

ORIGINAL ARTICLE

Impact of antihypertensive treatment on left ventricular systolic dyssynchrony in treatment-naïve hypertensive patients

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Dyssynchrony is common in asymptomatic patients with hypertension. We sought to investigate the impact of antihypertensive treatment on dyssynchrony in patients with hypertension. A total of sixty patients who had uncomplicated hypertension that had never been treated (treatment-naïve hypertensive patients) underwent echocardiographic evaluations of left ventricular (LV) dyssynchrony at baseline and after a 6-month treatment with antihypertensive drugs. The measured parameters were as follows: (1) the s.d. of 12 LV-segment time-to-peak systolic velocities (Ts-SD12), and (2) the maximal difference between peak systolic velocities of any 2 of the 12 segments (Ts-Max). Patients with Ts-SD12 ≥ 33 ms or Ts-Max ≥ 100 ms were regarded as having LV systolic dyssynchrony. Patients with systolic dyssynchrony (group 1, $n=29$) and without systolic dyssynchrony (group 2, $n=31$) were compared. Among the patients in group 1, antihypertensive treatment significantly improved LV systolic dyssynchrony (Δ Ts-SD12, -13.1 ms; $P<0.001$ and Δ Ts-Max, -34.0 ms; $P=0.003$), whereas it did not demonstrate additional benefit among group 2 patients. The change in LV systolic dyssynchrony was significantly associated with changes in the mean annulus E' velocity, mean annulus S' velocity and mean annulus E'/A' ratio, but not with changes in blood pressure and LV mass index. It is likely that chronic antihypertensive treatment could reverse the LV systolic dyssynchrony and simultaneously improve subclinical systolic and diastolic function in patients with hypertension and LV systolic dyssynchrony.

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INTRODUCTION

It is well known that left ventricular (LV) systolic or diastolic dyssynchrony is common in patients with heart failure (HF) and a normal QRS duration.¹ There has been increased recognition that LV dyssynchrony also exists in patients without HF but with other cardiac diseases, including hypertension,² coronary artery disease (CAD)³ and cardiomyopathy.^{4,5} Dyssynchrony has been measured using a variety of echocardiographic parameters based on different imaging techniques,⁶ including pulsed-wave tissue Doppler imaging (TDI), color-coded TDI, tissue tracking, displacement mapping, strain and strain rate imaging, and tissue synchronization imaging. TDI is the most extensively tested method.

Hypertension is a major risk factor for LV hypertrophy and HF. Epidemiological studies have demonstrated that hypertension accounts for 50% of patients with HF.⁷ Recently, it was demonstrated that LV systolic dyssynchrony was present in 24% of asymptomatic patients with hypertension.² Moreover, on the basis of results from the previous study,⁸ the proportion of treatment-naïve hypertensives with LV systolic dyssynchrony was found to be 44.5%.

Research has indicated that antihypertensive treatment reverses LV remodeling and LV hypertrophy in patients with hypertension;⁹ however, the impact of antihypertensive treatment on dyssynchrony has rarely been determined. We therefore designed a prospective study to identify the impact of antihypertensive treatment on dyssynchrony in patients who had uncomplicated hypertension that had never been treated.

METHODS

Study population

We consecutively enrolled patients who were diagnosed with primary hypertension between January 2009 and February 2010 at St Paul's Hospital (The Catholic University of Korea, Seoul, Korea). None of the patients had ever received antihypertensive treatment before they visited our hospital.

Hypertension was diagnosed based on clinical blood pressure (BP) measurements $\geq 140/90$ mm Hg on two separate occasions. Inclusion criteria were as follows: (1) outpatients of either gender, 18–75 years of age; (2) mild to moderate hypertension (diastolic BP <110 mmHg and systolic BP <180 mmHg); and (3) a normal QRS duration (<120 ms). Exclusion criteria

were as follows: (1) previous use of antihypertensive medications; (2) secondary hypertension; (3) diabetes mellitus, defined as a fasting plasma glucose ≥ 126 mg dl⁻¹ or a history of diabetes mellitus; (4) renal insufficiency, defined as a serum creatinine ≥ 1.5 mg dl⁻¹; (5) CAD; (6) HF, according to the Framingham criteria or a low LV ejection fraction (<50%); (7) cerebrovascular disease or peripheral artery disease; (8) echocardiographic evidence of valvular heart disease, LV regional wall motion abnormalities, pulmonary hypertension, or pericardial disease, or inaccurate delimitation of the endocardial border; and (9) rhythm disorders, including atrioventricular block, incomplete or complete bundle branch block, pre-excitation syndrome, ventricular arrhythmias or atrial fibrillation.

