Influence of White-Coat Hypertension on Left Ventricular Deformation 2- and 3-Dimensional Speckle Tracking Study

Marijana Tadic, Cesare Cuspidi, Branislava Ivanovic, Irena Ilic, Vera Celic, Vesna Kocijancic

Abstract—We sought to compare left ventricular deformation in subjects with white-coat hypertension to normotensive and sustained hypertensive patients. This cross-sectional study included 139 untreated subjects who underwent 24-hour ambulatory blood pressure monitoring and completed 2- and 3-dimensional examination. Two-dimensional left ventricular multilayer strain analysis was also performed. White-coat hypertension was diagnosed if clinical blood pressure was elevated and 24-hour blood pressure was normal. Our results showed that left ventricular longitudinal and circumferential strains gradually decreased from normotensive controls across subjects with white-coat hypertension to sustained hypertensive group. Two- and 3-dimensional left ventricular radial strain, as well as 3-dimensional area strain, was not different between groups. Two-dimensional left ventricular longitudinal and circumferential strains of subendocardial and mid-myocardial layers gradually decreased from normotensive control to sustained hypertensive group. Longitudinal and circumferential strains of subepicardial layer did not differ between the observed groups. We concluded that white-coat hypertension significantly affects left ventricular deformation assessed by 2-dimensional traditional strain, multilayer strain, and 3-dimensional strain. (Hypertension. 2016;67:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.06822.)

Key Words: ambulatory blood pressure monitoring ■ left ventricle ■ three-dimensional echocardiography ■ two-dimensional speckle tracking ■ white-coat hypertension

The effect of white-coat hypertension (WCH), a condition known by increased office blood pressure (BP) and normal ambulatory BP, on target organ damage, as well as on cardiovascular morbidity and mortality, has been a topic of discussion for >2 decades.1 Investigations also revealed that WCH significantly increased long-term risk of sustained arterial hypertension.2 Considering the fact that WCH phenomenon occurs in 13%–32% of subjects with increased office BP3 and findings that show elevated mortality risk in these individuals, it is of a great importance to determine cardiac changes that potentially could explain increased mortality.

Previous studies showed that WCH is associated with increased left ventricular (LV) mass and LV diastolic deterioration.4,5 However, there are also investigations that disagree.6,7 Our recent meta-analysis included 7382 untreated adult patients (2493 normotensive, 1705 WCH, and 3184 hypertensive individuals) and demonstrated that WCH is associated with structural and functional LV alterations.8 There is no available study that investigates cardiac mechanics in WCH subjects.

We sought to compare LV structure, function, and mechanics between patients with WCH and sustained hypertension and normotensive participants. Traditional 2-dimensional (2DE) and multilayer strain analysis, as well as 3-dimensional (3DE) strain analyses, were used for the investigation of LV mechanics.

Methods
This cross-sectional study included 139 untreated subjects referred to our outpatient clinic because of ambulatory BP monitoring in period from August 2014 to August 2015. Subjects with heart failure, coronary artery disease, previous cerebrovascular insult, atrial fibrillation, congenital heart disease, valvular heart disease, neoplastic disease, cirrhosis of the liver, kidney failure, sleeping disorders, obesity, or endocrinology diseases, including type 2 diabetes mellitus, were excluded from the study. For full details, see online-only Data Supplement and Figure S1 in the online-only Data Supplement.

Anthropometric measures and laboratory analyses were taken from all the subjects included in the study. Body mass index and body surface area were calculated for each patient. The study was approved by the local Ethics Committee, and informed consent was obtained from all the participants.

BP Measurement
Clinical arterial BP values were obtained in the morning hours by measuring the average value of the 3 consecutive measurements in the sitting position. BP was obtained in at least 2 separate occasions.
All the participants underwent a 24-hour BP monitoring, according to the current guidelines. For full details, see online-only Data Supplement.

WCH was defined as clinical systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg measured in at least 2 separate occasions associated with a 24-hour ambulatory systolic BP <130 mm Hg and diastolic BP <80 mm Hg, whereas those with sustained hypertension had clinical systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg, together with a 24-hour ambulatory systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg.

