proliferation of vascular smooth muscle cells by decreasing matrix metalloproteinase production and inducing cell cycle arrest or apoptosis and atherosclerotic effects in vascular cells in vitro and in diseased animal models. (Marx N, et al. Circ Res 2004)

2.1 Effects of thiazolidinedione on atherosclerosis and cardiovascular events

In the PROactive study, a double-blinded, placebo-controlled investigation, pioglitazone significantly reduced the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes, who have a high risk of macrovascular events. (Dormandy JA, et al. Lancet 2005) Nissen et al. conducted a double-blinded, randomized, multicenter trial in 543 patients with coronary disease and type 2 diabetes to compare the effects of an insulin sensitizer, pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes. (Nissen SE, et al. JAMA 2008) Treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS) compared with glimepiride in patients with type 2 diabetes and coronary artery disease. A meta-analysis showed that pioglitazone did not increase the risk of myocardial infarction or cardiovascular mortality. (Lincoff, et al. JAMA 2007)

In contrast, controversy persists regarding the effects of rosiglitazone therapy on myocardial infarction and cardiovascular mortality. A meta-analysis of 4 randomized controlled trials (N=14 291, including 6421 receiving rosiglitazone and 7870 receiving control therapy, with a follow-up duration of 1-4 years) showed that rosiglitazone use for ≥12 months is associated with a 42% increased risk of acute myocardial infarction and a doubling in the risk of heart failure among patients with impaired glucose tolerance or type 2 diabetes. (Singh S, et al. JAMA 2007) The most recent systematic review by Nissen and Wollski reported that rosiglitazone therapy significantly increased the risk of myocardial infarction (odds ratio (OR), 1.28; 95% confidence interval (CI), 1.02-1.63; P=.04), but not cardiovascular mortality (OR, 1.03; 95% CI, 0.78-1.36; P=.86). (Nissen SE, et al. Arch Intern Med 2010)

Both thiazolidinediones have been shown to increase the risk of heart failure compared with treatment with placebo or other antidiabetes medications. In order to compare the risk of serious cardiovascular harm by rosiglitazone and by pioglitazone, Graham DJ et al. conducted a nationwide, observational, retrospective, inception cohort of 227, 571 Medicare beneficiaries aged 65 years or older who initiated treatment with rosiglitazone or pioglitazone. The adjusted hazard ratio for rosiglitazone compared with pioglitazone was 1.06 (95% confidence interval [CI], 0.96-1.18) for AMI; 1.27 (95% CI, 1.12-1.45) for stroke; 1.25 (95% CI, 1.16-1.34) for heart failure; 1.14 (95% CI, 1.05-1.24) for death; and 1.18 (95% CI, 1.12-1.23) for the composite of AMI, stroke, heart failure, or death. Compared with prescription of pioglitazone, prescription of rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of AMI, stroke, heart failure, or all-cause mortality in patients 65 years or older. (Graham DJ et al. JAMA. 2010)

2.2 Effects of pioglitazone on in-stent restenosis in metabolic syndrome

We first demonstrated that treatment with pioglitazone reduces intimal index as assessed by IVUS as a parameter of neointimal hyperplasia after bare metal stent implantation in patients with non-diabetic metabolic syndrome using an open-labeled randomized

controlled study. (Katayama, et al. Am Heart J 2007) Before coronary stenting, 32 patients were randomly assigned to two treatment groups: the pioglitazone group; and the control group. All patients were successfully treated using IVUS-guided coronary stenting. After coronary stenting, patients in the pioglitazone group were treated with 30 mg/day of pioglitazone in addition to standard medications for 6 months, whereas patients in the control group were treated using only standard medications. After intracoronary administration of isosorbide dinitrate, a 40-MHz IVUS catheter was advanced to the distal side beyond the target lesion, and IVUS images were recorded using automatic pullback (0.5 mm/s). The lesion was defined as the site with smallest lumen, and the reference points were defined as the sites with the largest lumen within 10 mm proximal and distal to the lesion. Bare metal stents were implanted based on IVUS measurements. In accordance with the American College of Cardiology Task Force on Clinical Expert Consensus Documents on IVUS, (Mintz S, et al. J Am Coll Cardiol 2001) quantitative IVUS measurements were performed by a single observer who was blinded to the treatment assignments of patients. (Figure 1)