A treadmill exercise test, 24-h ECG monitoring, cardiac single photon emission computed tomography, coronary computed tomography and/or coronary angiography were performed if the patient was suspected to have ischemic heart disease. Body mass index was calculated as the body weight (kg) divided by the height (m) squared. Metabolic syndrome was defined according to the International Diabetes Federation criteria.¹⁰ Estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease formula.¹¹

The study protocol was approved by the Institutional Review Board for Biomedical Research at our institution. Written informed consent was obtained from all subjects.

Antihypertensive treatment

Antihypertensive treatment was initiated after baseline echocardiography was performed. The angiotensin II receptor blocker (ARB) is one of the first-line antihypertensive drugs for most patients, but monotherapy achieves the target BP recommended by the treatment guidelines^{12,13} in only a limited number of patients and, thus, combination therapy is required in a majority of patients.¹² A thiazide diuretic is commonly used in combination with an ARB because it has an additive effect on BP reduction because of its complementary mechanisms of action.¹² Patients first received monotherapy with ARB (Telmisartan, up to 80 mg). When the target BP (<140/90 mm Hg) was not reached within 4 weeks, we added hydrochlorothiazide (up to 50 mg) to the treatment regimen. Patients were followed up every 4 weeks thereafter. If the patient's clinical BP was greater than 140/90 mm Hg or intolerance to drugs occurred, a β -blocker (Cavedilol, up to 50 mg) was added. Finally, a calcium antagonist (Nifedipine, up to 60 mg) was added. The dose of medication could be down-titrated to the previous level in the event of hypotension, dizziness or intolerance. Once patients reached the target BP, they were maintained on the dose of antihypertensive drugs at which the target BP was reached for the study duration. Patients who could not obey this protocol were dropped from the study. Patients were followed up for 6 months.

Echocardiographic assessment

Standard TDI and strain echocardiography were performed with a commercially available echocardiography system (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway). Standard two-dimensional and color Doppler data (three consecutive beats), triggered to the QRS complex, were saved in a cine loop format. The averages of at least three consecutive beats were used for comparison, and all data were analyzed offline using a dedicated software package (EchoPAC version 6.0.1, GE Healthcare, Milwaukee, WI, USA) for TDI and TDI-derived parameters. All echocardiographic measurements were performed by one physician who was blinded to the clinical data to avoid interobserver variation. Echocardiography was performed at baseline and 6 months after antihypertensive therapy.

Standard echocardiography. The following parameters were evaluated, including Doppler and TDI studies: (1) the LV volumes and ejection fraction were assessed by biplane Simpson rule using manual tracing of digital images of the apical 4- and 2-chamber views according to the American Society of Echocardiography standard;¹⁴ (2) LV diameters were measured using two-dimensional-guided M-mode echocardiography according to the guidelines of the American Society of Echocardiography;¹⁵ and (3) transmitral flow velocities were recorded from the apical 4-chamber view using pulse-wave Doppler. The peak flow velocity in early diastole (E) and late diastole (A), the E/A ratio, the deceleration time of E-wave and the isovolumic relaxation time were obtained.

The filling time was measured from the onset of the E-wave to the end of the A-wave. Pulsed-TDI of the four sides of the mitral annulus (septal, lateral, inferior and anterior) was also obtained in 4- and 2-chamber views to assess global cardiac function.^{16,17} (4) The subaortic flow velocity was obtained by pulsed-wave Doppler from the apical 5-chamber view. The LV ejection time was measured as the interval between the onset of forward aortic flow and the aortic valve closure artifact.

