Journal of Nuclear Medicine, published on December 18, 2020 as doi:10.2967/jnumed.120.253419

Cardiac Beta-Adrenergic Receptor Downregulation, Evaluated by Cardiac Positron Emission Tomography, in Chronotropic Incompetence

Toshihiko Goto[1], Shohei Kikuchi[1], Kento Mori[1], Takafumi Nakayama[1], Hidekatsu Fukuta[2], Yoshihiro Seo[1], Hitomi Narita[3], Akihiko Iida[4], Nobuyuki Ohte[1]

[1] Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[2] Clinical Research Management Center, Nagoya City University Hospital, Nagoya, Japan

[3] Department of Internal Medicine, Nagoya City Rehabilitation Center Hospital, Nagoya, Japan

[4] Department of Radiology, Nagoya City Rehabilitation Center Hospital, Nagoya, Japan

For correspondence or reprints, contact:

Toshihiko Goto

Department of Cardiology, Nagoya City University Graduate School of Medical Sciences, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

Telephone: +81-52-853-8221

Fax: +81-52-852-3796

E-mail: t-goto@med.nagoya-cu.ac.jp

Word count: 2493

Financial support: This work was supported by a Grant-in-Aid for Scientific Research (no. 15K09966) from the Japan Society for Promotion of Science.

Short running title: β receptor in chronotropic incompetence

Abstract

The mechanism of chronotropic incompetence (CI), which has been associated with autonomic dysfunction, has not been elucidated in patients without heart failure (HF).

Methods: Cardiac positron emission tomography using ^{11}C-CGP12177 was performed to investigate the cardiac beta-adrenergic receptor density (β-ARD) in 13 patients with CI without HF and six healthy controls. The maximum number of available specific ^{11}C-CGP12177 binding sites per gram of tissue was calculated in regions of interest using an established graphical method.

Results: Peak heart rate was significantly lower in CI patients than in controls (116.9 ± 11.0 vs. 154.8 ± 14.4 beats/min, $p < 0.001$). β-ARD of the total myocardium was significantly lower in CI patients than in controls (4.3 ± 1.7 vs. 7.0 ± 1.7 pmol/mL, $p = 0.005$).

Conclusion: Beta-adrenergic receptor downregulation was demonstrated in patients with CI without HF. Decreased β-ARD is a common feature in patients with CI, with or without HF.

Key Words: β-adrenergic receptor; chronotropic incompetence; PET; sympathetic nervous system

Chronotropic incompetence (CI), defined as the inability of the heart to increase its rate commensurate with increased activity or demand, results in exercise intolerance that impairs quality of life (*1*). It is an independent predictor of major adverse cardiovascular events and overall mortality (*1*). CI is common in patients with cardiovascular disease, such as sinus node dysfunction (SND) (*1*) and heart failure (HF) (*2*). Cardiac autonomic dysfunction has been associated with CI (*3*), particularly in patients with HF (*2*). In contrast, the mechanisms underlying CI has not been elucidated in patients with CI without HF. To gain insight into the mechanism, we here investigated the cardiac beta-adrenergic receptor density (β-ARD) in patients with CI without HF using cardiac positron emission tomography (PET), using ^{11}C-(-)4-((S)-3-*tert*-butylamino-2-hydroxypropoxy)-1,3-dihydrobenzoimidazol-2-one (^{11}C-CGP12177), which is the most appropriate ligand for assessing β-ARD. Our hypothesis is that patients with CI without HF will have different levels of β-ARD than healthy volunteers without a history of heart disease.

MATERIALS AND METHODS

Study Subjects

The study was approved by Nagoya City Rehabilitation Center Institutional Review Board

(reference number: 201815), and all subjects provided written informed consent. The research was carried out in accordance with the Declaration of Helsinki.

The case-control study consisted of 13 patients with CI and 6 healthy volunteers who had no history of heart disease as controls (mean age: 65.7 ± 12.8 years; males: 63.2%). Five of 13 patients with CI had been implanted with a dual-chamber pacemaker due to SND, and none of them required ventricular pacing. Each participant underwent echocardiography immediately before the PET examination. The left ventricular (LV) end-diastolic and end-systolic volume indices and left ventricular ejection fraction (LVEF) were measured using the modified Simpson formula. Blood samples for B-type natriuretic peptide (BNP) and norepinephrine measurements were obtained immediately before the first ^{11}C-CGP infusion.