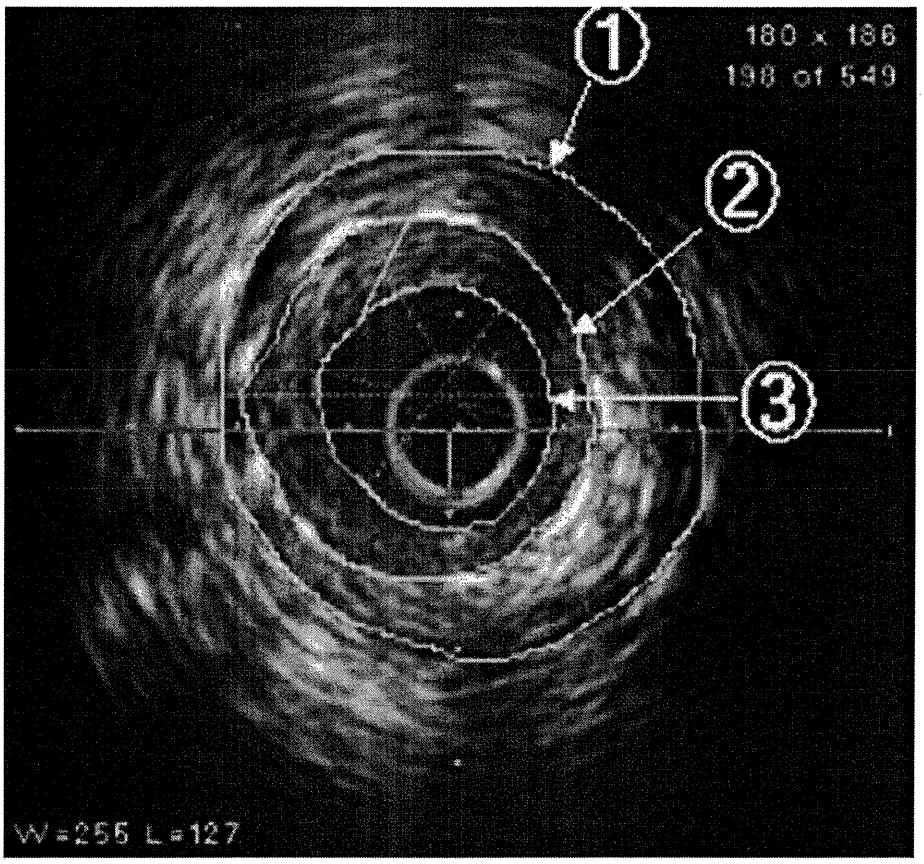

Fig. 1. The following parameters of IVUS were measured at 0.5-mm intervals through the stent site immediately and 6 months after stent implantation. 1) External elastic membrane cross-sectional lumen areas (mm^2); 2) Stent cross-sectional lumen areas (mm^2); 3) Lumen cross-sectional lumen areas (mm^2). Intimal area was calculated as the stent cross-sectional lumen area minus the lumen cross-sectional lumen areas, and the intimal index was defined as the intimal area divided by the stent cross-sectional lumen areas.

Two-dimensional tomographic images from IVUS allowed direct visualization of the 360° characterization of the coronary arterial lumen and neointimal hyperplasia at stent sites. IVUS is a safe, accurate and reproducible method and has thus been recognized as the reference method for quantification of restenosis in trials of anti-restenosis therapeutic interventions. Conversely, angiographic studies of progression/regression are limited because angiography shows the opacified silhouette of only the lumen. Furthermore, the variability of vascular remodeling prevents reliable assessment of plaque dimensions on the basis of lumen narrowing.

The primary end point of this study was the reduction of neointimal hyperplasia as evaluated by intimal index, a prespecified parameter for evaluating neointimal hyperplasia by IVUS. (Katayama, et al. Am Heart J 2007) Intimal index rather than intimal area is considered as a more reliable parameter for the assessment of neointimal hyperplasia. (Mintz GS, et al. J Am Coll Cardiol 2006) Secondary end points were intimal area, late loss of minimal lumen diameter, percentage diameter stenosis, binary restenosis rate, and target vessel revascularization.

Mean intimal index and maximal intimal index by IVUS were significantly reduced in the pioglitazone group compared with controls (Figure 2, panel a). Mean intimal area and maximal intimal area also tended to be reduced in the pioglitazone group compared with controls, but this difference was not significant (Figure 2, panel b). Late loss of minimal lumen diameter and percentage diameter stenosis by quantitative coronary angiography were significantly decreased in the pioglitazone group compared with controls (Figure 2, panels c, d).

The binary restenosis rate was 0% in the pioglitazone group, compared to 31% in controls (P=.043). Three patients in the control group underwent target vessel revascularization, whereas no patients in the pioglitazone group required such interventions. No significant differences in fasting plasma glucose levels, 2-h plasma glucose levels, or hemoglobin (Hb)A1c levels at baseline or follow-up were seen between the 2 groups. On the other hand, fasting insulin levels at baseline were significantly higher in the pioglitazone group compared with controls, and 2-h insulin levels at follow-up were lower in the pioglitazone group than in controls (67.1 ± 28.8 μU/mL vs. 151.9 ± 185.7 μU/mL; P=.027). Visceral fat areas as measured by abdominal computed tomography were significantly decreased at follow-up in the pioglitazone group compared with controls, although no significant differences in plasma lipid profiles (including total cholesterol, LDL, HDL and triglyceride levels) between groups. Pioglitazone treatment improved insulin resistance and decreased visceral fat accumulation, which is closely associated with insulin resistance, without significant changes in glucose or HbA1c levels, or lipid profiles. Our results indicate that reductions in neointimal hyperplasia by pioglitazone in non-diabetic patients with metabolic syndrome are likely attributable to improvements in insulin resistance. Our findings are consistent with previous reports of randomized controlled trials and meta-analyses in patients with impaired glucose tolerance or type 2 diabetes. However, no RCTs have demonstrated that rosiglitazone significantly reduces the risk of repeat target vessel revascularization following implantation of bare metal stents. A meta-analysis by Nishio et al. showed that rosiglitazone does not reduce the risk of repeat target vessel revascularization following PCI (Nishio et al. Cardiovasc Revasc Med 2010). The reasons behind these differing results for prevention of in-stent-restenosis by two thiazolidinediones remain unclear.