Dyssynchrony-related echocardiography.

- (1) LV systolic dyssynchrony: time-to-peak systolic velocity (Ts) and the standard deviation (s.d.) of 12 LV segments (Ts-SD12) were calculated with reference to the QRS complex.¹ Tissue Doppler time-velocity curves were derived from the following 12 sites: septal, lateral, anterior, inferior, antero-septal and posterior at both basal and mid-levels from the apical 4-, 3- and 2-chambers. The maximal difference between peak systolic velocities of any 2 of the 12 segments (Ts-Max) was also calculated.¹⁸ The time delay between Ts at the LV basal lateral and septal segments (Ts-LS) was measured.^{19,20} A Ts-SD12 ≥ 33 or Ts-Max ≥ 100 ms was regarded as the presence of LV systolic dyssynchrony.²¹
- (2) LV diastolic dyssynchrony: the time-to-peak myocardial early diastolic velocity (Te) of the 12 LV segments were measured with reference to the QRS complex and the s.d. of Te of all 12 LV segments (Te-SD12), and the maximal difference in Te between any 2 of the 12 LV segments (Te-Max) was calculated. A Te-SD12 ≥ 34 or Te-Max ≥ 113 ms was regarded as the presence of diastolic dyssynchrony.²¹
- (3) Contractile diastolic dyssynchrony: the sum of the time of strain tracing exceeding aortic valve closure on the overall 12 LV basal and mid-segments (oExcT) was measured.²²
- (4) Each parameter was obtained from three consecutive cardiac cycles and was only included in the algorithm for <10% beat-to-beat variation to improve reproducibility and accuracy. Intraobserver variability was calculated as the mean absolute difference in LV systolic dyssynchrony measurements divided by the original measurements and expressed as a percentage. The intraobserver variabilities of Ts-SD12, Ts-Max, Te-SD12, Te-Max and oExcT were found to be 6.8%, 7.0%, 6.5%, 6.6% and 5.9%, respectively.

Statistical analyses

On the basis of the results of the preliminary data comparing hypertensive patients with and without LV systolic dyssynchrony, we assumed 25% (derived from a one-half difference between two groups) improvement of Ts-SD12 in the group with LV systolic dyssynchrony and no interval change in the group without LV systolic dyssynchrony. Calculation of the sample size was based on a two-sided alpha level of 0.05 and 80% power. The total sample size was estimated to be 60 patients (1:1 assigned per group) for the trial on the expectation of 10% patient loss during echocardiography follow-up. The baseline characteristics of the patients were analyzed according to the presence or absence of LV systolic dyssynchrony. Continuous variables were expressed as the mean \pm s.d. and compared using an unpaired *t*-test. Categorical variables were expressed as a number (percentage) and compared using a χ^2 -test or Fisher's exact test (if there was an expected cell value <5). Changes of clinical and echocardiographic measurements before and after antihypertensive therapy were compared with paired *t*-tests. Linear associations between two variables were compared by Pearson's correlation coefficient (*r*) with additional adjustments for potential confounders. Analysis of covariance was performed to compare the parameters between the two groups after adjustments for potential confounders, which were $P < 0.20$ in the univariate analysis, age and gender. Statistical significance was set to $P < 0.05$. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient and baseline clinical characteristics

A total of 78 patients fulfilling the inclusion and exclusion criteria were initially evaluated and underwent echocardiographic examination. Of those, 18 were excluded because the images were not suitable for

