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Significance of Combined Angiotensin Ⅱ Receptor Blocker and Carvedilol Therapy in Patients With Congestive Heart Failure and Arginine Variant

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Abstract

Objectives. Angiotensin Ⅱ receptor blockers(ARBs)and β-blockers have contributed to longer life expectancies for patients with congestive heart failure. However, whether the use of ARBs is helpful for introducing carvedilol(β-blocker)is unclear when patients with symptomatic congestive heart failure are admitted to the hospital.

Methods. In this retrospective study, 27 patients with symptomatic congestive heart failure were given carvedilol upon admission. Five patients received carvedilol monotherapy(group A), and 22 were treated with a combination of carvedilol and ARBs(group B).

Results. There was no difference in medication between the groups except for ARBs. In addition, there were no significant differences in the decrease in plasma brain natriuretic peptide, or the improvement of left ventricular ejection fraction upon carvedilol treatment between the groups. Although there was no significant difference in the maintenance dose of carvedilol between the groups, the gross dose of carvedilol in group B was significantly lower than that in group A. In addition, the improvement of left ventricular ejection fraction in group B was positively correlated with the maintenance dose of carvedilol in patients who had wild-type β_1-adrenergic receptor at amino acid 389(arginine/arginine genotype).

Conclusions. These results suggest that ARBs are helpful for introducing carvedilol in patients with the wild-type β_1-adrenergic receptor gene, and that treatment with combined treatment with ARB or analysis of the β_1-adrenergic receptor genotype may offer advantages to control congestive heart failure in the short term.

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Key Words

■**Angiotensin Ⅱ** ■**Beta-adrenergic receptor blockers** ■**Genetics**
■**Heart failure**

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INTRODUCTION

Congestive heart failure is associated with high mortality and morbidity. Many trials have demonstrated significant improvements with regard to survival and reduced hospitalization for patients who received angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers, and these results have guided the recommendations of national and international guidelines for the management of heart failure. In patients with congestive heart failure and reduced left ventricular ejection fraction (LVEF), the results of clinical randomized trials have shown that ACEIs can provide life-saving and symptomatic benefits[1−3]. Furthermore, several double-blind, placebo-controlled, randomized studies performed in the United States and Europe have shown that β-blockers have beneficial effects on mortality and mobility in patients with congestive heart failure[4−8]. In addition, β-blocker carvedilol treatment for congestive heart failure patients is a highly cost-effective method of therapy in the Japanese medical environment[9].

However, as the prevalence of heart failure rises, its impact on morbidity, mortality, and healthcare costs exerts a heavy toll worldwide. A previous study[10] demonstrated that angiotensin II receptor blockers (ARBs) prevented patients with heart failure from worsening. A recent result showed that treatment with combinations of β-blockers and ACEIs reduced the mortality rate of patients with congestive heart failure[7]. Another study also demonstrated that the addition of ARBs to ACEIs and β-blockers and other conventional treatments leads to a further clinically important reduction in relevant cardiovascular death and hospital admissions for heart failure in patients with congestive heart failure and improves LVEF[10−13]. In addition, carvedilol and losartan alone and in combination prevent ventricular remodeling after acute myocardial infarction in rats, with almost equivalent effect[14]. Several genetic polymorphisms have been identified in the β_1-adrenergic receptor (AR) gene, and the genetic heterogeneity of β_1-AR correlates with a pathophysiological role in patients with congestive heart failure. A recent investigation suggested that heart failure patients with the amino acid residue arginine (Arg)^{389} β_1-AR variant showed improved left ventricular function when treated with carvedilol, a third-generation β-blocker with vasodilatory and antioxidant actions, when compared with glycine (Gly)^{389} patients[15].

It would be worthwhile to determine whether treatment with ARBs is useful for introducing β-blockers in patients with congestive heart failure. Therefore, we tested the hypothesis that the ARBs is useful for introducing carvedilol in patients with symptomatic congestive heart failure. We also examined the association between genetic variances of Arg^{389} in β_1-AR and the results of carvedilol treatment in congestive heart failure.

SUBJECTS AND METHODS

Subjects

The subjects consisted of 27 patients with symptomatic congestive heart failure who were admitted to Fukuoka University Hospital. Patients had ischemic or non-ischemic cardiomyopathy with symptoms [New York Heart Association (NYHA) functional class II−IV]. Patients with the following conditions were excluded: valvular heart disease, hypertrophic obstructive cardiomyopathy, cardiogenic shock, systolic blood pressure $<$ 90 mmHg, bradycardia ($<$ 60/min), grade II or III atrioventricular block, life-threatening arrhythmia, unstable angina, resting angina, cor-pulmonale, asthma, Raynaud phenomenon, and intermittent claudication. Hypertensive heart disease was defined by pressure of hypertension and left ventricular hypertrophy as assessed by echocardiography.

