Improvement in Left Ventricular Systolic Dyssynchrony in Hypertensive Patients After Treatment of Hypertension

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ABSTRACT

Background and Objectives: Left ventricular (LV) dyssynchrony has been commonly detected among hypertensive patients with normal LV systolic function and no evidence of congestive heart failure. The purpose of our study was to assess the changes in LV systolic dyssynchrony (SDS$_{LV}$) among hypertensive patients after antihypertensive treatment, and to determine the relationship between SDS$_{LV}$ and other conventional echocardiographic parameters. Subjects and Methods: Forty one hypertensive patients with normal LV ejection fraction were enrolled. By performing a conventional echocardiographic study, the SDS$_{LV}$ was measured as the time difference between the shortest and longest time of the peak myocardial systolic velocities among 12 segments of the basal and mid-levels of the 3 apical views, and radial dyssynchrony of the basal (RDS$_{base}$) and mid-levels (RDS$_{mid}$) measured as the time difference between the earliest and latest peak values on the radial strain curves of each level of the parasternal short-axis views. Results: Compared to baseline after six months of antihypertensive treatment, the SDS$_{LV}$ improved significantly (48.7 ± 37.9 ms vs. 29.5 ± 34.1 ms, p = 0.020). Also the RDS$_{base}$ and RDS$_{mid}$ improved significantly in respect to the baseline values (129.9 ± 136.3 ms vs. 38.8 ± 45.4 ms, p = 0.002 and 75.2 ± 63.8 ms vs. 28.2 ± 37.7 ms, respectively, p<0.001). Conclusion: The severity of SDS$_{LV}$ improved with antihypertensive treatment, and was associated with the regression of LV mass. Furthermore, it might precede improvement in the mitral inflow pattern, as assessed by conventional echocardiography, so that early detection of the benefit of antihypertensive treatment may be possible.

KEY WORDS: Hypertension; Left ventricular dyssynchrony.

Introduction

Hypertension has been regarded as a major cause of heart failure with preserved left ventricular (LV) systolic function as well as increased incidence of cardiovascular events. In hypertensive patients, abnormal LV diastolic properties detected by echocardiographic studies are implicated in the main underlying pathophysologies. Also a subtle but detectable LV systolic impairment has been reported, frequently accompanied by diastolic dysfunction despite a normal ejection fraction (EF).

Furthermore, mechanical dyssynchrony of LV contraction as measured by tissue Doppler imaging (TDI), as opposed to QRS complex width, has evolved as a parameter for identifying patients with severely decreased LV systolic function who might benefit from cardiac resynchronization therapy (CRT) through the reverse remodeling of the deteriorated LV. Recent studies have demonstrated that LV dyssynchrony is not confined to these patients and is widely found among patients with preserved LV systolic function. Furthermore, it is reported that LV systolic or diastolic dyssynchrony are commonly detected among hypertensive patients with a normal LV systolic function, even in patients with no evidence of congestive heart failure.

Whereas anatomical changes such as LV hypertrophy or enlargement in hypertensive patients have been known to regress as blood pressure is lowered, it has not been well determined...
whether LV dyssynchrony can be improved or not. The purpose of this study was to assess the changes in LV systolic dyssynchrony (SDS\textsubscript{LV}) among hypertensive patients after antihypertensive treatment, and to determine the relationship between SDS\textsubscript{LV} and other conventional echocardiographic parameters.

Subjects and Methods

Subjects

Newly diagnosed hypertensive patients, who needed antihypertensive medication according to the “Seventh Report of the Joint National Committee” guidelines,\textsuperscript{6} were enrolled into the study during echocardiography and confirmed as eligible for TDI and two dimensional speckle tracking image (2D-STI). Patients with a decreased left ventricular ejection fraction (LVEF: <50%) or symptoms of heart failure according to the Framingham criteria\textsuperscript{10} were excluded. Exclusion criteria were moderate to severe valvular heart disease, atrial fibrillation, a bundle branch block pattern on the surface electrocardiogram (ECG), cardiomyopathies on echocardiography, and coronary artery disease by a clinical assessment. A total of 41 patients were enrolled.