Table 1 Baseline clinical characteristics of the study population

	HT with LV systolic dyssynchrony (Group 1, n=29)	HT without LV systolic dyssynchrony (Group 2, n=31)	P-values
Age (years)	53 ± 9	55 ± 10	0.439
Male gender, n (%)	13 (44.8)	19 (61.3)	0.154
Body mass index (kg m ⁻²)	26.0 ± 2.8	25.0 ± 3.2	0.175
SBP (mm Hg) at office	162 ± 17	157 ± 17	0.264
DBP (mm Hg) at office	98 ± 14	96 ± 11	0.521
QRS duration (ms)	85 ± 15	86 ± 13	0.886
Heart rate (beats per minute)	68 ± 8	69 ± 10	0.711
Fasting plasma glucose (mg dl ⁻¹)	110 ± 11	108 ± 12	0.905
Hyperlipidemia, n (%)	13 (44.8)	22 (71.0)	0.040
Metabolic syndrome, n (%)	15 (51.7)	18 (41.9)	0.448
Estimated GFR by MDRD formula (ml min ⁻¹ per 1.73 m ²)	84.5 ± 16.6	81.5 ± 11.7	0.413
Current smoker, n (%)	3 (10.3)	12 (38.7)	0.011
Hs-CRP (mg dl ⁻¹)	0.22 ± 0.20	0.23 ± 0.18	0.786

Abbreviations: DBP, diastolic blood pressure; GFR, glomerular filtration rate; Hs-CRP, high-sensitive C-reactive protein; HT, hypertension; LV, left ventricular; MDRD, Modification of Diet in Renal Disease Study Group; n, number; SBP, systolic blood pressure. Values are arithmetic mean ± s.d.

Table 2 Classes of medical treatment in the hypertensive patients

	HT with LV systolic dyssynchrony (Group 1, n=29)	HT without LV systolic dyssynchrony (Group 2, n=31)	P-values
<i>Anti-hypertensive treatment</i>			
ARB, n (%)	29 (100.0)	31 (100.0)	—
Thiazide, n (%)	22 (75.9)	20 (64.5)	0.338
β-blockers, n (%)	12 (41.4)	9 (29.0)	0.316
Calcium antagonists, n (%)	1 (3.4)	0 (0.0)	0.297
Number of used drugs	2.2 ± 0.9	1.9 ± 0.8	0.214
Patients with achieving target BP goal, n (%)	25 (86.2)	26 (83.9)	0.800

Abbreviations: ARB, angiotensin receptor blocker; HT, hypertension; LV, left ventricular; n, number; target blood pressure (BP) goal, <140/90 mm Hg. Values are arithmetic mean ± s.d.

evaluating dyssynchrony parameters. Of the 60 patients enrolled, 29 revealed LV systolic dyssynchrony (group 1), whereas the others did not (group 2). Among the patients with LV systolic dyssynchrony, the proportion who had a Ts-SD12 ≥ 33 ms was 100% (29 of 29 patients), and the proportion who had a Ts-Max ≥ 100 ms was 82.8% (24 of 29 patients). Follow-up echocardiography was performed after a 6-month antihypertensive treatment.

The baseline clinical characteristics of the patients are summarized in Table 1. Patients in group 1 experienced less hyperlipidemia and represented fewer current smokers than those in group 2.

Antihypertensive treatment

There were no significant differences in the classes of medications, numbers of drugs or percentage of achieving a target BP goal (<140/90 mm Hg) between the two groups (Table 2).

Baseline echocardiographic measurements

The parameters of conventional echocardiography at baseline were not significantly different between groups 1 and 2 (Table 3). Both groups demonstrated normal systolic and diastolic function at baseline. However, as expected, patients in group 1 had severe LV systolic dyssynchrony (Ts-SD12, *P*<0.001; Ts-Max, *P*<0.001; and Ts-LS, *P*<0.001) compared with the group 2 patients (Table 4).

Changes in BP and conventional echocardiographic measurements after antihypertensive treatment

After 6 months of antihypertensive treatment, all of the patients experienced significant improvements in systolic BP, diastolic BP, the mean annulus E' and the mean annulus E'/A' ratio compared with baseline (Table 3). In addition, the group 1 patients demonstrated significant improvements in the LV mass index (LVMI), mitral E/A ratio and mean annulus S' after antihypertensive treatment, compared with baseline.

