Heart and Vessels (2019) 34:957–964
https://doi.org/10.1007/s00380-018-01326-5

ORIGINAL ARTICLE

Effect of carvedilol on heart rate response to cardiopulmonary exercise up to the anaerobic threshold in patients with subacute myocardial infarction

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Received: 19 July 2018 / Accepted: 21 December 2018 / Published online: 2 January 2019

Abstract

Resting heart rate (HR) plus 20 or 30 beats per minute (bpm), i.e., a simplified substitute for HR at the anaerobic threshold (AT), is used as a tool for exercise prescription without cardiopulmonary exercise testing data. While resting HR plus 20 bpm is recommended for patients undergoing beta-blocker therapy, the effects of specific beta blockers on HR response to exercise up to the AT (ΔAT HR) in patients with subacute myocardial infarction (MI) are unclear. This study examined whether carvedilol treatment affects ΔAT HR in subacute MI patients. MI patients were divided into two age- and sex-matched groups [carvedilol (+), $n=66$; carvedilol (−), $n=66$]. All patients underwent cardiopulmonary exercise testing at 1 month after MI onset. ΔAT HR was calculated by subtracting resting HR from HR at AT. ΔAT HR did not differ significantly between the carvedilol (+) and carvedilol (−) groups (35.64 ± 9.65 vs. 34.67 ± 11.68, $P=0.604$). Multiple regression analysis revealed that old age and heart failure after MI were significant predictors of lower ΔAT HR ($P=0.039$ and $P=0.013$, respectively), but not carvedilol treatment. Our results indicate that carvedilol treatment does not affect ΔAT HR in subacute MI patients. Therefore, exercise prescription based on HR plus 30 bpm may be feasible in this patient population, regardless of carvedilol use, without gas-exchange analysis data.

Keywords Myocardial infarction · Beta blocker · Anaerobic threshold · Heart rate response · Cardiac rehabilitation

Introduction

Exercise training reduces cardiovascular mortality after acute myocardial infarction (MI) [1]. Many guidelines recommend exercise for MI patients as part of prevention of cardiovascular death [2, 3]. When prescribing exercise intensity in patients with subacute MI, heart rate (HR) at anaerobic threshold (AT) is frequently measured by cardiopulmonary exercise testing (CPX) to ensure effectiveness and safety of training [2, 4, 5]. However, it is not feasible to perform CPX for all patients due to the high cost of equipment and need for manpower. Thus, exercise prescription based on resting HR plus 20 or 30 beats per minute (bpm), i.e., a simplified substitute for HR at AT [6, 7], is used as a way to determine exercise intensity without gas-exchange analysis data. This method is based on the physiologic HR response to exercise up to the AT.

The use of beta blockers is recommended to prevent cardiovascular death in MI patients [2], and consequently, many patients with subacute MI are administered beta

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blockers, including carvedilol, which is frequently prescribed worldwide due to its effectiveness [2, 8]. A recent study reported that beta blocker treatment decreased HR at rest and during exercise in patients with coronary artery disease [9]. Thus, experts recommend that a lower value (i.e., resting HR plus 20 bpm) should be used if patients are treated with beta blockers [6]. However, the previous study did not sufficiently evaluate HR response to cardiopulmonary exercise up to the AT in subacute MI patients treated with a specific kind of beta blocker. Therefore, the effect of single beta blocker treatment on HR response to exercise up to the AT in this patient population remains unclear. Accordingly, the present study aimed to examine whether carvedilol affects HR response to cardiopulmonary exercise up to the AT in patients with subacute MI, as this information may help physicians to prescribe appropriate exercise for subacute MI patients treated with beta blockers.

Methods

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of St. Marianna University School of Medicine (Chairperson of the ethics committee, Masashi Taki; Protocol number, No. 2258; date of approval by the ethics committee, November 30, 2012). Informed consent was obtained from each patient before conducting the CPX.