Blood pressure measurement and treatment

While screening, a sitting blood pressure was measured three times using a manual cuff and stethoscope, with at least five minute intervals between each measurement, after resting for more than five minutes. The study eligibility required an average systolic blood pressure (SBP) of more than 160 mmHg or an average diastolic blood pressure (DBP) of more than 100 mmHg. Combination therapy was initially prescribed using angiotensin II receptor blockers (ARBs) with hydrochlorothiazide. The average SBP and DBP were evaluated at two week intervals until a target blood pressure level that was recommended by the “Seventh Report of the Joint National Committee” guidelines was reached. Calcium channel blockers (CCBs) were added when the initial combination therapy did not achieve the target blood pressure level. The outcome of the antihypertensive treatment was assessed six months later.

Blood chemistry examinations and echocardiographic studies were performed twice, once at the initial enrollment and once after six months.

Conventional echocardiographic study

Two-dimensional and Doppler echocardiographic studies were performed using a 3.5 MHz transducer (Vivid 7, Vingmed-General Electric). The LVEF was measured in the apical 4-, and 2-chamber views using a modified Simpson’s formula. A preserved LVEF was regarded as an EF greater than or equal to 50%. The wall-motion score index was also examined in order to rule out any patients with regional wall motion abnormalities. As described in a previous study,\textsuperscript{11} pulsed-wave Doppler echocardiography was conducted in the apical 4-chamber view to obtain the mitral inflow profile measurements such as E-, A-wave velocity, E-deceleration time, and E/A ratio. TDI was also performed with a 1-2 mm sample volume at the septal side of the mitral annulus from the apical 4-chamber view in order to measure the systolic and diastolic mitral annulus velocities.

Assessment of left ventricular systolic dyssynchrony using tissue Doppler imaging and two dimensional speckle tracking image

After at least three consecutive beats were stored during the conventional echocardiographic studies, the images were analyzed offline with the aid of a customized software package (EchoPac, version 5.1.1, Vingmed-General Electric). To assess the SDS\textsubscript{LV}, the peak myocardial systolic velocity of the tissue Doppler signal was measured using the onset of the QRS complex as the reference point wherein the basal segments were scanned just above the mitral annulus, and the mid segments at the papillary muscle level. SDS\textsubscript{LV} was defined as a time difference between the shortest and longest time of the peak myocardial systolic velocities among the 12 segments (Fig. 1A).

At the basal and papillary muscle level of the short-axis view, routine gray scale images were also acquired to obtain the 2D-STI data as previously described in detail.\textsuperscript{12,13} An end-systolic circular region of interest (ROI) was traced through the cardiac border using a point-and-click technique to adjust the tracking of all 6 segments. The location shift of the acoustic markers (speckles) in the ROI from frame to frame, which represented tissue movement, provided the spatial and temporal data for calculating the velocity vectors as moving further apart or closer together. A series of regional strain vectors were calculated as the changes in the length independent of the initial length. Myocardial thickening was represented as a positive value of the strain, whereas myocardial thinning was represented as a negative value of the strain. The customized software package automatically analyzed and presented the radial strain curves of each segment, which were used to assess the radial dyssynchrony defined as the time difference between the earliest and latest peak values on the radial strain curves of each level (RDS\textsubscript{base} and RDS\textsubscript{mid} for the radial dyssynchrony of the mitral and papillary muscle levels of the parasternal short-axis view, respectively) (Fig. 1B).

Statistical analysis

Continuous data were presented as the mean value±standard deviation unless otherwise stated. The comparisons of the means between the initial and six month values were conducted by the paired t-test, and chi-square test for comparing categorical data. The relationship between the continuous variables was analyzed using a regression analysis, and the sel-
ection of the most powerful factor was performed using a forward stepwise multivariate analysis (Statistical Package for the Social Sciences version 17). A p ≤0.05 was used to define a significant result.

Interobserver and intraobserver variability were tested by independent analysis by two independent observers and by repeated measurement of these segments on another occasion by the same observer. To quantify the interobserver and intraobserver variability, the figure was expressed using Pearson’s correlation coefficient and also as the percentage (%) of the measured value as compared with the mean value.