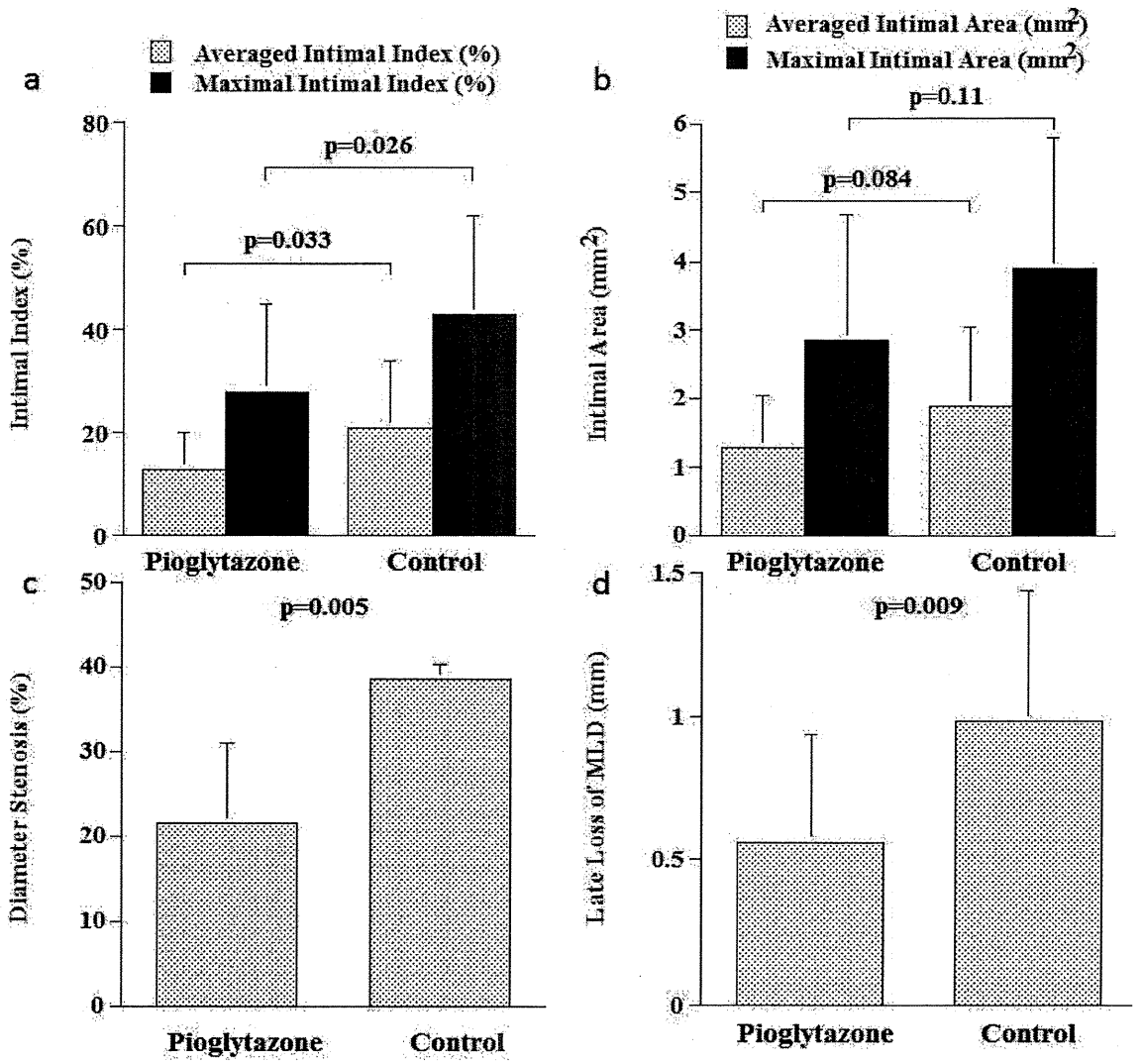

Fig. 2. Intimal index (a) and intimal area (b) as measured by IVUS and late loss (c) and diameter stenosis (d) as assessed by coronary angiography at 6-month follow-up. Mean intimal index and maximal intimal index (a) were significantly reduced in the patient group treated using pioglitazone (n=14) compared with controls (n=14). A non-significant reduction in intimal area was seen in the pioglitazone group compared with controls (b). Late loss of minimum lumen diameter and percentage diameter stenosis as assessed by quantitative coronary arteriography at 6-month follow-up. Late loss of minimum lumen diameter (c) and percentage diameter stenosis (d) were significantly decreased in the pioglitazone group compared with controls.

3. Conclusion

Thiazolidinediones, agonists of peroxisome proliferator-activated receptor (PPAR)-γ, improve insulin sensitivity in patients with type II diabetes mellitus and metabolic syndrome. Beyond the anti-diabetic actions, thiazolidinediones exert anti-inflammatory and anti-atherosclerotic effects in vascular cells in vitro and in diseased animal models. Pioglitazone shows reductions in neointimal hyperplasia leading to in-stent-restenosis after implantation of bare metal stents in patients with type 2 diabetes and metabolic syndrome by IVUS, without unfavorable effects such as increases in myocardial infarction or cardiovascular death. Rosiglitazone shows not only no significant reduction of in-stent-restenosis, but also a strong possibility of increased risk of myocardial infarction and cardiovascular death.

Two-dimensional tomographic imaging by IVUS allows direct visualization of the 360° characterization of coronary arterial lumen and neointimal hyperplasia at the stent sites. IVUS is a safe, accurate and reproducible method and has thus been recognized as the reference method for quantification of restenosis in trials of anti-restenosis therapeutic interventions.

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Efficacy of Out-Patient Cardiac Rehabilitation in Low Prognostic Risk Patients After Acute Myocardial Infarction in Primary Intervention Era

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Background: The efficacy of out-patient cardiac rehabilitation (OPCR) in patients with a low prognostic risk after acute myocardial infarction (AMI) is unclear in the recent primary intervention era.

Methods and Results: A total of 637 AMI patients who participated in in-hospital cardiac rehabilitation were divided into 2 groups; low prognostic risk group (n=219; age <65 years, successful reperfusion, Killip class I, peak serum creatine kinase <6,000 U/L, and left ventricular ejection fraction ≥40%) and non-low prognostic risk group (n=418). The prevalence of coronary risk factors (CRF) was compared between the 2 groups. Then, in the low-risk group, the efficacy of OPCR was compared between active OPCR participants (n=52; ≥20 sessions/3 months) and non-active participants (n=60; <6 sessions/3 months). Compared with the non-low prognostic risk group, the low prognostic risk group had a significantly higher prevalence of current smokers (72% vs. 49%, P<0.05) and patients with multiple CRF (3 or more; 49% vs. 39%, P<0.05). Among the low- risk group, active OPCR participants showed a significantly greater improvement in exercise capacity (peak $\dot{V}O_2$, P<0.05) and maintained a better CRF profile (total cholesterol, triglyceride and blood pressure, all P<0.05) than inactive participants at 3 months.

Conclusions: Low prognostic risk AMI patients have a higher prevalence of multiple CRF than non-low risk patients. Even in this low risk group, active participation in OPCR is associated with improved exercise capacity and better CRF profile. (*Circ J* 2011; **75:** 315–321)

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Coronary risk factors; Exercise capacity; Low prognostic risk

Cardiac rehabilitation (CR) is a comprehensive intervention including medically supervised exercise training, risk factor control, patient education, and psychosocial counseling. CR has been reported to be effective in improving numerous intermediate endpoints, including exertional ischemic symptoms, overall feelings of wellness, exercise tolerance, and coronary risk factors (CRF) in patients with coronary artery disease (CAD).[1–6] In addition, recent meta-analyses of randomized studies on the effects of exercise-based CR in patients with CAD have demonstrated a statistically significant reduction in total and cardiac mortality ranging from 20% to 32%[7–9] in patients undergoing CR compared with those receiving standard medical care. The guidelines from the American College of Cardiology/American Heart Association and Japanese Circulation Society recommend the use of CR after acute myocardial infarction (AMI) as Class I.[10–14]

Recently, the widespread use of primary percutaneous coronary interventions (PCI) has enabled early ambulation of patients with AMI by reducing acute phase complications, resulting in minimal physical deconditioning. As a result, many AMI patients leave a hospital early without participating in a recovery phase (phase II) out-patient CR (OPCR) program.[15] However, the necessity and efficacy of OPCR remain unclear in AMI patients who are anticipated to be at low risk in terms of long-term prognosis (ie, non-elderly, successful reperfusion, absence of heart failure, and preserved left ventricular (LV) systolic function).

