Relationship between chronotropic incompetence and $\beta$-blockers based on changes in chronotropic response during cardiopulmonary exercise testing☆

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A B S T R A C T
Background: Chronotropic incompetence (CI), an attenuated heart rate (HR) response to exercise, is common in patients with cardiovascular disease. The aim of this study was to assess changes in the chronotropic response (CR) during cardiopulmonary exercise testing (CPET) in patients undergoing cardiac rehabilitation and investigate the effects of $\beta$-blockers.

Methods: Patients undergoing cardiac rehabilitation performed CPET. Failure to achieve 80% of the age-predicted maximal HR (APMHR) defined CI. Values of the metabolic chronotropic relationship (MCR) were calculated from the ratio of the HR reserve to metabolic reserve at 4 stages, warm-up (MCR-Wu), anaerobic threshold (MCR-AT), respiratory compensation (MCR-Rc), and peak point (MCR-Pk), using the Wilkoff model. In patients who showed an increase in MCR at $\geq 3$ of the 4 exercise stages, CR was considered to have improved.

Results: Patients with high BNP levels ($\geq 80$ pg/ml) had a lower MCR at all stages compared with those with low BNP levels ($< 80$ pg/ml). Of the 80 patients, 47 showed an increase in both peak VO2 and AT, and of these 31 (66.0%) were taking $\beta$-blockers. Improvement in CR was observed in 30 of 47 patients with CI, and 70% of those taking $\beta$-blockers, MCR-AT was lower than MCR-Rc, whereas in those taking $\beta$-blockers MCR-AT was higher than MCR-Rc.

Conclusions: An attenuated HR response may occur during the early stages of exercise. The HR response according to the presence or absence of $\beta$-blockers is clearly identifiable by comparing MCR-AT and MCR-Rc using the Wilkoff model.

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1. Introduction

Chronotropic incompetence (CI), an attenuated heart rate (HR) response to exercise, is associated with increased cardiovascular risk and overall mortality [1–5]. The prevalence of CI in patients with chronic heart failure (CHF) is between 20% and 70% [6]. The variability is a result of multiple definitions, the confounding effects of aging and medications, and different characteristics of study populations. CI is believed to reflect an underlying autonomic nervous system imbalance involving various factors and complex interactions [7,8]. HR at rest is regulated by the parasympathetic nervous system. In the initial stages of exercise, HR increases with withdrawal of vagal activity. On commencing exercise, sympathetic nerve activity increases gradually and becomes dominant at a stress load greater than the anaerobic threshold (AT). However, patients with CHF have sympathetic overactivity with $\beta$-1-receptor down-regulation and reduced myocardial sensitivity to $\beta$-agonists [9], which may in turn lead to a reduction in HR response to exercise [7,10,11]

Currently, $\beta$-blocker therapy is pivotal in the treatment of heart disease including chronic ischemic syndromes, acute coronary syndromes, and heart failure. In clinical trials, $\beta$-blockers have been shown to lead to long-term improvement in left ventricular function, slowing the progression of heart failure, and increasing life expectancy [12]. Paradoxically, although $\beta$-blockers may result in pharmacologically induced CI, they may have a less detrimental effect on exercise capacity and may even improve exercise performance. Dobre et al. found that a CI < 0.6
was associated with adverse clinical outcomes in CHF patients receiving β-blocker therapy in the HF-ACTION trial [13].

Wilkoff et al. [14] used expired gas analysis to more objectively evaluate CI on the basis of the relationship between HR and oxygen consumption (VO2) during exercise. In this approach, the metabolic chronotropic relationship (MCR; also known as the chronotropic index) is calculated from the ratio of the HR reserve to the metabolic reserve during submaximal exercise. The advantage of using MCR is that it adjusts for age, physical fitness, and functional capacity and appears to be unaffected by the exercise testing mode or protocol. This is accomplished using the following formula, in which metabolic equivalents (METS) = VO2 (in mL·kg−1·min−1)/3.5:

Estimated HRstage = [(220 – age – HRrest)]
× [(METSstage − 1)/METSpeak − 1] + HRrest

The aims of the present study were to evaluate changes in HR response during cardiopulmonary exercise testing (CPET) in patients undergoing cardiac rehabilitation, using MCR values calculated using the Wilkoff model, and to assess the effects of β-blockers.

