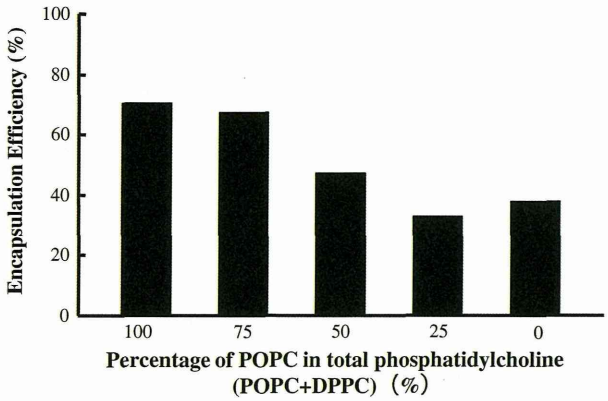

Fig. 1 Encapsulation efficiency of amiodarone in the liposomes. Amiodarone was loaded into liposomes containing POPC, DPPC, or a mixture of POPC and DPPC. The liposomal amiodarone was composed of phosphatidylcholine (POPC + DPPC):cholesterol:amiodarone at a 10:5:1 molar ratio. The percent molar ratio of POPC in total phosphatidylcholine (POPC + DPPC) is indicated in the figure. The encapsulation efficiency of amiodarone was determined as described in the Methods section

The dynamic light scatter analysis showed no significant differences between the mean diameter, polydispersity index, or ζ potential distribution of the empty and amiodarone-loaded PEGylated liposomes (Table 1).

Accumulation of Fluorescence-labeled Nano-sized Beads in the I/R Myocardium

Representative pictures obtained by fluorescence imaging are shown in Fig. 2a (whole heart) and b (sliced hearts). Quantitative analysis revealed that the average fluorescence intensity of the whole heart (Fig. 2c left) or the left ventricle (Fig. 2c right) of the I/R hearts was significantly higher than that in sham-operated hearts.

Amiodarone Concentration in the Blood and I/R Myocardium

The plasma concentration after the administration of liposomal amiodarone was significantly higher than that of free amiodarone (Table 2). Importantly, the amiodarone concentration in the I/R myocardium was detectable after the administration of liposomal, but not free, amiodarone (Table 2).

Hemodynamic Effects of Amiodarone and Liposomal Amiodarone

The baseline heart rates were 411±16, 426±14, 427±12, 409±8 and 414±6 beats/min in the saline, empty liposome, amiodarone (3 mg/kg), amiodarone (10 mg/kg) and liposomal amiodarone (3 mg/kg) groups, respectively. The baseline systolic BP was 113±7, 118±10, 111±5, 90±4 and 104±2 mmHg in the saline, empty liposome, amiodarone (3 mg/kg), amiodarone (10 mg/kg) and liposomal amiodarone (3 mg/kg) groups, respectively. There were no significant differences in the baseline HR or systolic BP among the groups tested. The intravenous administration of amiodarone (3 and 10 mg/kg) or liposomal amiodarone reduced both the HR and systolic BP from the baseline, whereas the saline or empty liposomes did not (Fig. 3). The time-course changes of both the HR and systolic BP were significantly smaller in the liposomal amiodarone group (3 mg/kg) compared with the corresponding dose in the free amiodarone group (3 mg/kg) (Fig. 3). The reductions in HR and systolic BP at 1, but not 3, minutes after liposomal amiodarone administration were significantly smaller compared with those following the corresponding dose of amiodarone.

Antiarrhythmic Effects of Amiodarone and Liposomal Amiodarone

Representative electrocardiograms of the rats that received saline, free amiodarone or liposomal amiodarone are shown in Fig. 4. The intravenous administration of liposomal amiodarone (3 mg/kg), but not amiodarone (3 mg/kg), significantly reduced the duration of VT/VF compared with saline (Table 3). Furthermore, the mortality in the group that received liposomal amiodarone (3 mg/kg), but not the corresponding dose of amiodarone (3 mg/kg), was significantly lower than that in the saline group. In the group of rats that received a high dose of amiodarone (10 mg/kg), the VT/VF duration was 36±12 s, and none of the rats died (Table 3), which was similar to the low dose of liposomal amiodarone group (3 mg/kg).

Discussion

In this study, we revealed that 1) liposomal amiodarone was successfully prepared using a thin-film method, 2) the

Table 1 Characterization of liposomes by dynamic light scatter analysis

	Mean diameter (nm)	Polydispersity index	ζ Potential (mV)
PEGylated liposomes (empty liposomes)	111±14	0.124±0.027	−2.1
PEGylated liposomal amiodarone	113±8	0.128±0.040	−3.7

Results represent 4 independent experiments. The values are expressed as the mean ± SD. *PEG* polyethylene glycol

