Impact of Arterial Stiffness on Regional Myocardial Function Assessed by Speckle Tracking Echocardiography in Patients with Hypertension

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BACKGROUND: Arterial stiffening may affect regional myocardial function in hypertensive patients with normal ejection fraction (EF).
METHODS: Brachial-ankle pulse wave velocity (PWV) was measured in 70 patients, of mean age 48 ± 14 years, with untreated hypertension and EF > 55%. Using two-dimensional-speckle tracking echocardiography, we measured longitudinal and circumferential strain (ε) and strain rate (SR). Basal and apical rotations were measured using short axis views.
RESULTS: The mean systolic and diastolic blood pressure in these patients was 152 ± 15 mmHg and 92 ± 11 mmHg, respectively. The mean value of PWV was 1578 ± 274 cm/s. PWV significantly correlated with age ($r = 0.682$, $p < 0.001$), body mass index ($r = -0.330$, $p = 0.005$), systolic blood pressure ($r = 0.386$, $p = 0.001$) and pulse pressure ($r = 0.509$, $p < 0.001$). PWV also significantly correlated with septal E' velocity ($r = -0.570$, $p < 0.001$), E/A ratio ($r = -0.414$, $p < 0.001$), E/E' ratio ($r = 0.589$, $p < 0.001$), systolic global longitudinal ε ($r = 0.300$, $p = 0.012$) and early diastolic SR (SR_E) ($r = -0.479$, $p < 0.001$) suggesting impaired abnormal relaxation. PWV was also correlated with basal rotation ($r = -0.301$, $p = 0.011$) and basal-to-apical twist ($r = -0.256$, $p = 0.032$). The increases in apical rotation and basal-to-apical twist were attenuated in patients with PWV > 1700 cm/s compared to those with PWV ≤ 1400 cm/s or those with PWV 1400-1700 cm/s.
CONCLUSION: In hypertensive patients with normal ejection fraction, arterial stiffening contributes to impaired systolic and diastolic function of the regional myocardium. Compensatory increases in ventricular twist were diminished in patients with advanced stage of vascular stiffening.

KEY WORDS: Arterial stiffening · Regional myocardial function · Speckle tracking echocardiography.

INTRODUCTION

Vascular remodeling and arterial stiffening, a marker of cardiovascular mortality and morbidity, are accelerated by systemic hypertension and aging. Chronic vascular stiffness is accompanied by reflected waves of high speed and magnitude and contributes to increase in end-systolic stiffness of the left ventricle (LV).[1)2)] Thus, ventricular systolic and diastolic stiffness linked to the interaction between the heart and vascular loads are affected by intrinsic changes in the ventricular myocardium.[3)]

Coupled ventricular-arterial stiffening may have a potent impact on limited systolic and diastolic reserve, blood pressure lability, coronary and peripheral flow regulation, and cardiac metabolic demand under stress. Although these adverse effects are thought to play a role in the pathophysiology of heart failure in patients with normal ejection fraction (EF),[4)] the mech-

anism by which chronic ventricular-arterial stiffening alters regional myocardial function remains unclear. The speckle tracking method has overcome several limitations of tissue Doppler imaging in terms of, tethering effect, translation movement and angle dependency. Thus, speckle tracking can provide useful information on three-dimensional myocardial deformations and cardiac torsion.[5)6)]

Using aortic pulse wave velocity (PWV) and speckle tracking echocardiography, we have evaluated the impact of chronic arterial stiffening, on the early changes in systolic and diastolic function of the regional myocardium, in hypertensive patients with normal EF.

METHODS

STUDY POPULATION

We evaluated 70 consecutive patients with untreated hypertension (repeated systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), who visited the outpatient clinic for the management of hypertension. None of these patients had received anti-hypertensive medications. All patients showed a normal EF (> 55%), as assessed by two-dimensional transthoracic echocardiography, and a normal sinus rhythm on electrocardiography. We excluded patients with positive exercise stress test, myocardial ischemia on thallium scan, presence of regional wall motion abnormality on echocardiography and significant coronary artery stenosis (diameter stenosis > 50%) on coronary angiography or coronary computed tomography. Patients with any evidence of secondary hypertension, diabetes mellitus, valvular heart disease, liver disease or systemic inflammatory disease were also excluded.

