J Cardiovasc Imaging. 2020 Oct;28(4):244-253
https://doi.org/10.4250/jcvi.2020.0025
pISSN 2586-7210·eISSN 2586-7296

Journal of Cardiovascular Imaging JCVI

Original Article

Check for updates

Changes in QRS Duration Are Associated with a Therapeutic Response to Sacubitril–valsartan in Heart Failure with Reduced Ejection Fraction

Bong-Joon Kim, MD*, Han-Su Park, MD*, Sung-Il Im, MD, PhD, Hyun-Su Kim, MD, PhD, Jung-Ho Heo, MD, PhD, Tae-Joon Cha, MD, PhD, and Kyoung-Im Cho, MD, PhD

Division of Cardiology, Department of Internal Medicine, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Korea

OPEN ACCESS

Received: Feb 19, 2020
Revised: Apr 30, 2020
Accepted: May 24, 2020

Address for Correspondence:
Kyoung-Im Cho, MD, PhD
Division of Cardiology, Department of Internal Medicine, Cardiovascular Research Institute, Kosin University School of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Korea.
E-mail: kyoungim74@gmail.com

*Bong-Joon Kim and Han-Su Park contributed equally to this work.

ORCID iDs
Bong-Joon Kim
https://orcid.org/0000-0002-5435-7449
Han-Su Park
https://orcid.org/0000-0001-5123-8383
Sung-Il Im
https://orcid.org/0000-0003-2544-2422
Jung-Ho Heo
https://orcid.org/0000-0002-6491-2426
Kyoung-Im Cho
https://orcid.org/0000-0002-5435-7449

ABSTRACT

BACKGROUND: Recent studies have demonstrated that angiotensin receptor neprilysin inhibitors (ARNIs) can reverse the cardiac remodeling effects that occur in heart failure with reduced ejection fraction (HFrEF). These studies have also suggested that ARNIs have favorable effects on ventricular dyssynchrony. We assessed the changes in QRS duration associated with ARNIs in patients with HFrEF.
METHODS: We retrospectively investigated patients with HFrEF (defined by a left ventricular ejection fraction [LVEF] ≤ 35%) who were treated with ARNIs for at least six months. We divided the patients into QRS shortening and non-QRS shortening groups according to their electrocardiogram (ECG) findings. We also compared changes in echocardiographic parameters between the groups.
RESULTS: A total of 68 patients with HFrEF were included (mean age: 62.5 years, 74.6% male). Twenty-one patients had significant ischemic heart disease (IHD). Thirty-five patients exhibited QRS-duration shortening on follow-up ECGs (mean change: −7.8 msec), and 33 patients showed no changes or increased QRS duration (mean change: 5.1 msec). The QRS shortening group exhibited significant improvement in LVEF (12.5 ± 15.3% vs. 1.7 ± 9.5%; p < 0.001) when compared with the non-QRS shortening group. The QRS shortening group also had significantly lower LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD) and LV mass index (LVMI) than did the non-QRS shortening group. The change in QRS duration was significantly correlated with the change in LVEF (r = -0.329, p = 0.011) and LVESD (r = 0.298, p = 0.022).
CONCLUSIONS: Among patients with HFrEF treated with ARNIs, the QRS shortening group showed favorable LV systolic function recovery, and reversal of cardiac remodeling compared to those of the non-QRS shortening group. Change in the QRS duration, which reflects LV synchrony, may be associated with response to ARNIs in patients with HFrEF.

Keywords: Heart failure reduced ejection fraction; Sacubitril–valsartan; QRS duration; Cardiac remodeling; Left ventricular synchrony

Journal of Cardiovascular Imaging JCVI

Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Angiotensin receptor neprilysin inhibitors (ARNIs), such as sacubitril/valsartan, are considered superior to enalapril in reducing the risks of death and hospitalization related to heart failure (HF) in symptomatic patients with reduced ejection fraction.[1] Sacubitril inhibits the enzyme neprilysin, which plays a role in the breakdown of natriuretic peptides, which ultimately increases natriuretic peptide levels and may have a natriuretic effect.[2] The inhibition of the renin–angiotensin–aldosterone system improves left ventricular ejection fraction (LVEF), antagonizes cardiac remodeling, and reduces the risk of cardiovascular death in patients with heart failure with reduced ejection fraction (HFrEF). ARNIs augment the inhibitory effects of valsartan alone by increasing the systemic exposure to the medication by 40%. This suggests that ARNIs would achieve greater anti-remodeling effects than does either valsartan or a neprilysin inhibitor alone. One meta-analysis showed that, even in the short-term, ARNIs distinctly improve LV size and hypertrophy compared to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in HFrEF patients.[3]

Cardiac reverse remodeling generally refers to improvements in damaged ventricular/atrial volume, dimension, and shape. The Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation (PRIME) study showed that ARNIs can reduce chronic functional mitral regurgitation (MR) in Korean patients with HFrEF.[4] These prior studies suggest that ARNIs have more favorable effects on ventricular dyssynchrony than do renin–angiotensin system blockers through cardiac reverse remodeling.