Study design and patients

Of the 641 consecutive acute MI patients who had undergone cardiac rehabilitation at St. Marianna University School of Medicine Yokohama City Seibu Hospital from August 1998 to November 2017, 289 patients who were able to undergo symptom-limited CPX at 1 month after the onset of MI were enrolled in this retrospective cross-sectional study. Exclusion criteria were the presence of atrial fibrillation, complex arrhythmia, a pacemaker, and recent myocardial infarction, a history of cardiac surgery, and the use of beta blockers other than carvedilol or any other drugs with negative or positive chronotropic effects (e.g., verapamil, diltiazrem hydrochloride). Of the 289 subacute MI patients, 229 met the study criteria. Patients were divided into the following two groups according to carvedilol treatment, matched by age (± 5 years) and sex: the carvedilol (+) group (66 patients) and the carvedilol (−) group (66 patients). Ultimately, these 132 patients were included in this study. All patients were clinically stable and examined while on stable doses of medication.

Clinical characteristics

Age, sex, body mass index, site of infarction, residual coronary artery stenosis, past medical history, complications, medications, time between MI onset and exercise testing, and year of hospitalization were evaluated using medical records. Maximum serum creatine kinase-myocardial band (max CK-MB) was measured using blood samples obtained during hospitalization. Left ventricular ejection fraction (LVEF) was echocardiographically determined using a modified Sympson's method and served as the index of left ventricular systolic function at hospital discharge.

Symptom-limited cardiopulmonary exercise testing

All patients underwent symptom-limited CPX on a treadmill (MAT-2700, Fukuda Denshi Co., Tokyo, Japan). After 3 min of rest in the seated position, patients performed exercise with an increasing load (speed or grade; every 60 s) [10] following 3 min of warm-up (speed, 1.0 mph; grade, 0%). A 12-lead electrocardiogram (ECG) was continuously monitored, and HR was measured from the R–R interval of the ECG (ML-9000, Fukuda Denshi Co., Tokyo, Japan) during the test. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the cuff method with an automatic blood pressure monitor (STBP-780, Colin Co., Aichi, Japan) at 1-min intervals. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), tidal volume (TV), end tidal O_2 (ETO_2), and end tidal CO_2 ($ETCO_2$) were measured with an aeromonitor (AE-310s, Minato Ikagaku Co., Tokyo, Japan) throughout the test. Expired gas was sampled using a breath-by-breath method. The endpoint of testing was determined as previously described [11]. Specifically, the appearance of a plateau in $\dot{V}O_2$ despite an increasing exercise intensity indicated the exercise endpoint.

Ventilatory equivalents were calculated for O_2 ($\dot{V}E/\dot{V}O_2$), CO_2 ($\dot{V}E/\dot{V}CO_2$), and the gas exchange ratio (GER) ($\dot{V}CO_2/\dot{V}O_2$) on a personal computer (Model PC-9801, NEC Co., Tokyo, Japan). AT was determined by the V-slope method [12].

HR at rest (HR_{rest}), HR at AT (HR_{AT}), and HR at peak $\dot{V}O_2$ (HR_{peak}) were determined from the recorded HR during the course of CPX. Increases from HR_{rest} to HR_{peak} (Δpeak HR), from HR_{rest} to HR_{AT} (ΔAT HR), and from HR_{AT} to HR_{peak} (ΔAT-peak HR) were calculated for all patients.

Statistical analysis

Results are expressed as mean ± SE. The Kolmogorov–Smirnov test was performed to assess the normality

of distribution. Differences in clinical characteristics among patients were analyzed using the unpaired *t* test, Mann–Whitney *U* test, and χ^2 test. Differences in the results of CPX between carvedilol (+) and carvedilol (−) groups were analyzed using the unpaired *t* test and Mann–Whitney *U* test. Analysis of covariance (ANCOVA) was used if GER at peak was determined to be a covariate according to the results of CPX. Clinically important factors and carvedilol treatment were entered into a multiple regression model for the prediction of ΔAT HR by the forced-entry method. In the carvedilol (+) group, Spearman's rank correlation coefficient was used to examine correlations between ΔAT HR and carvedilol doses. The χ^2 test was used to compare the number of patients with (HR_{rest} + 30 bpm − HR_{AT}) ≥ 10% HR_{AT} in each group, given that a difference of ≥ 10% HR_{AT} is considered clinically relevant [13]. $P < 0.05$ was considered statistically significant. All statistical analyzes were performed with JMP® pro 13 (SAS Institute Inc., Cary, NC, USA). A priori power analysis was performed for multiple regression analysis using G*Power 3 program (Heinrich-Heine-Universität, Düsseldorf, Germany). The sample size was calculated to be 123 in the regression model for ΔAT HR (effect size = 0.15, α error probability = 0.05, power (1 − β error probability) = 0.8, number of predictors = 11) and, thus, the sample size of the present study was considered sufficient for conducting multiple regression analysis. Effect sizes were also calculated using G*Power 3 program.