2. Methods

2.1. Subjects

We obtained data on 375 cases of CPET for performing ambulatory cardiac rehabilitation between January 2011 and December 2012 at the University of Tokyo Hospital. Patients were excluded, if: (a) they were not in sinus rhythm, (b) they were <45 years of age or >85 years of age, (c) they were heart transplant recipients, (d) they had a ventricular assist device, (e) they had a severe illness other than heart disease such as malignant tumors, and (f) they were unable to achieve an adequate pedal rotation speed and patients with maximum respiratory exchange ratio <1.05. Consequently, a total of 271 exercise tests from 140 patients were included in the final analysis. Sixty patients performed CPET once, 40 performed CPET twice, and 40 performed CPET more than twice. Standard echocardiographic imaging was performed for evaluation of left ventricular ejection function (LVEF) and assessment of right ventricular systolic pressure (RVSP). The B-type natriuretic peptide (BNP) level was measured prior to CPET. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Cardiopulmonary exercise testing

Symptom-limited CPET was performed on an electromagnetically braked upright cycle ergometer (Corival, Load, Holland) with a metabolic gas analyzer (AE-3005, Minato Medical Science, Osaka, Japan). After 4 min of rest on the cycle ergometer, exercise was commenced at 20 W for a 4-min warm-up, and then the work rate was increased by 1-W every 6 s. During CPET, blood pressure was measured by an automatic indirect cuff manometer (FB-300, Fukuda denshi, Tokyo, Japan) every min. HR and electrocardiography (ECG) were monitored using an exercise electrocardiogram (ML-9000, Fukuda Denshi, Tokyo, Japan) [15]. The criteria for discontinuation of CPET were (i) if pedal rotations were delayed, (ii) if the patient reached maximum symptom-limited performance determined by a Borg score of ≥17, (iii) when 85% of age-predicted maximal HR (APMHR) was achieved, (iv) if there was evidence of ST-T changes in ECG, or if any cardiac event such as arrhythmia or chest pain occurred. Expired gases were measured continuously in all subjects on a breath-by-breath basis. The anaerobic threshold (AT) was determined by gas exchange criteria as the point of nonlinear increase in ventilation equivalents for oxygen. The mean VO2 and HR at warm-up (Wu; 3–4 min after exercise commenced), AT, at the respiratory compensation point (Rc), and at the exercise peak (Pk) were all measured and recorded.

2.3. Definition of chronotropic incompetence

The patients who failed to achieve 80% APMHR were classified as having CI. Patients who achieved ≥80% of APMHR were classified as having chronotropic competence (CC). APMHR was calculated as 220 minus age in years and ΔHR was defined as the difference between the peak HR and the resting HR [16]; HR reserve (HRR) was calculated as the difference between APMHR and the resting HR, and the percent HR reserve (%HRR) was defined as the Δ HR divided by HRR [17,18]. The HR recovery was defined as the peak HR minus the HR at 1 min into the recovery period. These parameters have been widely used to assess CI in previous studies. The 80 patients who underwent CPET more than once, those with a higher peak VO2, were selected for the evaluation of the HR response.

2.4. Criteria and evaluation of chronotropic response (CR)

The Wilkoff model was applied at Wu, AT, Rc, and Pk to calculate the estimated HR at each stage. The ratios of estimated HRs to the measured HRs were calculated as MCR-Wu, MCR-AT, MCR-Rc, and MCR-Pk. In this model, the MCR-Pk was consistent with the %APMHR.

A total of 211 exercise tests by 80 patients were included to evaluate the progress of the CR during cardiac rehabilitation. The 40 patients who underwent CPET twice were evaluated by comparing the results of the first test with the second tests and the 40 who underwent CPET more than twice were evaluated by comparing the results of the first test with the mean results of the other tests. Patients who showed a change in %APMHR from <80% (CI) to ≥80% (CC), were considered to be normalized, and those who showed a change from ≥80% (CC) to <80% (CI), were considered to be worsening, and all other patients were considered to be stable (constant CI or CC). Furthermore, any improvement in the values of ≥3 of the 4 parameters MCR-Wu, MCR-AT, MCR-Rc, and MCR-Pk was considered to be an improvement in CR. An increase in 2 parameters was considered to be no change in CR, and an increase in ≤1 parameter was considered to be a deterioration in CR.

