Beta-Adrenergic Blockade Therapy for Autonomic Dysfunction is Less Effective for Elderly Patients with Heart Failure and Reduced Left Ventricular Ejection Fraction

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ABSTRACT

OBJECTIVE: Heart rate variability (HRV) has been reported to be an independent predictor of all-cause and sudden cardiac death in patients with heart failure. In the aging heart, however, both autonomic and cardiac functions appear to be altered. We assessed the relationship between aging and responsiveness of HRV and ventricular remodeling to beta-adrenergic blockade therapy in patients with heart failure and reduced ejection fraction (HFREF).

METHODS: Twenty-eight clinically stable patients with chronic heart failure, sinus rhythm, and left ventricular ejection fraction <50% as confirmed by echocardiography were included. At baseline and after carvedilol treatment, 24-hour ambulatory Holter monitor recording was used to analyze HRV indices by the maximum entropy method. Changes in these parameters were compared among three age groups.

RESULTS: HR decreased in all groups after carvedilol treatment, but was still highest in the youngest group despite the same treatment doses. Time and frequency domain variables improved. The response of time domain variables (the standard deviation of all normal sinus to normal sinus [NN] intervals and the standard deviation of the averages of NN intervals in all 5-minute or 30-minute segments) to carvedilol therapy significantly decreased with increasing age. Ventricular reverse remodeling induced by carvedilol therapy significantly decreased with increasing age. Increases in time domain variables and a low-frequency domain moderately correlated with left ventricular reverse remodeling.

CONCLUSION: Beta-adrenergic blockade therapy improved HRV variables and ventricular remodeling in HFREF patients; however, the response tended to be milder in the elderly. HRV improvement was associated with ventricular reverse remodeling.

KEYWORDS: heart rate variability, beta-adrenergic blockade, reverse remodeling, aging, heart failure

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Introduction

Heart failure is the final common pathway and end stage of cardiovascular disease. In patients with heart failure, the neurohormonal system is activated and plasma catecholamine release increases as a compensating mechanism. Prolonged cardiac sympathetic activation, however, contributes directly to cardiac myocyte deterioration and progressive failure. Heart failure is a progressive disorder with an incidence that increases with age. Some age-related cardiovascular changes are pertinent to heart failure. In healthy individuals, some changes in the aging process result in an aging heart, which ultimately leads to disability and death.[1] An aging heart exhibits some of the characteristic changes in autonomic control that are observed with heart failure. In addition, in elderly heart failure patients, neurohormonal imbalance accompanying aging may underlie and contribute to pathophysiological changes in heart failure. Beta-adrenergic blockade therapy in heart failure patients increases heart rate variability (HRV), which reflects the normalizing autonomic function and correlates with improved hemodynamics.[2,3] Although beta-adrenergic blockade therapy has been shown to provide mortality and morbidity benefits in non-elderly patients, relevant data specific to the elderly are lacking. The present study aimed to examine the effects of aging on the responsiveness of HRV and ventricular remodeling to beta-adrenergic blockade therapy in patients with heart failure and reduced ejection fraction (HFREF).

Methods

Study design and sample. This retrospective study investigated 28 patients (19 men and 9 women; mean age, 59.7 ± 14.6 years) with sinus rhythm and stable New York Heart Association class II systolic heart failure who visited our department between 2006 and 2010. For all patients, more than one cardiologist was asked to agree on diagnosis and severity according to the Framingham Criteria and New York Heart Association class. This investigation conformed to the principles outlined in the Declaration of Helsinki and was approved by the ethics committee of Tokyo Women's Medical University. All subjects provided written informed consent.

Systolic heart failure was determined on the basis of symptoms, signs, radiography findings, and ultrasonic echocardiographic criteria (ejection fraction, <50%). Patients with acute myocardial infarction, pathological valvular dysfunction, congenital heart disease, pericardial disease, symptomatic peripheral vascular disease, and/or obvious pulmonary disease were excluded. No patient received antiarrhythmic drugs. To assess the effects of age on changes in HRV and echocardiographic parameters and B-type natriuretic peptide (BNP) levels, patients were divided into three age groups (range A, ≤59 years; B, 60–69 years; C, ≥70 years).