All patients were given carvedilol upon admission: 5 received carvedilol monotherapy (group A), and 22 were treated with combined carvedilol and ARBs (group B). In group B, 27% ($n = 6$) received 5 ± 1 mg/day of candesartan, 46% ($n = 10$) received 52 ± 13 mg/day of valsartan and 27% ($n = 6$) received 33 ± 5 mg/day of losartan. All patients in group B were introduced to carvedilol after ARB administration on admission to a hospital. ARB on admission and diuretics, digitalis, calcium channel blockers, vasodilators, and antiarrhythmic agents could be used concomitantly if necessary for treatment of congestive heart failure. We investigated blood pressure, heart rate, echocardiography, plasma brain natriuretic peptide (BNP) level, and the maintenance and total doses of carvedilol at two points (on admission before treatment and when the patients left the hospital). The ethics committee of Fukuoka University Hospital approved this study.

Table 1 Baseline patient characteristics

	Group A (n=5)	Group B (n=22)
Age (yr)	56±4	66±2
Body mass index (m^2/kg)	22±2	23±1
Male (%)	60	65
Alcohol use (%)	40	36
Current smoker (%)	80	41
Heart disease cause (%)		
Ischemic heart disease	0	44*
Idiopathic cardiomyopathy	40	36
Hypertensive heart disease	40	16
Others	20	4
Concomitant disease (%)		
Hypertension	40	45
Diabetes mellitus	20	18
Hyperlipidemia	20	32
Medical treatment (%)		
Diuretics	80	82
Digitalis	20	23
NYHA class (%)		
Ⅱ/Ⅲ/Ⅳ	20/80/0	0/74/26
LVEF (%)	24±5	37±3
LVDd (mm)	60±6	57±2
Systolic BP (mmHg)	110±11	122±4
Diastolic BP (mmHg)	75±12	77±4
Heart rate (beats/min)	91±9	81±4
BNP level (pg/m*l*)	789±209	584±112

Continuous values are mean±SE. *$p<0.05$ vs group A.
Group A: Patients treated with carvediol. Group B: Patients treated with combined carvediol and angiotension Ⅱ receptor blockers.
NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; LVDd=left ventricular diastolic dimension; BP=blood pressure; BNP=brain natriuretic peptide.

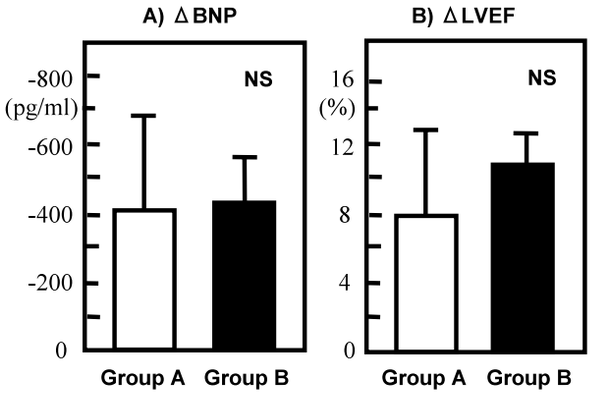

Fig. 1 Comparison of parameters in heart failure patients in groups A and B
No significant differences in the decrease in the BNP level (ΔBNP, Δ values after carvedilol treatment minus those before treatment; *A*) or the increase in LVEF (ΔLVEF; *B*) were observed between the groups.
Explanation of the groups and abbreviations as in Table 1.

Gene analysis

Genomic DNA was extracted from peripheral whole blood using the Genomix kit. For genotyping of the Arg389Gly polymorphism of the β_1-AR gene, the polymerase chain reaction and restriction enzyme digestion were performed as described previously[16].

Statistical analysis

Data are shown as the mean ± standard error. Categorical variables were compared between groups by chi-square analysis. Differences in individual variables were analyzed by the unpaired *t*-test. Correlation between variables was examined by the Pearson correlation. A value of $p<0.05$ was regarded as significant. Data were analyzed using commercially available statistical software (Statview-J 5.0; Abacus Concepts Inc.).

RESULTS

Baseline patient characteristics are shown in **Table 1**. There were no significant differences in baseline characteristics between the two groups, except for the etiology of heart failure. None and 44% of the patients in groups A and B, respectively, had ischemic heart disease ($p<0.05$).