Patient exclusion criteria were as follows: patients on β-blocker therapy, patients with any history of heart disease, including HF, LVEF <50%, atrioventricular block, or physical inability to undergo cardiopulmonary exercise testing (CPX).

CI

All participants underwent symptom-limited CPX by bicycle ergometry, with simultaneous expired ventilatory gas analysis. Peak oxygen consumption (peak VO_2) was defined as the highest VO_2 value during CPX. Peak heart rate (HR) was defined as HR at peak VO_2. HR

recovery, defined as the decrease in HR at 1 min after the cessation of CPX, was also obtained. The age-predicted maximal HR (APMHR) was defined by using the Astrand (220 - age) formula (*4*). HR reserve was determined from the change in HR from rest to peak exercise, divided by the difference of the resting HR and the APMHR (*5*). In this study, CI was defined as a measured HR reserve less than 80% of the reserve calculated with the APMHR.

^{11}C-CGP12177 PET

All participants underwent PET examination. After a transmission scan, we obtained dynamic ^{11}C-CGP12177 images according to the modified double-injection protocol. Briefly, during a 75-minute dynamic emission scan, the first dose of ^{11}C-CGP12177, with a high specific activity (124.0 ± 2.5 MBq, 2.1 ± 2.6 nmol), was infused intravenously over 2 minutes. After 30 minutes, the second dose of ^{11}C-CGP12177, with a low specific activity (234.1 ± 31.2 MBq, 78.4 ± 14.7 nmol), was infused over 2 minutes. A 54-frame dynamic emission scan was used to measure sequential distributions of the tracer *in vivo*. During the 30-minute period after the start of the first infusion, 24 timeframes were acquired (8 × 15, 4 × 30, 2 × 60, 2 × 120, and 8 × 150 seconds). After the second infusion, the scan was completed with 30 additional frames (8 × 15, 4 × 30, 2 × 60, 2 × 120, and 14 × 150 seconds). All emission sinograms were reconstructed using filtered back-projection with time-of-flight measurements. All data were corrected for dead time,

decay, and measured photon attenuation. Cardiac uptake of ^{11}C-CGP12177 was estimated using dedicated software. The total LV myocardium was divided into 17 segments, which were assigned to specific coronary artery territories of the left anterior descending artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA), according to the American Heart Association guidelines. The curve sections that corresponded to the two slow clearance phases, which represented the dissociation of ^{11}C-CGP12177 bound to beta-adrenergic receptors (β-ARs), were extrapolated back to the start of the infusions. β-ARD was then determined as the maximum number of available specific ^{11}C-CGP12177 binding sites per gram of tissue (Bmax) in the ROIs, based on the modified equation described by Delforge et al. (*6*).

Statistical Analysis

Continuous variables are presented as the mean ± standard deviation for normally distributed variables, and the median and interquartile range (IQR) for non-normally distributed variables. Categorical variables are summarized as frequencies (%). For the comparison of 2 groups, unpaired Student's *t*-tests were used for normally distributed continuous variables, and Mann-Whitney U-tests were used for non-normally distributed continuous variables. Differences in prevalence between the two groups were compared using the chi-square test. Relationships between the two parameters were evaluated by univariate regression analysis. Differences with p

< 0.05 were considered statistically significant.

RESULTS

The clinical characteristics did not differ between the groups. Peak HR (116.9 ± 11.0 vs. 154.8 ± 14.4 beats/min, $p < 0.001$), the double product (21800 ± 4200 vs. 31400 ± 4600 beats/min·mmHg, $p < 0.001$), and peak VO_2 (15.9 ± 3.7 vs. 23.5 ± 5.5 mL/kg/min, $p = 0.003$) were significantly lower in patients with CI than in controls. Peak O_2 pulse and HR recovery did not differ between the groups (Table1, Supplemental Table 1, Supplemental Table 2).

β-ARD was significantly correlated with peak HR ($r = 0.54$, $p = 0.02$). However, other parameters did not correlate with β-ARD (Supplemental Table 3). Fig. 1 shows the β-ARD in the total myocardium and in each region. β-ARD of the total myocardium was significantly lower in patients with CI than in controls (4.3 ± 1.7 vs. 7.0 ± 1.7 pmol/mL, $p = 0.005$). β-ARD in the LAD (4.4 ± 1.7 vs. 6.6 ± 1.8 pmol/mL, $p = 0.02$), LCX (3.9 ± 1.5 vs. 6.5 ± 1.4 pmol/mL, $p = 0.003$), and RCA (4.5 ± 1.7 vs. 7.9 ± 2.5 pmol/mL, $p = 0.003$) regions were also significantly lower in the CI group than in controls.