Therapy was initiated at a dose equivalent to 1.25 or 2.5 mg of carvedilol orally every 12–24 hours. If no adverse effects were observed, the dose was increased at 5–7-day intervals until either the maximum tolerated dose or the maximum allowed dose was reached. The maximum allowed dose was 20 mg of carvedilol twice per day. Therapy with angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), diuretics, and digitalis was kept constant throughout the study period. Holter monitor recordings over a 24-hour period were obtained before and 1–3 months after the titrated addition of carvedilol. Echocardiograms were obtained before treatment and at 1–3-month follow-up visits. Serial measurements of the left ventricular end-systolic diameter (LVESD) were obtained using echocardiography and were considered to be an appropriate surrogate parameter to assess the therapeutic effects on left ventricular remodeling.[4] BNP level was measured before and at 1–3 months after the titrated addition of carvedilol. After the patients were stabilized, blood was collected from the patients at rest for chemiluminescent enzyme immunoassay measurement of BNP levels.

Heart rate variability. A 24-hour ambulatory Holter recording using a heart rate monitor (model LRR03) and tracer (model AC300) (GMS Inc.) was obtained. HRV was analyzed by the maximum entropy method at a high resolution (MemCalc System software; Suwa Trust Co., Ltd.). Ectopic beats or artifacts, which may affect estimation of the power spectral densities of HRV, were automatically deleted from the data, and nonlinear predictive interpolation was performed. There were no differences in the deleted data among the three age groups. The data were visually reviewed to prevent processing artifacts after computer analysis of the QRS complex. Recordings with <24 hours of data or <80% qualified beats were excluded from our study.

In the MemCalc system, the spectrum of the power spectral analysis was separated into a total frequency (TF) domain in the range of 0.0001–0.5 Hz, an ultra-low-frequency (ULF) domain in the range of 0.0001–0.003 Hz, a very low-frequency (VLF) domain in the range of 0.003–0.04 Hz, a low-frequency (LF) domain in the range of 0.04–0.15 Hz, and a high-requency (HF) domain in the range of 0.15–0.4 Hz. The following definitions were used for the time domain variables: mean NN (mean of all normal sinus to normal sinus intervals), SDNN (standard deviation of all NN intervals), SDANN5 or 30 (standard deviation of the averages of NN intervals in all 5-minute or 30-minute segments), rMSSD (root mean square successive differences) and pNN50 (fraction of consecutive NN intervals that differed by >50 milliseconds).

A major component of SDNN or SDANN is attributable to the day–night difference in NN intervals, also known as circadian rhythm, and its decrease is associated with increased mortality. In the presence of normal sinus rhythm and normal atrioventricular nodal function, pNN50 and rMSSD quantify parasympathetic modulation of normal cardiac interbeat intervals driven by ventilation and approximately correspond to the HF component.[5] The HF component is regarded as a specific marker of parasympathetic activity. The LF component is a parameter that includes both sympathetic and parasympathetic influences, but the sympathetic influence predominates. LF has been reported to reflect the baroreflex function, not cardiac sympathetic innervation.[6] The exact physiological mechanism responsible for VLF and ULF components is in dispute, but both measurements are powerful predictors of cardiovascular disease risk. The VLF component is eliminated by atropine, suggesting that it reflects parasympathetic activity. In addition, the VLF component is reduced by ACE inhibition, reflects thermoregulation or vasomotor activity, and is affected by physical activity and disordered breathing during sleep. The ULF component is strongly associated with SDANN, which reflects the day–night difference in NN intervals.[5] Power-law scaling of NN interval variability was calculated over the frequency range of 10^{-4}–10^{-2} Hz. The long-term fractal component was plotted in a log-power vs. log-frequency plane (f^{β}plot), with the spectral exponent β estimated to be the slope of the linear regression of the plot. The $1/f$ signal properties (exponent value $\beta = -1$) have been shown to be fractal like, an organizing principle of physiological structure or function, and modestly correlated with the stability of sympathovagal balance.

