Influence of Complications of Diabetes Mellitus on Exercise Tolerance of Patients with Heart Failure: Focusing on autonomic nervous activity and heart rate response during cardiopulmonary exercise tests

Kodai Ishihara, MSc, PT1, Tomoyuki Morisawa, PhD, PT2, Junko Kawada, MT3, Yuko Nagare, MT3, Takuya Koyama, MT3, Hikari Yagi, MT3, Mayuko Sueoka, MT3, Toshinobu Yoshida, MD4 and Akira Tamaki, PhD, PT5

1) Department of Rehabilitation, the Sakakibara Heart Institute of Okayama
2) Department of Physical Therapy, Faculty of Health Sciences, Juntendo University
3) Department of Laboratory Medicine, the Sakakibara Heart Institute of Okayama
4) Department of Cardiovascular Medicine, the Sakakibara Heart Institute of Okayama
5) Graduate School of Health Sciences, Hyogo University of Health Sciences

ABSTRACT. Purpose: The purpose of this study was to clarify the influence of complications of diabetes on the exercise tolerance of patients with heart failure. Methods: The subjects of this study were 69 patients (44 men; mean age: 62.2 ± 13.4 years) who were hospitalized and diagnosed with heart failure between November 2016 and November 2017. The subjects all took part in a cardiopulmonary exercise test. The patients’ medical background, indexes obtained from lower-limb muscle strength and the cardiopulmonary exercise test, heart rate response indexes (Δ heart rate (ΔHR)), and autonomic nervous activities were measured, and these individual indexes were compared between the diabetic group and the non-diabetic group. Results: Compared with the non-diabetic group, the peak oxygen uptake (peak $\dot{V}$O2) and ΔHR in the diabetic group were significantly lower (13.0 ± 2.2 vs. 14.9 ± 4.4 ml/kg/min and 27.2 ± 11.7 vs. 36.7 ± 14.7 bpm, respectively) (p<0.05). Regarding the autonomic nervous activity during the cardiopulmonary exercise test in the diabetic group, there was a significant decrease of parasympathetic nerve activity and a significant lack of increase in sympathetic nerve activity (p<0.05). Conclusions: Patients with heart failure and diabetes had lower levels of exercise tolerance, as compared with patients without complications. It was suggested that the decrease in heart rate response was due to the decrease of autonomic nervous activity and that this may play a role in reduced exercise tolerance.

Key words: exercise tolerance, heart rate response, autonomic nervous activity, diabetes mellitus, heart failure

Clinical studies have reported that patients with heart failure (HF) and comorbid diabetes mellitus (DM) account for about 30% of all the patients with HF1, and there is a mutual relationship between HF and DM. Studies also suggested that patients with HF and comorbid DM have a poorer life expectancy, as compared with patients without DM2-4. Therefore, much emphasis has been placed on medical interventions for patients with HF and comorbid DM5.

Regarding physical capability of patients with HF, the exercise tolerance of patients with HF is lower than that of healthy individuals6. Moreover, heart rate recovery after the cardiopulmonary exercise test (CPX) is significantly related to many exercise and echocardiographic measures. And, the most significant predictors of abnormal heart rate recovery being related to indices of cardiorespiratory performance in...
patients with HF.

Regarding physical capability of patients with DM, the exercise tolerance of patients with DM is lower than that of healthy individuals. Moreover, there are clear differences in the heart rate response during CPX in patients with DM compared to healthy individuals. Therefore, it is possible that physical capability of patients with HF and comorbid DM decreases in an additive manner.

Regarding physical capability of the patients with heart disease and DM, it was reported that peak oxygen uptake (Peak VO2) and skeletal muscle strength of patients with acute myocardial infarction (AMI) and DM were lower than those of patients without DM. It was also reported that the decrease in the peak VO2 is associated with both attenuated heart rate response caused by autonomic disorder and the knee extension muscle strength, and that the heart rate response of patients with AMI and DM decreased during the exercise, unlike the patients without DM. Furthermore, it was revealed that the decrease in heart rate response was caused by reduced activities of sympathetic and parasympathetic nerves.