DISCUSSION

This present study demonstrated cardiac β-AR downregulation in patients with CI without HF; this has not been reported previously. It is noteworthy that our results indicate that decreased

β-ARD is a common feature in patients with CI, in both those with and without HF.

Post-Synaptic Status

CI in patients with HF has been suggested to be associated with downregulation of cardiac β-ARs (*2*). On the other hand, Kawasaki and colleagues evaluated CI using HR variability during CPX in patients without structural heart disease. They deduced that CI in such patients was mainly caused by a pathophysiological condition in which sympathetic activation was not well translated into an HR increase (*7*). The present study demonstrated downregulation of β-ARs in patients with CI without HF and showed a significant correlation between the β-ARD and peak HR during CPX. Therefore, our results are consistent with the speculations of these previous studies. Notably, decreased β-ARD is a common feature in patients with CI, whether in those with or without HF.

Pre-Synaptic Status

Elevated sympathetic nervous system activity, evaluated with iodine-123-meta-iodobenzylguanidine (MIBG), has been reported in patients with indications for a pacemaker due to SND; these patients included those with CI before pacemaker implantation, compared with normal healthy controls (*8*). The authors attributed the elevated norepinephrine to increased sympathetic nervous system activity due to abnormal adrenergic nerve function of the

LV myocardium in patients with SND. The increased sympathetic activity may also reflect the cardiac load caused by bradycardia in that study. In the current study, there was no significant increase in plasma BNP levels even in CI patients, i.e., the absence of bradycardia-induced cardiac load may have resulted in a lack of increase in plasma norepinephrine levels. On the other hand, Fukuoka et al. reported that cardiac sympathetic activity evaluated by MIBG did not differ between patients receiving atrial pacing and normal individuals without cardiac pacing (*9*). Our study is consistent with this because there were no patients requiring ventricular pacing. Further investigation regarding pre-synaptic status is needed in patients with CI without HF.

Mechanism underlying CI

HR during CPX is regulated by a reduction of vagal activity, an increase in sympathetic outflow, and the relative sensitivity of the sinoatrial node to catecholamines. In fact, the cardiac sympathetic nerves are particularly densely distributed around the sinoatrial node. The etiology of SND, which includes CI, often involves age-dependent, progressive, degenerative fibrosis of the sinus nodal tissue and the surrounding atrial myocardium (*10*). Therefore, it is possible that both the cardiac sympathetic pre-synapses and post-synapses are impaired. The abovementioned study showed that patients with SND had disturbances of global and regional cardiac ^{123}I-MIBG uptake before and after pacemaker implantation, indicating abnormal adrenergic nerve function (*8*). Contrary to sympathetic parameters, there was no difference in HR recovery as a

parasympathetic parameter between the groups. Therefore, sympathetic dysfunction may be key to understanding the mechanisms underlying CI in patients with CI without HF. Moreover, the mechanism underlying CI in such patients may involve both the pre-synaptic and post-synaptic states in the sympathetic nervous system.

Clinical Implications

No effective treatment for CI to improve prognosis has been established to date. No study has been able to demonstrate improved prognosis by rate-adaptive pacing. These suggest that mechanically increasing HR could not reverse β-AR downregulation. β-blockers are effective in chronic HF, where downregulation of β-AR is also observed. However, if the β-ARs themselves are already involved in degenerative fibrosis, the use of β-blockers is unlikely to be effective. The possibility of β-blocker use requires further study in patients with CI without HF.

Despite the limited number of patients and the varying definitions of CI, we believe that the results of this study, including the definition of CI, are appropriate and allow for generalization.

CONCLUSION

Cardiac β-AR downregulation was observed in patients with CI. Decreased β-ARD is a common feature in patients with CI, irrespective of whether they have HF.

KEY POINTS

Question:

- Could β-AR downregulation be a mechanism underlying CI without HF?

Pertinent findings:

- In this case-control study, β-ARD of the total myocardium was statistically significantly lower in CI patients without HF than in controls (4.3 ± 1.7 vs. 7.0 ± 1.7 pmol/ml).