Results

The clinical characteristics of patients are shown in Table 1. No significant differences were observed in clinical characteristics between the carvedilol (+) and carvedilol (−) groups, except that the proportion of patients hospitalized after 2006 was significantly higher in the carvedilol (+) group than in the carvedilol (−) group ($P < 0.001$).

The results of CPX are shown in Tables 2 and 3. None of the patients showed ischemic ST changes or experienced chest pain or serious arrhythmia during CPX. The variables obtained during cardiopulmonary exercise up to the AT are shown in Table 2. The values of HR_{rest} were significantly lower in the carvedilol (+) group compared to the carvedilol (−) group ($P = 0.047$; effect size, $d = 0.350$). The values of DBP_{rest} were significantly higher in the carvedilol (+) group compared to the carvedilol (−) group ($P = 0.011$; effect size, $d = 0.452$). Moreover, in the carvedilol (+) group, the values of HR_{AT} tended to be lower compared to the carvedilol (−) group ($P = 0.153$; effect size, $d = 0.250$). In contrast, the values of ΔAT HR did not differ significantly between the two groups ($P = 0.604$; effect size, $d = 0.091$).

The variables obtained during cardiopulmonary exercise up to peak $\dot{V}O_2$ are shown in Table 3. These results were analyzed by ANCOVA with GER at peak as the covariate, since the values of GER at peak were significantly lower in the carvedilol (+) group compared to the carvedilol (−) group (1.17 ± 0.09 vs. 1.13 ± 0.10; $P = 0.022$). In the carvedilol (+) group, HR_{peak} and ΔAT-peak HR were significantly lower compared to the carvedilol (−) group ($P = 0.009$ and $P = 0.010$, respectively). In contrast, Δpeak HR did not differ significantly between the two groups ($P = 0.440$).

The results of multiple regression analysis on the prediction of ΔAT HR are shown in Table 4. Old age (≥ 65 years) and heart failure after MI, but not carvedilol treatment, were significant predictors of ΔAT HR ($P = 0.039$ and $P = 0.013$, respectively).

Mean carvedilol dose was 5.76 ± 3.16 mg/day in the carvedilol (+) group (Table 1). No significant correlation was observed between ΔAT HR and carvedilol dose ($P = 0.903$) (Fig. 1).

No significant difference was observed in the number of patients with (HR_{rest} + 30 bpm − HR_{AT}) ≥10% HR_{AT} between the carvedilol (+) and carvedilol (−) groups ($P = 0.300$) (Table 5). A total of nine patients had values ≥ 10% HR_{AT}, and of these, three were treated with carvedilol (4.6% of all patients treated with carvedilol), five were older patients (7.8% of all older patients), and four had heart failure after MI (31% of all patients with heart failure after MI).

Discussion

In the present study, the values of ΔAT HR did not differ significantly between the carvedilol (+) and carvedilol (−) groups and the effect size (*d*) was very small. In addition, carvedilol treatment was not a significant predictor of ΔAT HR, even after adjusting for multiple factors. These results suggest that carvedilol treatment does not affect HR response to cardiopulmonary exercise up to the AT in subacute MI patients.

Differences in patient clinical characteristics between the two groups

Year of hospitalization significantly differed between the two groups. Almost all patients in the carvedilol (+) group were hospitalized after 2006. This likely reflects the fact that, in Japan, the administration of beta-blockers was first recommended by Guidelines for Secondary Prevention of MI in 2006 [14]. In fact, almost all patients in the carvedilol (−) group were hospitalized prior to 2006.