However, there are few studies that examined patients with HF and DM from the viewpoints of exercise tolerance and heart rate response. So, we hypothesized that complications of DM may result in the decrease of exercise tolerance in patients with HF, and that this decrease may be influenced by a decrease in heart rate response caused by lower autonomic nervous activity. Thus, the purpose of the present study was to examine the differences between exercise tolerance and heart rate response in patients with HF and DM.

Methods

Subjects

The chosen subjects for this study were patients diagnosed with HF and admitted to the Sakakibara Heart Institute of Okayama, to receive cardiac rehabilitation between November 2016 and November 2017. The subjects are 145 consecutive patients who were able to stabilize their HF via medical treatment and received CPX during their stay. Patients with New York Heart Association (NYHA) class II and III HF and those defined as stage C by the American Heart Association/American College of Cardiology (AHA/ACC) classification were included in this study. From the 145 patients, a total of 69 patients were selected to participate in the study, with the following cases excluded: those who didn’t signed the written informed consent form (n=14); those who had atrial fibrillation (n=22); those who had left bundle branch block (n=3); those who underwent pacemaker implantation (n=8); those who had an implantable cardiac defibrillator insertion (n=11); and those who received cardiac resynchronization therapy (n=19).

The subjects were categorized into the following 2 groups: patients with HF and DM (the DM group; n=14) and patients with HF without DM (the non-DM group; n=55). Patients in the DM group were those who were diagnosed with DM by a diabetologist at the beginning of this study.

This study was approved by the ethical committee of the Sakakibara Heart Institute of Okayama (approval number: 20160901), and by the ethical committee of Hyogo University of Health Sciences (approval number: 16034). Prior to participating in the study, participants were well informed about the objectives of the study, the procedures, and the handling of study results, and voluntarily signed the written informed consent form.

Measurement items

1) Information on attributes and patient backgrounds

Basic attributes and information of the patients included age, gender, height, body weight, body mass index (BMI), NYHA functional classification, primary disease status (ischemic heart disease, valvular disease, cardiomyopathy), diabetes duration, coefficient of variation of R-R interval (CVR-R), and the presence of comorbidity (hypertension and dyslipidemia). Items to be researched by biochemical blood examination included HbA1c and brain natriuretic peptide (BNP). Cardiac function tests included left ventricular ejection fraction (LVEF) and E/e’ (the ratio between the E-wave [the transmitial flow pattern] and the e’ wave [the mitral annular velocity]). Medication history to be researched included oral drugs used (angiotensin converting enzyme inhibitor, AI receptor antagonist, β blocker, Ca antagonist, oral hypoglycemic agent) and the use of insulin. These indexes were obtained through the medical records. In particular, data such as biochemical blood examination values, cardiac function test, and medication contents were extracted from the patients’ most recent CPX examination.

2) CPX

For CPX, a lumped loading test was performed using an upright-type ergometer (ergometer STB-3400, OG Wellness) with a 10 watt increase per minute. Termination conditions of the loading test was defined as the emergence of symptoms satisfying the exercise tolerance test discontinuation criteria of the American College of Sports Medicine and/or the emergence of leveling-off of oxygen uptake (VO2) despite the augmentation of loading intensity. During the test, blood pressure, heart rate (HR), ST-T wave changes, and arrhythmia were monitored continuously by using an exercise tolerance test monitoring device (stress test system ML-9000, Fukuda Denshi). During CPX, an expired gas analysis device (expired gas metabolic monitor Cpx-1, Inter Reha) was used to perform expired gas analysis (sampling frequency: 20 Hz) continuously by using the breath-by-breath method, and the following values were measured: VO2, HR, and oxygen pulse (O2 pulse) at rest, at
an anaerobic metabolic threshold (AT), and at peak exercise. AT was determined using the V-slope method\(^{14}\); \(\dot{V}O_2\) pulse was calculated as \(\dot{V}O_2/HR\); Peak \(\dot{V}O_2\) was calculated as the average of values obtained during the last 30 seconds of the exercise.

3) Heart rate response index

\(\Delta HR\) and chronotropic index were calculated as an index of heart rate incompetence with reference to the result of CPX\(^{11,12,13}\). \(\Delta HR\) was calculated from the difference between HR at rest and HR at peak exercise and was evaluated as the elevated value after the exercise\(^{16}\). Chronotropic index was accordingly defined as: chronotropic index = \((HR \text{ at peak exercise} – \text{resting HR})/ [(220 – age) – \text{resting HR})]\(^{15}\).