Changes in dyssynchrony parameters of echocardiography after 6 months of antihypertensive treatment

Table 4 summarizes the changes in the LV dyssynchrony parameters after antihypertensive treatment. Antihypertensive treatment significantly improved LV systolic dyssynchrony for the group 1, but not the group 2, patients. After adjustment for age, gender, body mass index, hyperlipidemia and current smoking status, the improvement of LV dyssynchrony among group 1 patients remained significant (Ts-SD12, *P*<0.001; Ts-Max, *P*=0.004; and Ts-LS, *P*<0.001). However, the values of Ts-SD12 and Ts-Max after antihypertensive treatment in group 1 patients were significantly greater than those of the group 2 patients (Ts-SD12, *P*=0.014; Ts-Max, *P*=0.024; and Ts-LS, *P*=0.015). In addition, global, atrioventricular and interventricular dyssynchrony

Table 3 Effects of antihypertensive treatment on clinical characteristics and standard echocardiography in the hypertensive patients

	HT with LV systolic dyssynchrony (Group 1, n=29)				HT without LV systolic dyssynchrony (Group 2, n=31)			
	Baseline	After 6 months	Δ change (95% CI)	P-values (paired t-test)	Baseline	After 6 months	Δ change (95% CI)	P-values (paired t-test)
SBP (mm Hg) at office	162 ± 17	128 ± 11	-34 (-39 to -28)	<0.001	157 ± 17	130 ± 10	-27 (-34 to -19)	<0.001
DBP (mm Hg) at office	98 ± 14	80 ± 6	-18 (-23 to -14)	<0.001	96 ± 11	83 ± 9	-13 (-18 to -9)	<0.001
QRS duration (ms)	85 ± 15	82 ± 13	-3 (-8 to 3)	0.250	86 ± 13	84 ± 13	-2 (-7 to 3)	0.323
Heart rate (beats per minute)	68 ± 8	68 ± 10	0.0 (-5 to 4)	0.936	69 ± 10	69 ± 11	0.0 (-4 to 3)	0.798
<i>LV size and function</i>								
Ejection fraction (%)	64.7 ± 5.6	66.1 ± 7.2	1.4 (-1.3 to 4.1)	0.294	64.4 ± 7.5	63.6 ± 7.5	-0.7 (-4.2 to 2.7)	0.672
End-diastolic volume (ml)	68.7 ± 18.9	66.0 ± 17.1	-2.7 (-9.1 to 3.7)	0.397	64.3 ± 20.0	63.4 ± 17.9	-0.9 (-7.3 to 5.6)	0.786
End-systolic volume (ml)	24.5 ± 8.4	22.6 ± 7.9	-1.9 (-5.4 to 1.5)	0.262	23.5 ± 10.5	22.8 ± 7.7	-0.7 (-4.5 to 3.0)	0.698
LV mass index (g m ⁻²)	102.5 ± 33.1	90.4 ± 24.2	-12.1 (-21.8 to -2.3)	0.017	106.0 ± 30.3	94.6 ± 25.7	-11.4 (-23.0 to 0.1)	0.052
Mitral E wave (cm s ⁻¹)	74.4 ± 18.1	76.8 ± 19.3	0.12 (0.02 to 0.22)	0.339	66.5 ± 14.6	68.2 ± 16.6	0.07 (-0.02 to 0.15)	0.551
Mitral E/A ratio	0.94 ± 0.26	1.05 ± 0.31	-4.1 (-24.0 to 15.7)	0.022	0.93 ± 0.36	1.00 ± 0.37	0.0 (-22 to 22)	0.135
Deceleration time of mitral E (ms)	181 ± 45	177 ± 37	-0.6 (-1.5 to 0.3)	0.672	199 ± 60	198 ± 51	-1.1 (-2.0 to -0.3)	0.979
Isovolumic relaxation time (ms)	84 ± 22	82 ± 21	0.7 (0.2 to 1.3)	0.315	86 ± 25	91 ± 21	0.5 (-0.1 to 1.0)	0.263
Mitral E/E' (average of septal and lateral annulus)	9.9 ± 2.2	9.3 ± 2.3	1.0 (0.5 to 1.5)	0.165	9.6 ± 2.0	8.5 ± 2.6	0.8 (0.4 to 1.2)	0.012
Mean annulus S' (cm s ⁻¹)	7.6 ± 1.0	8.3 ± 1.4	0.1 (-0.4 to 0.7)	0.012	7.9 ± 1.3	8.4 ± 1.3	0.1 (-0.4 to 0.5)	0.084
Mean annulus E' (cm s ⁻¹)	7.5 ± 2.3	8.6 ± 2.6	0.09 (0.01 to 0.17)	<0.001	7.4 ± 2.5	8.2 ± 2.5	0.08 (0.02 to 0.13)	<0.001
Mean annulus A' (cm s ⁻¹)	10.2 ± 1.6	10.3 ± 1.4	1.4 (-1.3 to 4.1)	0.670	9.5 ± 1.4	9.6 ± 1.3	-0.7 (-4.2 to 2.7)	0.833
Mean annulus E'/A' ratio	0.76 ± 0.26	0.85 ± 0.28	-2.7 (-9.1 to 3.7)	0.021	0.80 ± 0.31	0.87 ± 0.32	-0.9 (-7.3 to 5.6)	0.005