Effect of carvedilol on HR response during CPX in subacute MI patients

HR responses during exercise are greatly affected by autonomic nerve activity. A previous study suggested that a

Table 1 Patient clinical characteristics

	Carvedilol (+) group ($n=66$)	Carvedilol (−) group ($n=66$)	*P* value
Age (years)	64.35 ± 9.95	64.71 ± 9.30	0.829
Sex, men/women	58/8	58/8	1.000
Body mass index (kg/m^2)	23.30 ± 2.84	22.86 ± 2.65	0.369
MI			0.285
Inferior	24 (36.4)	33 (50.0)	
Anterior	36 (54.5)	28 (42.4)	
Lateral	6 (9.1)	5 (7.6)	
Residual coronary artery stenosis	24 (36.4)	28 (42.4)	0.476
Medical history			
Old MI	5 (7.6)	5 (7.6)	1.000
Hypertension	42 (63.6)	37 (56.1)	0.375
Dyslipidemia	35 (53.6)	41 (62.1)	0.291
Chronic kidney disease	6 (9.1)	7 (10.6)	0.770
Diabetes mellitus	20 (30.3)	22 (33.3)	0.709
Orthopedic disorder	1 (1.5)	2 (3.0)	0.559
Respiratory disease	0 (0)	1 (1.5)	0.315
Hyperuricemia	6 (9.1)	7 (10.6)	0.770
Peripheral arterial disease	0 (0)	2 (3.0)	0.154
Dementia	0 (0)	1 (1.5)	0.316
Heart failure after MI	6 (9.1)	7 (10.6)	0.770
Medication			
Renin–angiotensin system inhibitor	60 (90.9)	55 (83.3)	0.194
Calcium antagonist (dihydropyridine)	10 (15.2)	6 (9.1)	0.286
Cardiac stimulant	0 (0)	0 (0)	–
Anticlotting drug	2 (3.0)	2 (3.0)	1.000
Antiplatelet drug	66 (100)	66 (100)	1.000
Max CK-MB (≥ 300 ng/ml)	27 (40.9)	19 (28.8)	0.144
LVEF (< 50%)	44 (66.7)	52 (78.8)	0.118
Time between MI and exercise testing (days)	32.68 ± 12.35	31.62 ± 12.82	0.629
Carvedilol dose (mg/day)	5.76 ± 3.16		–
Hospitalization, before/after 2006	14/52	54/9	< 0.001

Patient clinical characteristics were compared between the carvedilol (+) and carvedilol (−) groups. Values are expressed as mean ± SD, No. (%), or No. /No

MI myocardial infarction, *LVEF* left ventricular ejection fraction, *Max CK-MB* maximum value of serum creatine kinase-myocardial band

decrease in parasympathetic nervous system activity mainly affects HR responses when exercise intensity is low to moderate and that an increase in sympathetic nervous system activity mainly affects HR responses when exercise intensity is moderate to high [15]. Parasympathetic nervous system activity is similarly affected during exercise in subacute MI patient [16]. On the other hand, beta blockers decrease sympathetic nervous system activity by inhibiting the interaction between noradrenaline and beta receptors. Beta blockers have been reported to mainly decrease HR responses when exercise intensity is moderate to high [17]. In the present study, although ΔAT HR did not differ significantly between the two groups, ΔAT-peak HR was significantly lower in the carvedilol (+) group than in the carvedilol (−) group. In addition, ΔAT HR represented a higher proportion of the HR response during exercise than ΔAT-peak HR. Therefore, Δpeak HR did not differ significantly between the two groups.

We conducted multiple regression analysis for predicting ΔAT HR. The analysis revealed that carvedilol treatment was not a significant predictor of ΔAT HR. In other words, carvedilol did not affect HR response to CPX up to the AT, after controlling for other main clinical factors. Old age and heart failure after MI were significant predictors of ΔAT HR. Previous studies suggested that old age decreases HR responses during exercise [18]. Moreover, chronotropic incompetence during maximal exercise is

Table 2 Variables of gas analysis during cardiopulmonary exercise up to the anaerobic threshold