4) Autonomic nerve activity

For spectral analysis of the R-R interval variability during CPX, a wireless vital sensor (RF-ECG, GMS) was used to measure the ECG data, which were then transmitted to a personal computer (Think pad X230i, IBM). The peak point of the R-wave was soon detected by the waveform recognition function of RF-ECG, and then frequency analysis of the R-R interval data of the last 30 seconds during exercise was performed using the MemCalc method\(^{16}\). The whole series of analyses were performed in real time, and the average of every 10 seconds of the low-frequency power (LF) components (0.04~0.15 Hz), high-frequency power (HF) components (0.15~0.4 Hz), and LF/HF components were calculated. The real-time analysis software for heart rate variability (Bonaly Light, GMS) was used for the analysis.

5) Lower-limb muscle strength

Isometric knee extension muscle strength was used as the index of lower-limb muscle strength. Isometric knee extension muscle strength was measured using a hand-held dynamometer (\(\mu\)-Tas F-1, Anima). The sensor pad was attached to the front of the distal lower leg in a seated position on a chair, and the length of the belt was adjusted with the knee joint at 90\(^\circ\) of flexion\(^{17}\). The maximum knee extension muscle strength was measured for about 5 seconds, in order to avoid the valsalva effect. Both the left and right legs were measured twice, and the higher value of the two attempts were recorded as the lower limb muscle strength (Kgf), and the average of the left and right muscle strength divided by the body weight (Kgf/kg) was recorded as the analytical value. The intra-class correlation (ICC), which represents the intra-rater reliability, was examined in advance, and the obtained ICC (1, 1) was very favorable at 0.972.

**Statistical analysis**

For the comparison between the DM group and the non-DM group, a Chi-square test, the Mann-Whitney U test, and Welch’s t-test were used to compare patient backgrounds, CPX indexes, lower-limb muscle strengths, and heart rate response indexes. The Shapiro-Wilk test was also used to confirm normality. When normality could not be confirmed, the Mann-Whitney U test was used. When normal distribution was confirmed, Levene’s test for equality of variance was performed. An unpaired t-test was performed when equality was established, but Welch’s t-test was performed when equality was not established. For the comparison of autonomic nervous activity (LF, HF, and LF/HF) during CPX, Mendoza’s multi-sample sphericity test was used in advance to test the equality of variance. Subsequently, a two-way factorial analysis of variance for split-plot factorial design and Tukey’s multiple comparison test were performed, with the between-group difference (an unpaired factor) and the load intensity being the two factors. Statistical analyses were conducted using R 2.8.1 software (The R Foundation for Statistical Computing, Vienna, Austria). Data were expressed as mean ± standard deviation. Statistical significance was defined as p<0.05.

**Results**

1. **Patient backgrounds**

Patient backgrounds in the DM group and the non-DM group are shown in Table 1. A significant difference was observed between the 2 groups in terms of HbA1c, LVEF, primary diseases (ischemic heart disease, valvular disease), and comorbidity (dyslipidemia) (p<0.05). There was no significant difference in all other basic attributes, primary disease status, comorbidity, and medication history between the 2 groups.

2. **Indexes of CPX, lower-limb muscle strength, and heart rate response**

Indexes of CPX, lower-limb muscle strength, and heart rate response are shown in Table 2. The results of CPX revealed a significantly low value for Peak \(\dot{V}O_2\) and Peak HR in the DM group, as compared with the non-DM group (p<0.05). There was no significant difference in all other CPX indexes between the 2 groups. Regarding the lower-limb muscle strength, there was no significant difference in the knee extension muscle strength between the 2 groups. Regarding the heart rate response index, \(\Delta HR\) and chronotropic index showed a significantly low value in the DM group, as compared with the non-DM group (p<0.05).