**Echocardiography**

Echocardiographic examinations were performed with a Vivid 7 ultrasound machine (GE Healthcare, Horten, Norway). 2DE LV and left atrial measurements followed standard recommendations. Transmirtal diastolic flow velocities were obtained by pulsed-wave and tissue Doppler. Specckle-tracking analysis for LV longitudinal strain was obtained in 2-chamber, long-axis and 4-chamber views. 2DE circumferential strain and radial strain, as well as corresponding strain rates, were assessed at the level of papillary muscles. Multilayer longitudinal and circumferential strains were determined by modified 2DE strain software. For full details, see online-only Data Supplement. 3DE LV analysis was obtained from an apical approach. For full details, see online-only Data Supplement.

**Statistical Analysis**

Continuous variables were presented as mean±standard deviation and were compared by the analysis of equal variance because they showed normal distribution confirmed by the Kolmogorov–Smirnov test. Bonferroni post hoc analysis was used for the comparison between different groups. Differences in proportions were compared by the χ² test. Intra- and interobserver variability for LV mechanical strains were determined by modified 2DE strain software. For full details, see Table S1.

**Results**

The observed groups were of similar age, sex distribution, body mass index, body surface area, heart rate, and smoking habits (Table 1). Clinical BPs were significantly higher in patients with WCH and sustained hypertension than in normotensive subjects. On the other hand, 24-hour, daytime, and nighttime BPs were significantly higher in patients with sustained hypertension than in other 2 groups (Table 1). Importantly, BP values obtained by 24-hour BP monitoring were similar between normotensive and WCH subjects.

**Conventional Echocardiographic Measurements**

LV diameters were similar among the groups, whereas LV posterior wall thickness, LV mass index, relative wall thickness, and left atrial volume index gradually increased from normotensive throughout WCH to hypertensive patients (Table 2). LV 2DE ejection fraction was similar between all 3 groups. However, midwall fractional shortening was lower in sustained hypertensive subjects than in controls (Table 2). Mitral E/A ratio decreased, whereas E/e' increased, progressively from normotensive to sustained hypertensive subjects (Table 2).

**2DE and 3DE Strain Analysis**

2DE LV longitudinal and circumferential strains gradually decreased from normotensive controls across WCH subjects to sustained hypertensive group (Table 3). Longitudinal and circumferential mechanical functions during systole and early and late diastole were similar between normotensive subjects and WCH patients, whereas individuals with sustained hypertension had significantly worsened LV mechanics during the...
whole cardiac cycle (Table 3). Radial mechanics was mostly similar between the groups. LV twist was higher in hypertensive subjects (Table 3).

Longitudinal and circumferential strains of subendocardial and mid-myocardial layers gradually decreased from normotensive control to sustained hypertensive group (Table 3). Subepicardial layer strains did not differ between the observed groups. 3DE longitudinal and circumferential strain decreased gradually and significantly from control to hypertensive individuals (Table 3). 3DE radial and area strains were lower in hypertensive patients than in normotensive subjects, but there was no difference between WCH individuals and other 2 groups (Table 3).

### Intra- and Interobserver Variability

Mean intra- and interobserver variability for multilayer strain measurements are presented in Table S1. Bland–Altman analysis showed a very good reproducibility, especially for subendocardial and mid-myocardial strains.

### Discussion

Deterioration of 2DE and 3DE multidirectional strain in hypertensive population has been shown previously.11,12 Our findings regarding patients with sustained hypertension are in line with the previous studies. However, for the first time, we provided the new insight to LV mechanical function in WCH patients. Our results revealed that longitudinal and circumferential LV functions are significantly deteriorated in WCH subjects and, particularly, in subendocardial and mid-myocardial layers. Kim et al have recently published a study that demonstrated significantly reduced longitudinal strain of all 3 LV myocardial layers (subepicardial, midendocardial, and subendocardial) in hypertensive subjects.13 The arterial hypertension increases the load on the cardiac chambers, and this could be normalized with the wall thickening or chamber lumen dilatation. Thus, structural cardiac remodeling in hypertension results in an increase in LV mass and LV hypertrophy.14 These alterations increase myocardial stiffness and decrease LV function. However, the load is not the same during the whole cardiac cycle, and the contribution of each layer is different. Therefore, in systole, endomyocardial layer is thickened and endocardium–epicardium gradient is reduced.15

Previous study revealed that subendocardium is the most vulnerable in hypertensive subjects and showed that the ratio between endomyocardial and epimyocardial radial strain is highest among hypertensive individuals.16 LV structural remodeling considers LV hypertrophy that includes myocytes hypertrophy, fibroblasts proliferation, and interstitial changes. These structural changes have different influence to each myocardial layer and occur from subendocardium to epicardium, which was demonstrated in animal model of arterial hypertension.17 The authors also detected relationship between reduced longitudinal strain and subendocardial layer fibrosis and proposed longitudinal strain as a useful marker for the risk stratification in hypertensive patients. Our findings showed that longitudinal and circumferential strains of subendocardial and mid-myocardial layers were affected in WCH subjects. This indicates that deterioration of LV mechanical function is spreading from endocardium to epicardium even in subjects who do not have sustained BP elevation.