Echocardiography. All subjects underwent standard two-dimensional echocardiography performed by using a commercially available system (Sonos 5500, Philips Medical Systems and Vivid 7, GE Medical Systems) with a multifrequency MHz transducer. Cardiac function was evaluated by M-mode echocardiography guided by two-dimensional imaging; left atrial diameter (LAD), interventricular septal thickness, posterior wall thickness, left ventricular end-diastolic diameter (LVEDD), LVESD, and left ventricular ejection fraction (LVEF) were measured. Right ventricular systolic pressure was measured by Doppler imaging.

Statistical analysis. Normally distributed data were presented as means ± standard deviations and analyzed using one-factor analysis of variance (ANOVA) to determine the baseline characteristics. The Kolmogorov–Smirnov test was used to analyze goodness of fit between sample distributions (the normal

distribution). The chi-square test for independence or Fisher's exact probability test was used to analyze differences between age groups as described by categorical variables. With regard to changes in HRV and echocardiographic parameters, the paired *t*-test was used for comparison of pre- and post-carvedilol therapeutic values. With regard to changes in echocardiographic and HRV parameters, one-factor ANOVA was used for intergroup comparisons of the three age groups, followed by the Tukey–Kramer post hoc test as appropriate. Simple linear regression analyses were performed to correlate changes in HRV with changes in LVESD. All *P* values of <0.05 were considered to indicate statistical significance. StatView 5.0 software (SAS Institute) was used to perform all statistical analyses.

Results

Table 1 demonstrates the clinical and echocardiographic variables for the entire patient population and each age group. Comprehensive statistics summarized for all of the examined variables at baseline revealed statistically negligible differences between the compared age groups, with the exception of history of diabetes mellitus and spironolactone use. Baseline echocardiographic parameters for the three age groups were similar. There were no significant differences in the carvedilol dose among groups.

The effects of carvedilol on HRV are listed in Table 2. Before carvedilol therapy, most HRV measures of vagal modulation had low values. The mean NN interval increased significantly, particularly in the youngest group. Carvedilol therapy resulted in a significant improvement in all HRV measures except LF/HF and fractal exponent β. There was a significant improvement in SDNN ($P < 0.0001$), SDANN5 ($P = 0.0005$), and SDANN30 ($P = 0.0021$). Carvedilol therapy was associated with statistically significant increases in rMSSD ($P = 0.0009$), pNN50 ($P = 0.0214$), and power spectral density of HF ($P = 0.0030$) and LF ($P = 0.0066$). There was an overall increase in other spectral parameters of HRV, namely,

Table 1. Baseline characteristics.