CONVENTIONAL ECHOCARDIOGRAPHIC MEASUREMENTS

Before starting anti-hypertensive medication, each patient underwent two-dimensional, M-mode and Doppler echocardiography using commercially available equipment (VIVID 7 machine, GE-Vingmed Ultrasound, Horten, Norway). The LV diameter of end-diastole (LVIDd) and end-systole, end-diastolic thickness of the ventricular septum (SWTd) and LV posterior wall (PWTd) were measured by M-mode echocardiography. LV mass and relative wall thickness was derived from ASE-recommended formula.[7)]

LV mass = $0.8 \times \{1.04 \times [(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]\} + 0.6$ g

Relative wall thickness = $(2 \times PWTd) / LVIDd$

LV mass index was determined by dividing the LV mass by the body surface area. End-systolic and end-diastolic LV volumes and EF were determined by a modified Simpson's method using the apical 4-chamber view. For each measurement, three cardiac cycles were averaged.

E and A velocities of transmitral inflow were measured and E/A ratio calculated. The mitral annular velocity was recorded at the LV septal wall by tissue Doppler echocardiography. The early diastolic velocity (E') and ratio of E/E' were determined.[8)]

TWO-DIMENSIONAL SPECKLE TRACKING ECHOCARDIOGRAPHY

All echocardiographic recordings were obtained in digital format and stored on magneto-optical disks for off-line analysis (Echopac TVI, GE Vingmed, Horten, Norway). Using a VIVID 7 machine with an M3S probe, we scanned apical 4-chamber and short axis views (at basal, mid and apical planes) of each patient to determine ventricular strain and rotation. Gain settings and pulse repetition frequencies were adjusted and sector size and depth were optimized to obtain a frame rate of 80-105 frames/s. Off-line analysis was performed using commercially available software on a personal computer workstation (EchoPAC platform, 2DS-software package, version 3.3, GE Medical Systems, Milwaukee, WI, USA).

Two-dimensional strain was measured as described.[5)6)] The endocardium was traced in an optimal frame, from which a region of interest (ROI) was automatically selected to approximate the myocardium between the endocardium and epicardium. The width of the ROI was adjusted to fit the wall thickness. The systolic peak of strain (ε) was selected between the aortic valve opening and closing times. We analyzed the strain rate curve and measured the early diastolic strain rate (SR_E). Longitudinal ε was defined as the average negative longitudinal strains of 6 segments of the septum and lateral walls on apical 4-chamber views. Radial and circumferential ε were measured in 6 mid-LV segments on the mid-short axis view and averaged.

As viewed from the apex, the LV apex rotates counterclockwise (positive angles) and the base rotates clockwise (negative angles) in systole. The proper basal level of the short-axis view was defined as that showing the tip of the mitral valve and the apical level as that just proximal to the level with LV cavity obliteration at end-systole. Basal-to-apical twist was defined as the net difference in LV rotation angle at the apical and basal short axis planes.

BRACHIAL-ANKLE PULSE WAVE VELOCITY MEASUREMENT

PWV was measured using an automatic wave form analyzer (VP-1000, Colin Medical Instruments, Komak, Japan). Before echocardiographic measurement, the PWV was recorded with the patient lying in the supine position at room temperature.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS (version 10.0, SPSS Inc., Chicago, IL, USA). All values are expressed as the means ± one standard deviation (continuous variables) or as counts and percentages (categorical variables). Continuous