Synchronous contraction in the LV is closely associated with its performance. LV dyssynchrony, the dispersion of electrical activation, and myocardial contraction, all have negative impacts on effective LV contraction. These changes lead to progressive LV remodeling and impaired LV function that contribute to the development of HF.[5] It is well known that the QRS complex is significantly associated with LV dyssynchrony in dilated cardiomyopathy (DCMP) patients, and may be used to predict prognosis in patients with idiopathic DCM.[6] However, few studies have addressed how changes in the QRS duration influence the effect of ARNIs in HFrEF. Therefore, we evaluated how changes in the QRS duration, which reflect LV synchrony, are associated with response to ARNIs in patients with HFrEF.

METHODS

Study design and study population

This was a retrospective, observational single-center cohort study. We reviewed the medical records of 173 patients with HFrEF who were treated with ARNIs between January 2017 and December 2018 at Kosin University Gospel Hospital. Patients who were not treated with ARNIs for at least six months or who had no follow-up electrocardiogram (ECG) or echocardiogram were excluded. The demographic and comorbidity data were obtained from the medical records. We divided study participants into two groups according to changes in the QRS duration between baseline and follow-up ECGs. We focused on whether or not QRS is reduced to assess the effect of LV reverse remodeling after sacubitril/valsartan treatment. Therefore, we used the expression 'QRS shortening/non-QRS shortening.' If the QRS duration was shortened by >1 msec on the follow-up ECG in comparison with the baseline ECG, the patient was included in the QRS shortening group. In contrast, if the QRS duration was the same or wider on follow-up ECG (compared to baseline), then the patient

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

was included in the non-QRS shortening group. We compared changes in the following echocardiographic parameters between the groups: LVEF, LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LV mass index (LVMI) and E/E′. We also compared changes in the N-terminal pro B-type natriuretic peptide (NT-pro BNP) level between the two groups.

Hypertension (HTN) was defined by a systolic blood pressure (BP) of >140 mmHg or a diastolic BP of >90 mmHg, as recorded by repeated BP measurements or a previous diagnosis. Diabetes mellitus (DM) was defined as a fasting plasma glucose level of 126 mg/dL during two consecutive assessments, or current treatment for DM. We defined chronic kidney disease as an eGFR ≤ 60 on a baseline laboratory test. The presence of dyslipidemia was assumed if subjects were taking lipid-lowering drugs or had high cholesterol levels. Ischemic heart disease (IHD) was defined by coronary artery stenosis >50% on a coronary angiography or coronary angio CT, or history of a previous coronary artery bypass graft or percutaneous coronary intervention.

This study was approved by the Ethics Committee of Kosin University Gospel Hospital, Busan, South Korea (No. 2019-11-010). The need for written informed consent was waived because of the retrospective nature of the study.

ECG measurement

We carefully reviewed resting 12-lead surface ECGs that were recorded closest to the time of echocardiography. The QRS duration was measured on these ECGs. All ECG measurements were performed using the MUSE Editor version 7.1.1 software program (General Electric Company, Boston, MA, USA). This software program provides an electronic caliper tool that is accurate to 4 msec. The filter settings included speed 25 mm/s, and voltage standardization 10 mm/mV. The specific measurements included the QRS duration in lead V1. A QRS complex was defined by the presence of various RSR′ patterns in two or more contiguous leads, including the presence of an additional R wave (R′), more than one R′, notching in the upstroke of the R wave or a nadir in the S wave.[7] The QT interval was measured from the global QRS–STT complex, which was derived from the standard 12-lead ECG as the interval from QRS onset to T-wave offset (end). We used a linear formula to calculate the rate-corrected QT as recommended by a task force sponsored by professional organizations.[8]

Echocardiography measurements

Standard two-dimensional echocardiography was performed on all subjects in the left lateral decubitus position using a 3.5-MHz transducer (Philips iE33; Philips Medical Systems, Bothell, WA, USA). The echocardiography examiners were blinded to the patient information. Measurements of the diameter of the LV cavity, LVEDV, LVESV, and the LVMI were performed according to criteria outlined by the American Society of Echocardiography.[9] The LVEF was measured using Simpson's method. The pulsed-wave Doppler imaging of the trans-mitral LV inflow was performed in the apical four-chamber view, with the sample volume placed at the level of the mitral valve tips. The doppler variables were analyzed during three consecutive beats. The following measurements of the global LV diastolic function were also recorded: peak early (E) and late (A) diastolic mitral flow velocity and their ratio E/A and early (E′) diastolic mitral annular velocity. The right ventricular systolic function (RVSP; in mmHg) was calculated from the maximal TR Vmax using the simplified Bernoulli formula, as follows: $4 \times (\text{TR Vmax})^2$ + right atrial (RA) pressure (RA pressure was determined according to the diameter and collapse of the inferior vena cava, as recommended by ASE guidelines).