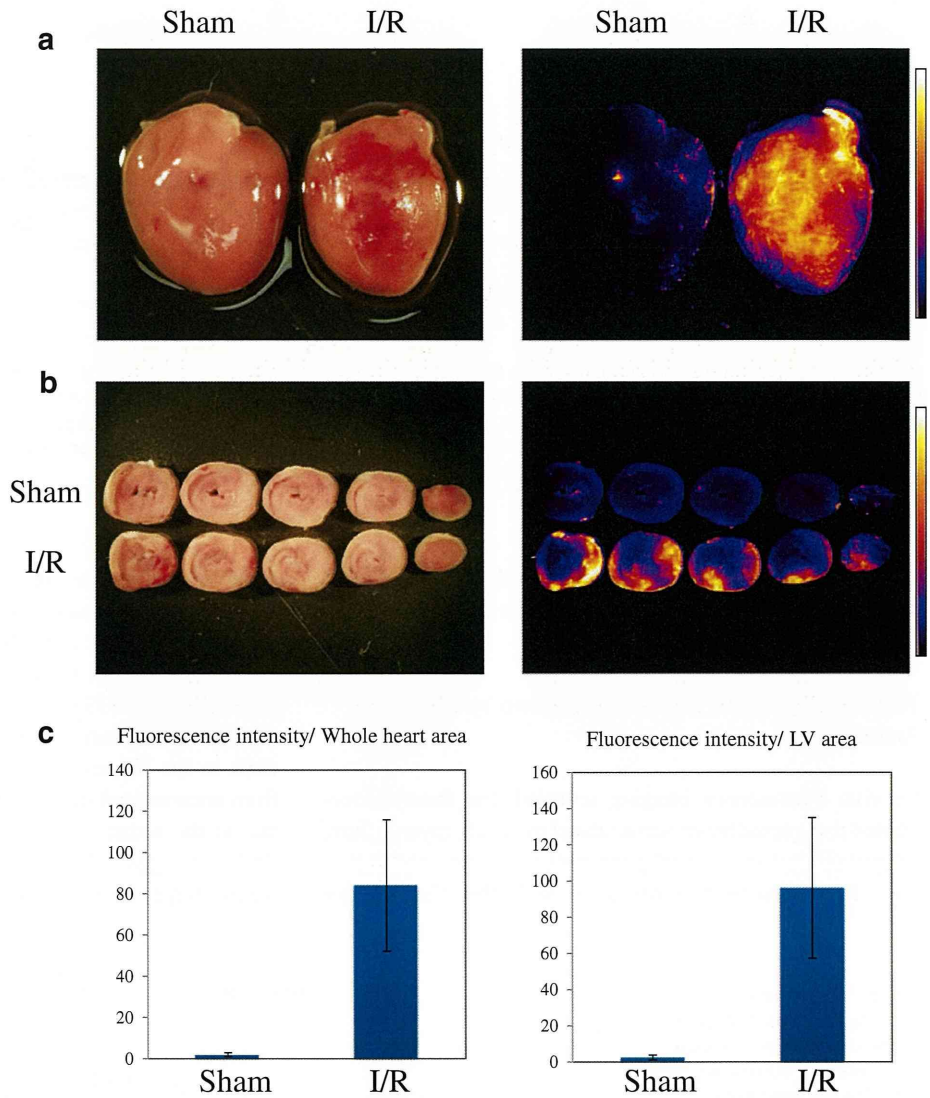

Fig. 2 Representative pictures of ischemia/reperfused myocardium with and without fluorescence-labeled nano-sized beads. Representative pictures obtained by fluorescent imaging are shown in **a** (*whole heart*) and **b** (*sliced hearts*). Quantitative analysis revealed that the average fluorescence intensity of the whole heart (**c** *left*) or the left ventricle (**c** *right*) of the I/R hearts was significantly higher than that of the sham-operated hearts

accumulation of nano-sized beads was observed in the I/R myocardium, 3) liposomal amiodarone showed a smaller reduction in the HR and systolic BP compared with free amiodarone, and 4) liposomal amiodarone, but not amiodarone, reduced the VT/VF duration and mortality during the reperfusion period compared with saline.

Table 2 Amiodarone concentration in the blood and I/R myocardium

Groups	Plasma, ng/mL	Myocardium, ng/mL
Saline	N.D.	N.D.
Free amiodarone	472±147	N.D.
Liposomal amiodarone	3872±378*	71±7*

Data are expressed as the mean ± SEM. *N.D.* not detected. n=3 rats in each group. * $p<0.05$ versus free amiodarone

Preparation of Liposomal Amiodarone

This study is the first to encapsulate amiodarone in PEGylated liposomes, although it has been previously encapsulated in other liposomes [22] and micelles [23]. We demonstrated that lipid bilayers composed of unsaturated lipids are more suitable for encapsulating amiodarone in PEGylated liposomes compared with those composed of saturated lipids. PEGylated liposomes have a long circulating time in the bloodstream because PEG endows a steric barrier to liposomes, allowing them to avoid interactions with opsonins and cells of the mononuclear phagocytic system [24]. Thus, they have been used to increase drug stability, safety, and bioavailability in clinical applications. In this study, we found that a higher concentration of amiodarone was retained in the blood when we administered liposomal amiodarone compared with the administration of