There were no significant differences in the decrease in the BNP level or the increase in LVEF (measured by M-mode echocardiography) during carvedilol treatment between groups A and B (**Fig. 1**). Since cardiac function in the groups recovered similarly, we did further statistical analysis. In addition, all patients in both groups became NYHA class Ⅰ after treatment.

The gross and maintenance doses of carvedilol before and after treatment for introducing carvedilol are shown in **Fig. 2**. The gross dose indicates total amount of carvedilol during hospitalization for patients. Although there was no significant difference in the maintenance dose of carvedilol (group A: 7.5 ± 1.6 mg/day, group B: 9.3 ± 1.1 mg/day), the gross dose of carvedilol in group B (125 ± 12 mg) was significantly lower than that in group A (204 ± 63 mg) ($p<0.05$). Group B

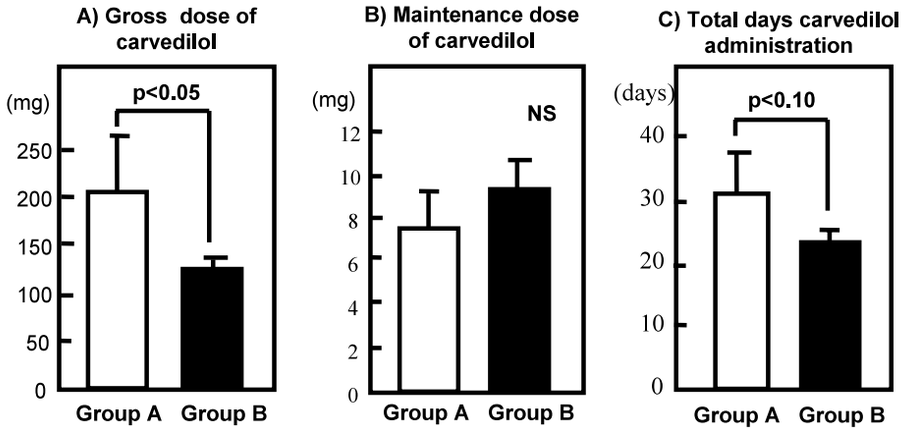

Fig. 2 Gross and maintenance doses of carvedilol for introducing carvedilol in groups A and B

Although there was no significant difference in the maintenance dose of carvedilol(*B*), the gross dose of carvedilol in group B was significantly lower than that in group A(*A*; $p < 0.05$). Total days of carvedilol administration is shown in(*C*).

Gross dose of carvedilol = dose of carvedilol × total days of administration. Explanation of the groups as in Table 1.

tended to have a shorter total period of carvedilol administration compared to group A(group A: 32 ± 7 days, group B: 23 ± 2 days, $p < 0.10$).

Fig. 3 compares the gross and maintenance doses of carvedilol before and after treatment for introducing carvedilol between the Arg/Arg($n = 14$)and Arg/Gly($n = 8$)groups in all patients. Five patients were excluded because of no approval to analyze DNA. There were no differences between the groups in baseline patient characteristics of age, body mass index, sex, drinking, smoking, heart disease cause, concomitant disease, medical treatment, NYHA class, LVEF, blood pressure, heart rate and BNP.

There were no significant differences in the gross or maintenance dose of carvedilol between the groups. Although there was no difference in the improvement of LVEF(ΔLVEF = value after carvedilol treatment minus that before treatment) between the Arg/Arg and Arg/Gly groups(**Fig. 4-A**)in all patients, ΔLVEF was positively correlated with the maintenance dose of carvedilol in group B patients who had the Arg/Arg genotype(**Fig. 4-B**). In the Arg/Gly group, there was no correlation between LVEF and the maintenance dose of carvedilol($p > 0.10$). If a patient with congestive heart failure and the wild-type β_1-AR gene(position 389 is Arg/Arg)receives combination therapy with ARBs for the introduction of carvedilol, a higher maintenance dose of carvedilol may more effectively improve cardiac function.

DISCUSSION

Our results support the hypothesis that ARBs and β-blockers have beneficial effects for patients with heart failure. Previous studies have demonstrated that ARBs have long-term benefits and reduce cardiovascular death and hospital admissions for heart failure. Our results suggest that ARBs also have a short-term benefit, *i.e.*, additional treatment with ARBs can reduce the gross dose of carvedilol. Therefore, the use of carvedilol combined with ARBs may be useful for introducing carvedilol in patients with heart failure.