	Carvedilol (+) group ($n=66$)	Carvedilol (−) group ($n=66$)	*P* value	Effect size *d*
Average time of exercise (min)	7.16 ± 1.54	7.22 ± 1.46	0.830	0.037
AT (ml/kg/min)	16.09 ± 3.38	16.18 ± 3.20	0.873	0.027
GER at AT	0.88 ± 0.05	0.87 ± 0.05	0.732	0.028
HR_{rest} (bpm)	71.86 ± 10.38	75.77 ± 11.93	0.047	0.350
HR_{AT} (bpm)	107.50 ± 10.67	110.44 ± 12.74	0.153	0.250
ΔAT HR (bpm)	35.64 ± 9.65	34.67 ± 11.68	0.604	0.091
SBP_{rest} (mmHg)	128.50 ± 15.20	125.96 ± 20.01	0.412	0.143
SBP_{AT} (mmHg)	161.03 ± 24.14	155.61 ± 29.29	0.248	0.202
DBP_{rest} (mmHg)	78.06 ± 11.34	72.97 ± 11.21	0.011	0.452
DBP_{AT} (mmHg)	79.20 ± 15.97	76.46 ± 12.83	0.986	0.189

Variables of gas analysis during cardiopulmonary exercise up to the anaerobic threshold were compared between the carvedilol (+) and carvedilol (−) groups using the unpaired t test and Mann–Whitney *U* test. Values are expressed as mean ± SD

AT anaerobic threshold, *GER* gas exchange ratio, *HR* heart rate, HR_{rest} HR at rest, HR_{AT} HR at AT, $\Delta AT\ HR$ (HR_{AT}) − (HR_{rest}), *SBP* systolic blood pressure, SBP_{rest} SBP at rest, SBP_{AT} SBP at AT, DBP_{rest}, DBP at rest, *DBP* diastolic blood pressure, DBP_{AT} DBP at AT

caused by heart failure [19]. Thus, old age and heart failure after MI might predict ΔAT HR.

Effect of carvedilol on resting HR and HR at AT in subacute MI patients

Resting HR is affected by both parasympathetic nervous system activity and sympathetic nervous system activity. In particular, resting sympathetic nervous system activity is increased in subacute MI patients [20]. On the other hand, beta blockers decrease sympathetic nervous system activity. In the present study, HR_{rest} was significantly lower in the carvedilol (+) group than in the carvedilol (−) group. Moreover, in the carvedilol (+) group, HR_{AT} tended to be lower compared to the carvedilol (−) group, because ΔAT HR did not differ significantly between the two groups. These findings were consistent with previously reported results [9].

Table 3 Variables of gas analysis during cardiopulmonary exercise up to peak oxygen uptake (results of analysis of covariance with GER at peak oxygen uptake as the covariate)

	Carvedilol (+) group ($n=66$)	Carvedilol (−) group ($n=66$)	*P* value	*F* value
HR_{peak} (bpm)	139.62 ± 13.37	144.94 ± 15.50	0.009	5.862
SBP_{peak} (mmHg)	186.70 ± 29.02	186.79 ± 30.33	0.966	0.046
DBP_{peak} (mmHg)	87.05 ± 21.11	84.24 ± 16.84	0.279	1.204
Δpeak HR (bpm)	67.76 ± 12.98	69.17 ± 15.81	0.440	0.794
ΔAT-peak HR (bpm)	32.12 ± 9.64	34.50 ± 11.36	0.010	18.80
Peak $\dot{V}O_2$ (ml/kg/min)	23.09 ± 5.44	23.57 ± 4.64	0.615	0.169

Variables of gas analysis during cardiopulmonary exercise up to peak oxygen uptake were compared between the carvedilol (+) and carvedilol (−) groups using the analysis of covariance (ANCOVA) with GER at peak oxygen uptake as the covariate. Values are expressed as mean ± SD

peak$\dot{V}O_2$ peak oxygen uptake, *GER* gas exchange ratio, *AT* anaerobic threshold, *HR* heart rate, HR_{AT} HR at AT, HR_{peak} HR at peak $\dot{V}O_2$, HR_{rest} HR at rest, $\Delta AT\ HR$ (HR_{AT}) − (HR_{rest}), $\Delta peak\ HR$ (HR_{peak}) − (HR_{rest}), $\Delta AT\text{-}peak\ HR$ (HR_{peak}) − (HR_{AT})

