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Abstract

Indications for Heart Failure Therapy and Evaluations Early Rehabilitation

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A body of evidence has proved that exercise therapy for heart failure improves exercise tolerance and subjective symptoms such as shortness of breath, and that exercise therapy is effective in improving survival and reducing re-hospitalization. However, the severity and clinical state of heart failure vary among patients. Adequate caution has to be exercised when prescribing exercise therapy for patients with severe heart failure. In addition to exercises, cardiac rehabilitation as an interdisciplinary treatment modality including evaluation of living environment and activities of daily living, adherence to medication, and nutritional guidance has attracted increasing attention recently. To prevent recurrence and ensure quality of life, comprehensive management based on good understanding of the disease is very important.

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Cardiac Rehabilitation Outcome Following Percutaneous Coronary Intervention Compared to Cardiac Surgery

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Abstract: To examine differences in objective and subjective outcomes in outpatients undergoing percutaneous coronary intervention (PCI) performed for acute myocardial infarction versus cardiac surgery (CS) following a phase II cardiac rehabilitation (CR). Longitudinal observational study of 437 consecutive cardiac outpatients after 8 weeks of phase II CR. Patients were divided into the PCI group (n = 281) and CS group (n = 156). Handgrip and knee extensor muscle strength, peak oxygen uptake (VO_2), upper- and lower-body self-efficacy for physical activity (SEPA), and physical component summary (PCS) and mental component summary (MCS) scores as assessed by Short Form-36 were measured at 1 and 3 months after PCI or CS. All outcomes increased significantly between months 1 and 3 in both groups. However, increases were greater in the CS versus PCI group in handgrip strength (+12.3 % *vs.* +8.1%, $P < 0.01$), knee extensor muscle strength (+19.3% *vs.* +17.5%, $P = 0.008$), peak VO_2 (+20.9% *vs.* +16.9%, $P < 0.01$), upper-body SEPA (+27.7% *vs.* +9.2%, $P = 0.001$), and PCS score (+6.5% *vs.* +4.1%, $P = 0.001$). Although this relatively short-term phase II CR increased all outcomes for both groups, outcomes showed the recovery process was different between the PCI and CS groups, slightly favoring CS patients. Furthermore, patents in the field of CR are presented.

Keywords: Cardiac rehabilitation, cardiac surgery, health-related quality of life, muscle strength, percutaneous coronary intervention, self-efficacy for physical activity.

INTRODUCTION

Traditionally, the effects of cardiac rehabilitation (CR) programs on objective outcomes such as exercise capacity, muscle strength, and reduction in coronary risk factors have been reported in patients with cardiac disease following percutaneous coronary intervention (PCI) due to angina pectoris or acute myocardial infarction (AMI) and cardiac surgery (CS) such as coronary artery bypass grafting (CABG) and valve replacement (VR) [1-6]. It is very important to improve measurement of the reported goals of CR programs for these patients, which have been to improve self-efficacy for physical activity (SEPA), the measure of self-confidence for performance of given activities or tasks and which represents patients' perceptions of their capability to performing specific activities or tasks, and health-related quality of life (HRQOL), both of which are subjective outcomes [6-8]. Many previous reports suggest that phase II CR programs after PCI or CS improve the objective and subjective outcomes for patients [3-6, 9]. To our knowledge, however, few studies have investigated differences in objective outcomes of PCI and CS patients in regard to clinical characteristics, and, in particular, short-term objective and subjective outcomes in Japanese cardiac patients are unknown.

A recent previous report [9] suggested that for both post-AMI and post-CS patients alike, measures of exercise tolerance such as peak oxygen uptake (peak $\dot{V}O_2$) were significantly increased as assessed by cardiopulmonary exercise testing (CPX), and lower muscle strength in both AMI and CS patients was also improved at baseline and at 6 months following a phase II CR program. Thus, despite the benefits of long-term supervised-recovery phase II CR outpatient programs for objective outcomes, limited data is available on short-term differences in subjective outcomes between PCI and CS patients.

Therefore, we aimed to investigate 1) differences between Japanese PCI and CS patients in regard to objective outcome measures of handgrip strength, knee extensor muscle strength (KEMS), and peak VO_2, and subjective outcome measures of SEPA and HRQOL at baseline, and 2) whether differences in these outcomes can be recognized at 3 months after PCI or CS in patients participating in a short-term supervised-recovery phase II CR outpatient program.

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METHODS

Subjects and Study Design

The present longitudinal study comprised consecutive patients selected from outpatients completing a routine 3-week, acute, phase I inpatient CR program at St. Marianna University School of Medicine Hospital from October 2000 to November 2008. Exclusion criteria included New York Heart Association functional class IV, and neurological, pulmonary, peripheral vascular, orthopedic, preexisting extensive comorbidities (e.g. cancer), or changes in treatment concepts such as a change in medication. Inclusion criteria were age > 40 years, first AMI, post CABG or VR, and successful completion of handgrip and KEMS testing and CPX at entry into an exercise-based supervised-recovery phase II CR outpatient program beginning 1 month (T1) after PCI was performed for AMI or after CS.

At the end of the acute, phase I CR inpatient program, objective outcomes of 601 patients were assessed, and the patients underwent subjective outcome testing. The present study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research (Approval No. 356). Informed consent was obtained from each patient.

Clinical Characteristics

We evaluated patient age, sex, body mass index (BMI), education, marital and employment status, left ventri-cular ejection fraction (LVEF), and medications. A cardio-logist assessed cardiac function and cardiac disease severity by echocardiographic measurement of LVEF. All patients underwent standard M-mode echocardiography (Apio, Toshiba, Tokyo, Japan) with a 3.5MHz transducer in the parasternal long-axis view to obtain the LVEF, as described elsewhere [4, 5].

Objective Outcomes Measurement

Handgrip strength, KEMS, and peak $\dot{V}O_2$ were measured to assess objective outcomes of each patient after PCI and CS at T1 and 3 months after PCI or CS (T2). Handgrip strength was measured by standard adjustable-handle JAMAR dynamometer (Bissell Healthcare Co., Grand Rapids, MI) that was set at the second grip position for all subjects [10, 11]. Attention was paid to a possible Valsalva effect, and measurements were made three times each on both hands. The index of handgrip strength was calculated by averaging the highest value of three measurements of the right- plus left-side handgrip strength / 2(kgf).

KEMS was measured by the Biodex System 2 isokinetic dynamometer (Biodex Medical Systems, Inc., New York, NY), and a maximum of five repetitions of knee extensions was performed at isokinetic speeds of 60°/sec [4,5]. Isokinetic test results were analyzed with Biodex System 2 software. After measurement, the index of KEMS was calculated by averaging the highest value of the right- plus left-side KEMS / 2(Nm/kg).

Symptom-limited exercise testing was performed on a MAT-2500 treadmill (Fukuda Denshi Co., Tokyo, Japan). Continuous monitoring of 12-lead ECG and calculation of heart rate during testing was performed with an ML-5000 ECG system (Fukuda Denshi Co.). The endpoint of exercise testing was determined according to the criteria of the American College of Sports Medicine [12]. Peak VO_2 was measured during the exercise period with an AE-300S aero monitor (Minato Ikagaku Co., Tokyo, Japan) and calculated with a personal computer.

Subjective Outcomes Measurement

SEPA and HRQOL tests were used to assess subjective outcomes of each patient at T1 and T2. SEPA was measured with the Japanese test version because of its reliability and validity [6, 7]. SEPA testing consists of 4 subscales: domains of walking, stair climbing, weight lifting, and push off. After testing the four domains, upper-body SEPA (U-SEPA) score (average scores of weight lifting + push off / 2) and lower-body SEPA (L-SEPA) score (average scores of walking + stair climbing / 2) were calculated. U-SEPA and L-SEPA subscale scores range from 0 to 100, with lower scores indicating poorer levels of SEPA [6, 7].

HRQOL was assessed with the Japanese version of the Medical Outcome Study 36-Item Short Form Health Survey (SF-36) consisting of 36 items representing 8 subscales covering the domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health [13]. It measures multi-dimensional properties of HRQOL on a 0 to 100 scale with higher scores representing higher HRQOL. The eight subscales in the SF-36 were further combined into the physical component summary (PCS) score and the mental component summary (MCS) score.

Exercise-Based Supervised-recovery Phase II CR Out-Patient Program

The 8-week exercise-based supervised-recovery phase II CR outpatient program continued until T2 and was customized for each patient based on the results of CPX and strength testing performed at the end of the acute, phase I CR inpatient program. At our hospital, physical therapists play a central role in the supervision of endurance and resistance exercise training in the exercise component of phase I and II CR. Patients participated in combined supervised endurance and resistance exercise training twice a week for 1 hour that comprised warm-up, resistance training, endurance exercise, and cool-down periods, as described elsewhere [4,5]. Exercise intensity during endurance exercise was maintained at anaerobic threshold heart-rate level during treadmill walking at a perceived exertion rating of 11 to 13.