	RANGE A	RANGE B	RANGE C	*P*
Sample size	11	9	8	
Age (years)	44 ± 10	64 ± 2	75 ± 3	
Sex: male (n)	8	7	4	0.4284#
Diabetes mellitus (n)	0	4	0	0.0073#
Hypertension (n)	5	5	2	0.4351#
Etiology (n)				
Idiopathic	11	5	5	0.1817#
Ischemic	0	3	2	
Hypertensive	0	1	1	
Systolic BP (mmHg)	133 ± 22	144 ± 23	136 ± 14	0.5132*
Diastolic BP (mmHg)	83 ± 11	86 ± 15	83 ± 14	0.9350*
Serum creatinine (mg/dL)	1.0 ± 0.4	1.2 ± 0.6	0.8 ± 0.3	0.1918*
BNP (pg/mL)	651.2 ± 624.9	622.0 ± 423.9	401.3 ± 360.0	0.5687*
Carvedilol doses (mg)	14.3 ± 5.8	9.2 ± 6.7	11.9 ± 5.9	0.1973*
Drug				
ACEI (n)	4	7	4	0.1763#
ARB (n)	6	2	4	0.3096#
Diuretics (n)	7	8	3	0.0874#
Spironolactone (n)	9	2	1	0.0034#
Digitalis (n)	4	1	2	0.4310#
UCG parameters				
LAD (mm)	41.5 ± 6.2	42.6 ± 8.1	39.9 ± 4.2	0.2010*
LVEDD (mm)	63.7 ± 6.4	57.8 ± 6.6	60.8 ± 4.8	0.2451*
LVESD (mm)	53.6 ± 7.2	47.1 ± 6.4	49.5 ± 6.9	0.1861*
LVEF (%)	33.5 ± 11.0	38.4 ± 6.9	38.0 ± 13.2	0.4745*
RVSP (mmHg)	33.6 ± 8.2	35.3 ± 10.0	29.8 ± 7.8	0.7736*

Notes: Data were measured by #Fisher's exact probability test and *one-factor ANOVA.
Abbreviations: LAD, Left atrial diameter; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; LVEF, Left ventricular ejection fraction; RVSP, Right ventricular systolic pressure; UCG, Ultrasound echocardiography; BP, Blood pressure; BNP, B-type natriuretic peptide; ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers.

Table 2. Effects of aging on changes in HRV parameters after carvedilol therapy.

CHANGES IN HRV (d-HRV)	ALL MEAN DIFFERENCE (CONFIDENCE INTERVAL)	*P**	RANGE A (MEAN ± SD)	RANGE B (MEAN ± SD)	RANGE C (MEAN ± SD)	*P*§
d-mean NN (ms)	100.6 (61.9–139.3)	<0.0001	157.9 ± 110.8#	43.1 ± 81.6	86.5 ± 60.3	0.0270
d-SDNN (ms)	24.7 (14.1–35.3)	<0.0001	41.1 ± 20.8‡	22.8 ± 29.0	4.2 ± 20.1	0.0090
d-SDANN5 (ms)	22.9 (12.6–33.2)	0.0005	37.7 ± 19.5‡	22.3 ± 28.6	3.2 ± 21.2	0.0136
d-SDANN30 (ms)	20.7 (9.9–31.4)	0.0021	35.0 ± 20.1‡	21.8 ± 28.6	−0.3 ± 24.8	0.0165
d-rMSSD (ms)	6.2 (2.8–9.6)	0.0009	5.9 ± 10.0	7.6 ± 9.5	4.9 ± 6.8	0.8186
d-pNN50 (%)	2.1 (0.3–3.9)	0.0214	1.2 ± 5.3	3.8 ± 5.4	1.5 ± 2.1	0.4177
d-TF (ms^2)	1768.6 (807.8–2729.5)	0.0008	2505.6 ± 2905.5	1609.1 ± 2061.5	934.9 ± 2255.0	0.3984
d-ULF (ms^2)	1122.6 (588.9–1856.2)	0.0005	1783.1 ± 2001.1	961.4 ± 1430.0	745.6 ± 1183.7	0.3446
d-VLF (ms^2)	394.1 (33.4–754.8)	0.0334	547.9 ± 1036.0	466.4 ± 600.9	101.2 ± 1117.8	0.5808
d-LF (ms^2)	89.4 (27.1–151.6)	0.0066	126.6 ± 183.0	67.1 ± 102.1	63.3 ± 189.9	0.6310
d-HF (ms^2)	42.2 (15.7–68.8)	0.0030	47.1 ± 77.6	45.7 ± 78.7	30.2 ± 46.7	0.8497
d-LF/HF	−0.36 (−1.3−0.6)	0.4361	−0.13 ± 2.17	−0.05 ± 0.61	−1.03 ± 3.82	0.6629
d-fractal exponent β	0.01 (−0.06−0.08)	0.8301	−0.02 ± 0.22	0.07 ± 0.15	−0.03 ± 0.13	0.4592

