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Myocardial β-Adrenergic Receptor Density Assessed by ^{11}C-CGP12177 PET Predicts Improvement of Cardiac Function After Carvedilol Treatment in Patients with Idiopathic Dilated Cardiomyopathy

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We evaluated whether myocardial β-adrenergic receptor (β-AR) density, as determined by ^{11}C-CGP12177 PET, could predict improvement of cardiac function by β-blocker carvedilol treatment in patients with idiopathic dilated cardiomyopathy (IDC). **Methods:** Ten patients with IDC (left ventricular ejection fraction [LVEF] < 45%) were studied. Myocardial β-AR density was estimated using ^{11}C-CGP12177 PET before treatment with carvedilol. Changes of LVEF in response to dobutamine infusion (ΔLVEF-dobutamine) were also measured by echocardiography. Changes of LVEF (ΔLVEF-carvedilol) were evaluated after 20 mo of carvedilol treatment. **Results:** Baseline myocardial β-AR density significantly correlated with ΔLVEF-carvedilol ($r = -0.88$, $P < 0.001$). In contrast, ΔLVEF-dobutamine did not correlate with ΔLVEF-carvedilol ($P = 0.65$). Myocardial β-AR density was the significant multivariate independent predictor of ΔLVEF-carvedilol ($\beta = -0.88$, $P < 0.001$) among univariate predictors, including functional class ($r = 0.76$, $P < 0.05$), plasma norepinephrine ($r = 0.85$, $P < 0.01$), LVEF ($r = -0.64$, $P < 0.05$), and age as confounding factors. Furthermore, myocardial β-AR density was significantly correlated with plasma norepinephrine ($r = -0.79$, $P < 0.01$) and LVEF ($r = 0.70$, $P < 0.05$). **Conclusion:** Myocardial β-AR density is more tightly related to improvement of LVEF-carvedilol than is cardiac contractile reserve in patients with IDC. Patients with decreased myocardial β-AR have higher resting adrenergic drive, as reflected by plasma norepinephrine, and may receive greater benefit from being treated by antiadrenergic drugs.

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Several clinical studies have demonstrated beneficial effects of β-blockers on the symptoms, hemodynamics, left ventricular ejection fraction (LVEF), neurohormonal parameters, and survival of patients with heart failure (*1–4*). β-blockers exert their benefits at least in part by inhibiting sympathetically mediated myocardial damage and necrosis (*3,5*). Previous studies have reported that cardiac contractile reserve during dobutamine stress predicts the improvement of cardiac function with β-blocker therapy in patients with idiopathic dilated cardiomyopathy (IDC) (*6,7*). However, it is generally still difficult to predict whether heart failure patients will respond favorably to β-blockers.

Myocardial β-adrenergic receptor (β-AR) density directly regulates left ventricular systolic function at rest and during dobutamine infusion (*8,9*). ^{11}C-CGP12177 PET has been established to allow us to measure myocardial β-AR density noninvasively (*8–11*). Recently, we demonstrated that a reduction in myocardial β-AR density, as measured by ^{11}C-CGP12177 PET, in patients with IDC was related to the severity of heart failure (*8*). Importantly, myocardial β-AR density inversely correlated with the ^{123}I-metaiodobenzylguanidine washout rate and positively correlated with a delayed heart-to-mediastinum ratio, indicating that decreased β-AR density was due to the increased presynaptic sympathetic tone. These results suggest that myocardial β-AR density is directly associated with the beneficial response to β-blocker carvedilol

treatment in patients with heart failure. However, the relationship between myocardial β-AR density assessed by ^{11}C-CGP12177 PET and the effects of long-term carvedilol treatment on left ventricular function have not been studied. We thus determined whether baseline myocardial β-AR density could predict the increase of LVEF after long-term carvedilol treatment (ΔLVEF-carvedilol) in patients with IDC. We also assessed cardiac contractile reserve by dobutamine stress echocardiography in the same patients.