Results

Baseline characteristics

The study included 20 women and 21 men: 41 patients in total. The mean age was 48.9±11.4 years ranging from 24 to 74 years. The mean body surface area and body mass index were 1.76±0.12 m² and 24.9±2.3 kg/m², respectively. Twelve patients had hyperlipidemia, and none had diabetes mellitus. For the initial management of the hypertension, a combination therapy (ARBs with diuretics) was prescribed for all patients. Fourteen patients additionally required CCBs to achieve the target blood pressure level (Table 1).

The initial SBP and DBP of the patients were 165.6±19.4 mmHg and 102.2±13.6 mmHg, respectively (mean BP: 123.3±12.6 mmHg, pulse pressure: 65.6±15.6 mmHg). The QRS duration and PR interval were 98.3±12.7 ms and 168.9±22.9 ms, respectively. According to the criteria of Sokolow and Lyon,[14] 25 of the patients presented with a left ventricular hypertrophic (LVH) pattern on the surface ECG (Table 1).

Changes in the hemodynamics, surface electrocardiogram parameters and pro B-type natriuretic peptide level after the antihypertensive treatment

After the antihypertensive treatment, the SBP and DBP averaged 131.9±5.4 mmHg and 82.5±9.1 mmHg respectively.
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Table 1. Baseline characteristics of hypertensive patients

| Parameters                        | Values          |
|----------------------------------|-----------------|
| Age (year)                       | 48.9±11.4       |
| Gender (M/F)                     | 21/20           |
| BSA (m²)                         | 1.76±0.12       |
| BMI (kg/m²)                      | 24.9±2.3        |
| Hyperlipidemia (n, %)            | 12 (29.3)       |
| Diabetes mellitus (n, %)         | None (0)        |
| Antihypertensive medication (n, %)|                |
| Initial combination therapy*     | 41/41 (100)     |
| CCB                             | 14/41 (34.2)    |

Calcium channel blockers (CCBs) were added when a target blood pressure was not achieved that was recommended by the “Seventh Report of the Joint National Committee” guidelines. *The initial combination therapy was composed of angiotensin II receptor blockers (ARBs) with hydrochlorothizide in all patients. M: male, F: female, BSA: body surface area, BMI: body mass index

These were significantly decreased (p<0.001, and p<0.001 respectively) and achieved the target blood pressure level. Also, the mean BP and pulse pressure decreased significantly (123.3±12.6 mmHg vs. 98.9±7.3 mmHg, p<0.001 and 65.6±15.6 mmHg vs. 49.4±7.2 mmHg, p<0.001, respectively). The QRS duration and PR interval had no significant changes while the LVH pattern decreased with marginal significance (25 (60.9%) vs. 12 (29.3%), p=0.070) (Table 2, Upper panel).

The level of pro B-type natriuretic peptide (pro-BNP) decreased from 142.6±294.7 pg/mL to 39.9±43.6 pg/mL with marginal significance after the antihypertensive treatment (p=0.053) (Table 2, Middle panel).

Analysis of the conventional echocardiographic parameters

The LV septal and posterior wall thicknesses during the end diastolic period significantly decreased after the antihypertensive treatment (1.15±0.19 cm vs. 1.07±0.14 cm, p=0.017 and 1.13±0.18 cm vs. 1.04±0.13 cm, p=0.031, respectively) whereas the LV dimension did not. In addition, the LV mass regressed significantly (227.6±57.5 g vs. 199.6±37.9 g, p=0.002), but the left atrial dimension represented no meaningful regression (Table 2, Lower panel). Furthermore, in the present study, among the parameters of blood pressure, the amount of regression in the LV mass was well correlated with the degree of decrease in the SBP (confidence interval (CI): 0.469-3.145, β=0.495, p=0.010).