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

The peak systolic strain was measured and averaged to assess global longitudinal myocardial regional function (GLS). The endocardial borders were traced at the end-systolic frame. An automated tracking algorithm outlined the myocardium in successive frames throughout the cardiac cycle. GLS was obtained by averaging all of the segment strain values from the apical 4-chamber, 2-chamber, and long axis views.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 25.0 for Windows software program (IBM Corp., Armonk, NY, USA). Data normality was tested using the Kolmogorov–Smirnov test. The values are expressed as means (± SD) for numerical variables or as numbers of participants and their percentages for categorical variables. Continuous variables were compared using the Student's t-test, Mann–Whitney U test and paired t-test. The categorical data were analyzed using the chi-squared test. Relationships between variables were examined with Pearson correlation coefficients. Multivariate logistic regression models for predicting a > 10% improvement in the LVEF were built to identify independently associated variables. Two-tailed p-values of <0.05 were considered statistically significant.

RESULTS

Of the 173 patients with HFrEF-treated ARNI, 68 patients were included in the final analysis. The mean patient age was 62.5 years old, and 74.6% were male. The mean follow up duration was 8.6 months. Twenty one patients had significant IHD and 19 patients had DCMP. Thirty-five patients exhibited QRS-duration shortening on follow-up ECG and 33 patients showed no changes or increased QRS duration (**Figure 1**). There were no differences in the following baseline characteristics between the groups: age, sex, prevalence of DM or chronic kidney disease (**Table 1**). The prevalence of HTN, in contrast, was statistically different between the groups (**Table 1**). Both groups had a similar prevalence of IHD (28.6% vs. 33.3%). During baseline echocardiography, the QRS shortening and non-QRS shortening groups demonstrated similar LVEF (29.8 ± 6.7 vs. 30.1 ± 7.5%; p = 0.878), LVEDD (59.7 ± 10.9 vs. 61.1 ± 6.9%; p = 0.550) and LVEDV (**Table 2**). There was no significant difference in the NT-pro BNP level (6,950.6 ± 10027.0 vs. 6,080.5 ± 10117.4 pg/dL, p = 0.731) between the two groups (**Supplementary Table 1**).

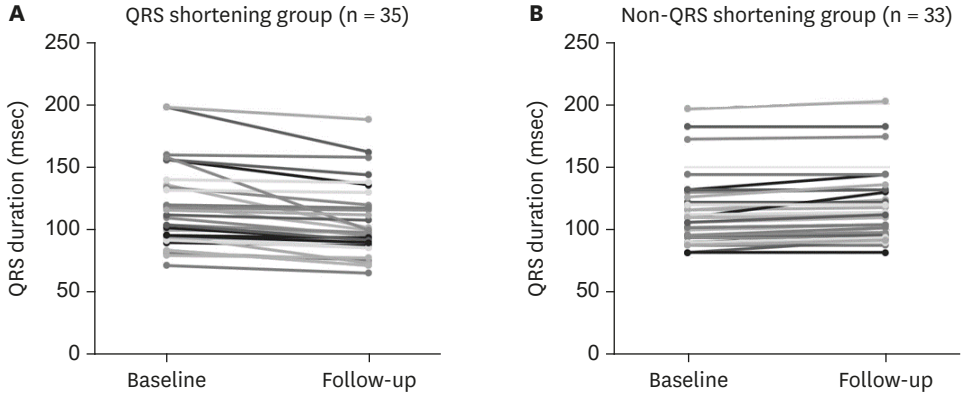

Figure 1. Change in QRS duration by group. Thirty-five patients exhibited QRS-duration shortening on follow-up electrocardiogram (A) and 33 patients showed no change or an increase in QRS duration (B).