2.5. Statistical analyses

Statistical significance in multiple-group comparison was assessed using nonrepeated measures one-way analysis of variance, followed by Tukey’s honestly significant test. We used an unpaired Student’s t-test for between group comparisons and a paired t-test for within group analyses. A p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS Base 11.0J software.

3. Results

3.1. Baseline characteristics

The indication for CPET at ambulatory cardiac rehabilitation from 140 patients was as follows: myocardial infarction (38.6%), unstable angina (10.0%), angina pectoris (32.9%), cardiac myopathy (7.1%), valvular heart disease (2.1%), arrhythmia (5.0%), and others (4.3%). Of the 114 patients who had ischemic heart diseases, 99 patients (86.8%) had treatment of percutaneous coronary intervention. There were 140 eligible patients, of whom 68 (48.6%) had CI. Of the 140 eligible patients, 45 (32.1%) were on optimal medical therapy without β-blockers (non-BB) and 95 (67.9%) were on optimal medical therapy with β-blockers (on-BB). Table 1 shows initial CPET parameters for the 140 patients divided into 4 groups on the basis of CC or CI and on-BB or non-BB. In the CI group, 59 of 68 patients (86.8%) were on BB and in the CC group, 36 of 72 patients (50%) were on BB. There were significant differences in
resting HR, peak HR, ΔHR, %HRR, MCR-Wu, MCR-AT, and MCR-Rc between the CC/non-BB and CI groups. Moreover, there were significant differences in resting HR, peak HR, recovery HR, ΔHR, %HRR, peak VO2/kg, MCR-Wu, MCR-AT, and MCR-Rc between the CC/non-BB group and the CI/on-BB group.

3.2. Relationship between CI, BNP, and β-blockers

The patients were divided into 4 groups on the basis of BNP [BNP ≥ 80 (H-BNP) and BNP < 80 (L-BNP)] and on-BB or non-BB (Table 2). Compared with the L-BNP/non-BB group, the H-BNP/non-BB group showed significant differences in peak HR, HR recovery, peak VO2, peak VO2/kg, and MCR-Wu. Compared with the L-BNP/on-BB group, the H-BNP/on-BB group showed significant differences in peak VO2, AT, and LVEF. There were significant differences in peak HR, %HRR, AT, MCR-AT, MCR-Rc, MCR-Pk, and LVEF between the non-BB and on-BB groups for both the L-BNP and H-BNP.

The changes in VO2 and the MCR values at each stage are shown in Fig. 1A and B. VO2 in the L-BNP/on-BB group was higher than in the H-BNP/on-BB group at AT, Rc, and Pk, whereas VO2 in the L-BNP/non-BB group was higher than in the H-BNP/non-BB group at Rc and Pk. MCR values were smaller at each stage in the on-BB group compared to the non-BB group.

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Table 1
Cardiopulmonary exercise test parameters for 4 groups based on chronotropic competence or incompetence and the presence or absence of β-blockers.