Implications for patient care:

- Clarifying the mechanisms underlying CI will contribute to the development of therapeutic strategies for CI.

FINANCIAL DISCLOSURE

This work was supported by a Grant-in-Aid for Scientific Research (no. 15K09966) from the Japan Society for Promotion of Science.

REFERENCES

1. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation.* 2011;123:1010-1020.

2. Colucci WS, Ribeiro JP, Rocco MB, et al. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic beta-adrenergic desensitization. *Circulation.* 1989;80:314-323.

3. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med.* 1971;285:877-883.

4. Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl.* 1960;49:1-92.

5. Okin PM, Lauer MS, Kligfield P. Chronotropic response to exercise. Improved performance of ST-segment depression criteria after adjustment for heart rate reserve. *Circulation.* 1996;94:3226-3231.

6. Delforge J, Mesangeau D, Dolle F, et al. In vivo quantification and parametric images of the cardiac beta-adrenergic receptor density. *J Nucl Med.* 2002;43:215-226.

7. Kawasaki T, Kaimoto S, Sakatani T, et al. Chronotropic incompetence and autonomic

dysfunction in patients without structural heart disease. *Europace.* 2010;12:561-566.

8. Marketou ME, Simantirakis EN, Prassopoulos VK, et al. Assessment of myocardial adrenergic innervation in patients with sick sinus syndrome: effect of asynchronous ventricular activation from ventricular apical stimulation. *Heart.* 2002;88:255-259.

9. Fukuoka S, Nakagawa S, Fukunaga T, Yamada H. Effect of long-term atrial-demand ventricular pacing on cardiac sympathetic activity. *Nucl Med Commun.* 2000;21:291-297.