Our findings revealed progressive deterioration of 2DE and 3DE LV longitudinal and circumferential functional mechanics from control subjects, throughout WCH participants, to hypertensive patients; which implies that longitudinal and circumferential function are the most sensitive to pressure

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**Table 2. Echocardiographic Parameters of Left Ventricular Structure and Function in the Study Population (2-Dimensional Echocardiography Evaluation)**

<table>
<thead>
<tr>
<th>Echocardiographic Parameters</th>
<th>Normal BP (n=45)</th>
<th>WCH (n=44)</th>
<th>HTA (n=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD, mm</td>
<td>48.1±4.2</td>
<td>48.6±4.4</td>
<td>49.6±4.8</td>
<td>0.254</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>30.4±3.3</td>
<td>30.7±3.5</td>
<td>31.8±3.9</td>
<td>0.136</td>
</tr>
<tr>
<td>IVS, mm</td>
<td>9.1±1</td>
<td>9.6±1.2</td>
<td>10.5±1.3†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PWT, mm</td>
<td>8.9±1</td>
<td>9.5±1.1</td>
<td>10.4±1.1</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>RWT</td>
<td>0.37±0.03</td>
<td>0.39±0.03</td>
<td>0.42±0.03</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>28.5±3.3</td>
<td>30.6±3.5</td>
<td>32.5±4.1</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>LVM, g</td>
<td>148±14</td>
<td>164±17</td>
<td>191±22</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>78±7.2</td>
<td>85±8.6</td>
<td>98±10.8</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>EF, %</td>
<td>63±3</td>
<td>64±3</td>
<td>63±4</td>
<td>0.275</td>
</tr>
<tr>
<td>Midwall FS, %</td>
<td>19±4</td>
<td>18±4</td>
<td>17±3</td>
<td></td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.24±0.27</td>
<td>1.10±0.22</td>
<td>0.95±0.24</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>DT, ms</td>
<td>180±20</td>
<td>197±24</td>
<td>215±23</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>E/e’</td>
<td>6.2±1.9</td>
<td>7.7±1.8</td>
<td>9±2.2</td>
<td>&lt;0.001§</td>
</tr>
</tbody>
</table>

A indicates late diastolic mitral flow (pulse Doppler); BP, blood pressure; DT, deceleration time; E, early diastolic mitral flow (pulsed Doppler); e’, average of the peak early diastolic relaxation velocity of the septal and lateral mitral annulus (tissue Doppler); EF, ejection fraction; FS, fractional shortening; HTA, hypertension; IVS, interventricular septum; LAVI, left atrial volume index; LVMi, left ventricular mass index; LVEDD, left ventricle end-diastolic dimension; LVESD, left ventricle end-systolic dimension; PWT, posterior wall thickness; RWT, relative wall thickness; and WCH, white-coat hypertension.

*P<0.01 vs normal BP. †P<0.01 vs WCH. ‡P<0.05 for all comparisons. §P<0.01 for all comparisons. ||P<0.05 vs normal BP.
overload in WCH and sustained hypertension. However, the reduction of layer-specific strain corresponds with the earliest stages of LV hypertrophy, which is why this analysis is expected to recognize the first signs of myocardial functional impairment in various myocardial diseases.

LV twist gradually decreased from controls to hypertensive patients in our study without significant difference between normotensives and WCH subjects. This has been reported previously in studies that investigated hypertensive patients. Increased LV twist seems to be a compensatory mechanism in hypertensive patients during the earlier stages (concentric remodeling and concentric hypertrophy). However, this hypertorsion is certainly lost in the patients with long-lasting hypertension (eccentric hypertrophy). This has been recently confirmed by Ikonomidis et al who reported significant relationship between LV twisting/untwisting and reduced exercise capacity and neurohumoral activation in hypertensive patients and suggested that a fibrotic process may be the common link between vascular dysfunction and abnormal myocardial deformation.