Resistance training comprised four sets of two upper extremity exercises (shoulder flexion and abduction from anatomic position) each performed with an iron weight array and handgrip at a resistance allowing completion of 5-10 repetitions with a 30-40% of 1 repetition maximum. Four sets of knee extensions, flexions, squats, and calf raises comprised the lower extremity exercises. Knee extension and flexion was performed with an ankle weight and at a resistance that allowed completion of 5-10 repetitions with a 40-60% of 1 repetition maximum. Exercise intensity for squats and calf raises was maintained at a perceived exertion rating of 11 to 13.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Unpaired *t*-test and χ^2 test were used to analyze differences in patient clinical profiles because comparisons between the PCI and CS groups were performed for handgrip, KEMS, and peak VO_2. Unpaired *t*-test was also used to test for differences in average U- and L-SEPA and SF-36 PCS and MCS scores between the two independent groups. Data at T1 and T2 were compared in each group by paired *t*-tests, and the changes in data between groups were analyzed with 2-factor (data at T1 and T2, and PCI *vs*. CS groups) repeated measures of analysis of variance with repeated measures in 1 factor (data T1 and T2), as described elsewhere [14, 15]. A *P*-value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 12.0J statistical software (SPSS Japan, Inc., Tokyo, Japan).

RESULTS

Study Participants

Flow of the participants through the present study is shown in Fig. (**1**). Of the 601 patients, 53 were excluded at T1 due to inability to measure handgrip and KEMS or peak VO_2 or because of inappropriate responses, such as missing data or answering the same question twice, to the subjective outcome tests. Therefore, 548 patients were recommended for participation in a supervised-recovery phase II CR outpatient program. However, 111 of these 548 patients were excluded due to refusal to undergo exercise testing or assessment of objective outcomes at T2 because they lived too far from the hospital or were too busy at work. Thus, we compared the differences in objective and subjective outcomes measured at T1 and T2 and the benefits gained from an exercise-based supervised-recovery phase II CR outpatient program from T1 to T2 in 437 patients comprising two groups: PCI group (n = 281) and CS group (n = 156; CABG, n = 109, VR, n = 47).

Clinical Characteristics

Clinical characteristics of all patients and differences between the PCI and CS groups at T1 are summarized in Table **1**. Age, sex, BMI, educational, marital status, employment status, LVEF, and medications were almost identical between the two groups.

Objective and Subjective Outcomes at T1

Objective outcome data collected from the two groups are presented in Table **2**. No patient showed ischemic ST changes or experienced chest pain or serious arrhythmia during CPX following the phase II CR outpatient program. Comparisons were performed across the two groups after muscle strength testing and CPX. Handgrip strength, KEMS, and peak VO_2 values in the CS group were all significantly lower than those in the PCI group (all $P < 0.05$).

U-SEPA, L-SEPA, and SF-36 PCS and MCS scores between the two groups at T1 are presented in Table **3**. U-SEPA and L-SEPA scores in the CS group patients were significantly lower than those in the PCI group patients ($P < 0.05$). PCS scores were significantly lower in the CS group than in the PCI group ($P < 0.05$). However, there was no significant difference in MCS scores between the CS and PCI groups.

Objective Outcomes Following CR

Following the phase II CR outpatient program, the PCI group showed statistically significant increases in handgrip strength (+8.1%, $P < 0.05$), KEMS (+17.5%, $P < 0.05$), and peak VO_2 (+16.9%, $P < 0.05$) from T1 to T2 Table **2**. Statistically significant increases also occurred in the CS group in

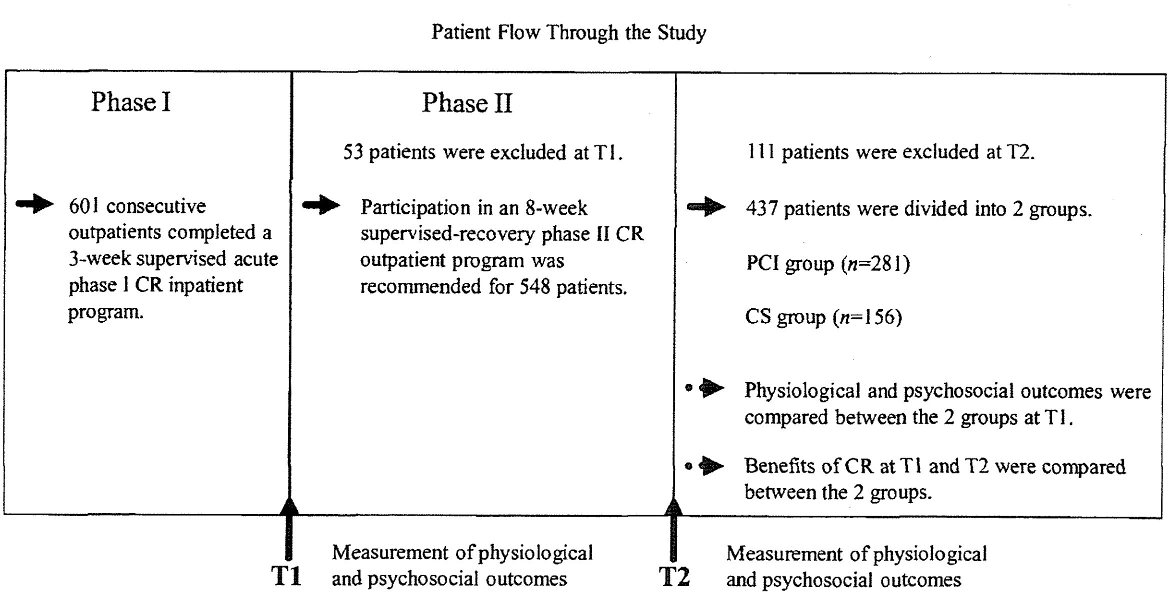

Fig. (1). Diagram of participant flow through the present study. CR - cardiac rehabilitation; CS - cardiac surgery; PCI - percutaneous coronary intervention; T1 - Time point at 1 month after PCI or CS; T2 - Time point at 3 months after PCI or CS.

Table 1. Clinical Characteristics of the Patients.

	PCI Group (n = 281)	CS Group (n = 156)	t or χ^2 Value	P-Value
Age (yrs.)	61.3 (10.1)	62.5 (10.0)	0.3	0.699
Male (%)	83.6	80.9	1.7*	0.098
BMI (kg/m²)	23.5 (2.9)	22.4 (2.4)	1.9	0.079
Education (yrs.)	13.1 (2.6)	12.4 (2.7)	1.7	0.086
Marital status (%)	83.7	88.9	2.1*	0.142
Employment status (%)	52.2	47.1	1.0*	0.315
LVEF (%)	51.9 (10.3)	52.2 (12.2)	0.1	0.910
Medications (%)				
B-Blockers	75.6	66.7	0.7*	0.387
ARB&ACEI	78.9	63.6	2.6*	0.102
Diuretic	30.4	42.4	1.5*	0.220

*χ^2 value.
BMI - Body mass index; CS - Cardiac surgery; LVEF - Left ventricular ejection fraction; PCI - Percutaneous coronary intervention; ARB - Angiotensin receptor blocker; ACEI - Angiotensin converting enzyme inhibitor.

Table 2. Differences in Objective Outcomes at T1 and T2.

	PCI Group (n = 281)			CS Group (n = 156)			F-Valne	P-Value
	T1	T2	%Change	T1	T2	%Change	Interaction	
Handgrip (kgf)	35.1 (9.5)	37.9 (9.7)*	+8.1	30.2 (8.1)$	33.9 (8.4)$*	+12.3	21.2	< 0.001
KEMS (Nm/kg)	1.60 (0.4)	1.88 (0.4)*	+17.5	1.50 (0.3)$	1.79 (0.4)$*	+19.3	8.8	0.008
Peak $\dot{V}O_2$ (L/kg/min)	23.0 (5.0)	26.9 (5.8)*	+16.9	20.1 (4.6)$	24.3 (5.3)$*	+20.9	14.5	< 0.001

Statistical analysis: $P < 0.05 between groups; *P < 0.05 between terms.
CS - Cardiac surgery; KEMS - Knee extensor muscle strength; PCI - Percutaneous coronary intervention; T1 - 1 Month after PCI or CS; T2 - 3 Months after PCI or CS.

handgrip strength (+12.3%, $P < 0.05$), KEMS (+19.3%, $P < 0.05$), and peak $\dot{V}O_2$ (+20.9%, $P < 0.05$) from T1 to T2 Table 2. Significant period (from T1 to T2) by group (PCI group and CS group) interactions in handgrip strength (F = 21.2, $P < 0.001$), KEMS (F = 8.8, $P = 0.008$), and peak $\dot{V}O_2$ (F = 14.5, $P < 0.001$) were detected. Therefore, a significant percent change occurred in response to the phase II CR outpatient program with the CS group showing greater increases in handgrip strength, KEMS, and peak $\dot{V}O_2$ than did the PCI group.

Subjective Outcomes Following CR

Following the phase II CR outpatient program, statistically significant increases from T1 to T2 occurred in both the PCI group in U-SEPA (+9.2%, $P < 0.05$), L-SEPA (+14.2%, $P < 0.05$), PCS (+4.1%, $P < 0.05$), and MCS scores (+4.6%, $P < 0.05$) and in the CS group in U-SEPA (+27.7%, $P < 0.05$), L-SEPA (+19.1%, $P < 0.05$), PCS (+6.5%, $P < 0.05$), and MCS scores (+5.1%, $p < 0.05$). Significant period by group interactions in U-SEPA (F = 23.4, $P < 0.001$) and PCS scores (F = 10.6, $P < 0.001$) were detected, as shown in Table 3. However, there were no significant period by group interactions in L-SEPA (F = 1.4, $P = 0.225$) and MCS scores (F = 0.1, $P = 0.749$). Therefore, a significant percent change occurred in response to CR with the CS group showing greater increases in U-SEPA and PCS scores than did the PCI group.

