EVALUATION OF MYOCARDIAL STIFFNESS IN HYPERTENSIVE PATIENTS BY INTRINSIC WAVE PROPAGATION OF THE MYOCARDIAL STRETCH

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Abstract—The objective of the study was to evaluate myocardial stiffness in hypertensive patients by measuring the intrinsic velocity propagation (IVP) of the myocardial stretch and to explore the correlation between IVP and cardiac systolic and diastolic functions. Eighty-one hypertensive patients and 53 healthy patients were prospectively enrolled in this study. IVP was measured using high-frame-rate tissue Doppler (350–450 frames per second). IVP was significantly higher in hypertensive patients than in the control group (1.53 ± 0.39 m/s vs. 1.40 ± 0.19 m/s, p = 0.031). In the hypertensive group, IVP was significantly higher in patients with electrocardiogram (ECG) strain than in those without ECG strain (1.63 ± 0.46 m/s vs. 1.45 ± 0.32 m/s, p = 0.047). Moreover, IVP exhibited a good correlation with interventricular septal thickness at end-diastole (r = 0.434, p < 0.001), left ventricular posterior wall thickness at end-diastole (r = 0.439, p < 0.001), E/A ratio (r = 0.245, p = 0.004) and global longitudinal systolic strain (r = 0.405, p < 0.001). IVP was significantly higher in hypertensive patients, which indicates elevated myocardial stiffness in this cohort of patients. This novel measurement exhibited great potential for use in clinical practice to assess myocardial stiffness in patients with hypertension non-invasively. (E-mail: bixiaojun185@aliyun.com) © 2020 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Echocardiography, Myocardial stiffness, Intrinsic wave velocity propagation, Hypertension.

INTRODUCTION

Hypertension is a significant risk factor for severe cardiac morbidity and mortality, and it remains a major public health problem. The main pathophysiological mechanism is myocardial fibrosis, which contributes to increased myocardial stiffness and leads to severe diastolic dysfunction, eventually triggering heart failure (Drazner 2011). Early detection of changes in myocardial stiffness is clinically significant in preventing myocardial fibrosis and remodeling. Previous researchers have concluded that left ventricular (LV) myocardial mass, diastolic function and pixel density distribution range (from using echocardiograms) with the analysis of reflected signal and integrated backscatter could be used to assess the degree of myocardial fibrosis (Maceira et al. 2002; Kobalava et al. 2011). However, few researchers have reported that myocardial stiffness is directly associated with myocardial fibrosis and remodeling in hypertension.

Ultrasound elastography is widely used for assessing tissue stiffness in liver (Dhyani et al. 2018), thyroid (Yoon et al. 2018), breast (Farrokh et al. 2019) and other organs. However, it is challenging to apply this technique to evaluate myocardial elasticity because of the difficulty of generating shear waves in a beating heart. Song et al. (2016a, 2016b) used acoustic radiation force (ARF) to excite shear waves in the myocardium with subsequent high-frame-rate imaging to detect the wave to quantitatively assess local myocardial stiffness non-invasively in adults and children. The limitation of this technology is that it provides diastolic myocardial stiffness measurement only, and the measurement can only be done for a small local region. Strain imaging is widely used to measure myocardial deformation...
and allow early detection of subclinical LV dysfunction, but it cannot measure the myocardial stiffness directly and quantitatively (Grondin et al. 2017). Voigt et al. (2002) described that the base-to-apex time delay in diastolic lengthening could be observed in both early diastole and atrial contraction. Kanai (2005) found that the pulsive wave spontaneously activated because of the aortic valve closure at the beginning of the isovolumic relaxation period and propagated along the interventricular septum from the base to the apex. Similarly, Pislaru et al. (2014) found that a wave inside the myocardial wall propagated from the base to the apex with a speed that is proportional to the stiffness of the myocardium at the onset of the ventricular filling after atrial systole. These findings opened up the possibility of developing a non-invasive echocardiographic technique to assess myocardial stiffness by measurement of intrinsic wave velocity propagation (IVP) of the myocardial stretch for the hypertensive population. Therefore, the aim of this study was to evaluate myocardial stiffness in hypertensive patients by measuring the IVP induced by the myocardial stretch and to explore its correlation with both cardiac systolic and diastolic functions.