Accordingly, the purpose of the present study was to clarify the prevalence of CRF and to determine the efficacy of a 3-month OPCR program in such presumably low prognostic risk patients after AMI.

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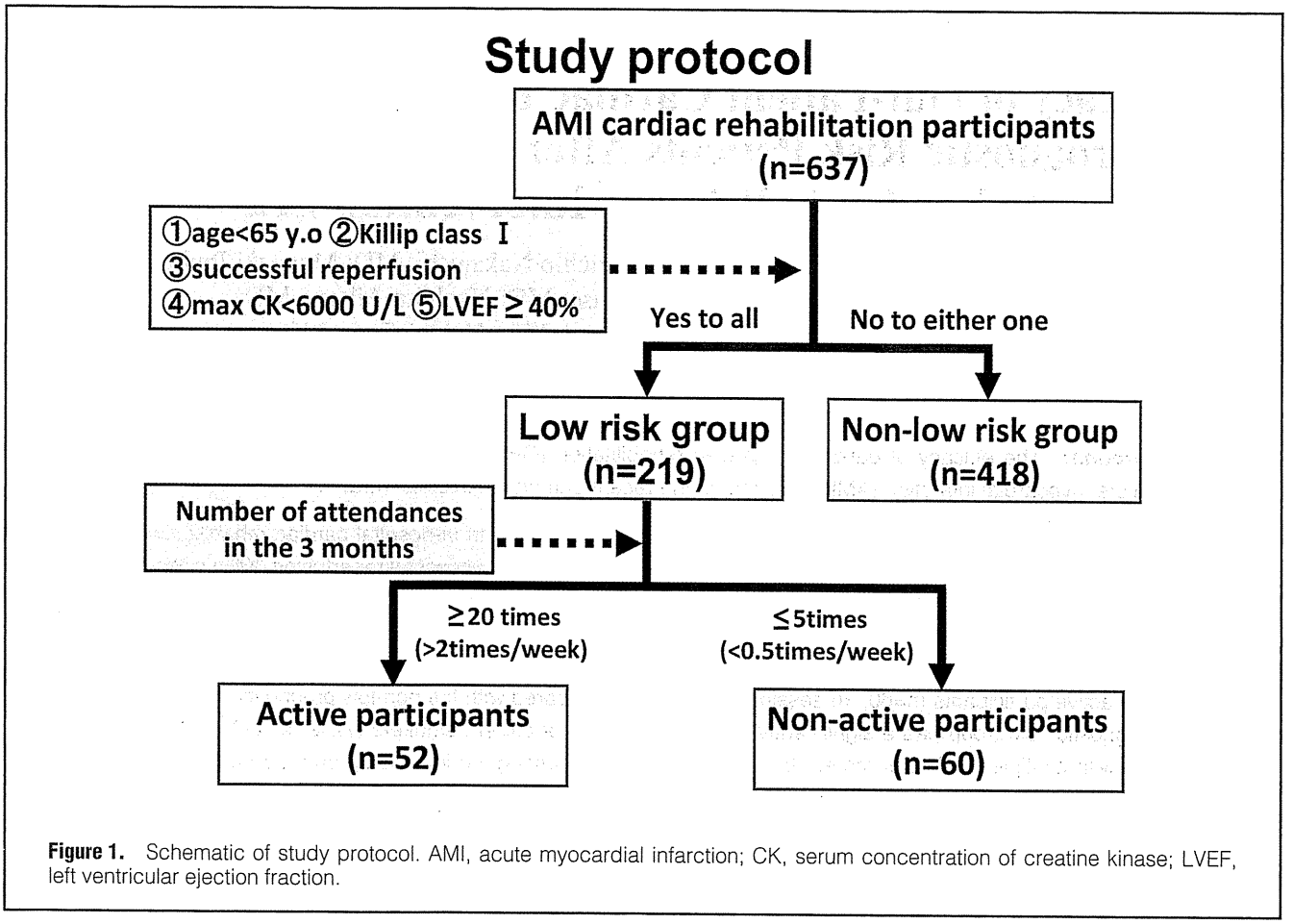

Figure 1. Schematic of study protocol. AMI, acute myocardial infarction; CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction.

Methods

Patients

We studied a total of 637 consecutive patients with AMI who participated in a recovery phase CR program and underwent cardiopulmonary exercise testing (CPX) at the beginning and end of a 3-month program in our hospital. The patients were divided into 2 groups: a low prognostic risk group and a non-low prognostic risk group. The low prognostic risk group comprised of 219 patients who fulfilled all of the following criteria indicative of favorable prognosis; age under 65 years, successful reperfusion, Killip class I (an indicator of absence of acute phase heart failure), peak serum creatine kinase (CK) <6,000 U/L, LV ejection fraction (LVEF) ≥40%. The remaining 417 patients who did not fulfill 1 or more of the above 5 criteria were referred to as the non-low prognostic risk group.

As the first step of data analysis, the prevalence each of the CRF (hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking habit) was compared between the low prognostic group and the non-low prognostic group.

As the second step, the efficacy of OPCR in AMI patients at low prognostic risk was examined by comparing the data for exercise capacity and CRF between active participants and non-active participants in the low prognostic risk group. Active participants were defined as patients who attended the OPCR sessions at least 20 times in 3 months (ie, approximately >2times/week), and non-active participants were those who attended OPCR less than 6 times in 3 months (ie, approximately <0.5times/week). There were 52 active participants and 60 non-active participants in the low prognostic group. We did not include the remaining 107 patients with intermediate attendance (patients with 6–19 attendances in 3 months) in the analysis, because the effect of OPCR in this patient group was considered to be modest, if any, and inclusion of this group in the analysis would dilute the measurable efficacy of OPCR. A schematic of the study protocol is provided in **Figure 1**.