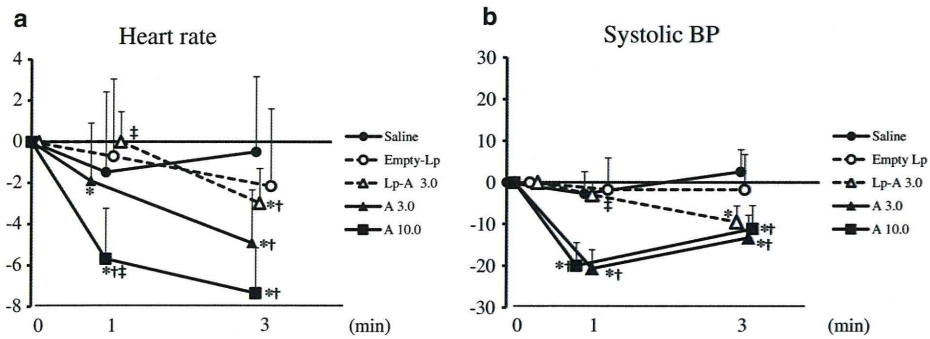

Fig. 3 Time-course changes in HR and systolic BP after drug administration. Shows the percent change from baseline for HR (**a**) and systolic BP (**b**) after intravenous administration of the tested drugs. The data are expressed as the mean ± SEM. *$P<0.05$ versus baseline, paired t-test. $P=0.0009$ (HR), 0.0002 (systolic BP) between amiodarone (3 mg/kg) and liposomal amiodarone (3 mg/kg), 1-way repeated-measurement ANOVA. †$P<0.05$ versus saline, ‡$P<0.05$ versus amiodarone (3 mg/kg), 1-way repeated-measurement ANOVA with Bonferroni's multiple comparison

free amiodarone, suggesting that encapsulation of amiodarone in PEGylated liposomes enhances the stability of amiodarone in the blood.

Targeted Delivery to the I/R Myocardium by Liposomal Amiodarone

Ex vivo fluorescence imaging revealed that fluorescence-labeled nano-sized beads accumulated in the I/R myocardium, suggesting that myocardial permeability can be enhanced in the I/R myocardium. Consistent with this finding, we observed that the amiodarone concentration in the I/R myocardium in the liposomal amiodarone group was much higher compared with that in the amiodarone group. Enhanced permeability in the I/R myocardium and the prolonged presence of amiodarone in PEGylated liposomes in the blood represent a possible mechanism for increased amiodarone concentrations in the I/R myocardium. Amiodarone will be released from accumulated liposomal amiodarone in I/R myocardium due to the natural decay and concentration gradient. These findings suggest that the I/R myocardium is a promising passive target for liposomal drug delivery.

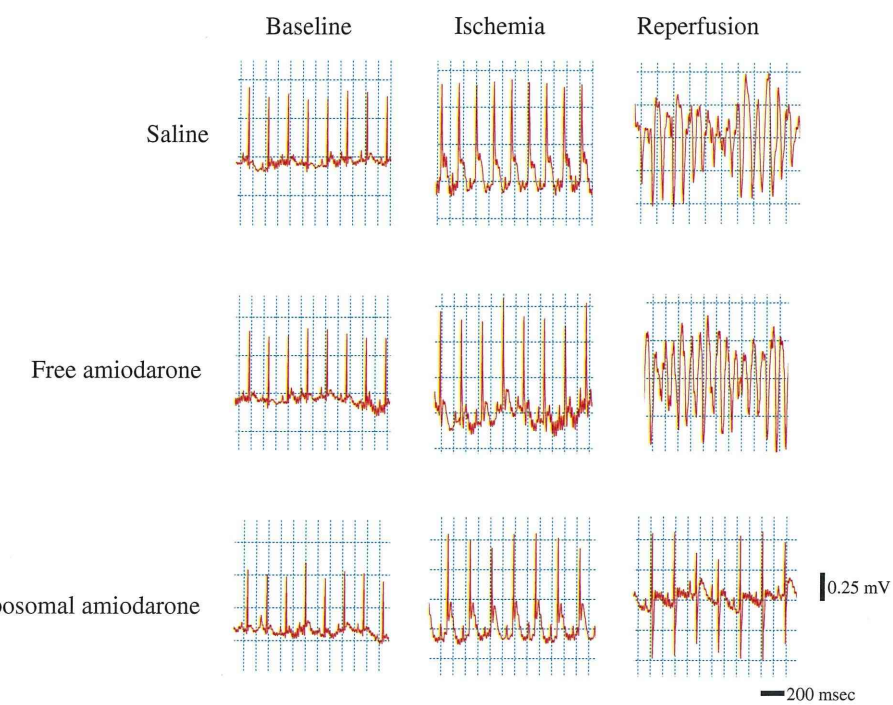

Fig. 4 Representative electrocardiograms. The *upper, middle and lower panels* show representative electrocardiograms under baseline conditions during ischemia and at the onset of reperfusion for rats that received saline, free amiodarone (3 mg/kg) and liposomal amiodarone (3 mg/kg), respectively

Table 3 Lethal arrhythmias and mortality in an I/R rat model

	Number	VT/VF duration (sec)	Mortality (%)
Saline	7	195±42	71
Empty liposomes	6	162±31	50
Amiodarone (3 mg/kg)	6	167±78	33
Amiodarone (10 mg/kg)	6	36±12*	0#
Liposomal Amiodarone (3 mg/kg)	6	18±9*	0#

*$p<0.05$ versus saline (VT/VF duration). #$p<0.05$ versus saline group (mortality). *VT* ventricular tachycardia, *VF* ventricular fibrillation

Minimal Negative Hemodynamic Effects of Liposomal Amiodarone

Amiodarone causes hypotension and bradycardia in clinical settings [4, 5]. In this study, both free and liposomal amiodarone significantly reduced the HR and systolic BP; however, the time-course changes for both the HR and systolic BP in the liposomal amiodarone group were significantly smaller compared with those following the corresponding dose of free amiodarone. Importantly, the reductions in HR and systolic BP at 1, but not 3, minutes after liposomal amiodarone administration were significantly smaller compared with those following the corresponding dose of amiodarone. These findings suggest that liposomal amiodarone may minimize the negative effects on systemic hemodynamics immediately after the administration of amiodarone. One possible mechanism to explain this finding is that amiodarone on the surface of the liposome membrane is covered with PEG so that amiodarone cannot act directly on cardiovascular cells. Gradual release of amiodarone from liposome may minimize the rapid hemodynamic changes, because systemic hemodynamic effects of liposomal amiodarone were significantly attenuated in liposomal amiodarone group than free amiodarone group.