DISCUSSION

The present study found that in measurements of objective and subjective outcomes, the CS group had lower handgrip, KEMS, and peak VO_2 values and lower U-SEPA, L-SEPA, and PCS scores than did the PCI group at entrance into an exercise-based supervised-recovery phase II CR outpatient program. However, the MCS score was not different between the two groups. Additionally, although significant increases occurred in all objective and subjective outcomes in both groups from T1 to T2, handgrip strength, KEMS, and peak VO_2 and U-SEPA and PCS scores in the CS group were greater than those in the PCI group. Thus, differences did occur between the two groups in measures of

Table 3. Differences in Subjective Outcomes at T1 and T2.

	PCI Group (*n*=281)			CS Group (*n*=156)			*F*-value	*P*-value
	T1	T2	% Change	T1	T2	% Change	Interaction	
SEPA								
U-SEPA	63.1(26.3)	68.9(23.0)#	+9.2	45.7(26.5)§	58.4(23.3)§#	+27.7	23.4	< 0.001
L-SEPA	68.2(20.7)	77.9(17.2)#	+14.2	61.7(23.5)§	73.5(22.2)§#	+19.1	1.4	0.225
HRQOL								
PCS	46.0(6.6)	47.9(4.9)#	+4.1	43.1(6.9)§	45.9(6.1)§#	+6.5	10.6	< 0.001
MCS	49.6(9.0)	51.9(7.0)#	+4.6	48.9(8.9)	51.4(7.5)#	+5.1	0.1	0.749

Statistical analysis: §P < 0.05 between groups. #P < 0.05 between terms.
CS - Cardiac surgery: HRQOL - Health-related quality of life; L-SEPA - Lower-body self-efficacy for physical activity; MCS - Mental component summary score: PCI - Percutaneous coronary intervention: PCS - Physical component summary score: T1 - 1 Month after PCI or CS: T2 - 3 Months after PCI or CS; U-SEPA - Upper-body self-efficacy for physical activity.

objective and subjective outcome during the recovery process following a phase II CR program.

Differences in Outcomes at T1

Previous studies reported that peak VO_2, handgrip strength and KEMS relate to prognosis, physical function, and HRQOL, as well as to the ability of an individual to perform the physical tasks necessary for daily living in cardiac patients [4-7]. Other previous studies have reported that CS patients consistently tend to have lower physiological outcomes than do other cardiac patients such as post-PCI or MI patients [9, 16]. Sumide *et al.* [9] reported that baseline exercise tolerance (peak VO_2) and lower-limb muscle strength measured in 104 cardiac patients entering phase II CR were decreased in CS patients compared to MI patients. Mroszczyk-McDonald *et al.* [16] reported that baseline handgrip strength measured with the same equipment used in the present study was lower in CABG patients than in patients with other diagnoses such as MI. Peak VO_2, handgrip, and KEMS values in the CS group were significantly lower than those in the PCI group, which strongly supports their findings. One reason for these findings may be that in comparison to that of PCI patients, leisure-time physical activity in the daily life of CS patients may be different due to shortness of breath on effort caused by coronary artery or valve problems in these patients before they undergo CS. Another reason may be that PCI was due to AMI, which is different than the kind of disease pre-existing in CS patients. We did not evaluate the daily life of our patients prior to undergoing CS or PCI; thus, future study may be required.

The extremely low objective outcomes scores of our patients, particularly those of the CS patients, on entry into phase II CR underscore the fact that one important goal of CR after a major cardiac event is improvement in physical function and prognosis. Particularly, CS has a significant impact on handgrip strength [16]. Weak handgrip strength and KEMS is associated with both the incidence and prevalence of disability, suggesting that loss of muscle mass and volitional muscle strength can be both a cause and a consequence of physical disability [16-18]. Resistance training should be enforced by concentrating on improving both upper- and lower-extremity muscle strength in CS patients.

With regard to subjective outcomes at baseline, U- and L-SEPA scores and HRQOL PCS scores in the CS group were also lower than those in the PCI group. Previous reports suggest a cross-sectional correlation between peak VO_2, handgrip strength, KEMS, self-efficacy, and HRQOL [7, 8]. In the present study, handgrip strength, KEMS, and peak VO_2 values in the CS group were lower than those in the PCI group, suggesting that these HRQOL scores may also be related to objective outcomes on entry into CR. However, the SF-36 MCS scores of the CS group were not significantly lower than those of the PCI group at T1. SF-36 MCS scores in CS and PCI patients are related to several factors such as lack of social support, anxiety and depression status, and ability to return to work after CS or PCI [5, 18]. In the present study, 47.1% of CS patients and 52.2% of PCI patients were employed before CS or PCI. A possible goal for some patients suffering a cardiac event is return to regular employment soon after discharge from hospital; however, the number of patients returning to work after hospital discharge is considered low, even in younger patients experiencing a short hospitalization [18]. In the present study, at T1, approximately 3 weeks after PCI or CS, many patients might not have been able to return to work. We did not investigate this or how it might relate to SF-36 MCS scores. Further study is required to evaluate the relation between these factors.

Differences in Objective and Subjective Outcomes Following CR

Attendance at exercise-based supervised-recovery phase II CR outpatient programs was shown to benefit objective and subjective outcomes from T1 to T2 in both groups. Previous reports suggested that such phase II CR outpatient programs for cardiac patients following AMI, CABG, and VR individually increase objective outcomes similar to those found in the present study [4, 5]. Important in the present study is that although all objective outcomes were lower in the CS group than in the PCI group at T2, there was a difference in the recovery process between groups in regard to handgrip strength, KEMS, and peak VO_2, all of which showed greater percent change in the CS than PCI group.

Although the data is inadequate to explain this difference in the recovery process between the two patient groups, a possible explanation might be that surgical patients require longer convalescence than do patients who do not undergo surgery [16]. Particularly, the percent change in handgrip strength in the CS group was greater than were changes in KEMS and peak VO_2. Compared to PCI patients, CS patients may either be limited in the amount of upper-extremity exercise training they can do while hospitalized, or they may limit upper-extremity use during daily living due to bone damage to the chest wall or injury to soft tissue in the shoulders and arms following CS [17]. However, our phase II CR outpatient program required middle-intensity effort during upper- and lower-extremity resistance training. Resistance training leads to neural adaptation and muscle hypertrophy [19]. Moreover, previous studies suggest a cross-sectional positive correlation between peak VO_2 and muscle strength in CS [9] and heart failure patients [20]. Percent change in objective outcomes increased in both groups in our study; however, this may be more an effective measure of the recovery process in CS patients versus PCI patients during exercise-based supervised-recovery phase II CR.

Significant increases in subjective outcomes measures of U-SEPA, L-SEPA, and SF-36 PCS and MCS scores occurred from T1 to T2 in both groups. One most important contribution of phase II CR outpatient programs may be to increase patient sense of well-being and self-efficacy, which should translate into enhanced QOL [21]. Previous reports suggest beneficial effects of resistance training on psychological well-being and quality of life in heart disease patients [22]. Arthur *et al.* [23] previously reported the effect of aerobic versus combined aerobic strength training over 1 year in women and suggested that perceived self-efficacy may be the mechanism through which both exercise modalities affected 6-month physical HRQOL. However, there was no placebo control in the present study, and we did not we confirm difference effects of both aerobic exercise and resistance training for self-efficacy and HRQOL. The combination of aerobic exercise and resistance training components in the present study might have affected the differences in subjective outcomes of SEPA and HRQOL between T1 and T2 in both groups.

Regardless of the percent change increases in U-SEPA, L-SEPA, and SF-36 PCS scores, the scores in the CS group during the recovery process were greater than those in the PCI group. Particularly, percent change in U-SEPA in CS patients versus PCI patients was 27.7% versus 9.2%, and L-SEPA was 19.1% versus 14.3%, respectively. Exercise of both the upper and lower extremities is important in helping patients regain strength and range of motion in the upper extremities and for returning to work or the activities of daily living [24].

Objective outcomes measures of handgrip strength and KEMS increased more greatly in the CS group than in the PCI group. Mroszczyk-McDonald *et al.* [16] reported that increase in handgrip strength in cardiac outpatients was associated with an increase in HRQOL. We also previously reported that increases in handgrip strength and KEMS in middle-aged and older-aged cardiac outpatients were associated with an increase in HRQOL [15]. Increase of objective outcomes in the CS group may have resulted in higher U-SEPA, L-SEPA, and SF-36 PCS scores in this group, indicating that increase of objective and subjective outcomes may offer greater clinical benefit to CS rather than PCI patients. SF-36 MCS scores were not different between the two groups, however, indicating that the recovery process may not affect the mental status of CS and PCI patients differently. The mental component of HRQOL is related not only to self-efficacy but to many other factors, such as social support, anxiety, and depression, for example [6-8].

There are several limitations in the present study. First, a control group was not included, so a more longitudinal study and evaluation of the effect of phase II CR outpatient programs on objective and subjective outcomes over the long term after CR is necessary. Second, many patients were excluded, particularly younger (< 40 years) patients, seriously ill patients (NYHA IV), and patients with coexisting illness such as neurological, pulmonary, peripheral vascular, or orthopedic disease. Finally, one other limitation is the patient population: the patients were mostly male and were not overweight. Thus, we do not know exactly whether the results would be the same in females or in overweight or obese patients in the present study. Despite these limitations, we believe that the current data support the beneficial differential effect of short-term phase II CR outpatient programs on objective and subjective outcomes for CS and PCI patients and that the sample size was large enough to yield significant results from the test instrument scores.