CR Program

The CR program began approximately 1 week after AMI and continued after hospital discharge for 3 months. Patients who had angina or evidence of ischemic changes in their electrocardiogram (ECG) at a low level of exercise (walking test), uncontrolled heart failure, and serious arrhythmia were excluded. Program components included supervised exercise sessions (walking, bicycle ergometer and calisthenics) and education, as previously described.[16,17] The exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen's equation, k=0.5–0.6)[18,19] or a heart rate of anaerobic threshold (AT) level obtained in a maximal symptom-limited CPX testing or at level 12–13 ('a little hard') of the 6–20 scale perceived rating of exercise (original Borg's scale).[20] The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30 to 60 min, 3–5 times a week.

Patients were encouraged to attend the education classes that were held 4 times a week with lectures on CAD, secondary prevention, diet, smoking cessation, medication, and

Table 1. Comparisons of Clinical Characteristics in the Low and Non-Low Prognostic Risk Groups

	Low-risk group (n=219)	Non-low-risk group (n=418)	P value
Age (years)	55±7	65±9	<0.01
Male (%)	88	83	NS
Killip class ≥II (%)	0	13	<0.01
Peak CK (U/L)	2,458±1,444	3,339±2,639	<0.01
CK ≥6,000 U/L (%)	0	17	<0.001
Unsuccessful reperfusion (%)	0	24	<0.001
LVEF (%)	49.1±6.8	44.4±10.4	<0.01
LVEF <40% (%)	0	34	<0.001
BNP (pg/ml)	75.7±70.9	209.8±202.0	<0.001
HT (%)	57	56	NS
DM/IGT (%)	47	42	NS
HLP (%)	59	49	<0.05
Obesity (%)	28	27	NS
Smoking habit (%)	72	49	<0.001
Coronary risk factors ≥3 (%)	49	39	<0.05

CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HT, hypertention; DM, diabetes mellitus; IGT, impaired glucose tolerance; HLP, hyperlipidemia.
Values are mean±SD.

Table 2. Baseline Characteristics of Active Participants and Non-Active Participants in the Low-Risk Group

	Active participants (n=52)	Non-active participants (n=60)	P value
Age (years)	57.0±7.3	52.8±7.0	<0.01
Male (%)	83	95	<0.001
Peak CK (U/L)	2,361.1±1,264.2	2,419.5±1,357.1	NS
LVEF (%)	51.4±7.5	47.4±5.7	<0.01
BNP (pg/ml)	83.7±106.0	82.8±74.8	NS
OPCR attendance (times/3 months)	25.5±5.1	1.3±1.7	<0.001
HT (%)	58	52	NS
DM/IGT (%)	44	52	NS
HLP (%)	58	58	NS
Obesity (%)	29	30	NS
Smoking habit (%)	56	75	<0.05
ACE-I/ARB (%)	42	52	NS
β-blocker (%)	19	43	<0.01
Ca channel blocker (%)	40	40	NS
DM medications (%)	8	15	NS
Statin (%)	44	43	NS
Rest HR (/min)	72.6±10.8	71.5±14.9	NS
Rest sBP (mmHg)	123.1±20.2	119.8±21.0	NS
Rest dBP (mmHg)	77.7±11.0	74.7±12.0	NS
Peak WR (W)	132.3±25.2	136.0±31.3	NS
AT ($ml \cdot min^{-1} \cdot kg^{-1}$)	11.1±2.5	11.6±2.6	NS
Peak $\dot{V}O_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	23.4±4.2	23.6±5.0	NS
Peak $\dot{V}O_2$ (%predict)	78.5±14.5	73.7±14.3	NS

Values are mean±SD.
OPCR, outpatient cardiac rehabilitation; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HR, heart rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; WR, work rate; AT, anaerobic threshold; Peak $\dot{V}O_2$, peak oxygen uptake. Other abbreviations see in Table 1.

physical activities given by physicians, nurses, dieticians, pharmacists and exercise instructors. In addition, all patients received individual counseling on exercise prescription, secondary prevention, and daily life activities by a physician and a nurse at the time of hospital discharge and the end of the 3-month CR program. Patients were scheduled to undergo blood tests at the beginning and the end of the 3-month CR program.