**METHODS**

**Study population**

From April 2016 to September 2017, 81 consecutive patients with a diagnosis of primary hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg), both outpatients and inpatients of our hospital, were enrolled in this study. Exclusion criteria included the presence of heart valve disease, congenital heart disease, coronary heart disease, myocardiopathy, history of cardiac surgery, secondary hypertension and suboptimal echocardiographic image quality. Fifty-three healthy volunteers with no evidence of hypertension or history of cardiovascular diseases and cardiac surgery (based on physical examination, laboratory testing, electrocardiography and echocardiographic examination) were also enrolled in the study. All study procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards and were approved by the local research ethics committee. Written informed consent was obtained from all participants.

All patients underwent blood pressure measurement, 12-lead electrocardiogram (ECG) and echocardiography. Echocardiographic images were analyzed by two experienced radiologists who were blind to each other’s findings. ECG strain was defined as ≥1-mm concave downsloping ST-segment depression with asymmetric T-wave inversion in the lateral leads (Shah et al. 2014). An analysis of ECG results was completed by an experienced clinician.

**Echocardiography**

Echocardiography was performed with a Vivid E9 digital ultrasonography system (GE Healthcare, Horten, Norway) equipped with an M5 S transducer. The imaging frequency was 1.7–3.4 MHz. Three cardiac cycles were stored in the cine loop format for analysis. Conventional 2-D images were obtained at a rate of at least 70 frames/s. Color flow M-mode images were acquired using the apical four-chamber view with a sweep speed of 50–100 mm per second. To obtain the longest column of flow, the ultrasound beam was adjusted to align with the LV filling flow. Aliasing in the early diastolic signal was produced by adjusting the color flow velocity scale. The cursor line was adjusted to be parallel with the ultrasound beam between the mitral valve leaflets. In addition, high-frame-rate tissue Doppler imaging data (350–450 frames/s) were acquired from the apical four-chamber, apical two-chamber and apical long-axis views. The imaging field-of-view was carefully adjusted so that each LV wall was aligned with the incident ultrasound beams to minimize the Doppler angle-induced bias.

**Imaging analysis**

All images were digitally stored on the hard drive of the ultrasound system and analyzed offline using EchoPac (GE Healthcare). Each measurement was obtained by averaging data acquired from three consecutive cardiac cycles. Standard echocardiographic measurements were performed according to the recommendations in joint publications of the American Society for Echocardiography and the European Association of Cardiovascular Imaging (Nagueh et al. 2016a, 2016b). Echocardiographic views used in this study included the apical four-chamber, two-chamber and parasternal long-axis views of the left ventricle. For data analysis, we first entered Q-analysis and then used the curved anatomic M-mode (CAMM) to trace the LV myocardium to reconstruct the axial tissue velocity maps. The tissue velocity map scale was adjusted to create velocity aliasing to better illustrate the isovelocity wave front that propagated in the myocardium during end-diastole induced by atrial contraction. Sweep speed was adjusted to maximum, and the slope of the isovelocity wave was measured as the propagation speed of the intrinsic wave (Fig. 1). The average wave velocity was calculated using all measurements from all six myocardial walls using the three apical views (Pislaru et al. 2017). The data processing time ranged from 10–15 min for each subject. Flow propagation velocity (FPV) was measured as the slope of the first aliasing velocity during early filling, from the mitral valve plane to 4 cm distally into the LV cavity on color M-mode imaging (Brun et al. 1992). Speckle tracking was used to measure the global longitudinal systolic strain (GLS), and the measurements were obtained from the apical four-chamber, two-chamber and long-axis views.
Reproducibility analysis

Measurements of IVP were repeated in 20 randomly selected data sets to test the reliability of measurements. The same observer who was blind to previous analysis results measured IVP again at least 2 wk apart to assess intra-observer variability. Inter-observer variability was evaluated between two independent observers who were blind to each other’s analysis results. Both observers were blind to the history, laboratory examination, ECG and other medical chart of each subject.