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

Table 1. Baseline characteristics

	QRS shortening group (n = 35)	non-QRS shortening group (n = 33)	p-value
Age (years)	62.7 ± 15.8	62.1 ± 14.3	0.853
Male	20 (58.8)	28 (77.8)	0.123
Height (cm)	162.7 ± 8.4	164.8 ± 7.0	0.273
Body weight (kg)	66.8 ± 19.4	67.5 ± 13.9	0.873
BMI	25.0 ± 5.6	24.5 ± 4.2	0.670
HTN	11 (31.4)	21 (63.6)	0.014
DM	15 (42.9)	15 (45.5)	0.829
Dyslipidemia	6 (17.1)	5 (15.2)	0.824
CKD ≥ stage 3	11 (31.4)	7 (21.2)	0.415
Hemodialysis	3	2	
Stroke	3 (8.6)	2 (6.1)	0.692
Thyroid disease	3 (8.8)	2 (5.6)	0.669
Ischemic heart disease	10 (28.6)	11 (33.3)	0.794
CAOD 1VD	5	4	
CAOD 2VD	3	5	
CAOD 3VD	2	2	
Dilated cardiomyopathy	12 (34.3)	8 (24.2)	0.431
Dose of ARNI			
100 mg/day	22	17	
200 mg/day	10	8	
400 mg/day	3	8	
Previous medication			
RAS blocker	35 (100)	33 (100)	
Beta-blocker	28 (80.0)	29 (87.9)	0.514
CCB	5 (17.1)	6 (12.1)	0.749
Ivabradine	6 (11.8)	4 (16.7)	0.735
Furosemide	23 (65.7)	25 (75.8)	0.246
Spironolactone	24 (70.6)	25 (69.4)	0.431
Aspirin	8 (22.9)	9 (27.3)	0.782
Clopidogrel	14 (40.0)	11 (33.3)	0.621
Statin	27 (81.8)	27 (77.1)	0.767
NOAC	12 (34.3)	8 (24.2)	0.431
Warfarin	3 (14.7)	7 (21.2)	0.181

All values are presented as means ± SDs or numbers of patients (%).
ARNI: angiotensin receptor neprilysin inhibitor, BMI: body mass index, CAOD: coronary artery obstructive disease, CCB: calcium channel blocker, CKD: chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, NOAC: new oral anticoagulant, RAS: renin-angiotensin system, VD: vessel disease.

Table 2. Baseline echocardiography parameters

	QRS shortening group (n = 35)	non-QRS shortening group (n = 33)	p-value
LVEF (%)	29.8 ± 6.7	30.1 ± 7.5	0.878
LVEDD (mm)	59.7 ± 10.9	61.1 ± 6.9	0.550
LVESD (mm)	51.5 ± 11.2	51.2 ± 8.1	0.754
LVEDV (mL)	157.2 ± 89.0	172.1 ± 56.8	0.425
LVESV (mL)	110.2 ± 73.1	115.0 ± 49.3	0.757
IVSTd (mm)	10.9 ± 2.1	10.1 ± 1.7	0.080
PWTd (mm)	10.3 ± 1.5	9.7 ± 1.4	0.105
LVMI (g/m^2)	154.5 ± 41.2	142.6 ± 26.2	0.210
LA diameter (mm)	43.5 ± 8.1	45.8 ± 8.1	0.266
Aorta diameter (mm)	33.5 ± 3.8	34.1 ± 5.3	0.592
E velocity (cm/sec)	0.8 ± 0.3	0.9 ± 0.5	0.172
A velocity (cm/sec)	0.6 ± 0.3	0.6 ± 0.3	0.815
E/A ratio	1.5 ± 1.1	1.9 ± 1.5	0.420
E′	0.05 ± 0.02	0.04 ± 0.01	0.363
E/E′	18.2 ± 8.9	21.3 ± 10.4	0.208
RVSP (mmHg)	38.4 ± 16.0	44.3 ± 18.6	0.084
GLS (%)	−7.6 ± 4.4	−7.9 ± 3.7	0.821

All values are presented as means ± SDs.
E: peak early diastolic mitral filling velocity, E′: early diastolic mitral annular velocity, GLS: global longitudinal strain, IVSTd: diastolic interventricular septal wall thickness, LA: left atrium, LVEDD: left ventricular end-diastolic diameter, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic diameter, LVESV: left ventricular end-systolic volume, LVMI: left ventricular mass index, PWTd: diastolic posterior wall thickness, RVSP: right ventricle systolic pressure.