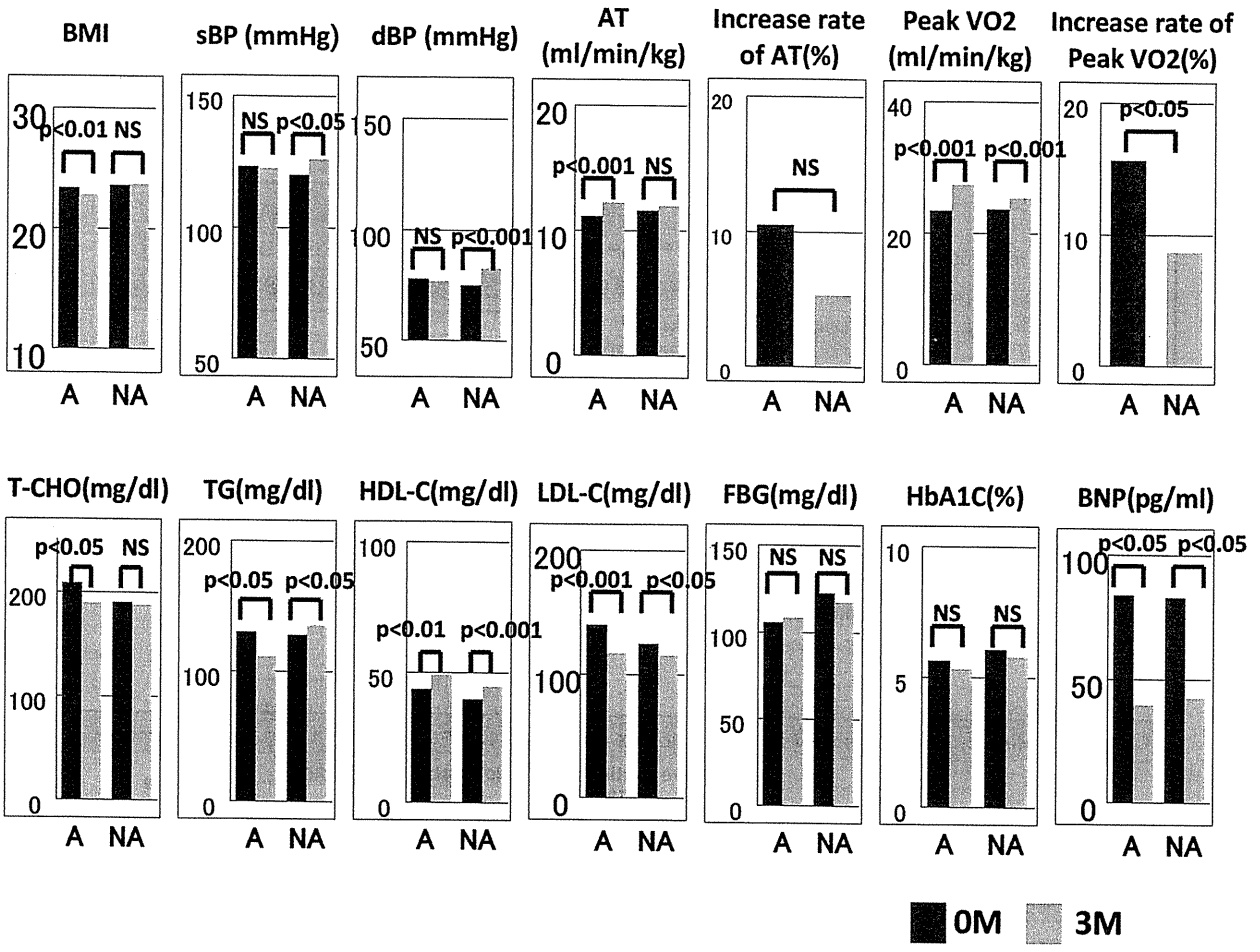

Figure 2. Comparison of the active participants and non-active participants before and after 3 months of outpatient cardiac rehabilitation program. A, active participants; NA, non-active participants; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; AT, anaerobic threshold; Peak $\dot{V}O_2$, peak oxygen uptake; T-CHO, serum concentration of total cholesterol; TG, serum concentration of triglyceride; HDL-C, serum concentration of high density lipoprotein cholesterol; LDL-C, serum concentration of low density lipoprotein cholesterol; FBG, fasting blood glucose; HbA_{1c}, hemoglobin A_{1c}; BNP, brain natriuretic peptide.

CPX

Patients were scheduled to undergo a symptom-limited CPX at the beginning and the end of the 3-month CR program.[21] After a 2-min rest on the bicycle ergometer in the upright position, the patients started pedaling at an intensity of 0 W for 1 min (warm-up), and then performed an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. Twelve-lead ECG was continuously monitored and blood pressure (BP) was measured once-a-min with a sphygmomanometer. Expired gas was collected and analyzed continuously with an AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak $\dot{V}O_2$) was defined as the highest $\dot{V}O_2$ value achieved at peak exercise. Ventilation ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$) were measured and the $\dot{V}O_2$ value at AT or ventilatory threshold was determined as the point at which $\dot{V}CO_2$ increased in a non-linear fashion relative to the rate of $\dot{V}O_2$ (according to the $\dot{V}E/\dot{V}O_2$ time trend, the respiratory exchange ratio flection point, or the V-slope method).[19,22]

Statistical Analysis

Baseline characteristics between the 2 groups were compared using unpaired t-test and chi-square test. Data at baseline and after the 3-month OPCR were compared by paired t-test. A P-value less than 0.05 was considered statistically significant. Data are presented as the mean±standard deviation.

Results

Prevalences of CRF in Low Prognostic Risk Group vs. Non-Low Prognostic Risk Group

Clinical characteristics in the low prognostic risk group and the non-low prognostic risk group are summarized in **Table 1**. Compared with the non-low prognostic risk group, the low prognostic risk group was on average significantly younger, and did not have heart failure on admission or unsuccessful reperfusion, but had lower peak CK and B-type natriuretic peptide (BNP) concentrations and preserved LVEF. Although these findings were anticipated by the definition of the group, they reconfirm that the patients in the low prognostic group were undoubtedly at low prognostic risk. However, when the prevalence of CRF was compared between the 2 groups, the percentage of patients with dyslipidemia, smoking habit and multiple CRF (equal to or more

than 3) was significantly higher in the low prognostic risk group than in the non-low prognostic risk group.

Efficacy of OPCR in Low Prognostic Risk Group: Comparison Between Active and Non-Active Participants

Baseline characteristics in active participants and non-active participants in the low prognostic risk group are summarized in **Table 2**. Although active participants were significantly older than the non-active participants, they were both non-elderly (less than 65 years old). Peak CK was low and LVEF was relatively preserved in both groups. These findings reconfirm that both active and non-active participants are apparently at low prognostic risk. Although there were minor differences in the prevalence of male patients, smokers and β-blocker use, there were no significant differences in exercise capacities at baseline between the 2 groups.

During the 3-month OPCR period, only a few patients experienced changes in medication; statins were introduced in 3 patients (5.8%) in the active participants and 2 patients (3.3%) in the non-active participants, and diabetic medications were started in 2 patients (3.3%) in the non-active participants. Thus, the baseline clinical characteristics of active and non-active participants were almost equivalent, except for the frequency of OPCR attendance.