|                      | Chronotropic competence (CI) | Chronotropic incompetence (CI) |
|----------------------|------------------------------|---------------------------------|
| %APMHR              | 91 ± 8                       | 71 ± 4***                      |
| β-blocker            | non-BB                       | on-BB                          |
| No. (m; f)           | 36 (23; 13)                 | 36 (28; 8)                    |
| Age, years           | 68.7 ± 7.4                   | 66.5 ± 6.7                     |
| BMI                  | 23.2 ± 3.5                   | 23.3 ± 3.4                     |
| DM, no.%             | 9 (25)                       | 3 (33)                         |
| BNP, pg/ml           | 660 ± 104.6                  | 747 ± 142.2                    |
| HR rest, bpm         | 75.2 ± 10.9                  | 65.6 ± 9.4***                  |
| HR peak, bpm         | 136.0 ± 12                   | 110.2 ± 13.3**                 |
| HR recovery, bpm     | 27.2 ± 12.9                  | 23.0 ± 7.2*                    |
| ΔHR, bpm             | 60.8 ± 14.6                  | 44.7 ± 11.2**                  |
| %HR reserve          | 81 ± 17                      | 50 ± 1.3***                    |
| VO2Pk, ml/min        | 1171.3 ± 431                 | 1064.8 ± 274.5                 |
| VO2Pk/kg, ml/min/kg  | 18.0 ± 5.0                   | 16.7 ± 4.5                     |
| AT, ml/kg/min        | 12.76 ± 2.69                 | 11.95 ± 2.2                    |
| MCR-Wu               | 0.87 ± 0.05                  | 0.78 ± 0.07**                  |
| MCR-AT               | 0.86 ± 0.07                  | 0.73 ± 0.08**                  |
| MCR-Rc               | 0.88 ± 0.07                  | 0.72 ± 0.08**                  |
| MCR-Pk               | 0.91 ± 0.08                  | 0.73 ± 0.09**                  |
| LVEF, %              | 68.0 ± 11.0**                | 66.2 ± 11.3                    |
| RVSP, mm Hg          | 20.0 ± 11.7                  | 24.1 ± 9.9                     |

Results are presented as mean (SD) or N (%), *p < 0.05 vs. CC/non-BB; **p < 0.05 vs. CC/non-BB; ***p < 0.01 vs. CC/non-BB; p < 0.05 vs. CC/on-BB; p < 0.05 CC/non-BB vs. CC/on-BB; BB, β-blockers; on-BB, presence of β-blockers. Significantly different differences in resting HR, peak HR, recovery HR, ΔHR, %HRR, peak VO2/kg, MCR-Wu, MCR-AT, and MCR-Rc between the CC/non-BB and CI groups. Moreover, there were significant differences in resting HR, peak HR, recovery HR, ΔHR, %HRR, peak VO2/kg, MCR-Wu, MCR-AT, and MCR-Rc between the CC/on-BB and the CI/on-BB group.

Table 2
Cardiopulmonary exercise test parameters for 4 based on BNP ≥ 80 and BNP < 80 and the presence or absence of β-blockers.

| β-blockers | L-BNP (<80) | H-BNP (≥80) |
|------------|-------------|-------------|
| non-BB     | on-BB       | non-BB      |
| No. (m; f) | 36 (23; 13) | 36 (28; 8)  |
| Age, years | 68.7 ± 7.4  | 66.5 ± 6.7  |
| BMI        | 23.2 ± 3.5  | 23.3 ± 3.4  |
| DM, no.%   | 9 (25)      | 3 (33)      |
| BNP, pg/ml | 660 ± 104.6 | 747 ± 142.2 |
| HR rest, bpm | 75.2 ± 10.9 | 65.6 ± 9.4*** |
| HR peak, bpm | 136.0 ± 12  | 110.2 ± 13.3** |
| HR recovery, bpm | 27.2 ± 12.9 | 23.0 ± 7.2* |
| ΔHR, bpm | 60.8 ± 14.6 | 44.7 ± 11.2** |
| %HR reserve | 81 ± 17 | 50 ± 1.3*** |
| VO2Pk, ml/min | 1171.3 ± 431 | 1064.8 ± 274.5 |
| VO2Pk/kg, ml/min/kg | 18.0 ± 5.0 | 16.7 ± 4.5 |