Augmented Anti-arrhythmic Effects of Liposomal Amiodarone

In this study, liposomal amiodarone (3 mg/kg), but not the corresponding dose of free amiodarone (3 mg/kg), significantly reduced the VT/VF duration and mortality compared with saline in an I/R rat model. Because the acute effects of amiodarone are known to be attributable to blockade of Na^+, Ca^{2+} and dose-dependent K^+ channels [2, 25], increasing the concentration of amiodarone in the I/R myocardium may augment its anti-arrhythmic effects through its tonic effects on cardiomyocytes caused by blocking cardiac ionic currents. Kishida et al. reported that amiodarone enhances nitric oxide production in cultured human endothelial cells [26]. Furthermore, amiodarone protects cardiac myocytes against oxidative injury by scavenging free radicals [27]. These pleiotropic effects of amiodarone are also enhanced by its increased concentration in the I/R myocardium via PEGylated liposomes, which may contribute to the reduction of lethal arrhythmias during reperfusion followed by ischemia. In the present study, since we did not do any procedure such as electrical conversion or cardiac massage for VT/VF, the mortality was higher than in our previous report [16].

Clinical Implications

In clinical settings, higher doses of amiodarone cause hypotension and non-cardiac death or induce worsening heart failure through negative inotropic effects [28]. These effects often diminish the beneficial effects of amiodarone for patients with AMI or heart failure [8, 9]. The present study demonstrated that liposomal amiodarone (3 mg/kg) exerts anti-arrhythmic effects similar to a high dose of free amiodarone (10 mg/kg) while reducing the extent of bradycardia and hypotension, suggesting that encapsulating amiodarone in liposomes augments its anti-arrhythmic effects and reduces its negative effects on hemodynamic parameters with reducing administrative dose. These findings can have a great impact on preventing lethal arrhythmias during reperfusion in AMI patients.

Study Limitations

There are several limitations in this study. We used a brief period of I/R without myocardial infarction in rats. Sakamoto et al. demonstrated that the incidence of VT/VF in a rodent model was 'bell-shaped' with a maximum at 5 min of ischemia and that most lethal arrhythmias occurred within first 20 s after the onset of reperfusion [29]. Consistently, our data showed that the mean time at which the lethal arrhythmia occurred after the onset of reperfusion was 3.3+/−1.6 s. Therefore, we chose the 5 min of ischemia followed by 15 min of reperfusion model. We also chose the timing of drug administration before the onset of ischemia to clarify whether liposomal-amiodarone could prevent the lethal arrhythmia that occurs in the early period of reperfusion. In addition, in clinical practice lethal arrhythmias often occur after a brief period of I/R without any irreversible damage to the heart, indicating that the anti-arrhythmic effects of liposomal amiodarone during a brief period of ischemia model could have clinical relevance [30]. However, careful interpretation is necessary when using liposomal amiodarone in acute myocardial infarction with irreversible damage to confirm the beneficial effects of liposomal amiodarone. Furthermore, because the electrophysiology of rats differs from that of humans and drug administration in our study started before the onset of

ischemia, additional pre-clinical studies including a longer period of I/R model to consider the timing of drug administration are needed using large animal models. We should also take into account that the potential side effects of amiodarone such as bradycardia are minimal in the left coronary artery occlusion model used in the present study.

Conclusion

In conclusion, the targeted delivery of liposomal amiodarone to the I/R myocardium exerted strong anti-arrhythmic effects and reduced the negative impact on systemic hemodynamics. Nano-sized liposomes may be a promising drug delivery system for targeting the I/R myocardium with cardioprotective agents.

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Original article

Switching from carvedilol to bisoprolol ameliorates adverse effects in heart failure patients with dizziness or hypotension

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ABSTRACT

Background: Treatment with carvedilol is an established primary therapy for patients with heart failure (HF). However, its most common adverse effects, dizziness and hypotension, often discourage continuation or dosage increase. The aim of this study was to examine whether switching to bisoprolol from carvedilol would help to avoid adverse symptoms and signs related to carvedilol administration.

Methods and subjects: Data were retrospectively collected from 23 patients with HF [age 57 ± 18 years, left ventricular ejection fraction (LVEF) 33 ± 15%] who could not increase the dosage of carvedilol because of dizziness or hypotension, defined as systolic blood pressure < 90 mmHg. Before and immediately after, and 6 months after switching to bisoprolol, we examined symptoms, vital signs, laboratory data, and New York Heart Association functional class. Furthermore, left ventricular (LV) dimension and ejection fraction (EF) were evaluated in 19 patients using echocardiography.

Results: All 13 patients with dizziness (100%) and 9 of 16 with hypotension (56%) were relieved of adverse symptoms or signs. The mean dose of carvedilol before switching was 5.60 ± 3.43 mg. Immediately after the switch, the mean dose of bisoprolol was 1.84 ± 1.08 mg and then increased to 3.13 ± 1.74 mg after 6 months ($p < 0.01$). At 6-month follow-up examinations, LV function determined by LVEF was significantly improved, which was accompanied by increased exercise tolerance.