Notes: Values are mean differences (confidence interval) or means ± SD. Data were measured by the paired *t*-test (*) and ANOVA (§). Tukey–Kramer post hoc test; #$P < 0.05$ vs. Range B; ‡$P < 0.05$ vs. Range C.
Abbreviations: HRV, Heart rate variability; SD, Standard deviation; NN, Normal sinus to normal sinus; SDNN, Standard deviation of all NN intervals; SDANN, Standard deviation of all NN intervals; rMSSD, Root mean square successive differences; TF, Total frequency; ULF, Ultra-low frequency; VLF, Very low frequency; LF, Low frequency; HF, High frequency.

TF ($P = 0.0008$), ULF ($P = 0.0005$), and VLF ($P = 0.0334$). LF/HF tended to decrease, but not significantly. Deviations in the power-law regression slopes from the 1/*f* curve were not observed.

The effects of aging on HRV indices before and after carvedilol therapy are shown in Table 2. The mean NN interval showed a large decrease in the youngest group, even though the same treatment doses were used. The effects of carvedilol on SDNN ($P = 0.0090$), SDANN5 ($P = 0.0136$), and SDANN30 ($P = 0.0165$) decreased significantly with increasing age (Fig. 1). Effects on frequency domain variables showed a decreasing trend with increasing age, but the decreases were not significant. There were no differences in LF/HF and fractal exponent β among the three age groups after carvedilol therapy.

The effects of carvedilol on ultrasound echocardiography parameters in all groups and each age group are listed in Table 3. There was a significant improvement in LAD ($P = 0.0069$), LVEDD ($P = 0.0024$), LVESD ($P = 0.0001$), and LVEF ($P = 0.0004$). The effects of carvedilol on LVEDD ($P = 0.0063$), LVESD ($P = 0.0015$), and LVEF ($P = 0.0229$) decreased significantly with increasing age (Fig. 1).

BNP levels decreased significantly after carvedilol therapy (mean difference, −399.3 ± 588.5; $P = 0.0036$), but there was no difference in BNP levels ($P = 0.3117$; range A, −584.3 ± 602.9; range B, −313.3 ± 676.9; range C, −112.1 ± 315.1) among the three age groups.

The correlations between the changes in HRV and LVESD are presented in Table 4. As illustrated in Figure 2, an intermediate inverse correlation was detected between the changes in SDNN and LVESD ($\gamma = -0.560$, $P = 0.0019$), particularly in the youngest group ($\gamma = -0.704$, $P = 0.0155$). A similar tendency was observed for SDANN and LVESD. The change in LF was also inversely correlated with the change in LVESD. Changes in the other HRV measures were