3. **Autonomic nerve activity during CPX**

1) Changes in LF during CPX are shown in Figure 1. The main effect between the groups, the main effect of the loading intensity, and interactions were observed in LF by using the two-way factorial analysis of variance and the multiple comparison test (p<0.05). In comparison between the 2 groups, LF of the loading intensity of HRrest, HRwu, HRrest+20%\(\Delta HR\), and HRrest+40%\(\Delta HR\) showed a signifi-
Table 1. Patient backgrounds in the DM group and the non-DM group

|                      | non-DM group (n=55) | DM group (n=14) | t, χ², Z value | p value |
|----------------------|---------------------|----------------|----------------|---------|
| Age (years)          | 60.8 ± 13.6         | 67.6 ± 11.6    | 0.213          | 0.076   |
| Sex (male/female)    | 32/23               | 12/2           | 3.661          | 0.056   |
| BMI (kg/m²)          | 23.4 ± 4.4          | 25.9 ± 5.1     | -1.826         | 0.072   |
| HbA1c (%)            | 5.7 ± 0.4           | 7.6 ± 1.5      | 0.632          | < 0.001 |
| Duration of diabetes (years) | -         | 12.0 ± 11.8    | -             | -       |
| CVR-R (%)            | 3.6 ± 1.9           | 3.4 ± 2.4      | 0.085          | 0.478   |
| BNP (pg/ml)          | 137.2 ± 174.7       | 279.9 ± 459.9  | 0.177          | 0.140   |
| LVEF (%)             | 58.6 ± 16.7         | 45.0 ± 15.6    | 0.355          | 0.003   |
| E/e'                 | 16.0 ± 7.7          | 19.5 ± 9.8     | 0.187          | 0.118   |
| NYHA class [n (%)]   | II: 47 (86)         | II: 9 (64)     | 3.270          | 0.071   |
| Primary disease [n (%)] |                       |                |                |         |
| Ischemic heart disease | 5 (9)              | 8 (57)         | 16.851         | < 0.001 |
| Valvular disease     | 38 (69)             | 4 (29)         | 7.692          | 0.006   |
| Cardiomyopathy       | 12 (22)             | 2 (14)         | 0.392          | 0.532   |
| Comorbidities [n (%)]|                      |                |                |         |
| Hypertension         | 20 (36)             | 8 (57)         | 1.998          | 0.158   |
| Dyslipidemia         | 7 (13)              | 8 (57)         | 12.940         | < 0.001 |
| Medication [n (%)]   |                      |                |                |         |
| ACE inhibitor        | 11 (20)             | 4 (29)         | 0.482          | 0.488   |
| ARB blocker          | 13 (24)             | 3 (21)         | 0.031          | 0.861   |
| β blocker            | 25 (46)             | 10 (71)        | 3.012          | 0.083   |
| Ca antagonist        | 9 (16)              | 3 (21)         | 0.199          | 0.655   |
| Oral hypoglycemic agent | -               | 9 (64)         | -             | -       |
| Insulin              | -                   | 2 (14)         | -             | -       |
| Diet                 | -                   | 3 (21)         | -             | -       |

Date are mean ± SD.
DM: diabetes mellitus; BMI: body mass index; HbA1c: hemoglobin A1c; CVR-R: coefficient of variation of R-R interval; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; NYHA: New York heart association; ACE: angiotensin converting enzyme.

Significantly low value in the DM group (p<0.05). In comparison of loading intensity, LF during rest in the non-DM group showed a significant decrease from HRwu (p<0.05), and also showed a significant decrease according to the escalation of the intensity (p<0.05). However, LF during rest in the DM group showed a significant decrease from HRrest+40%ΔHR (p<0.05).

2) Changes in HF during CPX are shown in Figure 2. The main effect between the groups, the main effect of the loading intensity, and interactions were observed in HF by using the two-way factorial analysis of variance and the multiple comparison test (p<0.05). In comparison between the 2 groups, HF of the loading intensity of HRrest, HRwu, HRrest+20%ΔHR, and HRrest+40%ΔHR showed a significantly low value in the DM group (p<0.05). In comparison of loading intensity, HF during rest in the non-DM group showed a significant decrease from HRwu (p<0.05), and also showed a significant decrease according to the escalation of the intensity (p<0.05). However, HF during rest in the DM group showed a significant decrease from HRrest+20%ΔHR (p<0.05).