MATERIALS AND METHODS

Study Patients

We studied 10 consecutive ambulatory patients with stable chronic heart failure due to IDC (5 men and 5 women; mean age [±SD], 61 ± 12 y; mean New York Heart Association [NYHA] class, 2.3 ± 0.8; LVEF < 45%), who were started on carvedilol at Hokkaido University Hospital from August 2003 to November 2005. IDC was diagnosed using echocardiography and endomyocardial biopsy findings. Patients who had significant coronary artery stenosis (>50%), other recognized etiologies, a history of β-blocker treatment, or severe heart failure (NYHA class IV) or were using continuous inotropic infusion were excluded. ^{11}C-CGP12177 PET, dobutamine stress echocardiography, and blood chemical analysis were performed within 2 wk during the stable stage of heart failure before carvedilol therapy. The study was approved by the institutional ethical committee, and the procedures were in accordance with institutional guidelines. Written informed consent was obtained from each study patient.

Carvedilol Therapy

After baseline studies, carvedilol was administrated at an initial dosage of 1.25 mg/d. The dosage was increased as tolerated to 2.5–20 mg/d (mean daily dose, 8.8 ± 6.7 mg) during 8 wk, and the target dosage was maintained during the follow-up period of 20 ± 5 mo. Neither side effects, worsening of heart failure, nor cardiac death was noted. Carvedilol was added to standard medical therapy including angiotensin-converting-enzyme inhibitors (n = 5), angiotensin II receptor blockers (n = 6), diuretics (n = 7), spironolactone (n = 3), and digoxin (n = 4) in all patients.

^{11}C-CGP12177 PET Scans

All PET scans were obtained using an ECAT EXACT HR+ (Siemens/CTI). A transmission scan was obtained with a ^{68}Ge source for 8 min to correct photon attenuation. ^{11}C-CGP12177 was synthesized as previously reported (*12*). Myocardial β-AR density was measured using ^{11}C-CGP12177 PET according to the modified double-injection protocol as previously reported (*11*). During a 75-min dynamic emission scan, the first dose of ^{11}C-CGP12177 (169 ± 59 MBq, 0.16 ± 0.07 μg) with a high specific activity (1,220 ± 578 MBq/μg) was infused intravenously for 2 min. Thirty minutes later, the second dose of ^{11}C-CGP12177 (306 ± 147 MBq, 21.3 ± 2.0 μg) with a low specific activity (14.7 ± 7.8 MBq/μg) was infused for 2 min. A 54-frame dynamic emission scan was used to measure the sequential distribution of the tracer in vivo. During the 30 min after the start of the first infusion, 24 time frames (eight 15-s frames, four 30-s frames, two 60-s frames, two 120-s frames, and eight 150-s frames) were acquired. After the second infusion, the scan was completed in 30 frames (eight 15-s frames, four 30-s frames, two 60-s frames, two 120-s frames, and fourteen 150-s frames).

All emission sinograms were reconstructed with backprojection using a Hann filter (cutoff frequency, 0.3 cycles per pixel). The in-plane resolution was 4.5 mm in full width at half maximum in images reconstructed into a 128 × 128 matrix. All data were corrected for dead time, decay, and measured photon attenuation. A whole-heart region of interest was set manually in each transaxial view. Myocardial time–activity curves in the regions of interest were corrected for radioactive decay. Myocardial activity in the regions of interest is affected by spillover from the left ventricular cavity, and also from myocardial blood activity because ^{11}C-CGP12177 binds red blood cells. Forty percent of left ventricular intracavity activity was reduced from left ventricular myocardial activity to correct myocardial time–activity curve according to the previous study by Delforge et al. (*13*). The sections of the curve corresponding to the 2 slow clearance phases, which represent the dissociation of ^{11}C-CGP12177 bound to β-AR, were extrapolated back to the start of the infusions. β-AR density was then determined as the maximum number of available specific ^{11}C-CGP12177 binding sites per gram of tissue in the regions of interest using a modified equation described by Delforge et al. (*11*).