Statistical analysis

Statistical analysis was performed using SPSS (Version 17.0, IBM Corp., Armonk, NY, USA) and MedCalc (Version 18.11.3, MedCalc Software, Ostend, Belgium). Continuous variables were expressed as the mean ± standard deviation. Categorical data were summarized as percentages. Student’s t-test was used to compare continuous data between the hypertensive group and the control group. Comparisons of continuous variables among more than two groups were performed using a one-way analysis of variance (ANOVA) test, with the Bonferroni test to compare the differences between two subgroups. The χ² test was used for comparisons of categorical data between groups. Correlations between IVP and clinical and echocardiographic parameters were calculated by linear regression analysis with Pearson’s correlation coefficient (r). p Values <0.05 were considered to indicate statistical significance. Intra-observer and inter-observer reproducibility for parameters of IVP were assessed using Bland–Altman analysis.

RESULTS

Clinical and echocardiographic characteristics

Baseline clinical characteristics of the hypertensive group and the control group are summarized in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive patients (n = 81)</th>
<th>Controls (n = 53)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53 ± 14</td>
<td>54 ± 11</td>
<td>0.698</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.5</td>
<td>52.8</td>
<td>0.38</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>159 ± 24</td>
<td>121 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
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</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>93 ± 18</td>
<td>75 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>66 ± 17</td>
<td>46 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Electrocardiogram strain</td>
<td>44.4</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
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</tr>
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</table>

There were no statistically significant differences between the two groups in age and gender. Systolic blood pressure, diastolic blood pressure, pulse pressure and percentage of patients with ECG strain were significantly higher in the hypertensive group than in the control group.

Echocardiographic parameters in the two groups are summarized in Table 2. For the hypertensive group, measurements including interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), mitral $A$ velocity and $E/E'$ ratio were significantly higher than those for the control group; and measurements including the $E/A$ ratio, mitral annular septal $e'$ velocity, FPV at early diastole and GLS were significantly lower than those for the control group. There was no statistically significant difference between the two groups with respect to left ventricular internal diameter at end-diastole (LVIDd), left ventricular ejection fraction (LVEF), left ventricular fraction shortening (LVFS) and mitral $E$ velocity.

IVP and correlations with clinical and echocardiographic findings

In all 134 patients, IVP was significantly higher in hypertensive patients than in the control group (1.53 ±
observer and inter-observer intra-class correlation coefficients of IVP measurement were 0.912 (95% confidence interval [CI]: 0.792–0.964) and 0.909 (95% CI: 0.784–0.963), respectively.

**DISCUSSION**

Measurements of the wave speed of the longitudinal myocardial stretch were proposed in this study to evaluate myocardial stiffness in hypertensive patients. We found that IVP was higher in hypertensive patients than in the control group and was well correlated with diastolic blood pressure, thickness of the LV wall and GLS. Furthermore, IVP was higher in patients with ECG strain than in patients without ECG strain, which suggests that myocardial stiffness may be higher in patients with ECG strain.