3) Changes in LF/HF during CPX are shown in Figure 3. Interactions were not observed, but the main effect between the groups and the main effect of the loading intensity were observed in LF/HF by using the two-way factorial analysis of variance and the multiple comparison test (p<0.05). In comparison between the 2 groups, LF/HF of the loading intensity of HRrest+20%ΔHR, HRrest+40%ΔHR, HRrest+60%ΔHR, HRrest+80%ΔHR, and HRpeak showed a significantly low value in the DM group (p<0.05). In comparison of loading intensity, LF/HF during rest in the non-DM group showed a significant increase from HRrest+20%ΔHR (p<0.05). However, LF/HF in the DM group showed a minimal increase even when the load-
Table 2. Indexes of CPX, lower-limb muscle strength, and heart rate response indexes

|                           | non-DM group (n=55) | DM group (n=14) | t, \(\chi^2\), Z value | p value |
|---------------------------|---------------------|-----------------|-----------------------|---------|
| CPX indexes               |                     |                 |                       |         |
| Peak values               |                     |                 |                       |         |
| VO\(_2\) (ml/kg/min)      | 14.9 ± 4.4          | 13.0 ± 2.2      | 2.263                 | 0.029   |
| HR (bpm)                  | 111.8 ± 20.4        | 99.4 ± 18.2     | 2.071                 | 0.042   |
| O\(_2\) pulse (ml/beat)   | 8.3 ± 2.9           | 8.9 ± 1.8       | -0.668                | 0.507   |
| RER                       | 1.2 ± 0.2           | 1.1 ± 0.1       | 0.227                 | 0.058   |
| AT values                 |                     |                 |                       |         |
| VO\(_2\) (ml/kg/min)      | 11.3 ± 2.6          | 10.2 ± 1.9      | 0.226                 | 0.060   |
| HR (bpm)                  | 93.3 ± 15.4         | 86.6 ± 14.6     | 1.449                 | 0.152   |
| O\(_2\) pulse (ml/beat)   | 7.4 ± 2.2           | 7.8 ± 1.6       | -0.717                | 0.480   |
| Rest values               |                     |                 |                       |         |
| VO\(_2\) (ml/kg/min)      | 4.3 ± 1.0           | 4.1 ± 0.9       | 0.847                 | 0.400   |
| HR (bpm)                  | 75.1 ± 12.1         | 72.2 ± 11.8     | 0.804                 | 0.425   |
| O\(_2\) pulse (ml/beat)   | 3.6 ± 1.1           | 3.7 ± 0.7       | 0.123                 | 0.303   |
| ΔVO\(_2\)/ΔWR (ml/min/watt)| 8.9 ± 4.3          | 8.8 ± 4.1       | 0.040                 | 0.732   |
| Lower-limb muscle strength|                     |                 |                       |         |
| Knee extension muscle strength (kgf/kg) | 0.48 ± 0.21 | 0.51 ± 0.16 | 0.091 | 0.455 |
| Heart rate response indexes|                     |                 |                       |         |
| ΔHR (bpm)                 | 36.7 ± 14.7         | 27.2 ± 11.7     | 2.245                 | 0.028   |
| Chronotropic index (%)    | 44.3 ± 16.0         | 34.5 ± 16.5     | 2.039                 | 0.045   |

Date are mean ± SD.

CPX: cardiopulmonary exercise test; DM: diabetes mellitus; VO\(_2\): oxygen uptake; HR: heart rate; O\(_2\) pulse: oxygen pulse; RER: respiratory exchange ratio; AT: anaerobic threshold; ΔVO\(_2\)/ΔWR: slope of the increase in VO\(_2\) with respect to the increase in work rate; ΔHR: change of HR from rest to peak exercise.

Figure 1. Changes in LF during CPX

- : Mean of non-DM group, ▲: Mean of DM group

\(\dagger\): p<0.05 (Comparison of groups), \(\dagger\): p<0.05 (Comparison of loading intensity)

CPX: cardiopulmonary exercise test; LF: low frequency power; DM: diabetes mellitus; HR: heart rate; ΔHR: change of HR from rest to peak exercise.
Figure 2. Changes in HF during CPX

- : Mean of non-DM group, ▲: Mean of DM group
*: p<0.05 (Comparison of groups), †: p<0.05 (Comparison of loading intensity)

CPX: cardiopulmonary exercise test; HF: high frequency power; DM: diabetes mellitus; HR: heart rate; ΔHR: change of HR from rest to peak exercise.