Echocardiography

Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF were measured from apical 2-chamber and 4-chamber views using the biplane disk-summation method according to the recommendation of the American Society of Echocardiography (*14*). Changes in LVEF before and after 20 mo of carvedilol treatment were calculated as ΔLVEF-carvedilol.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed at baseline in only 8 of the 10 patients because 2 patients refused the test. Dobutamine was intravenously infused at incremental dosages of 5, 10, and 20 μg/kg/min at 3-min intervals. A maximum of 20 μg of dobutamine per kilogram per minute was achieved in all patients. LVEF was measured at rest and during the maximum dobutamine infusion. Changes in LVEF at rest and during the maximum dobutamine infusion (ΔLVEF-dobutamine) were calculated to assess cardiac contractile reserve.

Blood Chemical Analysis

Venous blood samples were drawn after the patients had rested supine for 20 min. The plasma norepinephrine level was measured by high-performance liquid chromatography. The level of plasma brain natriuretic peptide was measured by chemiluminescent enzyme immunoassay.

Statistical Analyses

All data were expressed as mean ± SD. The changes in blood pressure, heart rate, NYHA class, and LVEF before and after carvedilol treatment were compared by a paired t test. Myocardial β-AR density and ΔLVEF-carvedilol were compared with baseline clinical variables. Regression analysis was used to determine univariate predictors of ΔLVEF-carvedilol, including clinical variables such as age, NYHA class, plasma brain natriuretic peptide and norepinephrine, echocardiographic parameters, ΔLVEF-dobutamine, and myocardial β-AR density. A multivariate stepwise regression model with forward selection was developed using the significant univariate predictors of ΔLVEF-carvedilol and age as confounding factors. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Table 1 shows the baseline characteristics of the study patients. Two patients were classified as NYHA functional class I, 3 patients as class II, and 5 patients as class III. LVEDV was 149 ± 44 mL, and LVESV was 109 ± 45 mL. All patients had an LVEF of less than 45%, and the average LVEF was 28%. The average myocardial β-AR density was 3.86 pmol/mL (range, 2.03–5.11 pmol/mL). ΔLVEF-dobutamine was greater than 15%, and the average value was 20%. Six of 10 patients had plasma brain natriuretic peptide levels greater than 100 pg/mL. Plasma norepinephrine was 342 ± 209 pg/mL.

Effects of Carvedilol Treatment on NYHA Class and LVEF

After 20 mo of carvedilol treatment, NYHA functional class significantly improved from 2.3 ± 0.8 to 1.5 ± 0.5 ($P < 0.01$) (Fig. 1A), whereas mean blood pressure and heart rate did not change (81 ± 11 vs. 85 ± 15 mm Hg, $P = 0.37$; 69 ± 16 vs. 73 ± 6 bpm, $P = 0.46$, respectively). LVEF significantly increased from 28% ± 11% to 46% ± 13% ($P < 0.01$) (Fig. 1B), and ΔLVEF-carvedilol was 18% ± 16% (Table 1).

Independent Determinants of ΔLVEF-Carvedilol

The correlation was estimated from regression analysis between ΔLVEF-carvedilol and the baseline variables. ΔLVEF-carvedilol correlated positively with baseline NYHA class and plasma norepinephrine. It also correlated inversely with LVEF and myocardial β-AR density by univariate analysis (Table 2; Fig. 2). In contrast, it did not correlate with age, plasma norepinephrine, LVEDV, LVESV, or ΔLVEF-dobutamine (Table 2; Fig. 3). Of 5 patients who had ΔLVEF-dobutamine greater than 20%, 2 patients had ΔLVEF-carvedilol less than 5%.

When age and these 4 univariate predictors of ΔLVEF-carvedilol were included in a multivariate model, only myocardial β-AR density was a significant independent predictor of ΔLVEF-carvedilol ($\beta = -0.88$, $P < 0.001$). On the basis of the estimated regression line, a decrease in myocardial β-AR density of 1 pmol/mL correlated with an increase in ΔLVEF-carvedilol of 12.5%.