Myocardial stiffness is determined not only by ventricular fibrosis (Yamamoto et al. 2002), but also by cardiomyocyte stiffness (Van Heerebeek 2006; Van Heerebeek et al. 2008). There are two types of assessments of diastolic function: those that reflect the process of active/auxotonic relaxation and those that reflect passive stiffness (Villemain et al. 2019). Abnormal passive ventricular stiffness is likely to be a major contributor to...
Fig. 2. Correlation between intrinsic velocity propagation (IVP) and diastolic blood pressure, interventricular septal thickness at end-diastole (IVSd), left ventricular posterior wall thickness at end-diastole (LVPWd), E/A ratio and global longitudinal systolic strain (GLS).
diastolic dysfunction (Ellims et al. 2014). At present, pressure–volume loops via cardiac catheterization are the clinical gold standard for assessing myocardial passive stiffness (Villemain et al. 2019). As an invasive examination, it is not widely used in the clinic. Wave speed is proportional to the elasticity of the medium in a solid elastic medium. A wave propagating from the base toward the apex with a speed proportional to the elasticity of the myocardial wall is produced when LV filling stretches at the late diastole phase. This means that the higher the wave speed, the higher is the myocardial stiffness. This hypothesis was confirmed in animal models (Pislaru et al. 2014), which indicated that IVP was associated with diastolic function. Pislaru et al. (2017) first reported the potential of intrinsic cardiac wave propagation in patients with aortic stenosis and mitral regurgitation, which revealed the feasibility of evaluating myocardial stiffness by IVP.

Similar to aortic stenosis, elevated afterload is the major pathophysiological consequence in hypertensive...
patients that results in subendocardial perfusion impairment, increased myocardial oxygen consumption and onset of abnormal collagen synthesis, myocardial fibrosis, necrosis and apoptosis. Cardiac remodeling, which manifests clinically as changes in size, shape and function of the heart after injury, occurs because of the genome expression, which causes molecular, cellular and interstitial changes in the chronic pressure-overloaded heart (Hein et al. 2003; Weidemann et al. 2009; Drazner 2011). In this study, IVP was significantly higher in hypertensive patients than in healthy patients, indicating increased myocardial stiffness in hypertensive patients. Previous research has indicated that ECG strain is a significant independent predictor for the development of, and death from, congestive cardiac failure in hypertensive patients (Okin et al. 2006). Our study found that IVP, IVSd, LVPWd and GLS were significantly higher in hypertensive patients without ECG strain than in patients without ECG strain. In hypertensive patients, myocardial cellular expansion and significantly increased interstitial fibrosis jointly lead to increased LV mass. Compared with the subgroup of hypertensive patients with LV hypertrophy but without ECG strain, patients with ECG strain have more interstitial fibrosis (Rodrigues et al. 2017). Therefore, myocardial stiffness was significantly higher in patients with ECG strain than in hypertensive patients with LV hypertrophy but without ECG strain.

Diastolic function is impaired in hypertensive patients. Pislaru et al. (2019) concluded that IVP correlated with mitral \( E/A \) ratio in patients with amyloidosis, another disease that may increase myocardial stiffness. This result is consistent with our study. \( E' \) velocity can be used to correct for the effect of LV relaxation on mitral \( E \) velocity, and the \( E'/e' \) ratio can be used to predict LV filling pressure (Nagueh et al. 2016a, 2016b). Pislaru et al. (2017, 2019) reported that IVP was well correlated with measures of LV preload \( (E'/e' \) ratio) in patients with aortic stenosis and amyloidosis. However, our study did not find any significant correlation between IVP and measures of \( E'/e' \) ratio. One possible reason may be that the value of the \( E'/e' \) ratio was 11.0 ± 3.9 (between 8 and 14), a “gray zone” of values in which LV filling pressures were indeterminate. FPV is an index that can be used to assess ventricular compliance to evaluate diastolic function. An FPV decrease indicates impaired LV diastolic function (Brun et al. 1992; Garcia et al. 1998).

In our study, FPV was significantly lower in hypertensive patients, but there was no evidence indicating that there was a significant correlation between myocardial stiffness and FPV.