Figure 3. Changes in LF/HF during CPX

- : Mean of non-DM group, ▲: Mean of DM group
*: p<0.05 (Comparison of groups), †: p<0.05 (Comparison of loading intensity)

CPX: cardiopulmonary exercise test; LF: low frequency power; HF: high frequency power; DM: diabetes mellitus; HR: heart rate; ΔHR: change of HR from rest to peak exercise.

A significant difference was observed only in LF/HF and HRrest+40%ΔHR at both HRwu and HRpeak, and in LF/HF at HRpeak (p<0.05).

Discussion

1. Decrease in exercise tolerance and its related factors in the DM group

Few studies have clarified the influence of the presence or absence complications of DM on the exercise tolerance in patients with HF and DM. So far, it has been clarified that the exercise tolerance in patients with DM is lower than that of patients without DM. Moreover, it was reported that even between patients with AMI, the level of exercise tolerance was lower in patients with DM than those without DM, and that the decrease in the level of exercise tolerance was associated with lower heart rate response caused by autonomic disorder and knee extension.
muscle strength\textsuperscript{10-12}. Since it was revealed in this study that the peak VO\textsubscript{2} was significantly lower in the DM group than in the non-DM group, we assumed that the level of exercise tolerance would decrease due to DM in patients with HF, as was reported in the previous study\textsuperscript{20}.

Firstly, there are reports regarding the influence of heart rate response on the decrease of exercise tolerance in the DM group; it was found that the heart rate response in patients with DM decreased during the incremental-load exercise, as compared with healthy control patients\textsuperscript{23}, and that the decrease of heart rate response in patients with DM was strongly associated with parasympathetic nerve malfunction\textsuperscript{27}. Furthermore, it was reported that lower heart response caused by autonomic disorder was associated as a factor of decrease in exercise tolerance in AMI patients complicated with DM\textsuperscript{21}. We also found in this study that \(\Delta HR\) and chronotropic index were significantly lower in the DM group than that in the non-DM group, so we assumed that heart rate response was decreased and this decrease might be a factor that contributed to the decrease of exercise tolerance in the DM group.

Secondly, regarding factors that contributed to the decrease of exercise tolerance in the DM group, ischemic heart disease accounted for a significant proportion of this study, and the level of LVEF was significantly low. Regarding the difference in LVEF between the 2 groups, it was reported that there was no relationship between LVEF during rest and peak VO\textsubscript{2}\textsuperscript{27}. In this study, no significant difference was found between the 2 groups of \(\Delta VO_2/\Delta WR\) during CPX and peak \(O_2\) pulse. \(\Delta VO_2/\Delta WR\) indicates the rate of increase of \(VO_2\) vs. the increase of the load during the load-incremental exercise, which is reported to reflect the rate of increase for cardiac output\textsuperscript{28}. It was reported that \(O_2\) pulse is equivalent to the stroke volume calculated by cardiac ultrasonography at HRmax during a load-incremental exercise\textsuperscript{21}, and \(O_2\) pulse is considered to reflect the stroke volume and works as a parameter of cardiac function during the exercise. For these reasons, the cardiac output and the stroke volume during CPX were equivalent between the 2 groups in this study, and therefore, the influence caused by the difference in patient backgrounds on the decrease in exercise tolerance in the DM group was considered to be minimal.

Lastly, regarding the influence of the lower-limb muscle strength on the decrease in exercise tolerance in the DM group, no significant difference was observed in the influence of the lower-limb muscle strength in the DM group, as compared with that in the non-DM group. Therefore, the influence caused by the lower-limb muscle strength exerted on the decrease in exercise tolerance in the DM group was considered to be minimal. A study that compared DM patients with age-matched healthy control patients reported that DM patients experienced no significant difference in the knee extension muscle strength was observed between the 2 groups\textsuperscript{27}. We also could not find a significant difference in the knee extension muscle strength in this study, so we assumed that the influence of DM on the knee extension muscle strength in patients with HF to be minimal.

