cm/%</td>
<td>0.01 (0.005, 0.014) ‡</td>
<td>-0.01 (-0.02, 0.002)</td>
<td>0.02 (0.01, 0.02) ‡</td>
</tr>
</tbody>
</table>

Coefficients represent change in the dependent variables per 1 decade increase in age or difference in the dependent variable for men compared to women, or hypertension with adjustments for multiple variables.

Age was adjusted for gender, ethnicity, height, heart rate, smoking, systolic BP, total-cholesterol, glucose, GFR, and the use of medication to control hypertension, lipidemia or diabetes.

Gender was adjusted for age, ethnicity, height, heart rate, smoking, systolic BP, total-cholesterol, glucose, GFR, and the use of medication to control hypertension, lipidemia or diabetes.

Hypertension was adjusted for age, gender, ethnicity, height, heart rate, smoking, total-cholesterol, glucose, GFR, and the use of medication to control lipidemia or diabetes.

*p <0.05, †p<0.01, ‡p<0.001

Table 3. Association of LV measurements with gradation of BP.

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP, mmHg</th>
<th>Diastolic BP, mmHg</th>
<th>Pulse pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV, ml</td>
<td>0.4 (-0.01, 0.8)</td>
<td>1.2 (0.4, 2.0) †</td>
<td>0.2 (-0.3, 0.7)</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>1.6 (0.9, 2.3) ‡</td>
<td>1.5 (0.1, 3.0) *</td>
<td>2.3 (1.4, 3.3) ‡</td>
</tr>
<tr>
<td>SV, ml</td>
<td>1.2 (0.8, 1.7) ‡</td>
<td>0.4 (-0.6, 1.3)</td>
<td>2.1 (1.5, 2.7) ‡</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.1 (-0.1, 0.3)</td>
<td>-0.6 (-0.9, -0.2) †</td>
<td>0.5 (0.2, 0.8) ‡</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>3.2 (2.4, 4.0) ‡</td>
<td>4.9 (3.3, 6.6) ‡</td>
<td>3.7 (2.6, 4.8) ‡</td>
</tr>
<tr>
<td>M/V ratio, g/ml</td>
<td>0.01 (0.003, 0.02) †</td>
<td>0.02 (0.01, 0.04) ‡</td>
<td>0.01 (-0.003, 0.001)</td>
</tr>
<tr>
<td>LV sphericity index, %</td>
<td>0.02 (-0.15, 0.18)</td>
<td>-0.12 (-0.45, 0.21)</td>
<td>0.008 (-0.14, 0.30)</td>
</tr>
<tr>
<td>Circumferential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shortening, %</td>
<td>-0.06 (-0.13, 0.00)</td>
<td>-0.29 (-0.43, -0.15) ‡</td>
<td>0.01 (-0.08, 0.10)</td>
</tr>
<tr>
<td>Torsion, °/cm</td>
<td>0.06 (0.03, 0.10)*</td>
<td>0.01 (-0.06, 0.07)</td>
<td>0.11 (0.07, 0.16) *</td>
</tr>
<tr>
<td>T/SV ratio, °/cm*L</td>
<td>-0.01 (-0.54, 0.51)</td>
<td>-0.67 (-1.74, 0.41)</td>
<td>0.27 (-0.44, 0.99)</td>
</tr>
<tr>
<td>T/CS ratio, °/cm/%</td>
<td>0.004 (0.003, 0.01) ‡</td>
<td>0.003 (-0.0005, 0.007)</td>
<td>0.01 (0.004, 0.01) ‡</td>
</tr>
</tbody>
</table>

Coefficients represent change in dependent variables per 10 mmHg increase in BP with adjustments for multiple variables; age, gender, ethnicity, height and heart rate, smoking, total-cholesterol, glucose, GFR, and the use of medication to control hypertension, lipidemia or diabetes.