In hypertensive patients, myocardial cells exhibit compensated hypertrophy, and both LVEF and LVFS can be preserved. However, this does not suggest that myocardial contractility is normal in hypertensive patients. Poulsen et al. (2003, 2005) reported decreased LV longitudinal contractility in patients with hypertension, most pronounced in patients with concomitant abnormal diastolic filling. They also found a significantly independent negative correlation between the plasma concentration of the plasma amino-terminal propeptide of procollagen type III and LV long-axis contractility, indicating that increased myocardial fibrosis affects the contractility of inner and outer longitudinally oriented myocardial fibers. In the present study, IVP correlated well with GLS, which is a sensitive marker of subclinical LV myocardial contractility, suggesting that increased myocardial stiffness may be closely related to decreased myocardial contractility. Moreover, IVP was significantly correlated with LVIDd and LVPWd, which were thicker in hypertensive patients than normal patients.

Myocardial stiffness measurements directly indicate the pathologic modifications of the myocardium, which are clinically significant for the evaluation of early variations of cardiac function, especially diastolic function. Several previous studies (Couade et al. 2011; Song et al. 2016a, 2016b) have reported the use of ARF-based ultrasound shear wave elastography (SWE) techniques for direct and quantitative assessment of myocardial stiffness. However, ARF-SWE is clinically challenging because of the poor imaging penetration and limited acoustic windows for imaging. The advantage of our
study is that the use of the heart’s intrinsic wave produced by physiologic events reduces the interference factor and obviates the need for using ARF. The objective of this study was to investigate the clinical feasibility of using intrinsic myocardial mechanical waves to quantify late diastolic myocardial stiffness in a cohort of a specific patient population. We found that IVP was obviously higher in hypertensive patients, which indicated increased myocardial stiffness. Although increased wall thickness always occurs in hypertensive patients, it is affected by some other factors. In general, athletes exhibit a 10%–20% increase in LV wall thickness compared with individuals of similar age and size (Sharma et al. 2015). Moreover, as a marker of advanced LV hypertrophy associated with increased interstitial fibrosis, ECG strain is a qualitative index. Although the definitive added clinical value of the proposed method needs to be investigated further, our study results indicated the potential for assessing myocardial stiffness conveniently and the possibility of early detection of abnormal diastolic function in hypertensive patients. Future studies will be conducted to systematically quantify myocardial stiffness in a large patient population to guide clinical treatment and prognosis.

There are some limitations to the present study. First, our study was limited by the relatively small size of both groups. Further research with larger samples will be conducted in the future. Second, a higher frame rate of imaging is needed to obtain more accurate measurements of IVP. Third, because of the Doppler angle dependency and narrow imaging range, the proposed method is not feasible in patients with LV globular enlargement. Another concern was that there was no ground truth and direct measurements of the myocardial stiffness. The conclusion of higher myocardial stiffness in hypertensive patients was derived only from the observation of a higher IVP value. To confirm our hypothesis, cardiac magnetic resonance or even endomyocardial biopsy needs to be performed to provide the reference standards in further studies. In addition, our study indicated that IVP correlated well with diastolic blood pressure, but only mildly with systolic blood pressure. However, this result may be influenced by many confounding factors. For example, blood pressure constantly fluctuates and is not a fixed value. The category and dosage of antihypertensive drugs in patients are affected by blood pressure and LV afterload. Therefore, it was challenging to accurately determine the correlation between myocardial stiffness and blood pressure.

CONCLUSIONS

To our knowledge, this is the first study to evaluate myocardial stiffness using the measurement of IVP in a cohort of hypertensive patients. IVP was significantly higher in hypertensive patients, which indicated elevated myocardial stiffness. We also found that IVP was well correlated with thickness of the LV wall and GLS. Furthermore, we speculated that myocardial stiffness was higher in patients with ECG strain than in patients without ECG strain. This novel measurement has great potential for use in clinical practice for non-invasive and convenient assessment of myocardial stiffness in patients with hypertension. Further studies with large samples are needed to investigate the clinical utility of this novel measurement for hypertensive patients as well as for other cardiovascular diseases.

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Conflict of interest disclosure—The authors have no conflicts of interest to declare.

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