Conclusion: Switching from carvedilol to bisoprolol may help with continuation of β-blocker treatment as well as dosage increase in HF patients with adverse symptoms or signs, allowing them to reach the target dose.

Introduction

Heart failure (HF) is one of the most serious causes of morbidity and mortality in both developed and developing countries [1], while increased survival was recently demonstrated with continuation of β-blocker therapy in patients with chronic HF and reduced ejection fraction [2–4]. Of the various β-blockers given to affected patients, carvedilol is a multiple action non-selective β-adrenergic receptor blocker that also induces α1-adrenergic receptor blockade and has been shown to improve the state of HF patients in a number of large-scale trials [5–7]. However, the most common adverse clinical effects of carvedilol are dizziness and hypotension [8], and some patients are not able to continue or up-titrate the drug because of these adverse symptoms/signs, which seem to be mainly related to an α1 blockade effect (vasodilation). On the other hand, bisoprolol, a highly selective β1-adrenergic receptor blocker, has also been shown to be effective for HF patients in several studies [9–11].

We speculated that switching from carvedilol to bisoprolol would be useful for avoiding adverse symptoms/signs, and lead to continuation or up-titration of β-blocker administration in HF patients who had adverse effects related to carvedilol administration. In the present study, we retrospectively examined changes in symptoms, blood pressure, heart rate, New York Heart Association (NYHA) functional class, laboratory data, and echocardiography parameters before and after switching to bisoprolol in patients who showed adverse effects due to carvedilol.

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Methods

Study patients

This retrospective study was conducted using data from a large university hospital. The protocol used complies with the Declaration of Helsinki and was approved by our Institutional Ethics Committee, which waived the need for patient consent because of the retrospective nature of the study. Between August 2005 and June 2011, we identified 1056 consecutive patients with left ventricular (LV) ejection fraction (EF) less than 50% who were receiving carvedilol in our hospital database. Among those, 23 in- and outpatients with chronic HF had switched medication because of persistent adverse effects of carvedilol, such as dizziness and hypotension with systolic blood pressure < 90 mmHg [12]. The diagnosis of heart failure was primarily based on signs and symptoms derived from a thorough history review and physical examination [1].

Data collection and study design

Baseline demographic information was retrospectively collected from the medical records, including age, sex, height, weight, NYHA functional class, dose of carvedilol, duration of carvedilol therapy, underlying heart disease (ischemic or non-ischemic), comorbidities (e.g. atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease), and medications (e.g. angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, calcium channel blocker, diuretic, mineralocorticoid receptor antagonist, digoxin, statin, pimobendan, aspirin, clopidogrel). The following assessments were performed: evaluation of adverse symptoms/signs, dose of β-blocker, laboratory data, B-type natriuretic peptide (BNP), echocardiographic parameters, NYHA functional class before the switch, and 6-month follow-up examination findings.

The effects of switching from carvedilol to bisoprolol on adverse symptoms/signs were evaluated immediately after the change or at the first follow-up visit, as well as at the 6-month follow-up examination. Improvement of dizziness was determined by subjective reports from the patient, and relief of hypotension was defined as a blood pressure increase of more than by 10 mmHg in 3 consecutive readings obtained before and after switching medications. To investigate the effects of the switch on cardiac reverse remodeling and symptoms, we also analyzed vital signs, echocardiographic and laboratory data, and NYHA functional class prior to and immediately after switching, and at the 6-month follow-up examination.

Initiation of and switching from carvedilol to bisoprolol

Principally, we treat our patients using optimal medical therapy in line with the guidelines for management of chronic HF (http://www.j-circ.or.jp/guideline/). Treatment with carvedilol was initiated at low doses (1.25 or 2.5 mg/day), followed by gradual increments (usually every 1–2 weeks) if the lower dose was well tolerated, during which the patient was closely monitored for changes in vital signs and symptoms. Planned dosage increases of carvedilol should be delayed until side effects observed with lower doses have disappeared. Every effort to achieve the target dose of carvedilol (usually, 10 mg twice daily) was made by the attending physician [7]. After the appearance of adverse effects, the attending physician switched from carvedilol to bisoprolol and up-titrated the dose of bisoprolol to accomplish the target dose of 5 mg once daily. The tolerable maximum dosage of bisoprolol was determined by the physician after the switch.

Echocardiography

Two-dimensional echo and Doppler recordings for each patient were obtained using a commercially available echocardiographic machine equipped with a 12-MHz transducer (Agilent Sonos 7500; Philips Medical Systems, Andover, MA, USA) at a standard clinical echocardiography laboratory. The investigators were blinded to the results of other tests and clinical examinations. LV end-diastolic dimension (LVDd) and end-systolic dimension (LVDs) were determined from 2-D transthoracic echocardiographic images using M-mode in parasternal long-axis views. LVEF was calculated using Simpson's biplane method with apical 2- and 4-chamber views [13].