Relationship Between Myocardial β-AR Density and Clinical Variables

Myocardial β-AR density was significantly lower in patients with NYHA class III ($n = 5$) than NYHA class I or II ($n = 5$) (3.02 ± 1.07 vs. 4.71 ± 0.13 pmol/mL, $P = 0.01$). By univariate analysis, myocardial β-AR density was significantly correlated with plasma norepinephrine ($r = -0.79$, $P < 0.01$) and LVEF ($r = 0.70$, $P < 0.05$) but not with LVEDV, LVESV, or plasma brain natriuretic peptide.

When age, NYHA class, LVEF, and plasma norepinephrine were included in a multivariate model, only plasma norepinephrine was a significant independent predictor of myocardial β-AR density ($\beta = -0.79$, $P < 0.01$).

DISCUSSION

The present study demonstrated that myocardial β-AR density as assessed by ^{11}C-CGP12177 PET could predict the improvement of cardiac function in patients with IDC after 20 mo of carvedilol treatment whereas cardiac contractile reserve as assessed by dobutamine stress echocardiography could not. Importantly, the elevated levels of plasma norepinephrine were significantly associated with the downregulation of myocardial β-AR. These results indicate that patients with advanced downregulation of β-AR have a higher resting adrenergic drive and may receive greater benefit from the antiadrenergic action of carvedilol treatment.

TABLE 1. Patient Characteristics

Patient no.	Age (y)	Sex	NYHA class	LVEDV (mL)	LVESV (mL)	LVEF (%)	Myocardial β-AR density (pmol/mL)	ΔLVEF-dobutamine (%)	ΔLVEF-carvedilol (%)	Plasma brain natriuretic peptide (pg/mL)	Plasma norepinephrine (pg/mL)
1	79	F	3	148	118	20	2.03	20	47	235	706
2	58	F	2	113	69	39	5.11	19	17	26	217
3	62	M	3	133	99	26	4.80	20	11	119	375
4	67	M	3	230	203	12	3.06	24	25	100	672
5	58	F	2	132	90	32	4.15	24	2	73	169
6	71	M	1	78	46	41	4.62	22	4	138	197
7	38	M	2	142	83	42	4.93	15	6	18	273
8	69	F	3	144	96	33	2.76	ND	27	59	303
9	44	M	3	157	137	13	2.42	17	40	430	563
10	67	F	1	213	152	29	4.75	ND	0	355	159
Mean ± SD	61 ± 12		2.3 ± 0.8	149 ± 44	109 ± 45	28 ± 11	3.86 ± 1.17	20 ± 3	18 ± 16	155 ± 141	343 ± 209

ND = not done.

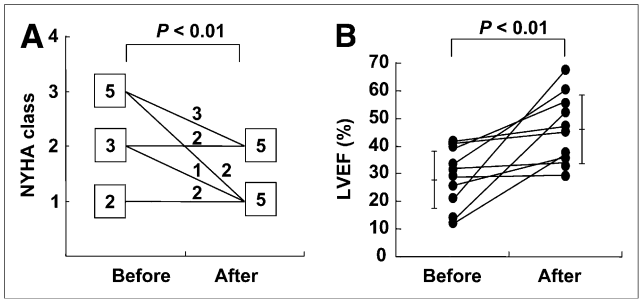

FIGURE 1. Changes in NYHA functional class (A) and LVEF (B) before and after 20 mo of carvedilol treatment.

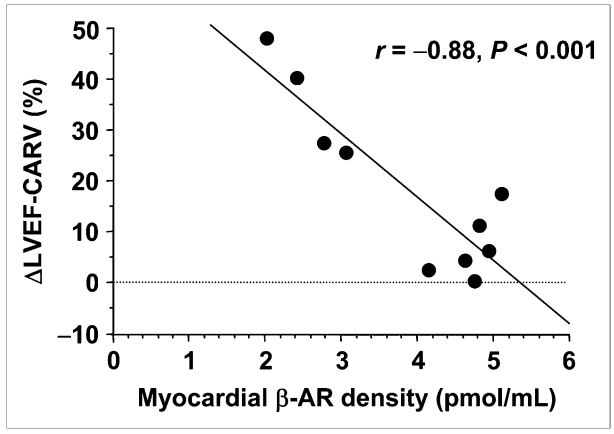

FIGURE 2. Relationship between ΔLVEF-carvedilol (CARV) and baseline myocardial β-AR density.