variables were compared by using unpaired t-tests or non-parametric Mann-Whitney tests; categorical variables were compared with χ^2 statistics or Fisher's exact test. Pearson's correlation analysis was utilized to assess the relationships between pairs of echocardiographic parameters. Intraobserver and interobserver variability of LV twist and strain were tested in 15 patients using the speckle tracking imaging method. Intraobserver and interobserver variability were tested by the Bland-Altman method and expressed as the mean ± standard deviation of the absolute differences between the two measurements divided by the mean value (%). A p-value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics and echocardiographic variables in the overall 70 hypertensive patients are summarized in Table 1. The age was 48 ± 14 years, and 39 (56%) were male. The systolic and diastolic blood pressure was 152 ± 15 mmHg and 92 ± 11 mmHg, respectively. PWV was 1578 ± 274 cm/s. PWV significantly correlated with age (r = 0.682, p < 0.001), body mass index (r = -0.330, p = 0.005), systolic blood pressure (r = 0.386, p = 0.001) and pulse pressure (r = 0.509, p < 0.001), septal E' velocity (r = -0.570, p < 0.001), E/A ratio (r = -0.414, p < 0.001) and E/E' ratio (r = 0.589, p < 0.001) (Table 2).

The parameters of regional myocardial function obtained by the speckle tracking method are shown in Table 3. PWV correlated with global longitudinal ε (r = 0.300, p = 0.012). More-

Table 1. Clinical data and conventional echocardiographic measurements

n = 70	Mean ± SD
Age (yr)	48 ± 14
Male	39 (56%)
PWV (cm/s)	1578 ± 274
Body mass index (kg/m^2)	25 ± 3
Systolic blood pressure (mmHg)	152 ± 15
Diastolic blood pressure (mmHg)	92 ± 11
Pulse pressure	60 ± 10
Septal wall thickness (mm)	11.0 ± 2.0
Posterior wall thickness (mm)	10.6 ± 1.7
LV mass index (g/m^2)	113 ± 27
E velocity (cm/s)	79 ± 20
A velocity (cm/s)	76 ± 19
E/A ratio	1.1 ± 0.4
Septal E' velocity (cm/s)	7.5 ± 2.4
E/E' ratio	11 ± 4

PWV: brachial-ankle pulse wave velocity, E velocity: peak mitral flow velocity of the early rapid filling wave, A velocity: peak mitral flow velocity of the late filling wave, E': early diastolic annulus velocity, LV: left ventricle
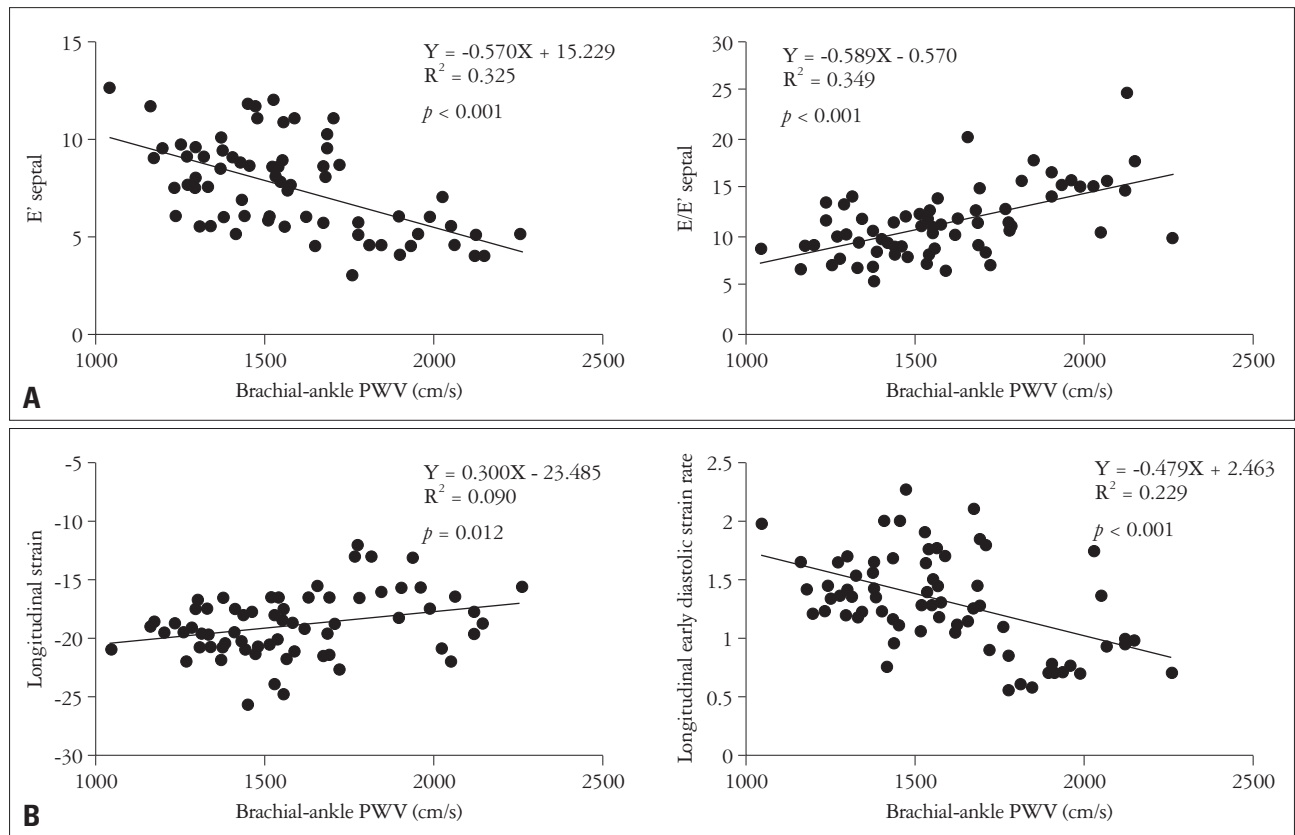