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HT, hypertension; LV, left ventricular; Mean annulus A', mean myocardial late diastolic velocity of four annulus of LV segments; Mean annulus E', mean myocardial early diastolic velocity of four annulus of LV ventricular segments; Mean annulus S', mean myocardial systolic velocity of four annulus of LV segments; Mitral E/A, peak early diastolic mitral flow velocity/peak late diastolic mitral flow velocity; n, number; SBP, systolic blood pressure; Δ , value of follow-up minus value of baseline. Values are arithmetic mean \pm s.d.

Table 4 Effects of antihypertensive treatment on dyssynchrony in the hypertensive patients

	HT with LV systolic dyssynchrony (Group 1, n=29)				HT without LV systolic dyssynchrony (Group 2, n=31)			
	Baseline	After 6 months	Δ change (95% CI)	P-values (paired t-test)	Baseline	After 6 months	Δ change (95% CI)	P-values (paired t-test)
<i>LV systolic dyssynchrony</i>								
Ts-SD12 (ms)	48.6 ± 11.1*	35.6 ± 16.5†	-13.1 (-19.8 to -6.4)††	<0.001	23.1 ± 8.3	25.0 ± 15.7	1.9 (-5.3 to 9.1)	0.592
Ts-Max (ms)	133.4 ± 38.2*	99.4 ± 43.6†	-34.0 (-55.2 to -12.9)††	0.003	99.4 ± 27.3	72.7 ± 45.1	4.7 (-16.8 to 26.1)	0.659
Ts-LS (ms)	89.4 ± 38.4*	57.7 ± 89.4†	-31.6 (-50.9 to -12.4)††	0.002	21.8 ± 23.9	32.5 ± 29.3	10.7 (-3.5 to 24.9)	0.134
<i>LV diastolic dyssynchrony</i>								
Te-SD12 (ms)	21.0 ± 8.1	19.8 ± 6.7	-1.2 (-4.1 to 1.7)	0.414	24.0 ± 12.9	23.7 ± 12.2	-0.3 (-5.1 to 4.5)	0.893
Te-Max (ms)	69.5 ± 26.1	61.2 ± 19.5	-8.3 (-18.3 to 1.8)	0.102	74.7 ± 36.8	74.4 ± 37.7	-0.3 (-14.2 to 13.5)	0.960
<i>Contractile diastolic dyssynchrony</i>								
oExcT (ms)	559.7 ± 329.4	431.0 ± 208.7	-128.7 (-275.4 to 18.0)	0.083	526.8 ± 305.4	400.4 ± 162.5	-126.4 (-243.8 to -9.0)	0.036

Abbreviations: CI, confidence interval; HT, hypertension; LV, left ventricular; n, number; oExcT, sum of the time of strain tracing exceeding aortic valve closure on the overall 12 LV segments; Te-Max, maximal difference between peak early diastolic velocities of any 2 of the 12 LV segments; Te-SD12, s.d. of 12 LV segments time-to-peak early diastolic velocities; Ts-LS, time delay between time-to-peak systolic velocities at the LV basal lateral and septal segments; Ts-Max, maximal difference between peak systolic velocities of any 2 of the 12 segments; Ts-SD12, s.d. of 12 LV segments time-to-peak systolic velocities; Δ , value of follow-up minus value of baseline. Values are arithmetic mean \pm s.d.