Figure 2 depicts comparisons of parameters before and after the 3-month OPCR between active and non-active participants in the low prognostic risk group. After the 3-month OPCR, only active participants, and not the non-active participants, showed significant improvements in body mass index (BMI; 23.3±2.5 to 22.9±2.5, P<0.01), AT (11.1±2.5 to 12.7±2.5 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001), total cholesterol (208.4±33.7 to 188.8±26.4 mg/dl, P<0.05), and triglyceride (130.0±77.4 to 111.0±63.7 mg/dl, P<0.05). In addition, while peak $\dot{V}O_2$ increased in both groups (active participants 23.4±4.2 to 27.3±5.0 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001; non-active participants 23.7±5.0 to 25.3±5.3 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001), the magnitude of the increase was significantly greater in the active participants (15.6% vs. 8.6%, P<0.05). In contrast, only non-active participants showed significant worsening in systolic and diastolic BP (systolic BP: from 119.8±21.0 to 126.1±20.4 mmHg, P<0.05, diastolic BP: from 74.7±12.0 to 82.4±11.8 mmHg, P<0.001) and triglyceride (128.0±57.1 to 135.3±63.9 mg/dl, P<0.05). The following parameters showed significant improvements both in the active and non-active participants; high density lipoprotein cholesterol (HDL-C: 43.6±14.1 to 49.0±12.2 mg/dl, P<0.01; 39.7±11.0 to 44.8±11.6 mg/dl, P<0.001), low density lipoprotein cholesterol (LDL-C: 140.1±31.9 to 117.6±25.9 mg/dl, P<0.001; 124.8±31.2 to 115.3±19.7 mg/dl, P<0.01), and BNP (83.7±106.0 to 39.7±44.8 pg/ml, P<0.05; 82.9±74.8 to 42.4±51.7 pg/ml, P<0.05).

Discussion

The major findings of the present study are that the low prognostic risk AMI patients had a higher prevalence of smoking habit, dyslipidemia and multiple CRF than the non-low prognostic risk patients, and that in the low prognostic risk group, active participation in OPCR was associated with better CRF profile (ie, BP, dyslipidemia, and obesity) and exercise capacity. These findings suggest that, by actively participating in OPCR after AMI, even the low prognostic risk patients might gain clinical benefits such as better CRF modification and physical functioning.

Previous Studies

Various guidelines for management of post-AMI (or established CAD) patients recommend aggressive modifications of CRF for secondary prevention,[10,12,13] and adherence to these recommendations and/or reduction of CRF have been shown to improve long-term prognosis.[23–26] In contrast, Thrombolysis In Myocardial Infarction (TIMI) risk score[27] and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) risk score[28] have demonstrated that 1-year mortality is very low in AMI patients with age <65 years, successful reperfusion, absence of acute phase heart failure, and preserved LV function, which are compatible with the patient characteristics of the low prognostic risk group in the present study. However, little is known about the prevalence of CRF or clinical significance of accumulation of multiple CRF in such low prognostic risk patients. In relation to this, it is of note that, Lloyd-Jones and colleagues demonstrated that young subjects with accumulated CRF, despite low short-term risk, have a higher 'lifetime risks for CAD' and greater progression of subclinical coronary atherosclerosis compared with those at low lifetime risk.[29,30] These data suggest that apparently low prognostic risk patients stratified by TIMI or CADILLAC risk score are likely to have superb short-term (1 year) prognosis, but not necessarily favorable long-term or lifetime prognosis.

Present Study

The present study has explicitly demonstrated that the low prognostic risk patients actually have higher prevalence of multiple CRF than the non-low prognostic risk patients. Although the finding that younger AMI patients have higher prevalences of smoking and hyperlipidemia than elderly patients is in accordance with previous studies,[31] there has been no report demonstrating higher prevalence of multiple CRF in low prognostic risk AMI patients with successful reperfusion and preserved LVEF. According to TIMI risk score[27] or CADILLAC risk score,[28] this finding might appear confusing or counterintuitive. However, from the viewpoint of lifetime CAD risk,[29,30] this finding might have a significant impact on the long-term prognosis of apparently low prognostic risk AMI patients.

The second major finding in the current study is that active participation in OPCR improved CRF (BP, dyslipidemia, and obesity) and exercise capacity even in the low prognostic risk group. There have been no studies that reported the effect of OPCR in the low prognostic risk AMI patients. Taylor et al[9] reported in a meta-analysis of randomized controlled trials that the effect of OPCR on total mortality did not differ between studies before and after year 1995 (odds ratio 0.84 before 1995 vs. 0.62 after 1995, NS), but they did not assess the effect of OPCR on the low prognostic risk patients after successful reperfusion. Witt et al recently reported that participation in OPCR after AMI was associated with improved survival and reduced recurrent myocardial infarction (MI) at 3 years, but the rate of reperfusion was only 33% in their patients.[32] Squires et al reported that a 3-year coronary disease management program in OPCR for CAD patients was effective in achieving the secondary prevention goals, but their assessment did not target the low prognostic risk patients.[33] Thus, the present study has demonstrated for the first time the favorable effects of OPCR on CRF and exercise capacity in the low prognostic AMI patients.

Clinical Implications

It remains unknown whether the improvements in CRF profiles and exercise capacity achieved by active participation in OPCR can lead to an improved long term prognosis in the low prognostic risk AMI patients. However, Tani et al reported that successful life style modification with exercise, body weight reduction and smoking cessation for 6 months was associated with coronary plaque volume regression in low prognostic risk CAD patients.[34] Belardinelli et al reported in the ETICA (Exercise Training Intervention after Coronary Angioplasty) trial that a 6-month OPCR for the relatively low risk CAD patients after successful PCI (49% having AMI) reduced cardiac events and hospital re-admission during the follow-up period (33±7 months).[35] In addition, because the magnitude of the improvement in endothelial function afforded by OPCR does not correlate with the improvements in CRF,[36] the general consensus at present is that the favorable effect of OPCR on the long-term prognosis is mediated by a direct anti-atherosclerosis effect of exercise training rather than by improvements in CRF.[4] Therefore, further study is necessary to determine the long term effect of OPCR in AMI patients with low prognostic risk.

In the present study, significant differences were found between active and inactive OPCR participants in BMI, total cholesterol, triglyceride and BP, but not in LDL-C or glucose tolerance. One might argue that the prognostic impacts of BMI, total cholesterol, triglyceride and BP might be less powerful compared with those of LDL-C and diabetes. However, Nakatani et al reported that the metabolic syndrome, diagnosed from the combination of BMI, HDL-C, triglyceride, BP, and fasting blood glucose, was an independent predictor of subsequent combined cardiac events of cardiac death and non-fatal MI in Japanese patients after AMI.[37] Therefore, it is plausible that the improvements in BMI, triglyceride and BP observed in the present study might contribute to the improvement in the long-term prognosis in Japanese AMI patients.