CONCLUSIONS

In conclusion, the present study identified differences in objective and subjective outcomes in PCI and CS patients at baseline and after undergoing a short-term exercise-based supervised-recovery phase II CR outpatient program. Baseline differences in outcomes indicated that CS patients may have lower strength, peak VO_2, and U-SEPA, L-SEPA and HRQOL PCS scores than PCI cardiac patients on entrance into such phase II CR outpatients programs. However, the HRQOL MCS scores of the two groups were not different at program entry. The exercise-based supervised-recovery phase II CR outpatient program was shown to have increase for all objective and subjective outcomes at T2 in both post-PCI and post-CS patient groups. However, there was a difference in the recovery process between groups in regard to handgrip strength, KEMS, and peak VO_2 values, all of which showed greater percent change in the CS group than in the PCI group. Increases in U-SEPA and SF-36 PCS scores in the CS group during the recovery process were also greater in the CS group. Although this relatively short-term phase II CR outpatient program increased all outcomes in both groups, the recovery process related to objective and subjective outcomes between the two groups was different and appeared to slightly favor CS patients.

CURRENT & FUTURE DEVELOPMENTS

The present study identified differences in objective and subjective outcomes in PCI and CS patients at baseline and after undergoing a short-term exercise-based supervised-recovery phase II CR outpatient program. Although this relatively short-term phase II CR outpatient program increased all outcomes in both groups, the recovery process related to objective and subjective outcomes between the two groups was different and appeared to slightly favor CS patients. However, in the present study, a control group was not included, so a more longitudinal study and evaluation of the effect of phase II CR outpatient programs on objective and subjective outcomes over the long term after CR is necessary. The patients were mostly male and were not overweight. Thus, we do not know exactly whether the results would be the same in females or in overweight or obese patients in the present study. Therefore, future trials are needed to evaluate whether these factors influence long-term outcomes and affect differences in PCI and CS patients over longer periods.

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CONFLICT OF INTEREST

Financial disclosure statements have been obtained, and no conflicts of interest have been reported by the authors or by any individuals in control of the content of this article.

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ORIGINAL INVESTIGATION

Global longitudinal strain by two-dimensional speckle tracking imaging predicts exercise capacity in patients with chronic heart failure

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Abstract
Background Left ventricular ejection fraction (LVEF) predicts mortality in patients with chronic heart failure (CHF). However, a weak correlation was found between LVEF and peak oxygen uptake ($\dot{V}O_2$) in CHF patients. Global longitudinal strain measured by two-dimensional (2D) strain is regarded as a more useful predictor of cardiac events than LVEF. We investigated whether 2D strain obtained at rest could predict peak $\dot{V}O_2$ in patients with CHF.
Methods Fifty-one patients (mean age of 54.0 ± 12.0 years, 14 females, LVEF 46.0 ± 15.0%) with stable CHF underwent resting echocardiography and cardiopulmonary exercise testing. Leg muscle strength was measured for the evaluation of peripheral factors. Global longitudinal strain (GLS) in the apical 4-, 3-, and 2-chamber views and global circumferential strain (GCS) in the parasternal mid short-axis view were measured.
Results In all patients, peak $\dot{V}O_2$ correlated with leg muscle strength ($r = 0.55$, $p < 0.0001$), LVEF ($r = 0.46$, $p < 0.001$), GLS ($r = -0.45$, $p < 0.001$), and GCS ($r = -0.41$, $p = 0.005$), respectively. No significant correlation was found between the ratio of early transmitral velocity to peak early diastolic mitral annulus velocity (E/E') and peak $\dot{V}O_2$. In the patients with heart failure and reduced LVEF, a multiple stepwise linear regression analysis based on leg muscle strength, LVEF, E/E', GLS, and GCS was performed to identify independent predictors of peak $\dot{V}O_2$, resulting in leg muscle strength and GLS ($R^2 = 0.888$) as independent predictors of peak $\dot{V}O_2$.
Conclusion Global longitudinal strain at rest could possibly predict exercise capacity, which appeared to be more useful than LVEF, E/E', and GCS in CHF patients with reduced LVEF.

Keywords Chronic heart failure · Exercise capacity · Ejection fraction · Speckle tracking imaging · Strain

Introduction

Chronic heart failure (CHF) is characterized by impaired exercise capacity, fatigue, and exertional dyspnea. Peak oxygen uptake (peak $\dot{V}O_2$) obtained from the results of cardiopulmonary exercise testing (CPX) is a useful index of exercise capacity and a strong prognostic indicator of mortality in patients with CHF [1]. Peak $\dot{V}O_2$ is defined by (1) a central component, cardiac output that describes the capacity of the heart to function as a pump and (2) peripheral factors (arteriovenous oxygen difference) that describe the capacity of the lung to oxygenate the blood delivered to it and the capacity of the working muscle to extract this oxygen from the blood. In particular, leg muscle strength, one of the peripheral factors, has been considered to be closely related to exercise capacity in patients with CHF [2, 3].

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Left ventricular ejection fraction (LVEF) has been regarded as the most extensively investigated echocardiographic parameter as a surrogate parameter of cardiac output. However, earlier studies reported LVEF is poorly associated with exercise capacity in patients with CHF [4–7], and its association remains unclear.

Recently, the reliability and reproducibility of echocardiography were improved by quantitative techniques; e.g., this is well demonstrated in the speckle tracking method which automatically obtains deformation measurements based on pure-gray ultrasound images. Brown et al. [8] reported that global longitudinal strain predicts cardiac output, measured by magnetic resonance imaging, more accurately than echocardiographic LVEF. Some studies also noted that two-dimensional (2D) strain is superior to LVEF for predicting all-cause mortality in patients with CHF [9, 10].

Here, this study tested the hypothesis that 2D strain obtained at rest could predict exercise capacity in patients with CHF.

Materials and methods

Subjects

This prospective study included 51 patients with CHF who underwent physical examination, 12-lead electrocardiography, comprehensive 2D echocardiography, and CPX. All patients were clinically stable: none were hospitalized within the last 1 month before enrollment. Patients with organic valvular disease, chronic obstructive pulmonary disease, atrial fibrillation, and paced rhythm were excluded. Ischemic heart disease was determined when a patient had either evidence of previous myocardial infarction or significant coronary artery disease detected by coronary angiography (stenosis > 50% in one of the major epicardial coronary arteries). No patients had a recent history of acute coronary syndrome or a revascularization procedure within the last 3 months. The patients were classified into the two groups on an LVEF basis, patients with heart failure and reduced LVEF (HFREF group; EF < 50%, $n = 23$) or those with heart failure and preserved LVEF (HFPEF; EF $\geq$ 50%, $n = 28$).

Ethics

The study protocol was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research (No. 340) in Kanagawa, Japan. Written informed consent was obtained from all patients prior to their enrollment.

Echocardiography

Echocardiography was performed in the left lateral decubitus position using a commercially available system (Vivid E9, General Electric-Vingmed, Milwaukee, Wisconsin). Images were obtained by using a 3.5-MHz transducer in the parasternal and apical views (apical long-axis, 2-chamber, and 4-chamber views). Recordings were performed according to the standard recommendations [11]. LVEF was calculated according to the biplane Simpson's method in apical 4- and 2-chamber views. The ratio of early (E) to late (A) transmitral velocities (E/A) and deceleration time of the E velocity were obtained by pulsed wave Doppler in the apical 4-chamber view. Peak early diastolic mitral annular velocity (E') was derived from the mean values obtained at the both septal and lateral mitral annulus in the apical 4-chamber view by placing sample volume at a sample size of 8 mm. The grade of mitral regurgitation (MR) was determined from color and continuous wave Doppler recordings based on the regurgitation flow intensity and classified into five grades [12]. Grade 0 denoted no regurgitation or regurgitation limited to a very small part of early systole; grade 1 indicated mild regurgitation weakly visible during the whole of systole; grade 2 was moderate regurgitation clearly visible throughout systole; grade 3 was defined by large regurgitation intensely visible during the whole of systole; and grade 4 was severe regurgitation as found, for example, in chordal rupture.

2D speckle tracking echocardiography

Global longitudinal strain (GLS) and circumferential strain (GCS) in the LV were quantified with 2D strain images [13]. We routinely checked for any foreshortening of the LV and ensured that 3 apical views did not differ by 10% of each LV long-axis length. A difference of 10% in 3 lengths would suggest the possibility of LV foreshortening in one view; in such a case, we measured LV long-axis length again to ensure accuracy. At least 3 cardiac cycles were acquired in each axis and view, and the highest quality view was used to measure strain. Images were digitally stored in the cine-loop format and transferred to commercially available software (EchoPac 8.0.0, GE Medical Systems, Horten, Norway) for off-line analysis to obtain LV strain. The software analyzes motion by tracking speckles in the ultrasonic images. Frame-to-frame changes of the speckles were used to derive motion and velocity; 1 single cardiac cycle was acquired in each view. The closure of the aortic valve was marked; the software measured the time interval between R wave and aortic valve closure. The automated algorithm provided peak systolic strain for each segment. GLS was averaged from the 3 apical views; GCS was measured at the papillary muscle level in the parasternal short-axis view. In general, GLS and GCS values have been presented as negative values; a larger negative value indicated a larger extent of longitudinal strain. The mean frame rate of the obtained images was 70 fps (range 40–100 fps; Fig. 1).