Data are presented as mean (SD) or N (%), *p < 0.05 vs. L-BNP/non-BB; **p < 0.05 vs. L-BNP/non-BB; ***p < 0.01 vs. L-BNP/on-BB; p < 0.05 vs. L-BNP/on-BB; p < 0.01 H-BNP/non-BB vs. H-BNP/on-BB; p < 0.05 H-BNP/non-BB vs. H-BNP/on-BB; BB, β-blockers; on-BB, presence of β-blockers; No. (m; f), number of patients (male; female); BMI, body mass index; DM, diabetes mellitus; BNP, brain natriuretic peptide; HR, heart rate; bpm, beats per minute; HR rest, heart rate at rest; HR peak, heart rate at the peak; ΔHR, difference between peak and rest heart rates; VO2Pk, peak oxygen consumption; VO2Pk/kg, peak exercise oxygen consumption per body weight; Wu, warm-up; AT, anaerobic threshold; Rc, respiratory compensation; Pk, peak; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure.
with the non-BB group, particularly compared with the H-BNP/on-BB group. Regardless of BNP levels, MCR values in the non-BB group decreased from Wu to AT and increased after AT (MCR-AT > MCR-Rc), whereas MCR values in the on-BB group decreased from Wu to Rc and increased after Rc (MCR-AT > MCR-Rc).

3.3. Classification based on an MCR-Wu

The patients were divided into 4 groups based on an impaired CR (ICR group) with an MCR-Wu ≥ 0.8, or a normal CR (NCR group) with an MCR-Wu < 0.8 and on-BB or non-BB (Table 3). Compared with the NCR/non-BB group, the ICR group showed significant differences in peak HR, ∆HR, %HRR, peak VO₂peak, peak VO₂/kg, and MCR values at all stages. Compared with the NCR/on-BB group, the ICR/on-BB group showed significant differences in resting HR, peak HR, ∆HR, %HRR, peak VO₂peak, peak VO₂/kg, AT, MCR-AT, MCR-Rc, MCR-Pk, and RVSP. Furthermore, there were significant differences in peak HR, %HRR, MCR-AT, MCR-Rc, MCR-Pk, and LVEF between the NCR/non-BB and NCR/on-BB groups, as well as in BNP, MCR-Rc, and LVEF between the ICR/non-BB and ICR on-BB groups.

Changes in MCR values for the 4 groups divided on the basis of NCR or ICR and non-BB or on-BB are shown in Fig. 2C. In the non-BB group, MCR values decreased from Wu to AT and increased after AT (MCR-AT > MCR-Rc). Conversely, in the on-BB group MCR values decreased from Wu to Rc and tended to increase after Rc (MCR-AT > MCR-Rc).

Table 3
Cardiopulmonary exercise test parameters for 4 groups based on MCR-Wu ≥ 0.8 or MCR-Wu < 0.8 and the presence or absence of β-blockers.

| β-blockers   | NCR (MCR-Wu ≥ 0.8) | ICR (MCR-Wu < 0.8) |
|--------------|--------------------|--------------------|
|              | non-BB             | on-BB              | non-BB             | on-BB              |
| No. (m; f)   | 36 (27.9)          | 51 (44.7)          | 9 (3.6)            | 44 (36.8)          |
| Age, years   | 69.5 ± 7.4         | 65.4 ± 10*         | 66.2 ± 7.3         | 65.1 ± 10.9*       |
| BMI          | 23.3 ± 3.4         | 24.6 ± 3.2*        | 23.0 ± 3.8         | 24.2 ± 2.6         |
| DM, no. (%)  | 10 (28)            | 23 (45)            | 2 (22)             | 15 (34)            |
| BNP, pg/ml   | 66.1 ± 104.8       | 72.2 ± 64.8        | 74.3 ± 62.9        | 131.7 ± 133.6**    |
| HR rest, bpm | 74.4 ± 10.8        | 72.2 ± 10.6        | 68.8 ± 11.8        | 65.1 ± 10.8**      |
| HR peak, bpm | 134.4 ± 14.0       | 126.4 ± 13.6**     | 116.7 ± 16.2**     | 107.1 ± 14.2**     |
| HR recovery, bpm | 26.3 ± 12.0   | 26.0 ± 10.0        | 25.1 ± 13.5        | 23.2 ± 9.5         |
| ∆HR, bpm     | 60.0 ± 14.6        | 54.2 ± 15.0        | 47.9 ± 16.0*       | 42.1 ± 14.0**      |
| %HRR reserve | 79.7 ± 18.8        | 66.3 ± 17.0**      | 56.7 ± 16.3*       | 47.0 ± 15.2**      |
| VO₂peak, ml/min | 11632 ± 4193  | 1226.6 ± 332.1     | 881.2 ± 222.7***   | 978.5 ± 298.1***   |
| VO₂peak/kg, ml/min/kg | 18.4 ± 5.0 | 18.1 ± 3.4       | 15.1 ± 3.4*        | 14.8 ± 3.6*        |
| AT, ml/kg   | 12.8 ± 2.7         | 12.0 ± 2.0         | 11.8 ± 2.2         | 10.7 ± 1.9**       |
| MCR-Wu       | 0.88 ± 0.05        | 0.87 ± 0.04        | 0.76 ± 0.06**      | 0.74 ± 0.06**      |
| MCR-AT       | 0.87 ± 0.06        | 0.83 ± 0.06**      | 0.72 ± 0.06**      | 0.70 ± 0.07**      |
| MCR-Rc       | 0.88 ± 0.08        | 0.82 ± 0.09**      | 0.76 ± 0.06**      | 0.69 ± 0.09***     |
| MCR-Pk       | 0.89 ± 0.09        | 0.80 ± 0.09*       | 0.76 ± 0.11**      | 0.69 ± 0.10*       |
| RVSP, mm Hg  | 66.7 ± 9.36        | 59.5 ± 13.22**     | 69.1 ± 10.5*       | 55.2 ± 13.8**      |