Fig. 1. Linear correlation of brachial-ankle pulse wave velocity with (A) the tissue Doppler parameter and (B) longitudinal peak systolic strain, and longitudinal early diastolic strain rate. PWV: brachial-ankle pulse wave velocity, E': early diastolic annulus velocity.

over, PWV correlated with SR_E (r = -0.479, p < 0.001), an indicator of abnormal relaxation on the longitudinal global SR curve (Table 4). Fig. 1 demonstrated the relation of PWV to the relaxation abnormality, filling pressure, and regional myocardial function of LV. PWV was also correlated with basal rotation (r = -0.301, p = 0.011) and basal-to-apical twist (r = -0.256, p = 0.032), while it did not correlate with apical rotation (r = 0.082, p = 0.498) (Fig. 2A). Multivariate regression analysis showed that age, body mass index, systolic blood pressure and basal to apical twist were independently related to brachial-ankle PWV (Table 5).

When the patients were classified by 3-quantile (tertile) of PWV (≤ 1400 cm/s, 1400-1700 cm/s, > 1700 cm/s), basal rotation showed a linear increase, whereas apical rotation revealed a biphasic pattern (Fig. 2C). Because basal and apical rotation differently responded according to the severity of aortic stiffness, the increase in basal-to-apical twist was attenuated in the 19 patients with PWV > 1700 cm/s. In the remaining 51 patients with PWV ≤ 1700 cm/s, PWV significantly correlated with both apical rotation (r = 0.461, p < 0.001) and

Table 2. Correlation between clinical data, and conventional echocardiographic measurements and brachial-ankle PWV

n = 70	r	p-value
Age (yr)	0.682	< 0.001
Body mass index (kg/m^2)	-0.330	0.005
Systolic blood pressure (mmHg)	0.386	0.001
Diastolic blood pressure (mmHg)	0.062	0.608
Pulse pressure	0.509	< 0.001
Septal wall thickness (mm)	0.176	0.145
Posterior wall thickness (mm)	0.149	0.219
LV mass index (g/m^2)	0.199	0.099
E velocity (cm/s)	-0.081	0.505
A velocity (cm/s)	0.447	< 0.001
E/A ratio	-0.414	< 0.001
Septal E' velocity (cm/s)	-0.570	< 0.001
E/E' ratio	0.589	< 0.001