CPX

All patients underwent CPX on a sitting cycle ergometer (Accura, Mitsubishi Electrical Engineering, Co., Tokyo, Japan) on different days within 2 weeks (mean ± SD 8.4 ± 2.2 days) before/after echocardiography and they did not have any changes in prescribed drugs. During the study period, no patients had cardiac events. After 3-min rest and 4-min warm up at 20 W, exercise load intensity was gradually and linearly increased by 1 or 2 W per 6 s according to the gradual increase intensity. A stress test system (ML-9000: Fukuda Denshi Co., Tokyo, Japan) monitored blood pressure, and 12-lead electrocardiography recorded heart rate response, ST-T changes, and arrhythmias every 1 min during CPX. Peripheral factors were assessed by measuring leg muscle strength with the Biodex System 2 isokinetic dynamometer (Biodex Medical Systems, Inc., New York, USA; Fig. 2a). Testing was performed at a maximum of 5 repetitions for knee extensors at isokinetic speeds of 60° per s. We measured the knee extensor muscle strength peak torque per body weight value (N m/kg) of both knees and used the maximum value obtained as the index of knee extensor muscle strength (Fig. 2b).

The criteria to halt the test were determined according to the guidelines described by the American College of Sports Medicine [14] or the appearance of so-called leveling off in which no increase in oxygen uptake was recognized in spite of an increase of exercise intensity. Expired gas analysis was performed continuously throughout the exercise testing on a breath-by-breath basis with an AE-300 cart (Minato Medical Science, Osaka, Japan). Anaerobic threshold, peak $\dot{V}O_2$, and the slope of the ventilatory equivalent to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$) were collected from the results of CPX. Blood samples were obtained just before CPX for measurements of brain natriuretic peptide (BNP).

Statistical analysis

A statistical analysis was performed with commercially available software (SPSS 18.0 software, SPSS Inc., Chicago, IL, USA). All continuous data were expressed as mean ± SD and categorical data in percentages. An unpaired Student's t test and a χ^2 test were used in comparison between the two groups. A multiple stepwise regression analysis evaluated the relationship between peak $\dot{V}O_2$ and echocardiographic parameters. Statistical significance was established at $p < 0.05$. A simple regression

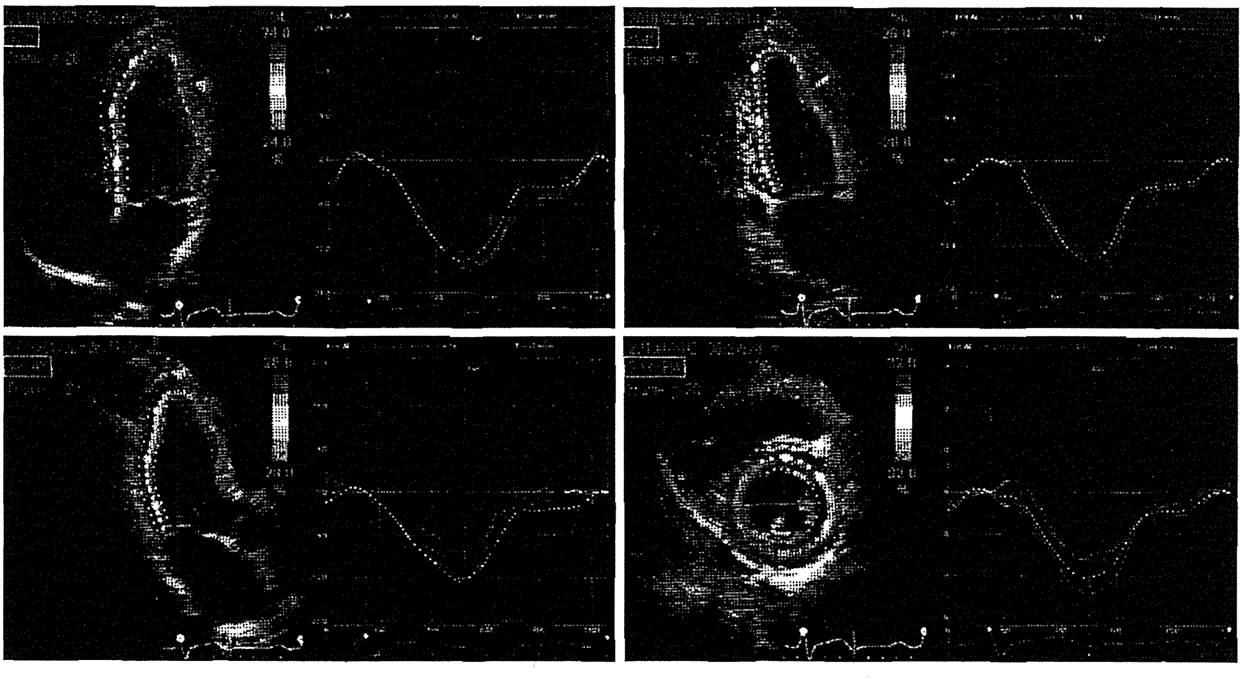

Fig. 1 Examples of global longitudinal strain measures from 3 standard apical views and global circumferential strain measures from the papillary muscle level in the parasternal short-axis view. The images obtained in the 4-chamber (*top left*), 2-chamber (*top right*), apical long-axis (*bottom left*), and short-axis (*bottom right*) are shown. The *color curves* indicate color-coded segmental strain and *dashed line* indicate global strain (color figure online)

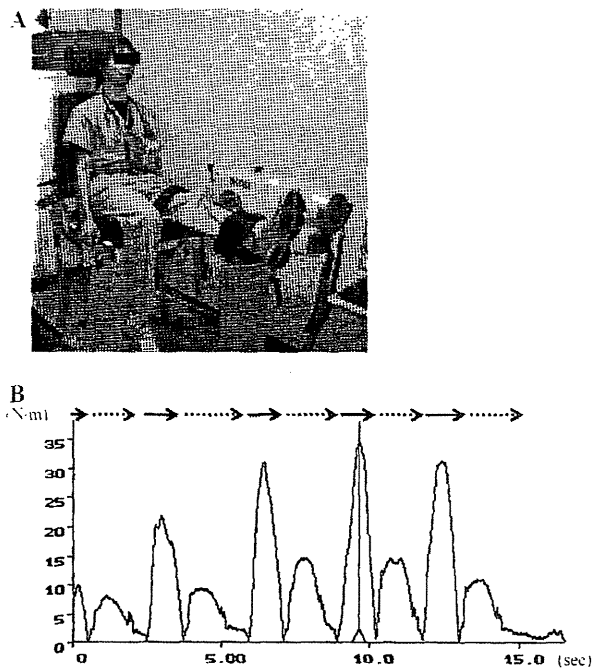

Fig. 2 **a** Measurements of leg muscle strength peripheral factors were assessed by measuring leg muscle strength with the Biodex System 2 isokinetic dynamometer (Biodex Medical Systems, Inc., New York, USA). **b** Measurements of the maximum leg muscle strength. The *curves* indicate knee extensor and flexor muscle strength torque; both values are expressed as positive values. *Continuous lines* depict the extension period and *dashed lines* indicate the flexion period. The maximum value during the extension period was measured. In this representative case, peak torque was 34.3 N m in the 4th extension period

analysis was performed to find parameters that had significant correlations with peak $\dot{V}O_2$. Reproducibility of GLS was analyzed with repeated measurements of GLS. Observer 1 measured and analyzed GLS of all patients at two different time points; meanwhile, observer 2 analyzed GLS of 25 randomly selected study patients. The two observers were blinded to the results obtained by the other observer. The limits of agreement for the Bland–Altman [15] analysis were calculated. Furthermore, intraclass correlation coefficient was calculated to assess reproducibility.

Results

Baseline characteristics

The study protocol was successfully completed, and technically adequate recordings were obtained for analysis in all patients (Table 1). The mean age was 54.0 ± 12.0 years. Of the study patients, 36 patients were in functional NYHA class I, 11 in class II, and 4 in class III. No significant differences in the age, gender, body mass index, or leg muscle strength were found between the HFREF and HFPEF groups. The HFREF group showed a significantly reduced anaerobic threshold and peak $\dot{V}O_2$, higher NYHA class, and increased BNP compared with the HFPEF group. Approximately 90% of the patients took β-blockers, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blocker (ARB). The number of patients who received ARB or diuretics was greater in the HFREF group than the HFPEF group.

Echocardiography

The left atrial and ventricular size, except LV end-diastolic volume, significantly increased in the HFREF group compared with the HFPEF group (Table 2). The LV wall thickness, *E/A*, deceleration time, *E′*, and *E/E′* were similar. The number of patients with MR grade 2 was greater in the HFREF group than HFPEF group; however, patients with MR grade 3 or above were not included in this study.

The GLS (−11.0 ± 4.5 vs. −19.2 ± 6.9%) and GCS (−10.2 ± 4.9 vs. −18.5 ± 6.9%, all $p < 0.0001$) were significantly lower in the HFREF than HFPEF group.

Predictors of peak $\dot{V}O_2$

In all study patients, peak $\dot{V}O_2$ correlated with muscle strength ($r = 0.55$, $p < 0.0001$), LVEF ($r = 0.45$, $p < 0.001$), GLS ($r = -0.47$, $p < 0.001$), and GCS ($r = -0.41$, $p < 0.005$), respectively (Table 3). No significant correlation was found between *E/A*, *E′*, deceleration time, *E/E′*, or peak $\dot{V}O_2$. Left atrial volume index (LAVI) showed significant correlation with peak $\dot{V}O_2$ ($r = -0.50$, $p < 0.001$). No significant correlation was found between peak $\dot{V}O_2$ versus *E/A*, *E′*, deceleration time, and *E/E′*, individually. The LAVI significantly correlated with the peak $\dot{V}O_2$ ($r = -0.50$, $p < 0.001$).