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

Table 3. Baseline and follow up electrocardiogram parameters

	QRS shortening group (n = 35)	non-QRS shortening group (n = 33)	p-value
Atrial fibrillation	10 (28.6)	9 (27.3)	0.905
RBBB	1	2	
LBBB	1	1	
RV pacing rhythm	1	1	
Baseline			
PR interval (msec)	183.0 ± 42.6	197.3 ± 56.6	0.330
QRS duration (msec)	115.3 ± 31.0	112.5 ± 28.6	0.704
QT interval (msec)	406.0 ± 54.9	404.7 ± 47.1	0.915
QTc interval (msec)	471.6 ± 43.9	470.1 ± 37.2	0.879
Follow up			
PR interval (msec)	188.2 ± 40.2	197.0 ± 46.4	0.489
QRS duration (msec)	108.4 ± 28.6	115.1 ± 28.0	0.339
QT interval (msec)	416.8 ± 70.0	423.0 ± 39.6	0.663
QTc interval (msec)	459.4 ± 37.5	466.0 ± 40.5	0.493

All values are presented means ± SDs or numbers (%).
LBBB: left bundle branch block, RBBB: right bundle branch block, RV: right ventricle.

With regard to ECG parameters (**Table 3**), both groups had a similar prevalence of atrial fibrillation (28.6% vs. 27.3%, p = 0.905). In the QRS shortening group, the baseline and follow-up QRS durations were 115.3 ± 31.0 msec and 108.4 ± 28.6 msec with a mean change of –7.8 msec. In the non-QRS shortening group, the baseline and follow-up QRS duration was 112.5 ± 28.6 msec and 115.1 ± 28.0 msec, respective, with a mean change of 5.1 msec.

On follow-up echocardiogram, the QRS shortening group exhibited more significant improvements in the LVEF (12.5 ± 15.3% vs. 1.7 ± 9.5%; p < 0.001) than the non-QRS shortening group (**Figure 2A**). The QRS shortening group also showed more a significant reduction in the LVEDD (-3.3 ± 6.1 mm vs. 0.5 ± 7.7 mm, p = 0.002), LVESD (-5.7 ± 8.1 mm vs. 0.9 ± 7.7 mm, p = 0.002), and LVMI (-16.4 ± 27.2 vs. -3.0 ± 16.9 g/m^2, p = 0.007) compared to those in the non-QRS shortening group (**Figure 2B**, **2C** and **2D**). On follow-up laboratory testing, the QRS shortening group showed a significant reduction in the NT-pro BNP level from baseline (5018.8 ± 8 vs. 7833.4 ± 11331.2 pg/dL, p = 0.034), while the non-QRS shortening group did not (10015.5 ± 12729.1 vs. 7774.8 ± 12070.3 pg/dL, p = 0.089). In the QRS shortening group, the E/E′ was reduced from baseline, but there was no statistical significance (p = 0.274).

According to Pearson correlation analysis, the change in QRS duration had a significant correlation with the change in LVEF (r = −0.329; p = 0.011) and LVESD (r = 0.298, p = 0.022) (**Figure 3**). The change in QRS duration also tended to be associated with changes in the LVEDD (r = 0.243, p = 0.064), LVMI (r = 0.259, p = 0.086) and E/E′ (r = 0.119, p = 0.390), although without statistical significance. Multivariate logistic regression analysis revealed that QRS shortening (odds ratio: 5.163; 95% confidence interval: 1.181–22.579; p = 0.029) was an independent predictor of LVEF (>10%) improvement after adjusting for age, sex, baseline LVEF and IHD (**Table 4**).

DISCUSSION

Patients with HFrEF have a highly variable prognosis. In clinical practice, it is important to predict a patient's response to medical treatment, especially when it may be poor, to identify those in whom an implantable cardioverter-defibrillator (ICD) or cardiac transplantation