Myocardial β-AR Density as a Predictor of ΔLVEF-Carvedilol

Although the assessment of myocardial β-AR density is expected to predict the effects of carvedilol on cardiac function in patients with heart failure, such information has been lacking. To our knowledge, this is the first study clearly demonstrating that the downregulation of myocardial β-AR can predict the increase of LVEF by carvedilol therapy in patients with IDC. In this study, elevated plasma norepinephrine was significantly correlated with decreased myocardial β-AR density. Elevated levels of norepinephrine within the synaptic cleft by increased sympathetic tone have been shown to be a major cause of downregulation of myocardial β-AR (*15*). We recently demonstrated that increased cardiac sympathetic tone is associated with the severity of symptoms, cardiac dysfunction, and remodeling in patients with heart failure (*8*). Moreover, in most patients with impaired presynaptic function, left ventricular function had a highly favorable response to carvedilol treatment (*5*). Reduction of cardiac sympathetic tone by treatment with β-blockers may result in a better prognosis in patients with heart failure (*3*). Taken together, our study findings suggest that the decrease of myocardial β-AR density implies the presence of higher cardiac sympathetic tone, which in turn predicts benefits from β-blocker treatment. Our findings have extended our own previous finding (*8*) and that of Spyrou et al. (*10*) that decreased myocardial β-AR density is associated with left ventricular remodeling. Our results are in contrast to those of Gilbert et al., who found that carvedilol improved cardiac function without altering myocardial β-AR density in patients with heart failure (*2*), indicating that myocardial β-AR density may not predict the efficacy of β-blocker therapy. However, Gilbert et al. did not examine the relationship between myocardial β-AR density and improvement in cardiac function. Furthermore, their measurement was based on small specimens obtained by endomyocardial biopsy. Therefore, in contrast to ^{11}C-CGP12177 PET in the present study, their measurements of myocardial β-AR density might not be representative of the heart as a whole. Another reason for the difference might be that Gilbert et al. measured all β-ARs whereas we measured the surface-active receptors that ^{11}C-CGP12177 PET reflects.

TABLE 2. Correlation Between ΔLVEF-Carvedilol and Baseline Variables

Variable	Correlation coefficient	*P*
Age (y)	0.19	0.60
NYHA class	0.76	<0.05
Plasma biomarkers		
Brain natriuretic peptide (pg/mL)	0.33	0.34
Norepinephrine (pg/mL)	0.85	<0.01
Echocardiographic parameters		
LVEDV (mL)	0.15	0.67
LVESV (mL)	0.34	0.34
LVEF (%)	−0.64	<0.05
ΔLVEF-dobutamine (%)	0.19	0.65
Myocardial β-AR density (pmol/mL)	−0.88	<0.001

Contractile Reserve and ΔLVEF-Carvedilol

The present study could not confirm previous results (*6,7*) showing that cardiac contractile reserve during dobu-

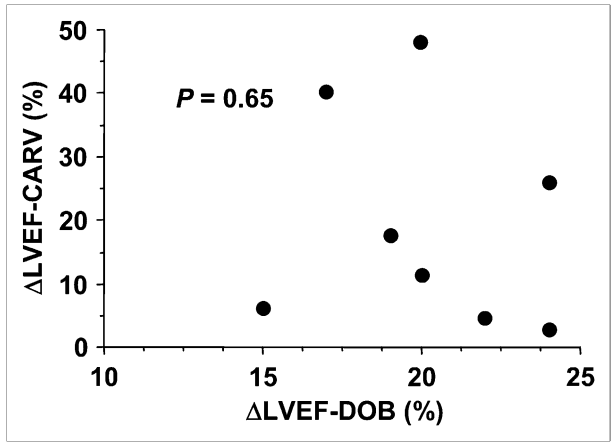

FIGURE 3. Relationship between ΔLVEF-carvedilol (CARV) and ΔLVEF-dobutamine (DOB).