Clinical application of the present study findings

In clinical practice, target HR for exercise prescription is often calculated as resting HR plus 20 or 30 bpm. This rate is used as a simplified substitute for HR at AT, as CPX is not feasible for all patients. Experts recommend a lower value (i.e., resting HR plus 20 bpm) for patients treated with beta blockers [6]. In the present study, carvedilol treatment did not affect HR response to exercise up to the AT in subacute MI patients. Moreover, no significant difference was observed in the number of patients with (HR_{rest} + 30 bpm − HR_{AT}) ≥ 10% HR_{AT} between the carvedilol (+) and carvedilol (−) groups. Furthermore, only 6.8% of all patients had values ≥ 10% HR_{AT}. This rate (i.e., 6.8%) is considered clinically valid compared with a previous study, in which the Karvonen formula was used to determine the target HR range (peak HR was obtained by stress test). In that study, 5.3% of subacute MI patients treated with beta-blockers had (target HR–HR_{AT}) ≥ 10% of HR_{AT} [21]. Thus, when prescribing exercise regimens for subacute MI patients, it may be feasible to use resting HR plus 30 bpm, regardless of carvedilol use. A previous study suggested that exercise tolerance is more readily improved by exercise training using an optimum target HR rather than a lower target HR [22]. It was also suggested that if exercise intensity determined by HR is lower by only 10 bpm as compared to recommended target HR, improvement in exercise tolerance is expected to be lower [22]. Therefore, the findings of this study may help

Table 4 Results of multiple regression analysis for the prediction of ΔAT HR

Independent variables	Dependent variable: ΔAT HR			
	$B \pm$ SE	β	95% CI	P value
Age (≥ 65 years)	− 2.063 ± 0.989	− 0.194	− 4.020 to − 0.105	0.039
Female	2.753 ± 1.426	0.169	− 0.070 to 5.576	0.056
Body mass index	0.436 ± 0.371	0.112	− 0.298 to 1.169	0.242
Max CK− MB (≥ 300 ng/ml)	0.925 ± 1.020	0.083	− 1.095 − 2.945	0.366
Inferior infarct[a]	− 0.276 ± 1.492	− 0.025	− 3.231 to 2.679	0.854
Lateral infarct[a]	− 0.581 ± 1.519	0.051	− 3.588 to 2.426	0.702
Residual coronary artery stenosis	− 0.498 ± 0.973	− 0.046	− 2.425 to 1.429	0.610
Heart failure after MI	− 4.239 ± 1.676	− 0.237	− 7.559 − 0.920	0.013
Diabetes mellitus	− 0.833 ± 1.004	− 0.073	− 2.821 to 1.154	0.408
LVEF (<50%)	− 0.761 ± 1.183	− 0.064	− 3.103 to 1.582	0.366
Treatment with carvedilol	0.377 ± 0.937	0.035	− 1.478 to 2.232	0.688
Constant	19.24 ± 9.550	0.000	0.324 to 38.144	0.046
			Coefficient of determination $R^2 = 0.158$, $F = 1.862$, $P = 0.046$	

The results of multiple regression analysis for the prediction of ΔAT HR by the forced-entry method are shown

ΔAT HR (HR_{AT}) − (HR_{rest}), *B ± SE* partial regression coefficient ± standard error, *β* standardized partial regression coefficient, *CI* confidence interval, *Max CK-MB* maximum value of serum creatine kinase-myocardial band, *MI* myocardial infarction

[a]Compared with anterior infarct

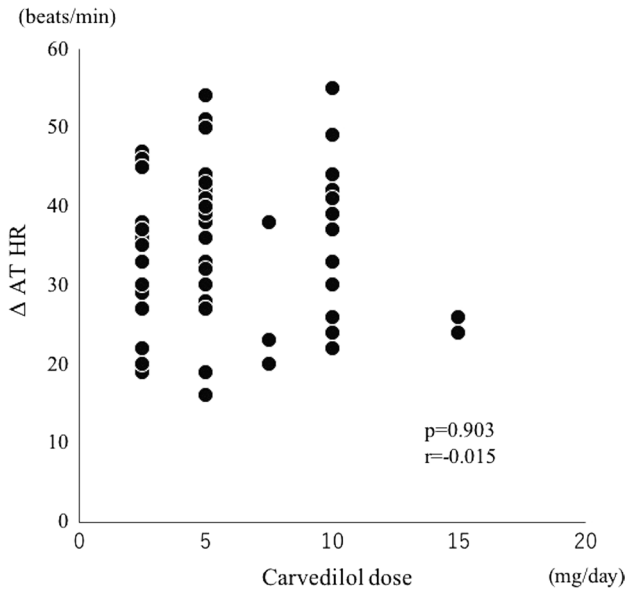

Fig. 1 Correlation between ΔAT HR and carvedilol dose. No significant correlation was observed between ΔAT HR and carvedilol dose in the carvedilol (+) group. *HR* heart rate, *AT* anaerobic threshold, HR_{AT} HR at AT, HR_{rest} HR at rest, *ΔAT HR* (HR_{AT}) − (HR_{rest})

physicians to prescribe appropriate exercise for subacute MI patients treated with beta blockers.