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

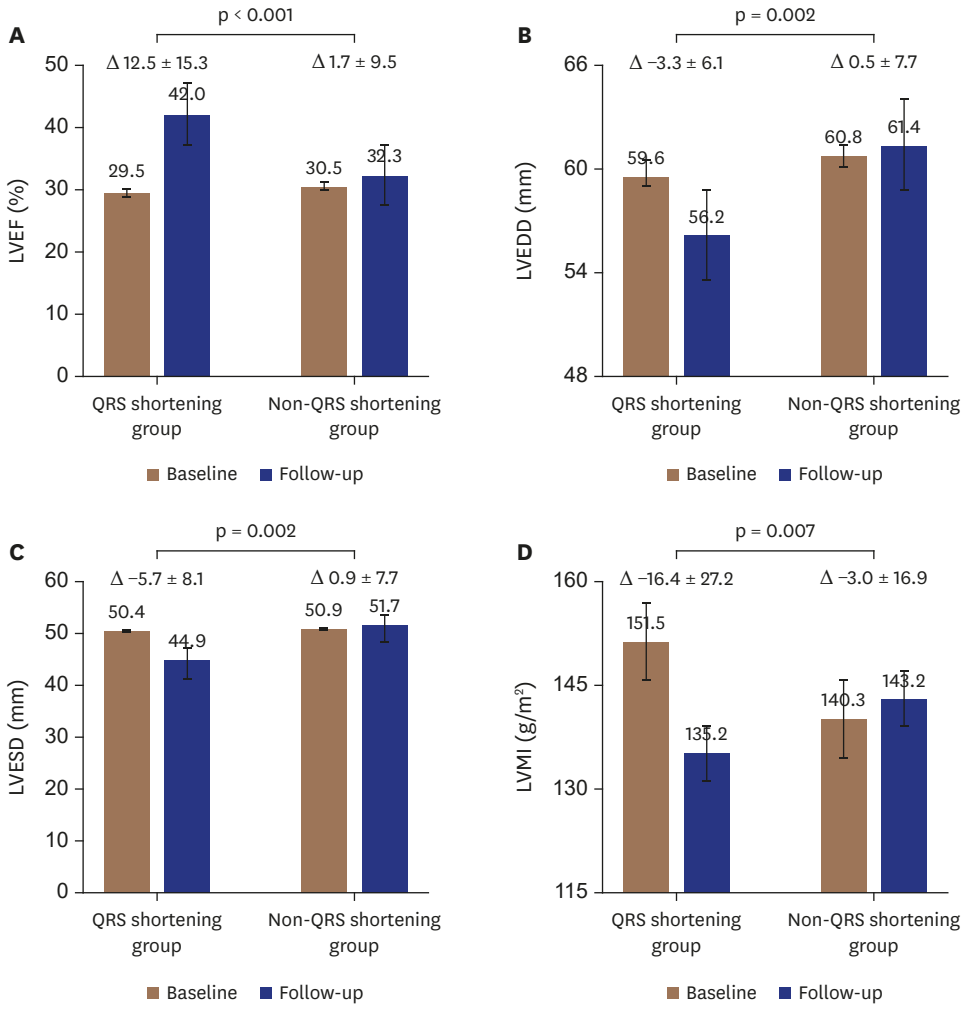

Figure 2. Change in echocardiographic parameters. (A) On follow-up echocardiogram, the QRS shortening group showed more significant improvement in LVEF than did the non-QRS shortening group (ΔLVEF; 12.5 ± 15.3% vs. 1.7 ± 9.5%; p < 0.001). (B, C and D) The QRS shortening group showed more significant reduction of LVEDD (-3.3 ± 6.1 mm vs. 0.5 ± 7.7 mm, p = 0.002), LVESD (-5.7 ± 8.1 mm vs. 0.9 ± 7.7 mm, p = 0.002) and LVMI (-16.4 ± 27.2 vs. -3.0 ± 16.9 g/m², p = 0.007) compared with the non-QRS shortening group. LVEDD: left ventricular end-diastolic dimension, LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic dimension, LVMI: left ventricular mass index.

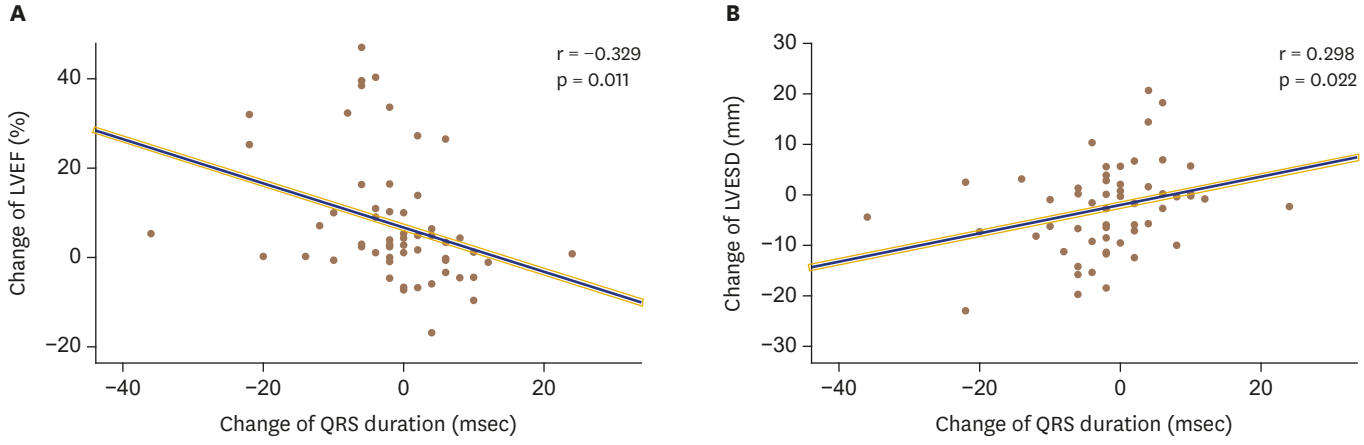

Figure 3. Pearson correlation with change in QRS duration. The change in the QRS duration was significantly correlated with the change in LVEF (r = −0.329, p = 0.011) (A) and LVESD (r = 0.298, p = 0.022) (B). LVEF: left ventricular ejection fraction, LVESD: left ventricular end-systolic dimension.