tamine stress is useful for predicting the efficacy of β-blockers in patients with IDC and heart failure. There are several explanations for this discrepancy. First, the characteristics of the patients differed between studies. In our patients, contractile reserve as assessed by dobutamine stress echocardiography was preserved at relatively normal levels; ΔLVEF-dobutamine was greater than 15% in all patients (Table 1). This result suggests that our patients had less severely impaired contractile reserve, as might be due to less myocyte death and fibrosis. Therefore, in assessing myocardial β-AR density, ^{11}C-CGP12177 PET can detect the efficacy of β-blockers on left ventricular function in patients with milder forms of IDC that may not be identified on dobutamine stress echocardiography. Second, the etiologies of heart failure were heterogeneous in the previous study, and most of the patients had ischemic heart failure (*7*), whereas all our patients were nonischemic. Narula et al. demonstrated that the scarred and remodeled myocardial segments were less amenable to contractile reserve than were the hibernating and stunned dysfunctional ones (*16*), indicating that the etiology of left ventricular systolic dysfunction could affect contractile reserve. Thus, contractile reserve in the remodeled myocardium of IDC may have failed to predict ΔLVEF-carvedilol in the present study. Third, follow-up in the present study was as long as 20 mo—longer than in the previous studies (3–7 mo) (*6,7*). More important, although partly reflecting β-adrenergic signaling pathways, contractile reserve in response to intravenous dobutamine infusion is not a direct measurement of myocardial β-AR density. Dobutamine alters not only myocardial contractility but also heart rate and systemic vascular resistance and increases oxygen demand. These multiple pharmacologic effects of dobutamine on cardiovascular hemodynamics might be responsible for the discrepancy between the direct assessment of myocardial β-AR density (as in the present study) and the indirect assessment of β-adrenergic signaling system by contractile reserve during dobutamine infusion to predict the efficacy of β-blockers in patients with IDC.

Study Limitations

Our study had few patients. However, the number of patients in the previous study, which demonstrated the relationship between myocardial β-AR density and the response to dobutamine using ^{11}C-CGP12177 PET, was as few as 10 (*9*). Furthermore, the relationship between myocardial β-AR density and ΔLVEF-carvedilol proved to be significant, and the number of patients was considered sufficient to perform this analysis. However, our study and its findings were preliminary, and a larger number of patients is definitely needed to confirm our results and convince clinicians to adopt this method of predicting improvement in cardiac function before initiating β-blockers in patients with IDC. Second, our dosage of carvedilol was less than that in previous studies, such as the Multicenter Oral Carvedilol Heart failure Assessment (MOCHA) trial (*1*). However, the Multicenter Carvedilol Heart Failure Dose Assessment (MUCHA) trial revealed that a mean dosage of 5 mg of carvedilol per day was beneficial in Japanese patients (*4*). Thus, a mean dosage of 8.8 mg of carvedilol per day could clinically benefit our study patients. Third, the maximum dosage of dobutamine in the present study (20 μg/kg/min) might not be enough to maximize ΔLVEF-dobutamine. Moreover, 2 patients were not included in the present study. These factors might explain the failure of ΔLVEF-dobutamine to demonstrate a relationship to ΔLVEF-carvedilol. However, a low-dosage infusion protocol (10–20 μg of dobutamine per kilogram per minute) has been established to evaluate contractile reserve in previous studies (*6,7*).

CONCLUSION

Myocardial β-AR density assessed by ^{11}C-CGP12177 PET predicts the improvement of cardiac function in patients with IDC after long-term carvedilol treatment. Patients with advanced downregulation of myocardial β-AR have higher resting adrenergic drive and may benefit more from the antiadrenergic effects of carvedilol treatment.

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