Once the onset of heart failure has occurred, a vicious cycle is initiated. After a sizable myocardial loss to precipitate heart failure, neurohormonal activation, especially of the sympathetic nerve system and the renin-angiotensin system, results in further losses of cardiac myocytes through apoptosis and necrosis. A primary objective of treatment is to prevent the further loss of cardiac myocytes[17], by reducing the recurrence of myocardial infarctions, myocarditis, or cardiomyopathic processes. The former can be effectively achieved by inhibiting the renin-angiotensin system or the sympathetic system. The latter can also be partly achieved by treatment with angiotensin converting enzyme inhibitors and possibly ARBs[18,19]. Administration of β-blocker normalized the abundance of

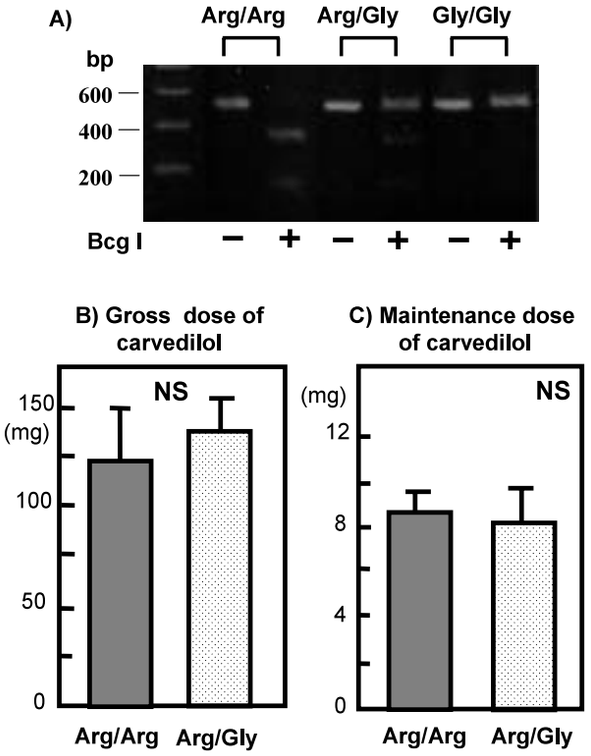

Fig. 3 Representative genetic variances in three individuals, gross and maintenance doses of carvediol

A: Representative genetic variances of β_1-AR at amino acid 389 in three individuals. Polymerase chain reaction fragments were digested with the restriction endonuclease Bcg Ⅰ, which did not digest the Arg-389 product because of the guanine to cytosine transition.

B,C: Gross(*B*)and maintenance(*C*)doses of carvedilol in the Arg/Arg($n=14$)and Arg/Gly groups($n=8$)are shown. None of the subjects in this study were Gly/Gly. There were no significant differences in the gross and maintenance doses of carvedilol between the groups.

Arg＝arginine; Gly＝glycine; bp＝base paire.

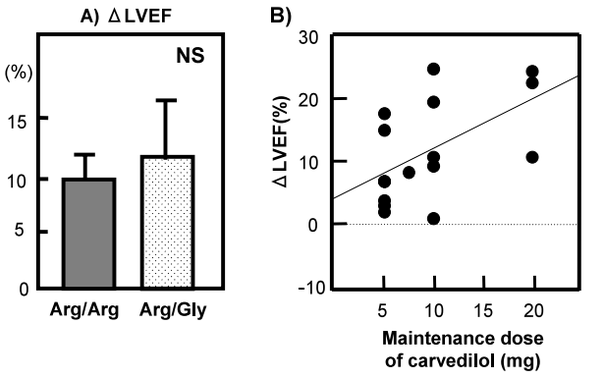

Fig. 4 ΔLVEF in the Arg/Arg and Arg/Gly groups (*A*), and ΔLVEF was positively correlated with the maintenance dose of carvedilol in group B patients who had the Arg/Arg genotype ($y=3.222+0.801x$, $r=0.674$, $p<0.05$; *B*).

Explanation of group B and abbreviation as in Table 1, Fig. 3.

myocyte Ca^{2+} regulatory proteins and improved Ca^{2+} handling[20]. In addition, β-blockers can effectively suppress the sympathetic system, thus interrupting the downward spiral caused by the vicious cycle in patients with heart failure, and prevent further losses of cardiac myocytes. Accordingly, the accelerated deterioration of cardiac pumping capability can be ameliorated by therapy aimed at inhibiting angiotensin and/or β-adrenergic effects using ARBs and/or β-blockers. The combination therapy with carvedilol and ARBs may be more potent than individual treatments through the combined beneficial mechanisms for controlling heart failure as seen in this study.