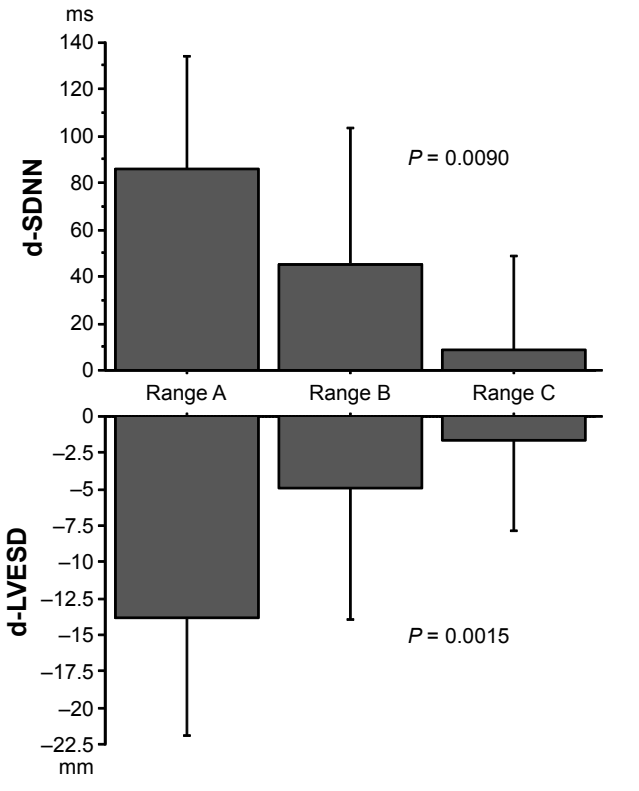

Figure 1. Improvements in SDNN and LVESD after carvedilol therapy decreased with increasing age.

Table 3. Effects of aging on changes in UCG parameters before and after carvedilol therapy.

CHANGES IN UCG PARAMETERS	ALL MEAN DIFFERENCE (CONFIDENCE INTERVAL)	*P**	RANGE A (MEAN ± SD)	RANGE B (MEAN ± SD)	RANGE C (MEAN ± SD)	*P*§
d-LAD (mm)	−5.2 (−5.9–1.1)	0.0069	−10.3 ± 14.4	−3.4 ± 3.7	−0.1 ± 5.5	0.1124
d-LVEDD (mm)	−4.8 (−7.7–1.9)	0.0024	−10.1 ± 7.6#,‡	−1.9 ± 6.8	−0.8 ± 3.5	0.0063
d-LVESD (mm)	−8.0 (−11.7–4.39)	0.0001	−15.2 ± 7.1#,‡	−4.9 ± 9.0	−1.6 ± 6.2	0.0015
d-LVEF (%)	11.8 (5.8–17.8)	0.0004	20.8 ± 10.9‡	9.1 ± 16.1	2.4 ± 14.5	0.0229
d-RVSP (mmHg)	−3.1 (−8.3–2.2)	0.2344	−7.3 ± 10.8	−0.2 ± 9.0	−3.1 ± 8.4	0.5316

Notes: Values are mean differences (confidence interval) or means ± SD. Data were measured by the paired *t*-test (*) and ANOVA (§). Tukey–Kramer post hoc test; #$P < 0.05$ vs. Range B; ‡$P < 0.05$ vs. Range C.
Abbreviations: LAD, Left atrial diameter; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; LVEF, Left ventricular ejection fraction; RVSP, Right ventricular systolic pressure; UCG, Ultrasound echocardiography; SD, Standard deviation.

Table 4. Attribution of changes in LVESD to changes in HRV.

	ALL	RANGE A	RANGE B	RANGE C
d-mean NN (ms)				
γ	−0.552	−0.467	−0.468	−0.109
R^2	0.278	0.131	0.107	–
P	0.0023	0.1478	0.2039	0.7964
d-SDNN (ms)				
γ	−0.560	−0.704	0.072	−0.701
R^2	0.287	0.440	–	0.407
P	0.0019	0.0155	0.8536	0.0525
d-SDANN5 (ms)				
γ	−0.479	−0.638	0.148	−0.448
R^2	0.200	0.341	–	0.068
P	0.0099	0.0346	0.7031	0.2656
d-SDANN30 (ms)				
γ	−0.424	−0.626	0.225	−0.242
R^2	0.149	0.324	–	–
P	0.0244	0.0394	0.5599	0.5638
d-rMSSD				
γ	−0.266	−0.638	0.161	−0.585
R^2	0.035	0.341	–	0.232
P	0.1708	0.0347	0.6799	0.1279
d-pNN50				
γ	−0.025	−0.512	0.471	−0.528
R^2	–	0.180	0.110	0.158
P	0.8995	0.1076	0.2011	0.1788
d-LF				
γ	−0.417	−0.416	−0.080	−0.923
R^2	0.142	0.081	–	0.828
P	0.0275	0.2037	0.8379	0.0011
d-HF				
γ	−0.289	−0.665	0.315	−0.773
R^2	0.048	0.380	–	0.531
P	0.1365	0.0257	0.4096	0.0244
d-LF/HF				
γ	0.006	0.259	−0.092	−0.018
R^2	–	–	–	–
P	0.9772	0.4415	0.8144	0.9668