**Limitations**

The present study has several limitations. The investigation included a relatively small number of subjects. However, we succeeded to show an important difference between different groups. 3DE assessment of LV structure and function could be significantly influenced by the quality of ultrasound images. There are several definitions of WCH that could partly interfere the comparison of our results with the other studies. Furthermore, we could not determine the causal relationship between WCH and LV mechanics because this represents a cross-sectional study. The WCH subjects analyzed in this study were referred patients and might therefore not be representative for low-risk WCH subjects in the general population.
Perspectives
The present study revealed impairment of LV mechanical function in WCH and sustained hypertensive patients. Multidirectional strain is progressively deteriorated from normotensive controls, across WCH subjects, to hypertensive patients. Subendocardial and mid-myocardial layers are particularly impacted by increased load in WCH and sustained hypertension, suggesting that LV remodeling in hypertensive patients might develop in the endocardium–epicardium direction. Further longitudinal studies are necessary to determine the possible predictive value of LV mechanics in WCH individuals.

Disclosures
None.

References

Novelty and Significance

What Is New?

- Two-dimensional and 3-dimensional left ventricular longitudinal and circumferential strains gradually decreased from normotensive controls across white-coat hypertensive subjects to sustained hypertensive group.
- Two-dimensional longitudinal and circumferential strains of subendocardial and mid-myocardial layers gradually decreased from normotensive control to sustained hypertensive group.

What Is Relevant?

- White-coat hypertension affects predominantly subendocardial and mid-myocardial longitudinal and circumferential layer strain.

Summary

White-coat hypertension significantly affects left ventricular deformation assessed by 2-dimensional traditional strain, 2-dimensional multilayer strain, and 3-dimensional strain.
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The influence of white-coat hypertension on left ventricular deformation: two- and three-dimensional speckle tracking study

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Potential conflict of interest: NONE

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Short title: White-coat hypertension and left ventricle
Methodology

This cross-sectional study included 139 untreated subjects referred to our outpatient clinic due to ambulatory blood pressure monitoring in period between August 2014 and August 2015. The whole process of selection of the patients is presented on the Figure S1. Shortly, during studied period 2120 subjects were referred to our outpatient clinic, 1706 individuals have already been treated with some of antihypertensive drugs and 217 patients were excluded due to the different reasons listed in the Figure S1. All comorbidities that are mentioned in the Figure S1 have already been described in some previous studies as conditions that could significantly change LV strain. There were also patients who had two or more of these comorbidities. However, these patients were classified according to the most prominent clinical feature. All exclusion criteria were predefined. From 197 subjects who fulfilled the inclusion criteria, 15 individuals had poor quality echocardiographic examination or 24-hour ambulatory BP monitoring and 13 refused to participate mainly because they did not want to perform additional tests (stress testing due to ECG changes) or had the personal reasons for refusal. Finally, 44 WCH subjects aged 39 to 62 years were included in the study. In order to avoid the potential influence of age, 30 healthy subjects and hypertensive patients out of this age range were excluded from the final analysis. The patients with masked hypertension were excluded due to exclusion criteria or disparity with age range. At the end, we included 45 individuals with normal BP, 44 WCH subjects and 50 patients with sustained arterial hypertension.

Clinic arterial BP values were obtained by E-mega aneroid manometer (Riester, Jungingen, Germany) in the morning hours by measuring the average value of the three consecutive measurements in the sitting position, taken within an interval of five minutes, after the subject had rested for at least five minutes in that position. BP was obtained in at least two separate occasions over a period of 1-2 months. The clinic BP was determined as the average of three measurements during each visit, and than the final value of clinic BP was the average value of two different visits. BP was measured by trained nurses. Both measurements occurred before ambulatory BP monitoring. The size of cuff of manometer or ambulatory BP device was adjusted to the patients.

All the participants underwent a 24-hour BP monitoring. The noninvasive 24-hour ambulatory BP monitoring was performed by Schiller BR-102 plus system (Schiller AG, Baar, Switzerland) according to the current guidelines /1/. The device was programmed to obtain BP readings at 20-min intervals during the day (07:00-23:00 o’clock) and at 30-min intervals during the night (23:00-07:00 o’clock). The patients were asked to keep the diary about their usual daily activities, including wake up time and bedtime. Nighttime BP was defined as the average of BPs from the time when the patients went to bed until the time they got out of the bed, and daytime BP as the average of BPs recorded during the rest of the day. The recording was then analyzed to obtain a 24-hour, daytime and nighttime average systolic BP, diastolic BP, mean BP, and heart rates. When the readings exceeded at least 70% of the total readings programmed for the testing period, the recording was considered valid and satisfactory.