Statistical analyses

All continuous values are expressed as the mean ± standard deviation, and data for categorical variables are expressed as the number and percentage of patients. All continuous variables were checked for normality using a Shapiro–Wilk test and normal probability plot. To assess the mean differences in continuous variables between before and after switching, and at the 6-month follow-up examination, we used a Student's paired *t*-test, while a Wilcoxon signed-rank test was performed to evaluate changes in non-normally distributed variables. The vital findings among the 3 different periods were tested using one-way analysis of variance (ANOVA) followed by a Tukey–Kramer multiple comparison test. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using commercially available statistical software JMP 10.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Characteristics of the 23 patients are shown in Table 1. The average age was 57 years and 74% were male. The majority of patients had NYHA class III or IV heart failure symptoms, while 10 (43%) had advanced systolic HF (LVEF < 30%). Nine patients (39%) had atrial fibrillation, 5 diabetes mellitus, and 1 chronic obstructive pulmonary disease (COPD) without bronchial asthma. There was no patient receiving both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in a concomitant manner. Fourteen patients were treated with enalapril (mean dose 2.68 ± 1.19 mg), 2 were taking candesartan (2 mg), and 1 was taking telmisartan (20 mg).

Adverse effects of carvedilol administration

None of the 23 patients was able to up-titrate carvedilol to the target dose of 20 mg because of adverse events. The reasons for switching from carvedilol to bisoprolol were dizziness in 13 patients and hypotension in 16; 6 were accompanied by dizziness but 10 were not. The dizziness disappeared in all 13 patients after switching, while hypotension improved in 9 of 16. Moreover, there were no new reports of dizziness or hypotension associated with bisoprolol use during the study period (Fig. 1).

Switching from carvedilol to bisoprolol

The median duration of carvedilol administration before switching was 128 days (interquartile range, 23–707 days) (Table 1). The daily dose of carvedilol before switching was 5.60 ± 3.43 mg. Immediately after the switch, the initial dose of bisoprolol was

Table 1
Patient characteristics.

Variable	$n=23$
Age, (years)	57 ± 18
Male, n (%)	17 (74)
Body weight (kg)	56 ± 11
Body surface area (m^2)	1.56 ± 0.16
Body mass index (kg/m^2)	20.2 ± 3.2
New York Heart Association class, *n* (%)	
II	11 (48)
III	10 (43)
IV	2 (9)
Duration of carvedilol therapy (days)	
Median	128
Interquartile range	23–707
Daily dose of carvedilol, *n* (%)	
<5.0 mg	8
5.0–7.4 mg	8
7.5–10.0 mg	7
>10.0 mg	0
Etiology, *n* (%)	
Ischemic cardiomyopathy	7 (30)
Non-ischemic (systolic failure)	16 (70)
Comorbidity, *n* (%)	
Atrial fibrillation, *n* (%)	9 (39)
Diabetes mellitus, *n* (%)	5 (22)
COPD, *n* (%)	1 (4)
Medication at baseline, *n* (%)	
ACE inhibitor (Enalapril), *n* (%)	14 (61)
Angiotensin receptor blocker, *n* (%)	3 (13)
Calcium channel blocker, *n* (%)	2 (9)
Diuretic, *n* (%)	17 (74)
Minaralocorticoid receptor antagonist, *n* (%)	17 (74)
Digoxin, *n* (%)	6 (23)
Statin, *n* (%)	4 (17)
Pimobendan, *n* (%)	6 (23)
Aspirin, *n* (%)	9 (39)
Clopidogrel, *n* (%)	3 (13)
Adverse symptoms/signs, *n* (%)	
Dizziness, *n* (%)	13 (57)
Hypotension (<90 mm Hg), *n* (%)	16 (70)
Vital signs	
Blood pressure (mmHg)	
Systolic	96 ± 19
Diastolic	58 ± 7
Heart rate (beats/min)	76 ± 11
Echocardiographic parameters	
LV end-diastolic dimension (mm)	60.1 ± 12.9
LV end-systolic dimension (mm)	51.1 ± 15.6
LV ejection fraction (%)	32.7 ± 14.8
B-type natriuretic peptide (pg/ml)	
Median	245
Interquartile range	111–460
Laboratory parameters	
Hemoglobin (g/dl)	11.7 ± 1.8
Blood urea nitrogen (mg/dl)	23.5 ± 10.5
Serum creatinine (mg/dl)	1.11 ± 0.43
eGFR (ml/min)	59.1 ± 23.4
Serum sodium (mEq/l)	136.2 ± 3.7
Serum potassium (mEq/l)	4.3 ± 0.4

Data given as mean ± SD or the number (percentage).
COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; LV, left ventricular; eGFR, estimated glomerular filtration rate

1.84 ± 1.08 mg and then increased to 3.13 ± 1.74 mg after 6 months ($p < 0.01$). Notably, the dose of bisoprolol reached the target dose in 9 of 23 patients (39%) at 6 months. Bisoprolol was continued in all of the patients and not replaced with another β-blocker during the study period.

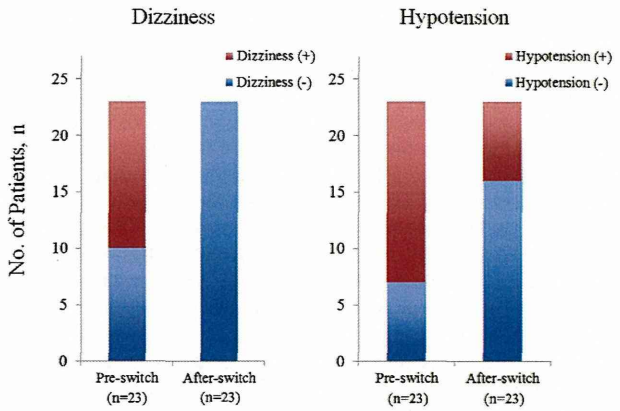

Fig. 1. Changes in dizziness and hypotension at pre-switch, and after-switch.