*p <0.05, †p<0.01, ‡p<0.001
Figure Legends:

**Figure 1.** Definition of rotational deformation and a sample of torsion curve. A. Tagged CMR short axis images and definition of rotational deformation. Torsion (°/cm) was calculated by dividing peak systolic LV twist by the inter-slice distance h (cm). B. Representative rotation, twist and torsion curves. C. The change in rotation by distance from basal to apex was as close to linear in the participants with 3 cm gap.

**Figure 2.** Gender specific torsion with age. Compared with younger ages, older women and men were more likely to have increased torsion (both tests for trends p<0.001). Torsion differed significantly between women and man in each age category (all p <0.001).

**Figure 3.** LV remodeling and torsion with gradation of BPs. Systolic BP increased LV mass/height$^{1.7}$ (A), Mass/volume ratio (B) and torsion (C). Pulse pressure was associated with torsion (D). Red, green and blue dots represents participants with medication for BP, all participants and participants without medication for BP (n=873), respectively.

**Figure 4.** The correlations between the torsion and rotation, ejection fraction and LV volume by CMR. There was a strong correlation between apical rotation and torsion (r=0.75, p<0.001). However the correlation between basal rotation and torsion was statistically significant but relatively weak (r=-0.21, p<0.001). 222 cases were excluded due to positive rotation at basal slice (A). Torsion correlated negatively with LVESV index (r=-0.44, p<0.001), LVEDV index (r=-0.30, p<0.001) (B), positively with LVEF (r=0.44, p<0.001) (C). Torsion correlated positively with circumferential shortening in all participant subgroups, and at any level of
circumferential shortening, the torsion was higher in hypertensive participants (n=705) compared to participants without hypertension (D). Torsion correlated negatively with LV mass/height\(^{1.7}\) in all groups, and torsion was higher in hypertensive participants at any level of LV mass/height\(^{1.7}\) (E). M/V ratio correlated negatively with circumferential shortening and the relations with torsion was nonlinear (F).

**Figure 5.** The influence of hypertension on torsion and age-related remodeling. Age was inversely associated with LVMI and positively with M/V ratio (A), and inversely with SV and circumferential shortening. However, torsion was positively correlated with age, along with LVEF (B). In hypertensive participants, remodeling was characterized primarily by an upward parallel shift compared to non hypertensive participants. At any age, hypertensive participants had higher LVMI and M/V ratio (C). Torsion was higher despite lower circumferential shortening compared to participants without hypertension (D). SV was lower with age, but was maintained to a larger degree in hypertensive individuals, indicating that increased torsion in part compensates for the reduced circumferential shortening in individuals with hypertension (E). CS; circumferential shortening, HT; hypertension, LVEF; left ventricular ejection fraction, LVMI; left ventricular mass index, M/V; mass/volume, SV; stroke volume
Rotation (°) = Angular displacement

Diastole  Systole

Base

Apex

Twist (°) = Apical rotation – Basal rotation

LV torsion (°/cm) = peak systolic Twist/h

C

mean ± SD

Slice gap, cm
LV torsion, °/cm

Age categories, years

45-54  55-64  65-74  75-84

Women ♀
Men ♂

mean ± 1 SD

* p < 0.001 for gender difference
† p < 0.001 for trend across age categories
A

LV mass / height $1.7 \text{ g/m}^2$

Systolic blood pressure, mmHg

B

Mass/volume ratio, g/ml

Systolic blood pressure, mmHg

C

Torsion, $^\circ$/cm

Systolic blood pressure, mmHg

D

Torsion, $^\circ$/cm

Pulse pressure, mmHg

- Red circle: Medication for blood pressure
- Green: All participants
- Blue circle: No medication for blood pressure
Age, Gender and Hypertension-Related Remodeling Influences Left Ventricular Torsion Assessed by Tagged Cardiac Magnetic Resonance in Asymptomatic Individuals: The Multi-Ethnic Study of Atherosclerosis
Kihei Yoneyama, Ola Gjesdal, Eui-Young Choi, Colin O. Wu, W. Gregory Hundley, Antoinette S. Gomes, Chia-Ying Liu, Robyn L. McClelland, David A. Bluemke and Joao A.C. Lima

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