On the other hand, 31% of patients with heart failure after MI had (HR_{rest} + 30 bpm − HR_{AT}) ≥ 10% HR_{AT}, suggesting that prescribing exercise intensity requires caution in this patient population, regardless of carvedilol use.

Table 5 Number of patients with (HR_{rest} + 30 bpm − HR_{AT}) < 10% or ≥ 10% HR_{AT}

	Carvedilol (+) group ($n = 66$)	Carvedilol (−) group ($n = 66$)	P value
(HR_{rest} + 30 bpm − HR_{AT}) < 10% HR_{AT}	63 (95.5)	60 (90.9)	0.300
(HR_{rest} + 30 bpm − HR_{AT}) ≥ 10% HR_{AT}	3 (4.5)	6 (9.1)	

Values are expressed as No. (%)

HR heart rate, *bpm* beat per minutes, HR_{rest} HR at rest, *AT* anaerobic threshold, HR_{AT} HR at AT

Carvedilol dosage

In the present study, mean carvedilol dose was 5.76 ± 3.16 mg/day in the carvedilol (+) group. Previously, a prospective, multi-center, open-label, randomized controlled study including 67 centers in Japan reported a mean carvedilol dose of 5.8 ± 3.9 mg among MI patients at 3 months from onset [23]. Moreover, despite that carvedilol was started from low doses and up-titrated to a target dose of 20 mg daily, only 3.8% of patients were administered 20 mg carvedilol (i.e., the maximum approved dose) at 12 month

from onset. Thus, the mean carvedilol dose in this study is likely considered clinically appropriate.

The negative chronotropic effect of carvedilol depends on its concentration in blood. However, in addition to dose [24–26], several clinical factors can affect the blood concentration of carvedilol, such as body weight, renal function, and liver function. In clinical practice, physicians determine appropriate doses for each MI patient based on these factors. In the present study, no significant correlation was observed between ΔAT HR and carvedilol dose in the carvedilol (+) group, as we could not examine effect of such factors on the blood concentration of carvedilol in our study population.

Limitations

The present study has several limitations worth noting. First, we did not demonstrate the effect of other beta blockers on HR response to CPX up to the AT in subacute MI patients. Previous studies suggested that carvedilol had the lowest negative chronotropic effect compared to other beta blockers [27, 28]. Thus, a future study will be needed to examine the effect of other beta blockers in this patient population. It should also be noted that the influence of potential factors (e.g., body weight, renal function, liver function, genetic polymorphism) on the blood concentration of carvedilol was not examined in the present study. Second, all patients underwent symptom-limited CPX using a treadmill in this study; therefore, the effect of carvedilol on HR responses during other symptom-limited CPX (e.g., on a bicycle ergometer) remains to be clarified. Third, patients in this study received low to moderate doses of carvedilol according to clinical decisions. Thus, whether carvedilol affects HR response to CPX up to the AT in patients receiving high doses remains unclear. Finally, this study has a selection bias in that patients who were unable to undergo symptom-limited CPX on a treadmill due to frailty were excluded from the study and that our patients were matched according to age (± 5 years) and sex by the authors. A future prospective study will be needed to verify the results of the present study.

Conclusions

Our data suggest that carvedilol treatment does not affect HR response to CPX up to the AT in subacute MI patients. Therefore, exercise prescription based on resting HR plus 30 bpm may be feasible in subacute MI patients, regardless of carvedilol use, if gas-exchange analysis data cannot be obtained.

Acknowledgements The authors thank the staff members of the Department of Rehabilitation Medicine and the Department of Cardiology at St. Marianna University School of Medicine Yokohama City Seibu Hospital for their assistance in data collection.

Funding This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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