E velocity: peak mitral flow velocity of the early rapid filling wave, A velocity: peak mitral flow velocity of the late filling wave, E': early diastolic annulus velocity, PWV: brachial-ankle pulse wave velocity, LV: left ventricle
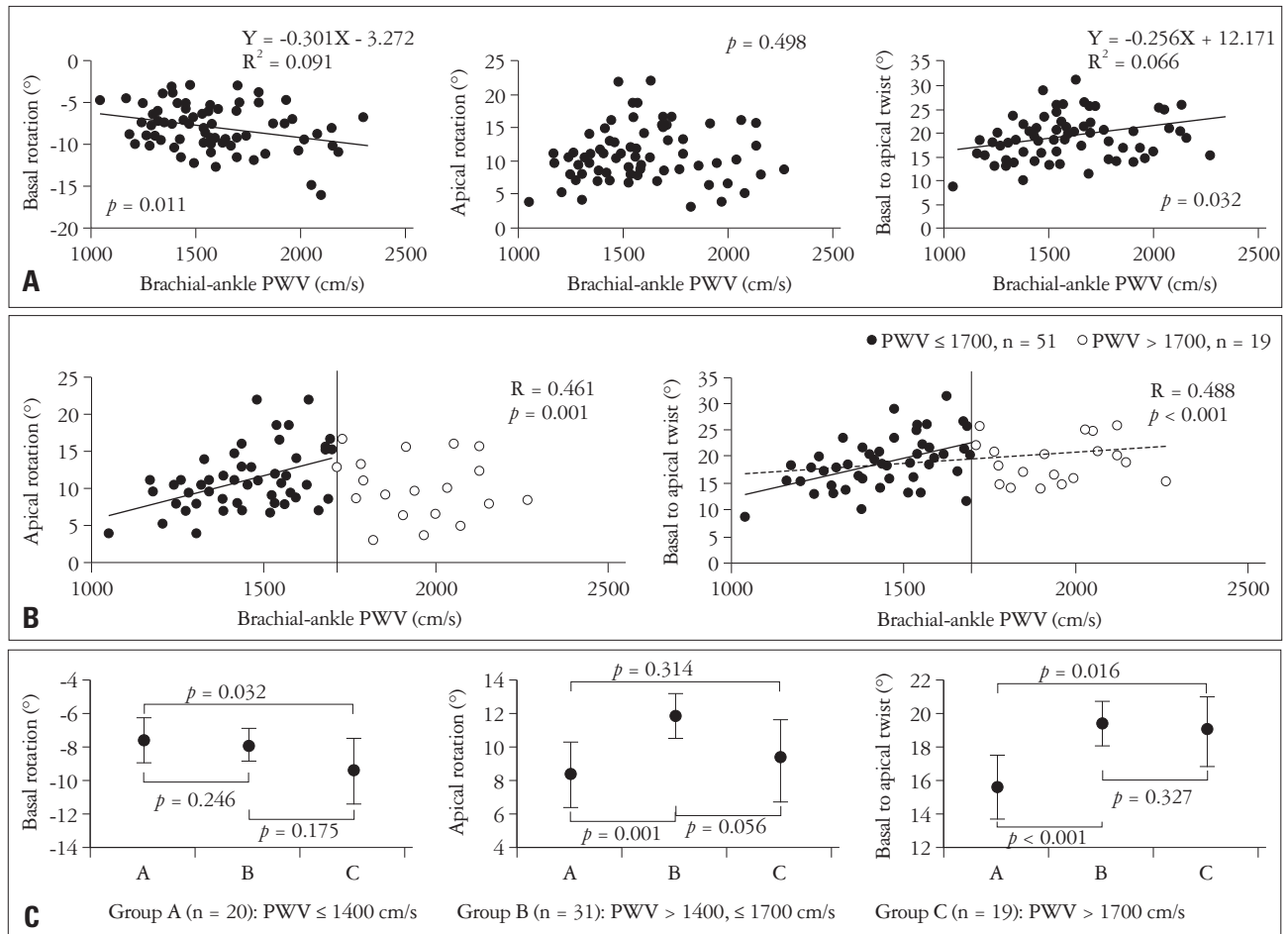

Fig. 2. Relationship between brachial-ankle pulse wave velocity and left ventricular rotation, and twist. A: Linear correlation of brachial-ankle pulse wave velocity with left ventricular rotation and twist. B: Changes in apical rotation and basal to apical twist in patients with brachial-ankle pulse wave velocity over 1700 cm/s. C: The changes of basal rotation, apical rotation, and basal to apical twist in 3 groups of brachial-ankle pulse wave velocity. PWV: brachial-ankle pulse wave velocity.