* $P < 0.05$ vs. baseline in group 2. † $P < 0.05$ vs. after 6 months in group 2. †† $P < 0.05$ vs. Δ change in group 2.

between two groups were not different before and after antihypertensive treatment (Supplementary Tables 1 and 2).

Relationships between changes in LV systolic dyssynchrony and other parameters

Linear relationships between changes in LV systolic dyssynchrony and other parameters that demonstrated significant changes after medical treatment were analyzed after adjustment for potential confounding

factors, including age, gender, body mass index, fasting plasma glucose, hyperlipidemia, estimated glomerular filtration rate, current smoking status and change in heart rate (Table 5). The changes in LV systolic dyssynchrony (Ts-SD12 and Ts-Max) were significantly associated with changes in the mean annulus E' velocity, the mean annulus S' velocity and the mean annulus E'/A' ratio, but not with BP and LVMI. In particular, mean annulus velocity was associated with the severity of LV systolic dyssynchrony at baseline (Supplementary Table 3).

Table 5 Linear correlations between changes of LV systolic dyssynchrony (Δ Ts-SD12 or Δ Ts-Max) and other parameters in all hypertensive patients

Variables	R	P-values
<i>Model^a for ΔTs-SD12</i>		
Δ SBP (mm Hg) at office	0.246	0.079
Δ DBP (mm Hg) at office	0.198	0.160
Δ LV mass index (g m^{-2})	0.069	0.627
Δ Mitral E/A ratio	-0.108	0.446
Δ Mean annulus E' (cm s^{-1})	-0.340	0.014
Δ Mean annulus S' (cm s^{-1})	-0.308	0.026
Δ Mean annulus E'/A' ratio	-0.289	0.038
<i>Model^a for ΔTs-Max</i>		
Δ SBP (mm Hg) at office	0.241	0.085
Δ DBP (mm Hg) at office	0.264	0.058
Δ LV mass index (g m^{-2})	0.051	0.719
Δ Mitral E/A ratio	-0.051	0.718
Δ Mean annulus E' (cm s^{-1})	-0.347	0.012
Δ Mean annulus S' (cm s^{-1})	-0.278	0.046
Δ Mean annulus E'/A' ratio	-0.271	0.052

Abbreviations: DBP, diastolic blood pressure; Δ , value of follow-up minus value of baseline; LV, left ventricular; Mean annulus A', mean myocardial late diastolic velocity of four annulus of LV segments; Mean annulus E', mean myocardial early diastolic velocity of four annulus of LV ventricular segments; Mean annulus S', mean myocardial systolic velocity of four annulus of LV segments; SBP, systolic blood pressure.

^aAdjusted for age, sex, body mass index, fasting plasma glucose, hyperlipidemia, estimated glomerular filtration rate, current smoker and change of heart rate.

DISCUSSION

In this trial of patients with uncomplicated primary hypertension that had never been treated, antihypertensive treatment significantly reversed LV systolic dyssynchrony. The benefit was observed among patients with LV systolic dyssynchrony at baseline, but not among patients without LV systolic dyssynchrony. After adjustment for confounding factors, medical treatment in patients with LV systolic dyssynchrony was also beneficial. In addition, the reversal of LV systolic dyssynchrony was significantly and independently associated with an improvement in subclinical systolic (annulus S' velocity) and diastolic (annulus E' velocity and annulus E'/A' ratio) function. Our results, together with those of a previous study,²³ provide evidence that a change in LV systolic dyssynchrony is associated with a transmitral flow pattern or annulus velocity. Our study population is representative of patients with new onset hypertension. All patients demonstrated narrow QRS complexes without HF and were naïve to antihypertensive medications.