In the pulsed-wave Doppler study, the parameters related to the mitral inflow patterns, as above-mentioned, did not show any significant alterations. However, the peak early diastolic mitral annulus velocity (E') and the ratio of the peak early diastolic mitral flow velocity to E' (E/E' ratio) exhibited a significant improvement in the TDI study (6.7±2.5 cm/sec vs. 8.0±2.6 cm/sec, p=0.017 and 13.0±4.9 cm/sec vs. 9.8±3.5 cm/sec, p=0.002) while the peak early systolic (Sm) and late diastolic annulus velocity (A') did not show any meaningful changes (Table 2, Lower panel).

Analysis of left ventricular the longitudinal dyssynchrony using tissue Doppler imaging

The SDS_LV exhibited a significant improvement after the an-
The present study demonstrated that the SDS$_{LV}$ in hypertensive patients can be improved by lowering blood pressure. At first, electrical dyssynchrony caused by left bundle branch block has been discerned to lead to further deterioration of LV systolic function in congestive heart failure, and is regarded as a surrogate for CRT. However, a widening of the QRS duration did not necessarily identify responders to CRT and a narrow QRS duration did not guarantee the absence of mechanical dyssynchrony in later studies. Furthermore, a number of myocardial imaging techniques based on echocardiography have been proven to be valuable for assessing mechanical dyssynchrony. Besides patients with systolic heart failure (SHF) or wide QRS complexes, LV systolic or diastolic dyssynchrony evaluated through these myocardial imaging techniques has been revealed to be more prevalent than expected with prevalences of 25.0% or 21.7%, respectively, in patients with a preserved LV systolic function (EF >50%), and they did not occur in parallel. While, for the purpose of a diagnosis, the threshold or cut-off value of dyssynchrony was arbitrarily determined to result in a prevalence of less than 5% of the normal population in the previous studies, the dyssynchrony itself was not an all-or-none phenomenon, but a continuous variable reflecting the discordance of the myocardial movement. Despite the variations in the cut-off values in the previous studies, dyssynchrony has a tendency to be less frequently observed in patients with diastolic heart failure (DHF) than in those with SHF, as well as being less common, but not rare, in the normal population. Wang et al. reported that medical therapy can improve LV dyssynchrony in patients with DHF, but not SDS$_{LV}$. This finding suggests that the pathophysiology of the LV dyssynchrony might, in part, be composed of reversible components depending on the cardiac status. To the best of our knowledge, there have been no studies evaluating the effects of antihypertensive treatment on the change in SDS$_{LV}$ among patients without heart failure. In the present study, performed in hypertensive patients with preserved LV systolic function, improvement in the SDS$_{LV}$ after antihypertensive treatment was seen when measured by the longitudinal and radial aspects.

In hypertensive patients, an abnormal LV relaxation with an elevated LV filling pressure secondary to a stiff, hypertrophied ventricle has been regarded as a cause of diastolic dysfunction. Recently, Yang et al. reported that SDS$_{LV}$ is common among hypertensive patients with a normal LV systolic function and no evidence of congestive heart failure when compared with baseline (129.9 ± 136.3 ms vs. 38.8 ± 45.4 ms, p=0.002 and 75.2 ± 63.8 ms vs. 28.2 ± 37.7 ms, respectively, p=0.001) (Table 3). In the multivariate regression analysis, the degree of improvement in the SDS$_{LV}$, r=0.94 (7.3%) and r=0.95 (6.5%) and r=0.94 (7.3%) for RDS$_{mid}$, r=0.98 (6.7%) and r=0.99 (7.8%) for RDS$_{base}$.