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

Table 4. Logistic regression analysis to predict >10% LVEF improvement

Risk factors	Univariable		Multivariable	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	0.998 (0.960 to 1.038)	0.937	0.988 (0.942 to 1.038)	0.636
Female gender	2.625 (0.773 to 8.914)	0.122	3.085 (0.715 to 13.307)	0.131
Ischemic heart disease	1.071 (0.308 to 3.728)	0.914	1.467 (0.346 to 6.289)	0.599
QRS shortening	5.263 (1.300 to 21.316)	0.020	5.163 (1.181 to 22.579)	0.029
Baseline LVEF	0.911 (0.828 to 1.003)	0.057	0.902 (0.809 to 1.005)	0.061

CI: confidence interval, LVEF: left ventricular ejection fraction.

would be most appropriate. However, it is not easy to perform echocardiography or NT-pro BNP measurement frequently in outpatient clinics. In addition, the clinical value of many echocardiographic parameters does not always reflect the status of LV dyssynchrony.[10] However, ECG can be performed frequently in the outpatient clinic, is inexpensive, and is convenient to analyze. Our results showed that, among patients treated with ARNIs for at least six months, patients with QRS shortening achieved significant improvements in their LV systolic function and reverse in cardiac remodeling compared to patients without QRS shortening. Changes in the QRS duration were significantly correlated to changes in the LVEF and LVESD. Although the number of patients was small, we also confirmed that the change in QRS duration was a significant factor in predicting the recovery of LV systolic function and reverse cardiac remodeling. This suggests that a change in QRS duration is closely related to LV synchrony and response to ARNIs in patients with HFrEF.

LV remodeling is a major mechanism underlying disease progression in patients with HFrEF.[11] In terms of cardiac structure remodeling, the LV size (including the LVEDV, LVESV, and LV dimensions) were strongly correlated with clinical outcomes, including survival.[12] Recently, the Prospective Study of Biomarkers, Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) study described a significant correlation between the change in the NT-pro BNP level, and echocardiographic markers of cardiac volume and function in HFrEF patients after ARNI treatment.[13] Interestingly, ARNIs had a favorable effect in the left atrial volume index (LAVi), and the ratio of early transmitral Doppler velocity to early diastolic annular velocity (E/E′). These findings suggest that favorable structural changes in the heart are associated with improved cardiac function in terms of cardiac remodeling. Therefore, ARNIs seem to hold a significantly meaningful role in HFrEF. Although our study had a small sample size and we did not detect a significant difference in the E/E′ between the groups, the observed trends were similar to those demonstrated in the PROVE-HF study.

It is difficult to clearly explain the mechanism of this structural change after ARNI treatment. One study regarding ARNI mechanisms suggested that ARNIs act synergistically against cardiomyocyte cell death and LV extracellular matrix remodeling via eight principal synergistic nodes.[14] Valsartan was found to improve cardiac remodeling by inhibiting members of the guanine nucleotide–binding protein family, while sacubitril attenuated cardiomyocyte cell death, hypertrophy, and impaired myocyte contractility by inhibiting PTEN. Recent studies suggest that ARNIs appear to play a role in demonstrating LV synchrony. The importance of LV synchrony in HF is well-known. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial showed that the combination of CRT and ICD technology significantly decreased the risk of death and HF events in patients with HFrEF with wide QRS complex.[15] Furthermore, the CRT group had a more significant reduction in LVEDV and LVESV compared to those of the

https://doi.org/10.4250/jcvi.2020.0025

Journal of Cardiovascular Imaging JCVI

ICD-only group. Another study found that, in HF patients with CRT therapy, a higher rate (> 92%) of biventricular pacing ensured significantly lower HF hospitalization or all-cause mortality when compared to a lower rate of biventricular pacing.[16] These results suggest that improving ventricular synchrony is strongly associated with favorable cardiac reverse remodeling. As mentioned in the introduction, the PRIME study found that ARNIs reduced chronic functional MR in Korean patients with HFrEF.[4] Here, we found that LV dyssynchrony with involvement of the posterior papillary muscle resulted in immediate functional MR changes. In contrast, LV dyssynchrony in the lateral wall preceded a late response to the resynchronization therapy.[17][18] Of course, the mitral valve and LV and LA sizes are complicated for functional MR. However, improvement in the LV synchrony may also play a role in improving functional MR.