Echocardiography

Echocardiographic examination was performed by a Vivid 7 ultrasound machine (GE Healthcare, Horten, Norway). Three experienced echocardiographers (MT, II, VC) performed exams and MT performed off-line analyses. However, the
other persons were responsible for the selection of subjects based on 24-hour ambulatory BP monitoring (BI, VK), thus echocardiographers did not have information regarding subjects’ characteristics (BP measurements). The values of all 2DE parameters were obtained as the average value of three consecutive cardiac cycles. LV ejection fraction was assessed by the biplane method. LV midwall fractional shortening has been also calculated. LV mass was calculated by using the formula of the American Society of Echocardiography, and indexed for body surface area. Left atrial volume was measured by the biplane method in 4- and 2-chamber views and indexed for BSA. Transmitral Doppler inflow and tissue Doppler velocities were obtained in the apical 4-chamber view. Pulsed Doppler measurements included the ratio between the transmitral early and late diastolic peak flow velocity (E/A). Tissue Doppler imaging was used to obtain LV myocardial velocities at the septal and lateral segment of the mitral annulus during early and late diastole (e’ and a’), and systole (s).

2DE LV strain analysis

2DE strain imaging was performed by using three consecutive cardiac cycles \(^/2/\), and a commercially available software (EchoPAC 113, GE-Healthcare, Horten, Norway) was used for 2DE strain analysis. The 2DE longitudinal strain was calculated in 2-chamber, long axis and 4-chamber views. 2DE circumferential strain and radial strain, as well as corresponding strain rates, were assessed at the level of papillary muscles. At least 2 echocardiographic clips of each view that will be used in strain analysis were taken from each participant. Using the same software we determined the rotation of the base and apex, and calculated LV twist value.

Multilayer longitudinal and circumferential strains were determined by modified 2DE strain software. The modified 2DE strain speckle tracking includes the delineation of the endocardial border, similarly to traditional 2DE strain, but instead of a single chain of nodes, the myocardial wall is automatically defined with multiple chains of nodes, allowing investigation of 3 myocardial layers: subendocardial, mid-myocardial and subepicardial \(^/3/\).

3DE examination and strain analysis

A full-volume acquisition of the LV required for further analyses was obtained from an apical approach. All data sets were analyzed by commercially available software LVQ software (EchoPAC 113, GE-Healthcare, Horten, Norway). 3DE-derived LV mass was also indexed for BSA. The 3DE deformation parameters: global longitudinal, circumferential, radial and area strain were calculated from the 17 myocardial segments at end-systole \(^/4/\).

Statistical analysis

The data were analyzed by using a standard statistical software SPSS (version 21, Chicago, IL, USA). Intra- and interobserver variability for LV mechanical parameters were analyzed in 20 study subjects using Bland-Altman method (S2). To obtain intraobserver variability one observer evaluated the same studies on two separate occasions. For the interobserver variability evaluation, two independent observers performed the analysis. Each observer individually determined which echocardiographic image will use and worked alone, without any influence of the other observer. Time interval between repeat measurements was between around 14 days. The p-value <0.05 was considered statistically significant.
References


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<tr>
<th>Variability parameters</th>
<th>Longitudinal strain</th>
<th>Circumferential strain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Intraobserver variability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>-0.17</td>
<td>-0.46 – 0.17</td>
</tr>
<tr>
<td>Mid-miocardial</td>
<td>0.24</td>
<td>-0.12 – 0.73</td>
</tr>
<tr>
<td>Subepicardial</td>
<td>-0.48</td>
<td>-1.15 – 0.24</td>
</tr>
<tr>
<td><strong>Interobserver variability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendocardial</td>
<td>0.24</td>
<td>-0.19 – 0.72</td>
</tr>
<tr>
<td>Mid-miocardial</td>
<td>-0.38</td>
<td>-0.85 – 0.14</td>
</tr>
<tr>
<td>Subepicardial</td>
<td>0.63</td>
<td>-0.42 – 1.09</td>
</tr>
</tbody>
</table>

**Table S1.** Variability of 2DE left ventricular multilayer longitudinal and circumferential strain.

CI – confidence interval
Figure S1. Flow chart showing patient selection for the study.