Data are presented as means (SD) or N (%); *p < 0.01 vs. NCR/non-BB; **p < 0.05 vs. NCR/non-BB; $p < 0.01 vs. NCR/non-BB; **p < 0.05 vs. NCR/on-BB; \(*p < 0.05\) ICR/non-BB vs. ICR/on-BB.

NCR, normal chronotropic response; ICR, impaired chronotropic response; BNP, brain natriuretic peptide; H-BNP, high BNP group with BNP ≥ 80; L-BNP, low BNP group with BNP < 80; Wu, warming up; AT, anaerobic threshold; Rc, respiratory compensation; Pk, peak; β-blockers; non-BB, absence of β-blockers; on-BB, presence of β-blockers; DM, diabetes mellitus; BMI, body mass index; BNP, brain natriuretic peptide; HR, heart rate; bpm, beats per minute; AT, heart rate at the peak; ∆HR, difference between peak and rest heart rates; VO₂peak, peak oxygen consumption; VO₂peak/kg, peak exercise oxygen consumption per body weight; Wu, warm-up; AT, anaerobic threshold; Rc, respiratory compensation; Pk, peak; LVEF, left ventricular ejection fraction; RVSP, right ventricular systolic pressure.
3.4. Progress of the chronotropic response

Of the 80 patients selected to evaluate the progress of CR, 29 (36.2%) were in the non-BB group and 51 (63.8%) were in the on-BB group (Table 4). Both peak VO\textsubscript{2} and AT increased in 47 patients (58.8%), 31 of whom were on BB (66.0%). Of the 47 patients who showed an increase in both peak VO\textsubscript{2} and AT, CI was normalized in 8 (7 of these 8 [87.5%] were on BB), and 32 patients (23 of these 32 [71.9%] were on BB) showed an improvement in CR according to the criteria stipulated in the present study. In 22 patients, CI was maintained regardless of improvement in VO\textsubscript{2} and AT, but 14 of them did show an improvement in CR (12 of these 14 [85.7%] were on BB; data not shown). Fig. 3 shows changes in MCR values during cardiac rehabilitation. MCR values increased overall, particularly in the on-BB group.

4. Discussion

4.1. Staging of CI assessment

Both BNP and peak VO\textsubscript{2} are strong predictors of mortality in patients with CHF\textsuperscript{[18,19]. Our findings that the H-BNP group had more severe CI and lower peak VO\textsubscript{2} and AT compared with the L-BNP group are not unexpected and support the results of previous studies. The finding that MCR-Wu and MCR-AT in the CI group were significantly smaller than