10. Evans R, Shaw DB. Pathological studies in sinoatrial disorder (sick sinus syndrome). *Br Heart J.* 1977;39:778-786.

Figure Legends

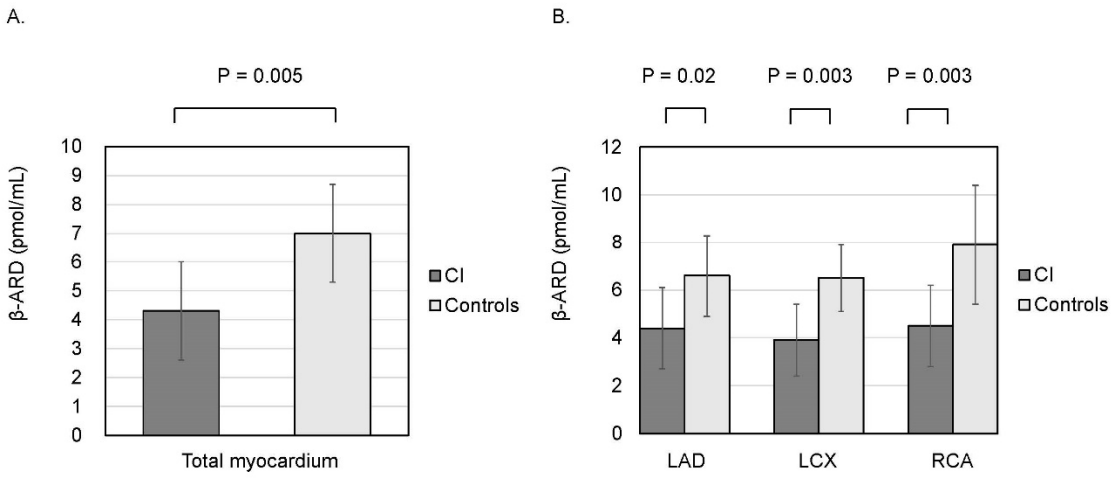


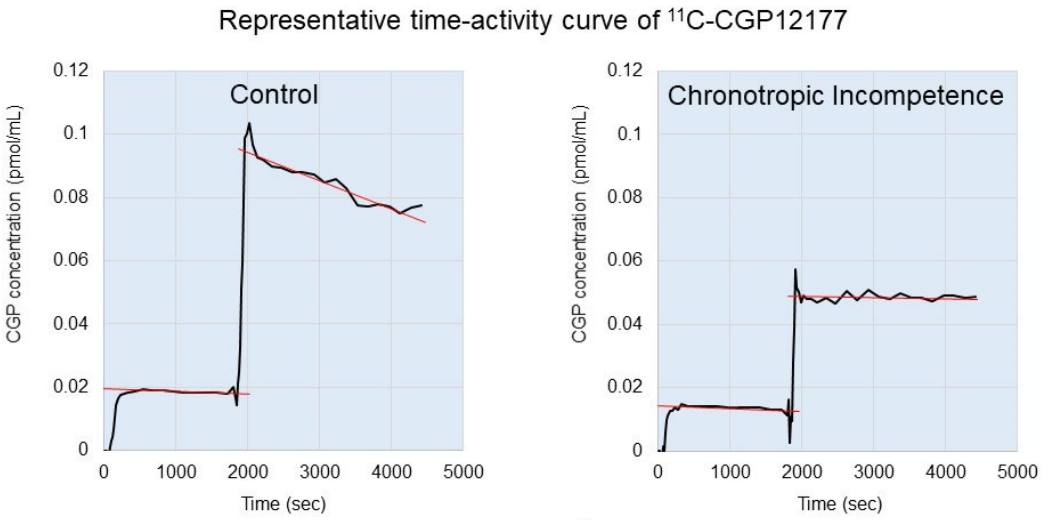
FIGURE 1. A. The cardiac beta-adrenergic receptor density (β-ARD) of the total myocardium. B. The β-ARD in the left anterior descending artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA) regions. CI, chronotropic incompetence.

Table 1. Comparisons of clinical characteristics between the patients with CI and controls

Characteristic	CI (n=13)	Controls (n=6)	*P*
Male/female	7/6	5/1	0.22
Age (years)	70.4 ± 8.9	55.5 ± 14.8	0.06
Height (cm)	160.3 ± 7.1	164.6 ± 10.0	0.30
Weight (kg)	58.5 ± 7.0	65.5 ± 11.7	0.12
Rest heart rate (beats/min)	66.7 ± 13.8	67.8 ± 12.2	0.86
Peak heart rate (beats/min)	116.9 ± 11.0	154.8 ± 14.4	<0.001
Peak systolic blood pressure (mm Hg)	183.5 ± 23.3	203.2 ± 17.6	0.09
Double product (beats/min*mm Hg)	21800 ± 4200	31400 ± 4600	<0.001
Peak VO_2 (mL/kg/min)	15.9 ± 3.7	23.5 ± 5.5	0.003
Peak O_2 pulse (mL/beats)	7.8 ± 2.4	10.0 ± 2.5	0.08
Peak work (watt)	85.4 ± 30.1	131.8 ± 37.2	0.01
Heart rate recovery (beats/min)	19.9 ± 14.6	18.3 ± 7.6	0.81

Data are expressed as mean ± standard deviation. CI, chronotropic incompetence; VO_2, oxygen consumption.

Graphical Abstract. Representative time-activity curve of ^{11}C-CGP12177



Two slow clearance phase represent the dissociation after injection of ^{11}C-CGP 12177 bound to beta-adrenergic receptor.
The slope of the curve after the second injection was slower in a patient with chronotropic incompetence than in a control subject.

Supplemental Table 1

Comparisons of clinical characteristics and hemodynamic data between the patients with CI and the controls

Characteristic	CI	Controls	p value
Number	13	6	
Male/female	7/6	5/1	0.22
Age (years)	70.4 ± 8.9	55.5 ± 14.8	0.06
Height (cm)	160.3 ± 7.1	164.6 ± 10.0	0.30
Weight (kg)	58.5 ± 7.0	65.5 ± 11.7	0.12
Body mass index (kg/m^2)	22.8 ± 2.9	24.1 ± 2.9	0.40
Hypertension (%)	7 (53.8)	2 (33.3)	0.41
Diabetes (%)	2 (15.4)	2 (33.3)	0.37
Echocardiographic parameters			
LVEF (%)	67.8 ± 10.8	68.4 ± 7.6	0.90
LVEDVI (ml/m^2)	66.4 ± 11.7	65.5 ± 9.4	0.86
LVESVI (ml/m^2)	21.0 ± 5.4	20.6 ± 4.7	0.88
LAD (mm)	36.3 ± 5.4	33.7 ± 3.7	0.29
E (cm/sec)	59.1 ± 17.6	60.7 ± 8.3	0.84
e’ mean (cm/sec)	8.0 ± 1.8	8.9 ± 1.5	0.30
E/e’ mean	7.6 ± 2.4	7.0 ± 1.6	0.60
Laboratory data			
BNP (pg/mL)	26.6 [IQR, 10.1–96.4]	12.0 [IQR, 7.9–19.4]	0.11
Serum creatinine (mg/dL)	0.69 ± 0.17	0.70 ± 0.19	0.88