**Discussion**

The present study demonstrated that the SDS$_{LV}$ in hypertensive patients can be improved by lowering blood pressure. At first, electrical dyssynchrony caused by left bundle branch block has been discerned to lead to further deterioration of LV systolic function in congestive heart failure, and is regarded as a surrogate for CRT. However, a widening of the QRS duration did not necessarily identify responders to CRT and a narrow QRS duration did not guarantee the absence of mechanical dyssynchrony in later studies. Furthermore, a number of myocardial imaging techniques based on echocardiography have been proven to be valuable for assessing mechanical dyssynchrony. Besides patients with systolic heart failure (SHF) or wide QRS complexes, LV systolic or diastolic dyssynchrony evaluated through these myocardial imaging techniques has been revealed to be more prevalent than expected with prevalences of 25.0% or 21.7%, respectively, in patients with a preserved LV systolic function (EF >50%), and they did not occur in parallel. While, for the purpose of a diagnosis, the threshold or cut-off value of dyssynchrony was arbitrarily determined to result in a prevalence of less than 5% of the normal population in the previous studies, the dyssynchrony itself was not an all-or-none phenomenon, but a continuous variable reflecting the discordance of the myocardial movement. Despite the variations in the cut-off values in the previous studies, dyssynchrony has a tendency to be less frequently observed in patients with diastolic heart failure (DHF) than in those with SHF, as well as being less common, but not rare, in the normal population. Wang et al. reported that medical therapy can improve LV dyssynchrony in patients with DHF, but not SDS$_{LV}$. This finding suggests that the pathophysiology of the LV dyssynchrony might, in part, be composed of reversible components depending on the cardiac status. To the best of our knowledge, there have been no studies evaluating the effects of antihypertensive treatment on the change in SDS$_{LV}$ among patients without heart failure. In the present study, performed in hypertensive patients with preserved LV systolic function, improvement in the SDS$_{LV}$ after antihypertensive treatment was seen when measured by the longitudinal and radial aspects.

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pared to normotensive controls: SDS_{LV} was assessed by the “maximum T-P”, which is the maximal difference in the interval from the onset of the QRS complex to the peak of the systolic velocity on the pulsed tissue Doppler waveform in the 3 apical views, and deterioration of the LV synchrony seems to be associated with the LV remodeling process. Wang et al.\(^\text{20}\) reported that exercise could aggravate the SDS_{LV} in hypertensive patients when comparing those in a post-exercise state with those in a resting state. This finding suggests that an increase in the LV wall tension caused by an elevation in blood pressure during exercise could result in a temporal deterioration of the LV synchrony in susceptible conditions. Also a positive correlation with the N-terminal pro-BNP (NT-proBNP) level was found between the resting and post-exercise states. In the present study, the level of NT-proBNP tended to decrease with marginal significance after antihypertensive treatment.

We submit two possible mechanisms for the improvement in SDS_{LV}. The first possibility is the regression in LV hypertrophy that was observed in the present study, resulting in the decrease of LV mass from 227.6± 57.5 g at baseline to 199.6± 37.9 g after antihypertensive therapy. However, the degree of regression of LV mass after antihypertensive treatment, dependent on individual susceptibility, varied between patients to such an extent that we were unable to find an obvious linear correlation between the reduction of LV mass and the improvement of LV dyssynchrony. The second possible explanation is that the effect of lowering BP itself accounted to some extent for the immediate restoration of the LV synchrony, regardless of the regression in the LV hypertrophy, because decreased LV wall stress could ameliorate any regional heterogeneity of the coronary blood flow and regional wall motion.

Additionally, in the conventional echocardiographic studies, the pulsed-Doppler parameters of the mitral inflow and LVEF did not change significantly after antihypertensive therapy. But the parameters related with mitral annulus velocity such as E' and E/E' ratio were improved after antihypertensive treatment in the TDI study, which suggested that LV diastolic function improved with antihypertensive treatment. Also, improvements in the SDS_{LV} were elucidated by the TDI and 2D-STI studies. Therefore, as a clinical implication, measurement of longitudinal or radial dyssynchrony could be used for the early detection of any improvement in the LV mechanical function during antihypertensive treatment.

### Study limitations
The number of patients was relatively small in the present study. Therefore, it was not possible to elucidate the quantitative relationship between the degree of improvement in the SDS_{LV} and the amount of regression of LV hypertrophy. An examination with a larger number of patients is warranted to achieve a more accurate representation of improvement in SDS_{LV} associated with antihypertensive treatment.

In conclusion, the degree of SDS_{LV} can be improved by antihypertensive treatment. Furthermore, it might precede an improvement in the pulsed-Doppler parameters of mitral inflow, so that early detection of the benefit of antihypertensive treatment for LV myocardium may be possible.

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