Study limitations

Our study has several limitations. First, the number of enrolled patients was too small to generalize. Second, we did not strictly control for the use of heart failure medications. However, there was no significant difference between the use of b-blockers and spironolactone. A third limitation is that although we defined the follow-up period to be six months or more, the exact duration of follow up was not constant among all patients. Fourth, we evaluated the recovery of cardiac function with LVEF, which has many limitations in achieving accurate measurements. Furthermore, LVEF is just an indicator of the systolic function of the LV and does not directly reflect patient outcomes. Fifth, the non-QRS shortening group had more HTN than the QRS shortening group. Therefore, LV hypertrophy or fibrosis due to HTN may have influenced our results. Finally, this was a retrospective study performed at a single-center. However, to the best of our knowledge, it is the first study to describe the association between QRS duration changes, improvements in the LV systolic function and reverse cardiac remodeling in patients treated with ARNIs. Our results suggest that ECG can be used to predict the treatment response to ARNIs in HFrEF patients.

Conclusion

Among patients with HFrEF treated with ARNIs, patients with QRS shortening showed favorable recovery of the LV systolic function and reverse cardiac remodeling compared to those without QRS shortening. Changes in the QRS duration, which reflects LV synchrony, may be associated with response to ARNIs in patients with HFrEF.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Baseline laboratory test

Click here to view

REFERENCES

1. McMurray JJ, Packer M, Desai AS, et al.. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
PUBMED | CROSSREF

2. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. *JACC Heart Fail* 2014;2:663-70.
PUBMED | CROSSREF

3. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. *J Am Heart Assoc* 2019;8:e012272.
PUBMED | CROSSREF

4. Kang DH, Park SJ, Shin SH, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019;139:1354-65.
PUBMED | CROSSREF

5. Kim SA, Kim MN, Shim WJ, Park SM. Layer-specific dyssynchrony and its relationship to the change of left ventricular function in hypertensive patients. *Heart Vessels* 2016;31:528-34.
PUBMED | CROSSREF

6. Zhao L, Lu J, Cui ZM, et al. Changes in left ventricular synchrony and systolic function in dilated cardiomyopathy patients with fragmented QRS complexes. *Europace* 2015;17:1712-9.
PUBMED | CROSSREF

7. Tigen K, Karaahmet T, Gurel E, et al. The utility of fragmented QRS complexes to predict significant intraventricular dyssynchrony in nonischemic dilated cardiomyopathy patients with a narrow QRS interval. *Can J Cardiol* 2009;25:517-22.
PUBMED | CROSSREF

8. Rautaharju PM, Surawicz B, Gettes LS, et al.. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:982-91.
PUBMED | CROSSREF

9. Levy D, Savage DD, Garrison RJ, Anderson KM, Kannel WB, Castelli WP. Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;59:956-60.
PUBMED | CROSSREF

10. Smiseth OA, Russell K, Skulstad H. The role of echocardiography in quantification of left ventricular dyssynchrony: state of the art and future directions. *Eur Heart J Cardiovasc Imaging* 2012;13:61-8.
PUBMED | CROSSREF

11. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Levy D. Left ventricular dilatation and the risk of congestive heart failure in people without myocardial infarction. *N Engl J Med* 1997;336:1350-5.
PUBMED | CROSSREF

12. Wong M, Johnson G, Shabetai R, et al. Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure. Veterans Affairs cooperative studies V-HeFT I and II. V-HeFT VA Cooperative Studies Group. *Circulation* 1993;87:VI65-70.
PUBMED

13. Januzzi JL Jr, Prescott MF, Butler J, et al.. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019;322:1-11.
PUBMED | CROSSREF

14. Iborra-Egea O, Gálvez-Montón C, Roura S, et al. Mechanisms of action of sacubitril/valsartan on cardiac remodeling: a systems biology approach. *NPJ Syst Biol Appl* 2017;3:12.
PUBMED | CROSSREF

15. Moss AJ, Hall WJ, Cannom DS, et al.. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-38.
PUBMED | CROSSREF

16. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;53:355-60.
PUBMED | CROSSREF

17. Ypenburg C, Lancellotti P, Tops LF, et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. *Eur Heart J* 2008;29:757-65.
PUBMED | CROSSREF

18. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J 3rd. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. *J Am Coll Cardiol* 2004;44:1619-25.
PUBMED | CROSSREF