In the HFREF group, the multiple stepwise linear regression analysis based on leg muscle strength, LVEF, *E/E′*, GLS, and GCS was performed to identify an independent predictor of peak $\dot{V}O_2$, resulting in leg muscle strength and GLS as independent predictors ($p < 0.0001$, Table 3, Fig. 3a). In the HFPEF group, echocardiographic parameters were not used to identify independent predictors of peak $\dot{V}O_2$ (Fig. 3b).

Reproducibility

The average difference of the intraobserver agreement for GLS was −0.3 ± 0.6% and intraclass correlation coefficient was 0.95 (mean ± 2 SD). Similarly, the average difference agreement of measurements by the 2 different observers was −0.2 ± 2.6% and intraclass correlation coefficient was 0.92 (mean ± 2 SD).

Table 1 Clinical characteristics

	LVEF < 50% ($n = 23$)	LVEF ≥ 50% ($n = 28$)	p Value
Age (years)	51.3 ± 13.5	56.3 ± 14.3	ns
Sex (male/female)	19/4	18/10	ns
Body mass index (kg/m^2)	23.6 ± 4.1	22.7 ± 2.9	ns
NYHA classifications	1.7 ± 0.8	1.1 ± 0.3	<0.001
AT (ml/min/kg)	15.1 ± 4.8	18.4 ± 3.7	0.008
Peak $\dot{V}O_2$ (ml/min/kg)	19.6 ± 5.9	23.9 ± 5.6	0.01
$\dot{V}E/\dot{V}CO_2$	31.5 ± 6.0	30.3 ± 4.9	ns
Leg muscle strength (N m/kg)	1.8 ± 0.4	1.9 ± 0.5	ns
BNP (pg/ml)	207.5 ± 197.4	82.7 ± 68.2	<0.0001
Etiology			
Dilated cardiomyopathy (%)	17 (74)	6 (21)	0.001
Ischemic heart disease	6 (26)	19 (68)	0.001
Others	0 (0)	3 (11)	ns
Medications			
Calcium antagonists	2 (9)	4 (14)	ns
Beta blockers	23 (100)	24 (86)	ns
ACE inhibitors	14 (61)	19 (68)	ns
ARB	9 (39)	4 (14)	0.043
Diuretics	16 (70)	10 (36)	0.016

NYHA New York Heart Association, *AT* anaerobic threshold, $\dot{V}O_2$ oxygen uptake, $\dot{V}E$ ventilatory equivalent, $\dot{V}CO_2$ carbon dioxide output, *BNP* brain natriuretic peptide, *ACE* angiotensin II-converting enzyme, *ARB* angiotensin receptor blocker

Table 2 Echocardiographic data

	LVEF < 50% ($n = 23$)	LVEF ≥ 50% ($n = 28$)	p Value
Septal thickness (mm)	8.9 ± 2.0	8.8 ± 1.7	ns
PW thickness (mm)	9.5 ± 1.2	8.9 ± 1.4	ns
LVDd (mm)	61.7 ± 9.8	48.5 ± 4.9	<0.0001
LVDs (mm)	51.3 ± 12.3	32.9 ± 5.1	<0.0001
LVEDV (ml)	180.0 ± 68.6	131.5 ± 65.5	ns
LVESV (ml)	128.9 ± 68.4	43.7 ± 13.5	<0.0001
LVEF (%)	32.5 ± 12.1	57.0 ± 3.9	<0.0001
LAD (mm)	40.1 ± 6.6	32.9 ± 4.2	<0.0001
LAVI (ml/m^2)	29.5 ± 15.0	20.0 ± 7.3	0.01
E/A	1.15 ± 0.75	0.95 ± 0.36	ns
Deceleration time (ms)	179.1 ± 51.5	216.3 ± 48.0	<0.05
E' (cm/s)	7.1 ± 2.2	7.4 ± 2.1	ns
E/E'	9.2 ± 3.7	9.0 ± 3.0	ns
MR grade I	10 (44%)	19 (68%)	ns
MR grade II	6 (26%)	0 (0%)	<0.05
Global longitudinal strain (%)	−11.0 ± 4.5	−19.2 ± 3.3	<0.0001
Global circumferential strain (%)	−10.2 ± 4.9	−18.5 ± 6.9	<0.0001

PW posterior wall, *LVDd* left ventricular end-diastolic diameter, *LVDs* left ventricular end-systolic diameter, *LVEF* left ventricular ejection fraction, *LAD* left atrial diameter, *LAVI* left artial volume index, *E/A* ratio of peak velocities of early (*E*) to late (*A*) of transmitral flow, *E/E'* ratio of peak velocity of early transmitral flow (*E*) to early mitral annular motion (*E'*), *MR* mitral regurgitation, *ns* not significant

Discussion

Relationship between leg muscle strength and exercise capacity in CHF

In the present study, we observed a strong relationship between leg muscle strength and exercise capacity ($r = 0.55$, $p < 0.0001$). Clark et al. [16] found that reduced muscle function affected both knee flexors and extensors in patients with CHF. In our previous study [3], the improvement of exercise capacity was determined by muscle strength. Reduced muscle strength correlates with the ventilatory response to exercise. These observations lend support to the importance of peripheral factors in patients with CHF.

Table 3 Regression correlations for exercise capacity versus leg muscle strength and echocardiographic parameters

	Univariate analysis		Multiple stepwise regression analysis	
	r	p Value	Standard regression coefficient	p Value
All subjects independent variable				
Leg muscle strength	0.55	<0.0001	0.53	<0.0001
LVEF	0.45	0.001		
Global longitudinal strain	−0.47	0.001		
Global circumferential strain	−0.41	0.005		
E/E'	−0.27	ns		
$R^2 = 0.261$	ANOVA $p = 0.001$			
LVEF $\geq$ 50% independent variable				
Leg muscle strength	0.51	0.005	0.49	0.014
LVEF	0.11	ns		
Global longitudinal strain	0.08	ns		
Global circumferential strain	−0.09	ns		
E/E'	−0.39	ns		
$R^2 = 0.203$	ANOVA $p = 0.014$			
LVEF < 50% independent variable				
Leg muscle strength	0.68	0.005	0.70	<0.0001
LVEF	0.50	0.015		
Global longitudinal strain	−0.61	0.002	−0.62	<0.0001
Global circumferential strain	−0.38	ns		
E/E'	−0.17	ns		
$R^2 = 0.888$	ANOVA $p < 0.0001$			

Peak $\dot{V}O_2 = -7.953 + 8.799 \times$ leg muscle strength $- 1.076 \times$ global longitudinal strain

Relationship between LVEF and exercise capacity in CHF

The evaluation of LVEF is somewhat subjective, which requires considerable experience, as demonstrated by differences between novices and experienced operators. Even when the stroke volume is correctly measured. LVEF may be overestimated due to MR. LVEF is also affected by patients' preload conditions.

Left ventricular ejection fraction has been regarded as the most extensively investigated echocardiographic parameter for the evaluation of cardiac systolic function and a powerful predictor of mortality in patients with systolic heart failure [17, 18]. Nevertheless, some studies have reported LVEF as a poor predictor of exercise capacity [4–7, 19, 20]. Multiple stepwise regression analysis did not show LVEF as a predictor of peak $\dot{V}O_2$ in this study; however, univariate analysis showed that LVEF had a moderate correlation with peak $\dot{V}O_2$ ($r = 0.45$, $p = 0.001$). Of note, this correlation was remarkable in the HFREF group ($r = 0.50$, $p = 0.015$).

In the present study, we excluded patients with organic valvular disease, which might affect our study result. We assume this is the reason why we could only observe a moderate correlation between peak $\dot{V}O_2$ and LVEF.

Relationship between E/E' and exercise capacity in CHF

Several studies reported E/E', a significant marker of LV end-diastolic pressure, was useful for predicting exercise capacity. However, the result of this study demonstrated no significant correlation between E/E' and peak $\dot{V}O_2$, which was different from the results of Hadano et al. [21] and Podolec et al. [22]. Meanwhile, the LAVI, a significant marker of LV diastolic dysfunction, correlated with peak $\dot{V}O_2$. E/E' is an important determinant of exercise capacity. We presume this is due to relatively maintained exercise capacity and optimal medication in our study patients, which leads to lower LV filling pressure.