eGFR (mL/min/1.73 m^2)	75.3 ± 13.1	87.0 ± 21.1	0.15
Norepinephrine (pg/mL)	596.9 ± 175.9	444.3 ± 148.4	0.08
Medication			
Loop diuretics (%)	1 (7.7)	1 (16.7)	0.55
ACEIs (%)	2 (15.4)	0 (0)	0.31
ARBs (%)	2 (15.4)	0 (0)	0.31
CCBs (%)	5 (38.5)	2 (33.3)	0.83
Statins (%)	1 (7.7)	0 (0)	0.49
β-blockers (%)	0	0	N/A

Data are expressed as mean ± standard deviation or number or frequency (%).

B-type natriuretic peptide (BNP) is represented by the median and interquartile range (IQR).

CI, chronotropic incompetence; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LAD, left atrium diameter; E, Early diastolic transmitral flow velocity; e', mitral annular velocity during early diastole; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Supplemental Table 2. The results of CPX

Rest	CI	Controls	P value
Heart rate (beats/min)	66.7 ± 13.8	67.8 ± 12.2	0.86
Systolic BP (mm Hg)	128.2 ± 13.8	129.8 ± 15.0	0.81
Diastolic BP (mm Hg)	68.7 ± 11.5	73.3 ± 8.7	0.40
Peak exercise			
Heart rate (beats/min)	116.9 ± 11.0	154.8 ± 14.4	<0.001
Systolic BP (mm Hg)	183.5 ± 23.3	203.2 ± 17.6	0.09
Diastolic BP (mm Hg)	86.5 ± 16.8	94.2 ± 19.7	0.39
Double product (beats/min∗mm Hg)	21800 ± 4200	31400 ± 4600	<0.001
Percent predicted heart rate (%)	80.7 ± 8.2	93.7 ± 5.1	0.003
Anaerobic threshold (mL/kg/min)	11.9 ± 2.9	14.9 ± 2.2	0.04
Peak VO_2 (mL/kg/min)	15.9 ± 3.7	23.5 ± 5.5	0.003
Percent predicted peak VO_2 (%)	74.5 ± 19.1	80.5 ± 18.0	0.52
VE/VCO_2 slope	34.6 ± 5.9	33.8 ± 5.4	0.79
Peak RER	1.23 ± 0.06	1.27 ± 0.07	0.21
Peak O_2 pulse (mL/beats)	7.8 ± 2.4	10.0 ± 2.5	0.08
Exercise time (min)	5.4 ± 2.3	8.1 ± 1.2	0.02
Peak work (watt)	85.4 ± 30.1	131.8 ± 37.2	0.01
Heart rate recovery (beats/min)	19.9 ± 14.6	18.3 ± 7.6	0.81

Data represent mean ± standard deviation.

CI, chronotropic incompetence; BP, blood pressure; VO_2, oxygen consumption, VE/VCO_2, minute ventilation/carbon dioxide production; RER, respiratory exchange rate.

Supplemental Table 3. Results of univariate regression analysis for the β-AR density.

Variable	r	*P*
Age (years)	-0.42	0.08
Height (cm)	0.21	0.39
Weight (kg)	0.09	0.73
Body mass index (kg/m^2)	-0.07	0.78
LVEF (%)	-0.29	0.23
e' mean (cm/sec)	0.37	0.12
E/e' mean	-0.14	0.56
Rest heart rate (beats/min)	-0.01	0.98
Rest systolic BP (mm Hg)	0.08	0.74
Rest diastolic BP (mm Hg)	0.001	0.99
Peak heart rate (beats/min)	0.54	0.02
Peak systolic BP (mm Hg)	0.47	0.05
Peak diastolic BP (mm Hg)	0.12	0.64
Log BNP (pg/mL)	-0.39	0.10
Norepinephrine (pg/mL)	-0.29	0.22
eGFR (mL/min/1.73m^2)	0.41	0.08

Abbreviations as in Supplement 1 and 2.