Changes in vital findings, and echocardiographic and laboratory parameters after switching

Of the 23 studied patients, only 19 provided complete echocardiographic and laboratory data at 6 months after switching. Data for 4 who underwent 6-month follow-up examinations at the referring hospital were not included in this analysis.

There was a significant increase in both systolic and diastolic blood pressure from before the switch to 6 months after, whereas heart rate showed no significant difference and plasma BNP concentration was not significantly improved (Table 2). Blood pressure changed from 94.4 ± 18.7 mmHg at baseline to 99.1 ± 17.0 mmHg immediately after switching (p = NS) and increased to 110.3 ± 21.2 mmHg at 6 months ($p < 0.05$). In the 11 patients with dizziness, blood pressure changed from 101 ± 22 to 103 ± 20 mmHg (p = NS) from baseline to immediately after switch, while that change was from 85 ± 3 to 92 ± 8 mmHg ($p = 0.007$) in the 14 with hypotension.

LVDd did not significantly change and LVDs was significantly decreased at 6 months after switching. As a consequence, LVEF showed a significant improvement, suggesting that significant LV reverse remodeling had occurred.

Plasma BNP concentration was not significantly improved, suggesting that no significant changes in cardiac wall stress occurred after switching. As for laboratory parameters, renal function, determined by serum creatinine level and estimated glomerular filtration rate, was slightly decreased after switching.

Exercise tolerance

NYHA functional class was significantly improved from before to 6 months after switching, as the proportion of patients rated as NYHA class I (no symptoms) or II heart failure increased, and that of those with class III or IV heart failure decreased during the interval from baseline to the 6-month follow-up visit (Fig. 2).

Discussion

Our results demonstrated that switching to bisoprolol from carvedilol is useful for avoiding adverse symptoms/signs, and can lead to continuation or up-titration of β-blocker administration in HF patients experiencing adverse effects related to carvedilol. The major findings of the present study were (1) all patients with dizziness could be relieved from that adverse symptom and hypotension was improved in more than half after switching to bisoprolol, and (2) at 6 months after switching from carvedilol to bisoprolol, the majority of patients showed significant reverse LV remodeling

and improvement in symptoms, while no significant reduction in plasma BNP level occurred.

Previous US trial data have shown that dizziness accounts for 33% and hypotension 9% of all adverse effects related to carvedilol administration [5]. In addition, the GESICA registry states that hypotension is the main reason for not achieving the target dose of carvedilol [14]. One possible explanation for the favorable result of switching could be differences in α1-blocking effect. In a previous review article, dizziness and hypotension were attributed to relaxation of blood vessels induced by α1 adrenoceptor blockade [15], while the same investigator also demonstrated that dizziness was not related to changes in blood pressure, but rather to central nervous system effects [16]. Of note, there were 6 patients with dizziness regardless of the absence of hypotension. Since autonomic nervous system dysfunction was not assessed, we were unable to definitively diagnose any of the present patients with autonomic dysregulation, such as orthostatic hypotension. Nevertheless, our results suggest that switching from carvedilol to bisoprolol is a practical and safe method for clinically stable patients with LV dysfunction.

In addition, we found that the dose of bisoprolol was significantly increased at 6 months after switching, which was accompanied by disappearance of carvedilol-related side-effects. Given that the equivalent dose of bisoprolol is 1/5 that of carvedilol, as shown in some large trials [12,17], the mean dose of carvedilol (5.60 mg) at pre-switch was equivalent to 1.12 mg of bisoprolol. The patients were switched to bisoprolol at 1.84 mg and the dose was finally increased to 3.13 mg during the study period, thus the bisoprolol dosage after 6 months was significantly increased. Based on our findings, we consider that switching from carvedilol to bisoprolol may also help with up-titration of the β-adrenergic receptor blocker agent in such settings.

Several studies have shown that the mortality benefits of carvedilol and other β-blockers are dose dependent [7,18,19]. Also, major society guidelines recommend that every effort be given to achieve the target dose of administered β-blockers [1,20], although the dose-dependent benefits remain controversial [21]. It is also important to exercise caution in Japan where the recommended maximum doses of β-blockers are less than half of those in Western countries, while there is limited evidence of the tolerability of daily carvedilol doses higher than 20 mg in Japanese chronic HF patients. In our study, LVEF and NYHA functional class were significantly improved after switching from carvedilol to bisoprolol. It is well known that β-blocker administration reduces LV volume along with improvement in systolic function, leading to improvement in prognosis [22], which also occurs in a dose-dependent manner [7]. Therefore, switching from carvedilol to bisoprolol may provide beneficial effects in regard to prognosis and/or reverse remodeling in patients who experience difficulty with continuation or up-titration of carvedilol because of adverse effects such as dizziness or hypotension.