Over the past decade, increasing evidence has accumulated to indicate that angiotensin Ⅱ is involved in the development of atherosclerosis, myocardial infarction, vascular and myocardial remodeling, and heart failure[21,22]. In the case of heart failure, angiotension Ⅱ type 1(AT_1)receptors expressed in myocardial cells are activated, which causes consequent cellular hypertrophy, proliferation, and apoptosis. ARBs strongly block AT_1 receptors, and reduce cardiovascular death and hospital admissions for heart failure. Up-regulation of angiotension Ⅱ caused by ARBs stimulates AT_2 receptor. Other mechanisms of action, such as AT_2 receptor effects, and the anti-oxidant[23] or anti-fibrotic effects of ARBs[24], may also contribute to the improvement of heart failure.

According to a previous epidemiological study, the β_1-AR Ser49Gly variant might be associated with a decreased risk of morbidity and mortality in patients with congestive heart failure[25]. Also, a lack of polymorphic α_{2c}-AR(α_{2c} Del322−325)and abnormality of β_1-AR(Arg389Gly)act synergistically to increase the risk of heart failure in blacks[26]. A recent study demonstrated that the human Arg^{389} variant predisposes patients to heart failure by instigating hyperactive signaling programs which lead to depressed receptor coupling and ventricular dysfunction, and influences the therapeutic response to β_1-AR blockade. Heart failure patients with Arg^{389} homozygosis showed improved left ventricular function during long-term carvedilol treatment compared to Gly^{389} patients.

Although we did not note any differences in the improvement of left ventricular function for introducing carvedilol between the Arg/Arg and Arg/Gly groups, this may have been due to the short duration of this study. This study found that the Arg^{389} variant in β_1-AR may be useful for introducing carvedilol in heart failure patients because a higher maintenance dose of carvedilol was more effective for improving cardiac function in patients with the wild-type β_1-AR gene(Arg/Arg at position 389). If heart failure patients who have the Arg/Arg genotype and receive combination therapy with ARBs for introducing carvedilol, a higher maintenance dose of carvedilol might be recommended.

Study limitations

This study has several important limitations. First, there was a difference in the etiology of heart failure between groups A and B. However, this difference did not affect our main conclusion that ARBs are helpful for introducing carvedilol in patients with the wild-type β_1-AR gene. Second, the sample size is small, which limited our ability to determine significance. Our study was a nonrandomized, retrospective, observational study. A large randomized controlled trial of statins in patients with coronary artery disease is warranted to evaluate the potential benefits of these agents.

CONCLUSIONS

Additional treatment with ARBs and the analysis of Arg^{389} variant in β_1-AR in patients with congestive heart failure may be helpful for introducing carvedilol, and treatment with the combination of carvedilol and ARBs may have advantages over

要　　約

うっ血性心不全患者のアンジオテンシンⅡ受容体遮断薬併用によるカルベジロール導入とβ$_1$アドレナジック受容体アルギニン^{389}バリアントの意義

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目　的: アンジオテンシンⅡ受容体遮断薬(ARB)とβ遮断薬は，うっ血性心不全患者の予後を改善する．しかし，カルベジロール(β遮断薬)の導入にARBの併用が有効であるかについては明らかでない．

方　法: 入院後，カルベジロールを導入された症状を有する27例のうっ血性心不全患者を後ろ向きに検討した．2群に分け，5例をカルベジロール投与群，22例をカルベジロール＋ARB投与群とした．

結　果: 投薬内容は，ARB投与を除いて両群間に有意差はなかった．また，脳性Na利尿ペプチド，左室駆出率にも有意差はなかった．カルベジロールの維持量は，両群間に有意差はなかったが，カルベジロール＋ARB投与群では，カルベジロール投与群に比べて有意にカルベジロールの総投与量が減少していた．さらに，カルベジロール＋ARB投与群における左室駆出率の改善度は，β$_1$アドレナジック受容体の389番のアミノ酸がArg/Arg遺伝子型(野生型)を有する患者においてカルベジロールの維持量と正相関していた．

結　論: ARBは，β$_1$アドレナジック受容体の389番のアミノ酸がArg/Arg遺伝子型を有する心不全患者のカルベジロール導入を容易にし，ARBの併用療法およびβ$_1$受容体の遺伝子解析は，短期に心不全患者に対してカルベジロールを導入する場合に有用であることが示唆された．

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