Table 3. Measurements of speckle tracking echocardiography

n = 70	Mean ± SD
Peak systolic strain (%)	
Longitudinal	-18.9 ± 2.7
Radial, mid	64 ± 19
Circumferential, mid (%)	-20.5 ± 3.5
Systolic strain rate (s⁻¹)	
Longitudinal	-1.0 ± 0.2
Radial, mid	2.5 ± 0.6
Circumferential, mid (%)	1.7 ± 0.6
Diastolic strain rate (s⁻¹)	
Longitudinal	1.3 ± 0.4
Radial, mid	-2.7 ± 0.8
Circumferential, mid	-1.3 ± 0.3
LV rotation (°)	
Basal rotation	-8.0 ± 2.8
Apical rotation	10.9 ± 4.1
Basal-to-apical twist	18.9 ± 4.6

LV: left ventricle

Table 4. Correlation between speckle tracking echocardiographic measurements and brachial-ankle PWV

n = 70	r	p-value
Peak systolic strain (%)		
Longitudinal	0.300	0.012
Radial, mid	0.029	0.814
Circumferential, mid (%)	0.028	0.815
Systolic strain rate (s⁻¹)		
Longitudinal	0.192	0.111
Radial, mid	0.015	0.920
Circumferential, mid (%)	-0.108	0.372
Diastolic strain rate (s⁻¹)		
Longitudinal	-0.479	< 0.001
Radial, mid	0.209	0.150
Circumferential, mid	-0.034	0.779
LV rotation (°)		
Basal rotation	-0.301	0.011
Apical rotation	0.082	0.498
Basal-to-apical twist	-0.256	0.032

PWV: brachial-ankle pulse wave velocity, LV: left ventricle

basal-to-apical twist (r = 0.488, p < 0.001) (Fig. 2B).

E/E' ratio was related to old age (r = 0.582, p < 0.001), high systolic blood pressure (r = 0.246, p = 0.040), wide pulse pressure (r = 0.33, p = 0.001) and large LV mass index (r = 0.387, p = 0.001). In addition, E/E' ratio was associated with the reduced longitudinal ε (r = 0.329, p = 0.005), systolic longitudinal SR_E (r = 0.440, p < 0.001), diastolic longitudinal SR_E (r = -0.401, p < 0.001) and basal-to-apical twist (ß = -0.208, p = 0.030).

Intra- and interobserver variabilities were 7 ± 5% and 10 ±

Table 5. Multivariate regression analysis to determine the predictor of brachial-ankle PWV

R^2 = 0.718	β	p-value
Age	0.478	< 0.001
Body mass index	-0.216	0.010
Systolic blood pressure	0.264	0.001
A velocity	0.024	0.834
Septal E' velocity	0.105	0.493
E/E' ratio	0.230	0.076
Longitudinal ε	0.115	0.221
Longitudinal SR_E	-0.145	0.286
Basal rotation	0.152	0.105
Basal to apical twist	0.289	0.003

PWV: brachial-ankle pulse wave velocity, A velocity: peak mitral flow velocity of the late filling wave, E': early diastolic annulus velocity, ε: strain, SR_E: early diastolic strain rate

7% in longitudinal ε. Those of radial and circumferential ε were 12 ± 9% and 13 ± 11%, and, 11 ± 8% and 13 ± 9%, respectively. In basal-to-apical twist, intra- and interobserver variability were measured as 8 ± 6% and 11 ± 8%.