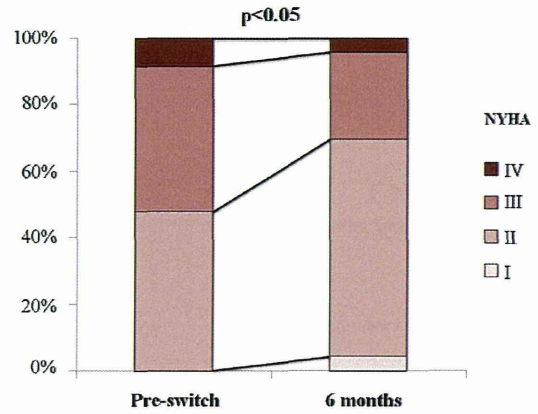

Fig. 2. Effects of switching from carvedilol to bisoprolol on New York Heart Association (NYHA) functional class.

Despite LV reverse remodeling and improvement in NYHA class, there was no significant change in BNP level. BNP is a hormone of cardiac origin that is secreted specifically from the ventricle in response to volume expansion and pressure overload [23], as well as abnormal constructive change such as hypertrophy and/or fibrosis. Our data suggest that the improvements in functional class and

Table 2
Vital signs, laboratory data, and echocardiographic parameters.

Variables	Pre-switch $n=19$	After-switch $n=19$	6 months $n=19$	*P*-Value
Vital signs				
Blood pressure (mmHg)				
Systolic	94.4± 18.7	99.1 ± 17.0	110.3 ± 21.2‡	<0.05†
Diastolic	58.6 ± 5.5	55.6 ± 7.8	63.5 ± 10.3§	<0.05†
Heart rate (beats/min)	76 ± 12	74 ± 13	74 ± 12	NS
Echocardiographic parameters, *n* (%)				
LV end-diastolic dimension (mm)	61.1± 13.7	n.a.	59.3 ± 14.4	NS
LV end-systolic dimension (mm)	52.6± 15.8	n.a.	47.6 ± 16.8	$p<0.01$
LV ejection fraction (%)	30.7± 13.5	n.a.	39.9 ± 13.8	$p<0.001$
B-type natriuretic peptide (pg/ml)				
Median	223	n.a.	194	NS*
Interquartile range	114–458	n.a.	86–331	
Laboratory parameters, *n* (%)				
Hemoglobin (g/dl)	11.6 ± 1.8	n.a.	12.0 ± 1.6	NS
Blood urea nitrogen (mg/dl)	23.8 ± 8.7	n.a.	27.2 ± 11.6	$p=0.054$
Serum creatinine (mg/dl)	1.1 ± 0.5	n.a.	1.2 ± 0.5	<0.01
eGFR (mL/min per 1.73 m^2)	59.9 ± 25.4	n.a.	53.9 ± 18.5	<0.05
Serum sodium (mEq/l)	137 ± 3	n.a.	138 ± 4	NS
Serum potassium (mEq/l)	4.3 ± 0.5	n.a.	4.5 ± 0.4	NS

Data given as mean ± SD or the number (percentage).
LV, left ventricular; eGFR, estimated glomerular filtration rate.
* Tested with Wilcoxon signed-rank method.
† Tested with one-way analysis of variant (ANOVA).
‡ >Pre-switch, Tukey–Kramer test $P<0.05$.
§ >After-switch, Tukey–Kramer test $P<0.05$.

LV reverse remodeling after switching may be mainly mediated by neurohormonal modulations of the adrenergic receptor blockers themselves, rather than by a reduction in circulating plasma/blood volume and subsequent decreased wall stress, or decreased pressure overload.

Although a favorable effect of switching to bisoprolol was shown in patients with adverse effects due to carvedilol administration in our study, there were two unexpected results. First, heart rate was not significantly changed, although there was improvement in blood pressure after switching to and increasing the dose of bisoprolol, which might have been due to the highly selected population with hypotension in our study. It is also conceivable that our study patients had already taken carvedilol before switching, thus no heart rate reduction could be achieved with an increase in dose. Second, there was significant exacerbation of renal function found in the present subjects, which was recently reported to be a strong predictor of prognosis in patients with HF [24]. It is also well known that renal function is progressively worsened in HF patients. Konishi et al. reported that there was no difference regarding impact on renal function between carvedilol and bisoprolol [25], while worsening renal function was attributed to use of diuretics in that study. On the other hand, it has been reported to be important whether the pharmacological intervention improves clinical outcomes even in such HF patients [26]. As there was no control group without β-blocker administration in the present study, we cannot conclude whether the change in estimated glomerular filtration rate during 6 months could be attributed to the switch of carvedilol to bisoprolol, other drugs (diuretics, etc.), or the natural course of HF. Additional well-designed prospective large-scale investigations are needed to more closely examine the efficacy of this switching strategy.

Study limitations

The main limitations of the present study are the small number of enrolled patients and absence of a control group. Moreover, although clinical data obtained at 6 months after switching are considered to be integral to understand the immediate effect of the β-blocker itself and LV reverse remodeling, we were unable to assess laboratory and echocardiographic data immediately after the switch. Therefore, it is not possible to definitively conclude from our findings that switching from carvedilol to bisoprolol will produce favorable effects in patients with chronic HF in all settings. It is well known that systolic blood pressure increases later in HF patients with hypotension who respond to β-blockers [27], thus the clinical implications of our observations are also limited. Nevertheless, our retrospective series consisted of consecutive patients with impediments caused by carvedilol administration in actual clinical settings, thus the results may provide helpful insight for determining effective β-blockade strategies for HF patients.

Conclusion

Switching from carvedilol to bisoprolol may help with continuation of β-blocker treatment as well as dosage increase in patients with adverse symptoms or signs, allowing them to reach the target dose.

Disclosures

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