Previous trials have focused on patients with structural heart disease, including CAD,³ hypertrophic cardiomyopathy,⁵ dilated cardiomyopathy⁴ and subsequent HF.¹ LV dyssynchrony is known to impair the function of a failing ventricle, resulting in the worsening of symptoms and clinical outcomes in patients with HF.^{24,25} LV dyssynchrony is associated with the development of LV remodeling after acute myocardial infarction²⁶ and increases the risk of new-onset HF in patients with hypertension.²⁷ The effects of medical treatment on dyssynchrony in patients with CAD,²⁸ hypertrophic cardiomyopathy,²⁹ dilated cardiomyopathy³⁰ and HF³⁰⁻³² have been reported, but patients with hypertension and a structurally normal heart have not been evaluated. Our trial demonstrated the benefit of chronic antihypertensive treatment on dyssynchrony in patients with early stage hypertension. These findings emphasize the potential importance of dyssynchrony as a pharmacological target and predictor of adverse clinical events. Specifically in early stage hypertension,

dyssynchrony measurement may be a parameter for pharmacological interference on the transition from uncomplicated hypertension to HF. A longer-term study will be required to determine whether changes of LV dyssynchrony in hypertension are associated with the subsequent development of HF. The clinical implications and impacts of LV systolic dyssynchrony on morbidities and prognosis still remain unclear in hypertensive patients.

In this trial, the LVMI was significantly decreased after antihypertensive treatment. It is well known that angiotensin-converting enzyme inhibitors, ARBs and β -blockers, can reverse LV remodeling and LV hypertrophy.^{9,33} Our study lends further support to the notion that antihypertensive treatment can reduce LV hypertrophy; however, there was no significant relationship between the LVMI and the LV systolic dyssynchrony, which is in accordance with the results from a previous trial.³⁴ The benefits of antihypertensive treatment on LV systolic dyssynchrony may be independent of LVMI regression. In contrast, Yang *et al.*³⁵ demonstrated the association between LV systolic dyssynchrony and LV mass. Several factors could explain this discrepancy. First, in a study by Yang *et al.*, 24% of the patients had diabetes, and all of the patients had already been taking antihypertensive medication, whereas we included only treatment-naïve hypertensives and non-diabetics. Second, although there were many confounding factors, including cardiac status, comorbidities and medications, they only performed univariate analysis; the significance can be changed in a multivariate analysis.

The high severity and prevalence of dyssynchrony in treatment-naïve patients with uncomplicated hypertension⁸ may be explained, at least in part, by myocardial fibrosis,³⁶ exaggerated accumulation of collagen fibers,³⁷ altered myocardial glucose metabolism,³⁸ amplified transmural repolarization dispersion caused by LV hypertrophy³⁹ and long-term cardiac memory.⁴⁰ Therefore, the mechanisms by which medical treatment could lead to the reversal of LV systolic dyssynchrony can be explained by substantial improvements in the above-mentioned causes. In addition, the BP-lowering effect and subsequent reduction of afterload may have an important role.

Some regional contractile events can be shifted in the diastolic phase. Mechanical dyssynchrony in the systolic phase has been an important issue, but delayed LV contractions in the diastolic phase after aortic valve closure have not received focus. Contractile diastolic dyssynchrony can occur independently of delayed activation in various conditions, such as ischemia, LV hypertrophy or LV overload.⁴¹ The finding of an improvement in contractile diastolic dyssynchrony demonstrated that antihypertensive treatment may have a benefit in the diastolic as well as the systolic phase, in terms of longitudinal contraction. Further clinical investigations are needed to determine the real clinical impact of an improvement in contractile diastolic dyssynchrony.

The present study had some limitations. First, the study population was relatively small, and whether the subjects of this study represented the general population was not established. Second, we used the most popular TDI method to measure LV dyssynchrony, but there is no gold standard method for detecting mechanical dyssynchrony.⁴² Third, it is unclear whether our results were dependent on the escalation protocol of the antihypertensive drugs. Finally, it is uncertain whether the improvement of LV systolic dyssynchrony by antihypertensive treatment could be maintained beyond 6 months.

In conclusion, the present study confirmed that chronic antihypertensive treatment significantly reverses LV systolic dyssynchrony and simultaneously improves subclinical systolic and diastolic function in treatment-naïve hypertensive patients. Further studies are warranted to determine whether improvements in dyssynchrony prevent HF and adverse cardiovascular events.

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Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)