Note: Data were measured by simple linear regression analyses.
Abbreviations: LVESD, Left ventricular end-systolic diameter; HRV, Heart rate variability; NN, Normal sinus to normal sinus; SDNN, Standard deviation of all NN intervals; SDANN, Standard deviation of the averages of NN intervals; rMSSD, root mean square successive differences; LF, low frequency; HF, high frequency.

unrelated to the change in LVESD. The change in LAD was not associated with HRV.

Discussion

This study indicates that beta-adrenergic blockade therapy improves autonomic function and ventricular remodeling in HFREF patients. The increase in HRV seems to be more pronounced with additional beta-adrenergic blockade therapy with ACEI or ARB. In addition, we found that autonomic responsiveness to beta-adrenergic blockade therapy decreased with increasing age in heart failure patients for the first time. Furthermore, changes in HRV were correlated with ventricular dimension (ie, ventricular reverse remodeling) and its effects were attenuated with increasing age.

Although HRV is a reliable measure of parasympathetic function, it is considered to be a flawed index of sympathetic activity.[7,8] The mechanism by which beta-adrenergic blockade directly influences the parasympathetic system remains unclear. Parasympathetic activity certainly appears to be decreased in chronic heart failure patients, but the number of cardiac muscarinic receptors is not altered.[9] In ischemic animal models, the sensory endings of both vagal and sympathetic afferent fibers are mechanoreceptors and fire with cardiac ischemia.[10,11]

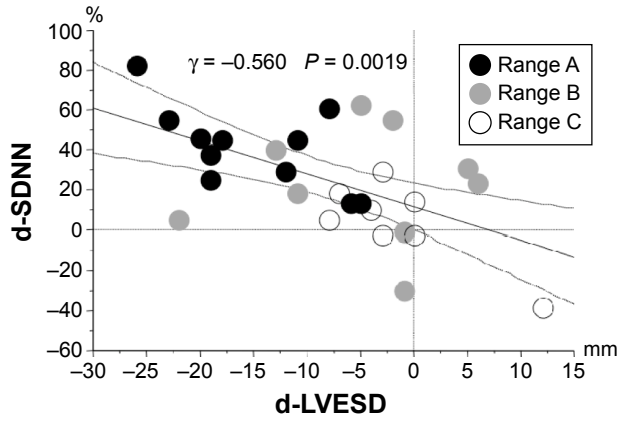

Figure 2. Regression plots of the change in SDNN vs. the change in LVESD. The filled circle, the gray filled circle, and the open circle represent range A, ≤59 years; range B, 60–69 years; and range C, ≥70 years, respectively.

In addition, this cardiac sympathetic afferent activity produces a tonic and reflex inhibition of cardiac vagal efferent activity, namely, the cardiocardiac sympathetic reflex.[12] This mechanism can be applied to autonomic dysfunction in patients with other heart disease accompanied by cardiac dilatation and can be antagonized or limited by beta-adrenergic blockade.

In the elderly, autonomic changes are similar to those in heart failure patients, but there are some differences between the two. The decrease in parasympathetic activity with increasing age can be explained by several mechanisms, such as the decrease in sinus node responsiveness and disturbance in the central oscillation of parasympathetic outflow, ultimately leading to the onset and progression of cardiovascular disease.[13–15] Unlike those in the failing heart, the number and responsiveness of muscarinic receptors seem to be decreased in the aging human heart. The release of acetylcholine from atrial tissue, which is stimulated electrically, decreases in the elderly.[16] The frequency of occurrence of autoantibodies to the muscarinic M2 receptor in healthy individuals significantly increases with age.[17]