2. Autonomic nerve activity during CPX in the DM group

It was found that the heart rate response during exercise was adjusted by the balance between sympathetic and parasympathetic nerve activities\textsuperscript{20}, and that insufficient heart rate response caused by malfunction of the sympathetic nervous system during exercise, would affect the decrease of exercise tolerance in patients with DM\textsuperscript{21}. It was also reported that norepinephrine secretion from peripheral sympathetic nerve terminals was decreased during exercise in patients with DM, as compared with healthy control patients\textsuperscript{27}, and that heart rate response against norepinephrine secretion was decreased in patients with AMI complicated with DM\textsuperscript{111}. Moreover, it was revealed that patients with DM had malfunctions of not only sympathetic nerves but also parasympathetic nerves\textsuperscript{29}.

Similarly, we found that exercise tolerance and heart rate response in patients with HF and DM were lower than those of patients without DM in this study. Based on the analysis results of HF and LF/HF during CPX, a decrease of sympathetic and parasympathetic nerve activities was also confirmed. And, we also could not find a significant difference in the CVR,\textsubscript{R} in this study, so we assumed that the influence of diabetic autonomic neuropathy to be minimal. It might suggest from these observations that attenuation of heart rate response caused by the DM-induced decrease in autonomic nerve activities functioned as a mechanism to decrease exercise tolerance in patients with HF and DM, as similarly shown in previous studies.

3. Limitations of this study

There were some limitations for this study. Firstly, we only compared the DM group with the non-DM group, so we were unable to perform a factorial analysis using a multiple regression analysis, due to the lack of subjects in the DM group and the lack of statistical power. These point was severe limitations in this study and important issues to be solved in the future study. Secondly, since our study was a cross-sectional study, we did not mention whether the changes of autonomic nervous activity and heart rate response could lead to the improvement of exercise tolerance. Thus, further research that includes a factorial analysis using a multiple regression analysis and a longitudinal study are needed in the future in order to clarify factors that define exercise tolerance of patients with HF and comorbid DM. Lastly, since the target of our study were patients with HF and DM, those with ischemic heart disease accounted for the most part, and the level of LVEF was low. In this regard, although there were no differences reflected in the indexes between the cardiac output and the stroke volume...
during the exercise, we could not go so far as to say that the influence affecting the decrease in exercise tolerance in the DM group was removed completely. We also could not find any difference in the medications, such as β blocker, that would affect the heart rate response between the 2 groups, but we could not go so far as to say that this influence was removed completely either. Thus, these issues remain to be resolved in future study.

4. Clinical implications

The presence or absence of complications of DM and the decrease of physical capability in patients with HF are also associated with re-hospitalization and life expectancy. Our expectation is that clarifying the influence of complications of DM on the exercise tolerance of patients with HF will allow for the implementation of cardiac rehabilitation interventions to deal with the cause later on, thereby improving exercise tolerance and life expectancy of patients with HF and comorbid DM.

Conclusions

In this study, we found that exercise tolerance and heart rate response was reduced in patients with HF and DM, as compared with patients without DM. In addition, sympathetic and parasympathetic nerve activities of patients with HF and DM were decreased during CPX, as compared with patients without DM. These findings might suggest that lower heart rate response caused by the decrease in autonomic nerve activities might be associated with the decrease of exercise tolerance in patients with HF and DM.

Acknowledgments: We thank the staff members of Sakakibara Heart Institute of Okayama and Hyogo University of Health Sciences who collaborated in this study.

Conflict of Interest: There is no conflict of interest to disclose.