Relationship between GLS and exercise capacity in CHF

Strain and strain rate imaging quantify the regional myocardial deformation. Both techniques possibly differentiate

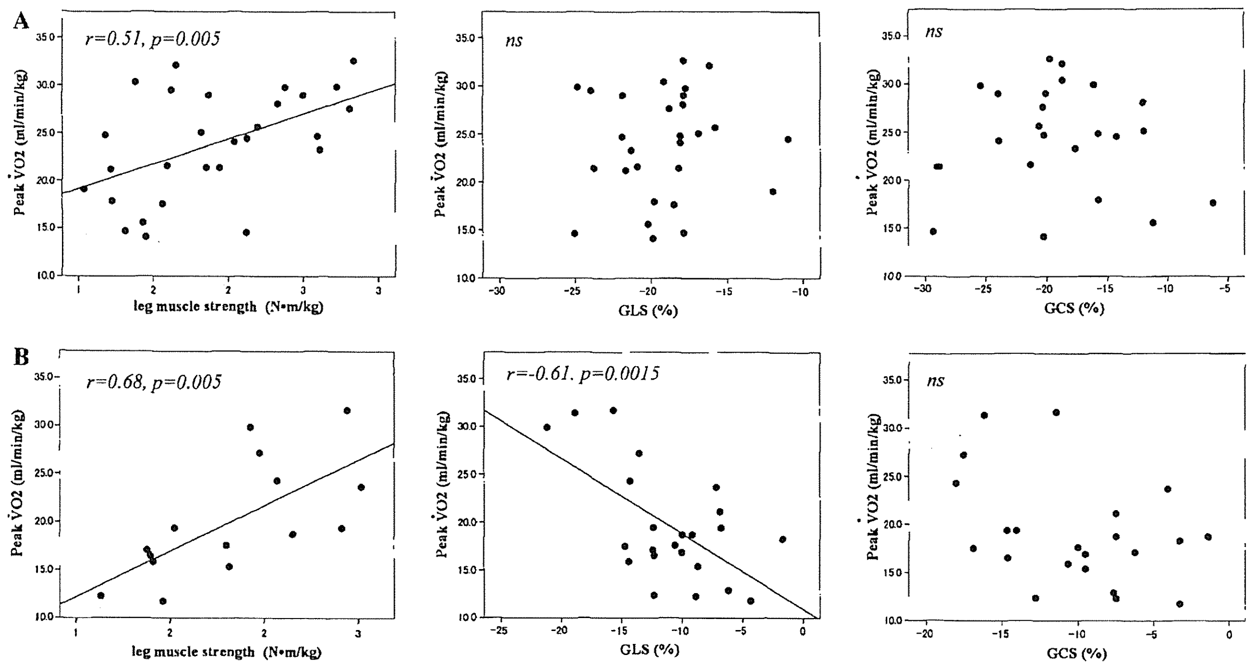

Fig. 3 **a** Relation between peak $\dot{V}O_2$ versus leg muscle strength, global longitudinal strain (*GLS*), and global circumferential strain (*GCS*), individually, in the patients with heart failure and preserved left ventricular ejection fraction (*LVEF*). GLS and GCS values are presented as *negative values*; a larger negative value indicated a larger extent of longitudinal strain. **b** Relation between peak $\dot{V}O_2$ versus leg muscle strength, global GLS, and global GCS, individually, in the patients with heart failure and preserved LVEF. Leg muscle strength significantly correlated with peak $\dot{V}O_2$ in both patients with heart failure and preserved LVEF (LVEF < 50%) and patients with heart failure and reduced LVEF (LVEF < 50%). In patients with heart failure and reduced LVEF, GLS significantly correlated with peak $\dot{V}O_2$

those myocardial segments with an active contraction from passive motion caused by tethering [23]. In one recent study, biplane LVEF in all patients was related to global LV longitudinal strain quantified by the novel algorithm GLS [24] and linearly related to the GLS. Delgado et al. [25] demonstrated a good correlation between GLS and LVEF in a large study population with a wide range of LVEF. Although the correlation between GLS and biplane LVEF was good in the overall population, the correlation was less strong in patients with coronary artery disease (ST-segment elevation myocardial infarction or chronic ischemic heart failure). This finding suggests that these two parameters should not be identical, but rather reflect different aspects of LV systolic function.

Lim et al. [26] proposed the use of the strain delay index with longitudinal strain by speckle tracking as a strong predictor of response to cardiac resynchronization therapy. This index, which quantifies the amount of wasted energy due to LV dyssynchrony, suggested that GLS should reflect LV systolic function rather than LVEF. We consider that not LVEF but GLS responds well to exercise capacity, which is attributed to the fact that GLS not only evaluates cross-sectional area changes but also reflects LV systolic function. In the HFPEF group, compared with the HFREF group, the rate of patients with ischemic heart disease was greater, there were not many patients complicated by MR, and GLS was significantly preserved. Accordingly, the rate of patients with relatively good cardiac function was greater in the HFPEF group, resulting in these patients not having many central factors responsible for exercise capacity.

Clinical implications and study limitations

The result of this study demonstrated that GLS, a central component, was an independent predictor of peak $\dot{V}O_2$ in CHF patients with reduced LVEF. Even though echocardiography in the present study was performed at rest, GLS could estimate exercise capacity. Our findings lend support to earlier studies suggesting GLS can predict cardiac output [8] and all-cause mortality in CHF patients [10] more accurately than LVEF. GLS is probably useful for the evaluation both after medical therapy and cardiac transplantation [11] in patients with CHF. GCS is also regarded as a useful parameter; however, a poor correlation between GCS and exercise capacity is pointed out. This correlation is due to single view recording in the short-axis view at the papillary muscle level and insufficient quality recording in the basal and apical short-axis views. In addition, strong and significant correlations between peak $\dot{V}O_2$ and diastolic parameters were not shown in the present study because of the small study population. Further studies with a larger population are required for understanding torsion, a circumferential direction parameter which has a good correlation with τ [27]. In addition, it is indispensable to analyze the strain deformation measured by three-dimensional echocardiography, particularly in patients with preserved EF in whom the longitudinal velocities can not predict exercise capacity. To our knowledge, this is the first study to identify the determinants of exercise capacity using strain imaging in patients with reduced LVEF. In the present study, we could have a clinically significant finding that GLS could predict peak $\dot{V}O_2$ even at rest.

Conclusions

Global longitudinal strain at rest was a useful predictor of exercise capacity, which appeared to be a better parameter than LVEF, *E/E'*, and GCS in CHF patients with reduced LVEF.

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Conflict of interest There are no conflicts of interest related to this study.

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研究論文

糖尿病を合併した急性心筋梗塞患者の運動耐容能低下の関連要因*

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要旨

【目的】糖尿病（DM）を合併した急性心筋梗塞（AMI）患者における運動耐容能低下への身体機能の関与の有無を明らかにする。【方法】対象はAMI男性患者190例（DM群47例，非DM群143例）。最高酸素摂取量（Peak $\dot{V}O_2$），身体機能指標（膝伸展筋力，握力，片脚立位時間，前方リーチ距離，体脂肪率，筋肉量），自律神経指標（% HRR，⊿HR）を測定した。【結果】DM群は非DM群に比しPeak $\dot{V}O_2$ 24.3, 27.1 ml/kg /min（$p < 0.01$），膝伸展筋力1.75, 1.93 Nm/kg（$p < 0.01$），握力38.1, 41.3 kgf（p=0.02），片脚立位時間22.2, 28.5秒（$p < 0.01$），% HRR 79.1, 85.6%（p=0.04），⊿HR 66.0, 75.4 bpm（$p < 0.01$）と低値を示した。DM群のPeak $\dot{V}O_2$の関連要因を検討した結果，膝伸展筋力と⊿HRが抽出された（r=0.58, R^2=0.301，$p < 0.01$）。【結論】DM群の運動耐容能低下には，膝伸展筋力の低下と自律神経指標（⊿HR）が関与することが明らかとなった。

キーワード　糖尿病，急性心筋梗塞，運動耐容能

はじめに

本邦では，高齢化に加え食生活の欧米化と運動不足などの原因により，糖尿病（diabetes mellitus：DM）とその予備軍が急増しており，社会的な問題となっている。厚生労働省による平成19年国民健康・栄養調査[1)]では，DMおよびDM予備軍の合計は約2,210万人と推定されており，10年前の同調査と比較しその数は約840万人も増加している。

DMは心筋梗塞や脳梗塞など動脈硬化性疾患の重要なリスクファクターのひとつである。DM患者では健常人と比較して心筋梗塞の発症危険度は3倍以上高く，境界型の段階よりすでにそのリスクは上昇することが指摘されている[2)]。さらに，欧米ではDM患者の40～50%が心筋梗塞を直接死因としているが，我が国でも冠動脈疾患が直接死因となるDM患者が増加している[3)]。また，DMを合併した急性心筋梗塞（acute myocardial infarction：AMI）患者では，DMの合併症である神経障害の影響により無症候性の心筋虚血や複数枝での冠動脈病変を認めるなどの特徴を有し，かつ心筋を栄養する微小血管の障害を伴うため潜在的心筋障害が多く予後不良とされている[4)]。最近では，DM患者の増加の背景を受け，AMI患者におけるDMの合併率が増加していることが指摘されている[5)]。

これらDMを合併したAMI患者ではDMを合併していないAMI患者と比較して運動耐容能が低下していると報告されている[6-11)]。一般に運動耐容能を規定する因子には年齢，性別，心機能，下肢筋力など多くの指標があげられている[13-16)]。DMを合併したAMI患者における運動耐容能低下の要因としては，DMの合併症に代表される自律神経障害による心拍応答不良が報告されており[9-12)]，運動機能を考慮した報告は極めて少ない。このことからも，我々が知る限り，患者背景，心機能，自律神経，および運動機能を含む多角的な検討をした報告はなく，DMを合併したAMI患者における運動耐容

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能低下への自律神経障害以外の要因の関わりについては明らかではない。

本研究の目的は，DMを合併したAMI患者の運動耐容能低下の機序に身体機能の変化が関与しているのかを明らかにすることである。

対象および方法

1. 倫理的配慮

本研究は，聖マリアンナ医科大学生命倫理委員会の承認を得て実施した（承認番号：第1480号）。本研究に際し，事前に患者に研究の趣旨，内容および調査結果の取り扱い等に関して説明し同意を得た。

2. 対象

2003年5月から2009年4月の6年間に，聖マリアンナ医科大学病院ハートセンターにて入院期心リハを終了し，初発のAMI発症後1ヵ月時点で心肺運動負荷試験（Cardiopulmonary Exercise Test：CPX）が実施できた連続236例を本研究の対象とした。なお，本研究ではDMを合併したAMI患者の回復期心臓リハビリテーション開始時における実態を把握すべく，発症1ヵ月時点のCPX結果を採用した。そのうちから，女性，負荷試験中に心電図上の虚血や不整脈のため途中終了した症例，心房細動例，およびガス交換比1.0未満の症例は除外し，残りの190例を本研究の分析対象とした。