| Table 4 | Progress of exercise tolerance capacity and heart rate responses throughout cardiac rehabilitation. |
|---------|--------------------------------------------------------------------------------------------------|
| AT      | Peak VO\textsubscript{2}                                                                 | Chronotropic incompetence | Chronotropic response | Total no. |
|         |                                                                                             | CI → CC                   | CC → CI                | CI → CI              | Improvement | Deterioration | No change |         |
| ↑       | ↑                                                                                           | 8 [7]                     | 3 [1]                  | 14 [4]               | 22 [19]      | 32 [23]       | 11 [6]     | 4 [2]    | 47 [31]  |
| ↓       | ↓                                                                                           | 2 [2]                     | 0                      | 6 [5]                | 6 [3]        | 10 [6]        | 3 [3]      | 1 [1]    | 14 [10]  |
| ↓       | ↓                                                                                           | 0                        | 1 [0]                  | 0                    | 3 [2]        | 0             | 3 [2]      | 1 [0]    | 4 [2]    |
| ↓       | ↓                                                                                           | 1 [0]                     | 3 [2]                  | 6 [2]                | 5 [4]        | 5 [2]         | 9 [6]      | 1 [0]    | 15 [8]   |
| CR      | Improvement                                                                                 | 11 [9]                   | 0                      | 17 [8]               | 19 [14]      | –             | –          | –        | 47 [3]   |
|         | Deterioration                                                                               | 0                        | 6 [2]                  | 6 [2]                | 14 [13]      | –             | –          | –        | 26 [1]   |
|         | No change                                                                                   | 0                        | 1 [1]                  | 3 [1]                | 3 [1]        | –             | –          | –        | 7 [3]    |
| Total no.|                                                                                           | 11 [9]                   | 7 [3]                  | 26 [11]              | 36 [28]      | 47 [31]       | 26 [17]    | 7 [3]    | 89 [51]  |

[No. on-BB].

AT, anaerobic threshold; Peak VO\textsubscript{2}, peak oxygen consumption; CI, chronotropic incompetence; CR, chronotropic response; No., number of patients; on-BB, presence of β-blockers.
The HR response is related to the severity of heart failure; therefore CI may be not only a cause of the reduction in exercise capacity in patients with CHF but also an indicator of autonomous nervous system dysfunction resulting from cardiac disease. Witte et al. supported the concept that chronotropy is not a major factor in determining exercise capacity in patients with CHF [19], suggesting that HR limitation is unlikely to be the cause, but rather the consequence, of exercise intolerance in CHF patients [21]. Fukuda et al. demonstrated that CHF patients with impaired exercise capacity had attenuated increments in cardiac output during exercise [22].

Using conventional evaluation methods, CI showed no change in 62 (77.5%) of the patients in the present study. However, according to the evaluation criteria stipulated in the present study, 73 patients showed subtle changes in CR. Throughout the course of cardiac rehabilitation, we found a significant improvement in CR related to β-blocker administration. Therefore, β-blockers may in fact contribute to the improvement in CR by protecting the myocardium from the cardiotoxic effects of increased catecholamine levels and by restoration of down-regulated β1 receptors. In addition, endurance exercise training may improve chronotropic function in patients with CHF, probably by increasing baroreflex sensitivity and reducing sympathetic outflow and plasma levels of neurohormones [23].

4.4. Limitations

There are several limitations to the present study. The study population was relatively small and there was no control group. The disease severity in our patients was mild, and the New York Heart Association classification was low. Because the participation of the study patients in ambulatory cardiac rehabilitation was voluntary, the frequency and intensity of the execution varied among patients. We did not have information on death rates, cause of death, or hospitalization.

5. Conclusions

An attenuated HR response may occur during the early stages of exercise because the MCR-Wu and MCR-AT in the CI group were significantly smaller than those in the CC group. In the non-BB group, MCR values decreased from Wu to AT and increased after AT with MCR-AT < MCR-Rc. Conversely, in the on-BB group, MCR values decreased from Wu to Rc and tended to increase after Rc with MCR-AT > MCR-Rc. The differences in MCR values between the non-BB group and the on-BB group may reflect the HR response under β-blocker administration. Cardiac rehabilitation increased both peak VO2 and AT with an improvement in CR, particularly in the on-BB group. Here, we have presented a method for evaluating CI objectively using widely available exercise testing methods and standardized definitions based on the Wilkoff model.

Conflict of interest statement

The authors report no relationships that could be construed as a conflict of interest.

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