References

1) Pfeffer MA, Swedberg K, et al.: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003; 362: 759-766.
2) Kannel WB, Hjortland M, et al.: Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974; 34: 29-34.
3) Fumelli P, Romagnoli F, et al.: Diabetes mellitus and chronic heart failure. Arch Gerontol Geriatr. 1996; 23: 277-281.
4) Varela-Roman A, Grigorian Shamagian L, et al.: Influence of diabetes on the survival of patients hospitalized with heart failure: a 12-year study. Eur J Heart Fail. 2005; 7: 859-864.
5) Rydén L, Grant PJ, et al.: ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013; 34: 3035-3087.
6) Koike A, Hiro M, et al.: Anaerobic metabolism as an indicator of aerobic function during exercise in cardiac patients. J Am Coll Cardiol. 1992; 20: 120-126.
7) Cahalin LP, Arena R, et al.: Predictors of abnormal heart rate recovery in patients with heart failure reduced and preserved ejection fraction. Eur J Prev Cardiol. 2014; 21: 906-914.
8) Baldi JC, Aoina JL, et al.: Reduced exercise arteriovenous O2 difference in Type 2 diabetes. J Appl Physiol. 2003; 94: 1033-1038.
9) Moser O, Tschakert G, et al.: Different Heart Rate Patterns During Cardio-Pulmonary Exercise (CPX) Testing in Individuals With Type 1 Diabetes. Front Endocrinol. 2018; 9: 585.
10) Hiraki K, Izawa K, et al.: Determinants of exercise capacity in acute myocardial infarction patients with diabetes mellitus. Jpn Physic Ther Ass. 2011; 38: 343-350. (In Japanese).
11) Izawa K, Tanabe K, et al.: Impaired chronotropic response to exercise in acute myocardial infarction patients with type 2 diabetes mellitus. Jpn Heart J. 2003; 44: 187-199.
12) Kasahara Y, Izawa K, et al.: Influence of autonomic nervous dysfunction characterizing effect of diabetes mellitus on heart rate response and exercise capacity in patients undergoing cardiac rehabilitation for acute myocardial infarction. Circ J. 2006; 70: 1017-1025.
13) American College of Sports Medicine: ACSM’s guidelines for exercise testing and prescription. 6th ed, Williams & Wilkins, Baltimore, 2000.
14) Beaver WL, Wasserman K, et al.: A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol. 1986; 60: 2020-2027.
15) Gulati M, Shaw LJ, et al.: Heart rate response to exercise stress testing in asymptomatic women: the st. James women take heart project. Circulation. 2010; 122: 130-137.
16) Ohtomo N, Kamo T, et al.: Power spectral densities of temporal variations of blood pressures. Jpn J Appl Physiol. 1996; 35: 5571-5582.
17) Bohannon RW: Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. Arch Phys Med Rehabil. 1997; 78: 26-32.
18) Ozdirenç M, Bibero lu S, et al.: Evaluation of physical fitness in patients with Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2003; 60: 171-176.
19) Fang ZY, Sharman J, et al.: Determinants of exercise capacity in patients with type 2 diabetes. Diabetes Care. 2005; 28: 1643-1648.
20) Tibb AS, Ennezat PV, et al.: Diabetes lowers aerobic capacity in heart failure. J Am Coll Cardiol. 2005; 46: 930-931.
21) Kremer CB, Levitt NS, et al.: Oxygen uptake kinetics during exercise in diabetic neuropathy. J Appl Physiol. 1988; 65: 2665-2671.
22) Roy TM, Peterson HR, et al.: Autonomic influence on cardio-
vascular performance in diabetic subjects. Am J Med. 1989; 87: 382-388.
23) Franciosa JA, Park M, et al.: Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol. 1981; 47: 33-39.
24) Sundstedt M, Hedberg P, et al.: Left ventricular volumes during exercise in endurance athletes assessed by contrast echocardiography. Acta Physiol Scand. 2004; 182: 45-51.
25) Andersen H, Nielsen S, et al.: Muscle strength in type 2 diabetes. Diabetes. 2004; 53: 1543-1548.
26) Robinson BF, Epstein SE, et al.: Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. Circ Res. 1966; 19: 400-411.
27) Bottini P, Tantucci C, et al.: Cardiovascular response to exercise in diabetic patients: influence of autonomic neuropathy of different severity. Diabetologia. 1995; 38: 244-250.
28) Bernardi L, Ricordi L, et al.: Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. Circulation. 1992; 86: 1443-1452.
29) Yu CM, Lau CP, et al.: Clinical predictors of morbidity and mortality in patients with myocardial infarction or revascularization who underwent cardiac rehabilitation, and importance of diabetes mellitus and exercise capacity. Am J Cardiol. 2000; 85: 344-349.