女性は運動機能への性差の影響を除くために除外した。最高ガス交換比が1.0未満の場合には十分な運動負荷が実施できていない可能性があるため除外した。さらに，虚血性心電図変化や心房細動を含む不整脈の増加が認められた場合は，その出現する運動強度に依存してCPXが終了してしまうために除外した。なお，運動麻痺や関節痛などの運動器疾患を有する者は，対象から除外した。

これらの対象者を，DMを合併したAMI患者（DM群）47例とDM非合併のAMI患者（非DM群）143例の2群に分類した。本研究では，日本糖尿病学会による糖尿病診断基準[17]にしたがって，空腹時血糖値，随時血糖値，グリコヘモグロビン値（HbA_{1c}）の結果をもとに糖尿病と診断されたものをDM群とした。なお，本研究におけるHbA_{1c}値はJDS（Japan Diabetes Society）値を採用した。

3. 調査測定項目

1）属性および患者背景に関する情報

調査項目は，基本属性に関する情報として，年齢，身長，体重，Body Mass Index（BMI），併存疾患（高血圧と脂質異常症）の有無を，血液生化学検査値はHbA_{1c}，心筋逸脱酵素（CK-MB）を，心機能検査は有意冠動脈狭窄枝数と左室駆出率（Left ventricular ejection fraction：LVEF）を，投薬内容は経口薬の内容（循環器および糖尿病）とインスリン使用の有無とした。これらの指標は診療記録より調査し，そのうち基本属性，HbA_{1c}，心機能検査，投薬内容の情報はCPXの検査日から直近のものを採用した。また，CK-MBは発症後の最高値を採用した。

2）最高酸素摂取量（Peak $\dot{V}O_2$）

CPXはトレッドミル（フクダ電子社製，MAT-2500®）を使用した1分ごとに漸増するランプ負荷を用いて実施した[18]。試験中は，運動負荷試験監視装置（フクダ電子社製，STRESS TEST System ML-9000®）によって，心拍数，ST-T変化および不整脈を連続的に監視し，12誘導心電図を1分ごとに記録した。CPX中は，呼気ガス分析装置（ミナト医科学社製，エアロモニタ300S®）を用いてbreath by breath法で連続的に呼気ガス分析を施行し，最高酸素摂取量（Peak $\dot{V}O_2$）を測定（ml/kg /min）した。負荷試験の終了条件は，米国スポーツ医学会の運動負荷試験中止基準[19]を満たす徴候の出現，あるいは負荷強度の増加にも関わらず酸素摂取量が増加しない，いわゆるleveling offの状態の出現とした。

3）身体機能指標

身体機能指標の測定はCPXとすべて同一測定日に実施した。

(1) 上下肢筋力

筋力の指標には等速性膝伸展筋力と握力を採用した。筋力の測定は先行研究に準じて実施した[20]。膝伸展筋力の測定は等速性筋力測定器（BIODEX社製，SYSTEM2®）を使用した。測定姿勢は，背もたれに背中を密着させ，下腿を下垂させた坐位をとり，体幹と骨盤および大腿部をバンドで固定した。測定中は両手で座面外側にある握りを把持させた。下肢の可動範囲は膝屈曲90～0度とし，角速度60度/秒で5回繰り返し，その最高値を計測した。そして左右の平均値を体重で除した値を膝伸展筋力（Nm/kg）として採用した。

握力は握力計（PRESTON社製，JAMAR®ハンドダイナモメーター）を用い，座位で肘屈曲90度前腕中間位にて測定し，最高値を計測した。そして左右の平均値を算出した値を握力（Kgf）として採用した。

(2) バランス機能

バランス機能の指標としては片脚立位時間と前方リーチ距離を採用し，先行研究に準じて測定した[21]。片脚立位時間は開眼にて上肢の支持なく一側の下肢を挙上させ，検者はできるだけ長く片足で立ち続けるように指示し，上限を30秒として測定した。2回ずつ測定し，その最高値を採用した。

前方リーチ距離は伸縮可能な指示棒を用いたModified

Functional Reach Test（M-FRT）にて測定（cm）した[21]。測定はM-FRT専用の測定機器（レモン社製，M-FR ROD®）を使用した。最長（60 cm）に伸ばした指示棒を被検者の利き手で把持させ，肩関節屈曲90度挙上にて指示棒の先端が壁に接する位置に立たせた。測定は，被検者に可能な限り前方へリーチさせ，手に持った指示棒で壁を押してそれを短くさせた。短縮した指示棒の長さをメジャーで測定し，その長さを60 cmから差し引いた長さを前方リーチ距離とした。なお，それぞれの測定は十分な練習を行った後に2回測定し，その最高値を採用した。

(3) 体組成

本研究における体組成の指標には体脂肪率と筋肉量を採用し，先行研究に準じて測定した[22]。測定は体組成計（Physion社製，生体電気インピーダンス方式体組成計®）を用い，単周波生体電気インピーダンス方式にて行った[23]。体液バランス変動の影響を取り除くために背臥位として四肢に電極を装着した。

(4) 自律神経指標

CPXの結果を参考に心拍数予備能（Heart Rate Reserve：% HRR）と⊿HRの心拍応答不全の指標を採用した[10)12)]。% HRRは，（最高心拍数－安静時心拍数）／（220－年齢－安静時心拍数）× 100で算出した。⊿HRは，安静時心拍数と最大運動時の心拍数の差により算出し，運動による心拍数の上昇値として評価した。

4) 統計解析

各指標は平均値±標準偏差で示した。DM群，非DM群の2群間での患者背景の比較にはχ二乗検定，対応のないt検定，Mann-WhitneyのU検定を用いた。DM群と非DM群におけるPeak $\dot{V}O_2$の比較には，対応のないt検定を用いた。また，2群間の運動機能指標と自律神経指標の比較には，対応のないt検定およびMann-WhitneyのU検定を用いた。さらに，DM群におけるPeak $\dot{V}O_2$と患者背景，身体機能，自律神経指標の各要因との関連については，Pearsonの積率相関係数を用いた。次に，これらの有意に単相関を認めた因子を独立変数に，Peak $\dot{V}O_2$を従属変数とするステップワイズ重回帰分析を施行した。分析にはSPSS ver.12.0J for Windowsを使用し，統計学的有意差判定基準は5%未満とした。

結　　果

1. 患者背景

表1にDM群と非DM群の患者背景を示した。両群間には血糖コントロールの指標であるHbA_{1c}のみに有意差を認めた（$p < 0.01$）。その他の基本属性，心機能検査，投薬内容には両群間ですべて有意差を認めなかった。

2. 最高酸素摂取量，身体機能指標，自律神経指標

Peak $\dot{V}O_2$，身体機能指標，自律神経指標の結果を表2に示す。Peak $\dot{V}O_2$はDM群24.3 ml/kg /min，非DM群27.1 ml/kg /minとDM群で有意に低値を示した（$p < 0.01$）。次に，DM群，非DM群の順にそれぞれ身体機能指標は膝伸展筋力1.75 Nm/kg，1.93 Nm/kg（$p < 0.01$），握力38.1 kg，41.3 kgf（p=0.02）片脚立位時間22.2秒，28.5秒（$p < 0.01$）でありDM群は有意に低値を示した。しかし，もうひとつのバランスの指標である前方リーチ距離や体組成の体脂肪率や筋肉量には有意差を認めなかった。自律神経の指標は% HRR 79.1%，85.6%（p=0.04），⊿HR 66.0 bpm，75.4 bpm（$p < 0.01$）と，両指標ともにDM群で有意に低値を示した。なお，本研究ではCPXの中止基準に該当する症例は除外基準としているため，CPXの終了理由は両群で差はなかった。

3. DM群の運動耐容能を規定する要因

先行研究と同様にDM群の運動耐容能が低下していることを確認できたので，DM群のみを分析の対象として運動耐容能を規定する要因を検討した。まず，Peak $\dot{V}O_2$と関係のある因子を単変量解析で検討した結果，年齢（r=−0.44，$p < 0.01$），膝伸展筋力（r=0.43，$p < 0.01$），握力（r=0.34，p=0.02），体脂肪率（r=−0.38，$p < 0.01$），⊿HR（r=0.48，$p < 0.01$）が有意な相関を示した。次に，DM群のPeak $\dot{V}O_2$に関連する要因についてステップワイズ重回帰分析を行った結果を表3に示す。Peak $\dot{V}O_2$を従属変数とし，上記の単相関のみられた各指標を独立変数とした結果，膝伸展筋力と⊿HRのみがDM群の運動耐容能を規定する要因として抽出された（r=0.58，R^2=0.301，$p < 0.01$）。

考　　察

本研究では，DM群の運動耐容能低下に関与する要因を重回帰分析により検討した。その結果，DM群の運動耐容能低下には，先行研究でその関与が指摘されていた自律神経指標（⊿HR）以外に，今回新たに膝伸展筋力の低下が関与することが明らかとなった。

1. 患者背景について

心筋の虚血は運動耐容能の制限因子[24]とされているが，両群間の心機能指標である左室駆出率および有意冠動脈狭窄枝数に有意差はなく，安静時の心機能は両群ともに同等であった。その他，年齢および投薬内容も両群で同等であったことから，DM群の運動耐容能の低下に患者背景の因子が関与していた可能性は低いものと考えられた。ただし，関らは[25]，DMを合併したAMI患者の運動耐容能低下の規定因子のひとつとして左室拡張能