In chronic heart failure patients, activated sympathetic nerves and elevated plasma noradrenaline levels persist in stimulating beta-adrenoreceptors (ie, cardiac noradrenaline spillover), which results in alterations of downstream mechanisms. For example, upregulation of the G-protein-coupled receptor kinase (GRK) and downregulation of the beta-1-adrenoreceptor induce a decrease in beta-1-adrenoreceptor function. In elderly patients and those with heart failure, the sympathetic activity is also enhanced and plasma noradrenaline levels increase. Functional responsiveness of beta-adrenoreceptors appears to decrease in the aging human heart. Whether the number of beta-adrenoreceptors may be affected by age remains unknown. In contrast to the failing human heart, GRK activity also appears to have an insignificant role in beta-adrenoreceptor desensitization in the aging human heart.[18,19] One of the reasons for the different behaviors of autonomic regulation between aging and failing hearts may be the differences in the time course and intensity of changes in autonomic regulation.[20] In the failing heart, the autonomic receptor systems are altered toward attenuation of beta-adrenoreceptor responses to oversympathetic activation. In the aging heart, however, the autonomic receptor systems are altered in a direction that prepares for a decrease in beta-adrenoreceptor responsiveness.[20] Age-related cardiac changes (ie, aging heart) pertinent to heart failure include cardiac fibrosis, enhanced intracellular generation of oxidative stress, increase in advanced glycation end products and angiotensin and endothelin levels, and telomeric shortening.[1] The adult heart has a significant capacity for myocyte regeneration, which is markedly enhanced in heart failure.[21] Even in the normal heart, the rate of cell death increases with age and is not balanced by a concomitant increase in new myocyte formation after middle age. Recently, the poor clinical outcome of aging patients with cardiovascular disease was reported to be recapitulated at the cellular level; specifically, aging is characterized by impaired cardiomyocyte division, cardiac stem cell senescence, decreased efficiency in autophagy, activation of apoptosis, and cardiac fibroblast dysfunction.[22] It is conceivable that these factors influence responsiveness to beta-adrenergic blockade therapy in elderly heart failure patients. Heart failure reaches epidemic proportions in the elderly, and the clinical manifestations and prognosis worsen with increasing age.

Study Limitations

One possible limitation of our study was the small sample size. For this reason, our findings cannot be generalized. Further larger-scale study is required to confirm our results. This study was designed to test age-related differences in response to beta-blocker therapy. It was considered inappropriate to use a placebo-controlled study design because the use of beta-blockers is standard in heart failure therapy. In this study, the etiology of heart failure varied, which may have affected the improvement in cardiac function. HRV is affected by various factors, such as diabetes mellitus, and the use of some drugs, such as ARB, ACEI, and digoxin. There was a statistically significant difference in the prevalence of diabetes mellitus among the three groups; this may have affected HRV responsiveness. Drugs such as ARB, ACEI, digitalis, and spironolactone restore the autonomic nervous system and cardiac function toward normal, and their use or dose difference may have affected our result because of the small sample size. In this study, we used LVESD as a surrogate parameter to assess the therapeutic effects on left ventricular remodeling. However, we can gain almost the same results by using LVEF or LVEDD. The 24-hour ambulatory Holter monitor recordings were not obtained under strict control of external conditions; however, they were useful for risk stratification in a variety of pathological entities and for clinical quantification of autonomic dysfunction.

Conclusions

Beta-adrenergic blockade therapy in addition to ACEI or ARB may improve HRV measures in heart failure patients, although the response may be decreased in the elderly. HRV improvement seems to be correlated with reverse remodeling of the left ventricle. Pharmacotherapy of heart failure in the elderly needs to be individualized, and age-related changes should be considered.

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Author Contributions

Conceived and designed this study, carried out data analysis and statistical analysis, and drafted the manuscript: KS. Helped to draft the manuscript and added important

intellectual content: MK. Both authors read and approved the final manuscript.

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