DISCUSSION

The major findings of this study are: 1) PWV significantly correlated with echocardiographic parameters of abnormal myocardial relaxation and high LV filling pressure; 2) PWV also correlated with the indicators of regional myocardial function, including global longitudinal ε and early diastolic SR_E; 3) Although there were positive correlations between PWV and basal rotation and basal-to-apical twist, the increase in the apical rotation and basal-to apical twist, was attenuated in patients with PWV > 1700 cm/s.

Vascular stiffening causes arterial pulse pressure to widen and affects mechanical vascular stimulation by increasing pulsatile shear and pressure. Chronic vascular stiffness increases the speed and magnitude of reflected waves, amplifying late systolic pressure and, thus, systolic load on the LV. This chronic vascular alteration is coupled with an increase in ventricular end-systolic stiffness.[1-3] Although chronic systolic ventricular-arterial coupling maintains stroke work, it also predisposes to adverse effects including a high sensitivity to change in volume, change in myocardial perfusion patterns and reduction in systolic reserve.[9,10] These adverse effects are thought to play a role in the pathophysiology of heart failure in patients with normal EF.[4] Because heart ejecting into a stiffer arterial system generates the higher end-systolic pressure for the net stroke volume, the greater energy may be required for a given level of ejected flow.[11] As a result, chronic ejection into a stiffer vasculature induces structural and functional changes in myocardium, even at the similar level of mean arterial pressure.[12]

Although obesity has been considered to have a relationship with arterial stiffness, the current data showed a negative cor-

relation between body mass index and PWV. This inconsistent result may be explained by a relatively low body mass index in our patients and confounding factors such as an effect of age on the arterial stiffness.

The speckle tracking method has overcome some technical limitations of tissue Doppler imaging, including angle dependency, tethering and translational effects, high signal-to-noise ratio and high measurement variability.[5)6)] Speckle tracking has made it possible to quantify different components of complex cardiac motions, namely longitudinal, circumferential and radial deformation and torsion. Using the speckle tracking method, our data showed that progressive vascular stiffening contributed to the impairment of systolic and diastolic regional myocardial function. Furthermore, the compensatory increases in apical rotation and basal-to-apical twist were attenuated in patients with advanced arterial stiffening.

We previously reported that hypertensive patients with normal EF had a decreased longitudinal ε and a paradoxically increased LV torsion.[13)] The quantitative parameters of regional myocardial function correlated with the serum concentration of TIMP-1, which controls myocardial collagen turnover. Although the precise mechanisms associated with variable changes in different types of regional function remain unclear, paradoxically increased LV torsion with normal EF has been observed in patients with diabetes, aortic stenosis and hypertrophic cardiomyopathy.[14-18)] Because the changes in torsion occur long before irreversible tissue damage, these may be an early indicator of systolic dysfunction. The increase in basal-to-apical twist was primarily due to the increase in basal rotation that is affected by age-related changes in diastolic filling.[19)]

LIMITATIONS

Although we excluded patients with diabetes mellitus, we included 7 patients with impaired glucose tolerance. Nevertheless, our patients had fasting blood glucose concentrations ranging from 112 to 123 mg/dL, and all had serum HbA1C concentrations < 7.0%. Second, the current study used apical 4-chamber view to assess longitudinal ε. The lack of 2-chamber view and apical long axis view may be another limitation of this analysis. Third, our study could not demonstrate the precise mechanism underlying increased LV twist. Although a few explanations have been proposed,[15-18)] it is unclear whether high torsion is a compensatory response to maintain intracavitary pressure or a secondary change in abnormal fiber structure caused by subendocardial dysfunction in a hypertensive heart with normal EF. Further investigations are needed to clarify its clinical impact on the progression of hypertensive heart disease.

CONCLUSIONS

In hypertensive patients with normal EF, arterial stiffness contributed to the impairment of systolic and diastolic function of the regional myocardium. Although the paradoxical increase in LV twist may be a compensatory mechanism, LV twist decreased in patients with advanced vascular stiffening.

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