Future Direction

In the present study, the rate of active OPCR participation was only 24% (52/219 patients) in the low prognostic risk group. To reduce lifetime CAD risk in these low prognostic risk AMI patients, a substantial increase in participation rate in OPCR is necessary. However, according to a recent nation-wide survey in 526 Japanese Circulation Society authorized cardiology training hospitals,[15] the implementation rate was 92% for emergency PCI, but only 9% for OPCR. In addition, Ades et al reported that, by multivariate analysis, the strength of the physician's recommendation for participation was the most powerful predictor of OPCR participation.[38] Thus, to increase the participation rate in OPCR, it is critically important to greatly increase the number of CR facilities and to enhance physicians' understanding of the benefits of OPCR after AMI.

Study Limitations

First, this study was a retrospective analysis and the number of patients was relatively small. The more active patients would be expected to participate in OPCR and this might have introduced a selection bias.

Second, the low prognostic risk group is anticipated to be at low risk in terms of short-term prognosis[27,28] and hence, whether improvements in CRF profile in such low prognostic risk patients are associated with actual improvements in outcome is uncertain. A longer follow-up in a larger number of patients is necessary to increase the statistical power to demonstrate the beneficial effect of OPCR on the long-term prognosis.

Conclusions

The low prognostic risk AMI patients have a higher prevalence of multiple CRF than the non-low risk patients. Active participation in OPCR program is associated with improved exercise capacity and CRF profile in such low prognostic risk patients. OPCR program can be effective in achieving secondary prevention goals even in the low prognostic risk AMI patients.

Disclosure

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ORIGINAL ARTICLE
Cardiac Rehabilitation

Effects of Exercise Training in Patients With Chronic Heart Failure and Advanced Left Ventricular Systolic Dysfunction Receiving β-Blockers

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Background: It remains unclear whether patients with chronic heart failure (CHF) and advanced left ventricular (LV) dysfunction on β-blocker therapy benefit from exercise training (ET).

Methods and Results: We studied 45 CHF patients with advanced LV dysfunction [ejection fraction (LVEF) <25%] and impaired exercise tolerance [normalized peak oxygen uptake ($P\dot{V}O_2$) <70%] receiving a β-blocker: 33 patients participated in a cardiac rehabilitation program with ET (ET group) and 12 did not (inactive control group). Exercise capacity, LV dimension and plasma B-type natriuretic peptide (BNP) were assessed before and after a 3-month study period. At baseline, both groups had markedly reduced LVEF (ET group 18±4% vs. Control group 18±5%, NS) and impaired exercise capacity (normalized $P\dot{V}O_2$ 51±10% vs. 55±9%, NS). Although one patient in the ET group withdrew from the program due to worsening CHF, no serious cardiac events occurred during the ET sessions. After 3 months, the ET group (n=24) had significantly improved $P\dot{V}O_2$ by 16±15% (1,005± 295 to 1,167±397 ml/min, P<0.001), while the $P\dot{V}O_2$ of the control group was unchanged. LV end-diastolic dimension decreased in both groups to a similar extent, but plasma BNP was significantly decreased only in the ET group (432 to 214 pg/ml, P<0.05).

Conclusions: The data indicate that in CHF patients with advanced LV dysfunction on β-blocker therapy, ET successfully improves exercise capacity and BNP without adversely affecting LV remodeling or causing serious cardiac complications. (*Circ J* 2011; **75:** 1649–1655)

Key Words: Advanced left ventricular dysfunction; Beta-blocker; Chronic heart failure; Exercise capacity; Exercise training

In patients with chronic heart failure (CHF), exercise training (ET) improves exercise capacity, quality of life, and prognosis.[1–4] The ACC/AHA guidelines for the management of CHF recommend ET as an adjunct therapy to improve the clinical status of ambulatory patients with current or prior symptoms of heart failure (HF) and reduced left ventricular (LV) ejection fraction (LVEF).[5] However, previous studies of ET in patients with CHF have primarily examined patients with an LVEF in the range of 25–40%, and few studies enrolled patients with advanced LV dysfunction (LVEF <25%).[6] Thus, the therapeutic benefits and safety of ET in patients with advanced LV dysfunction remain unknown.

β-blocker therapy improves the long-term prognosis of patients with advanced HF,[7–9] and β-blockers are recommended as a class I standard medication by the ACC/AHA and ESC guidelines.[5,10] However, β-blockers were prescribed in only 0–70% of eligible patients in previous studies of ET in patients with advanced LV dysfunction.[6,11–14] A large randomized controlled trial, HF-ACTION,[15] was designed to examine the efficacy and safety of ET in patients with CHF, and the results of this study were recently reported. β-blockers were prescribed in 95% of the patients in HF-ACTION, but the median LVEF of study participants was 25%, indicating that half of the patients had an LVEF higher than 25%. Thus, in the current era of widespread β-blocker use, it remains unclear whether patients with CHF and advanced LV dysfunction on β-blocker therapy benefit from ET. Accordingly, the purpose of the present study was to determine whether ET safely improves the exercise capacity of CHF patients on β-blocker therapy with advanced LV dysfunction.

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Table 1. Clinical Characteristics and Baseline Data

	ET group	Inactive control group	P value
n	33	12	
Age (years)	51±14	52±16	NS
Male (%)	88	83	NS
NYHA class (II/III) (%)	39/61	33/67	NS
NIsCM/IsCM (%)	64/36	83/17	NS
HT (%)	41	17	NS
HL (%)	36	67	NS
IGT/DM (%)	36	25	NS
BMI	21.4±3.1	23.1±2.6	NS
Medications			
Digitalis (%)	70	58	NS
Diuretics (%)	97	92	NS
ACEI/ARB (%)	91	92	NS
BB (Car/Meto/Biso [%])	88/9/3	92/0/8	
Ca antagonist (%)	9	8	NS
Nitrate (%)	24	8	NS
Cardiotonic (%)	36	8	NS
Antiarrhythmic agent (%)	48	25	NS
Baseline data			
Plasma BNP (pg/ml)	365±390	215±129	NS
LVEDD (mm)	70±7	70±9	NS
LVEF (%)	18±4	18±5	NS
Peak $\dot{V}O_2$ (ml/min)	979±285	1,122±283	NS
Normalized peak $\dot{V}O_2$ (%)	51±10	55±9	NS
$\dot{V}E$-$\dot{V}CO_2$ slope	35.3±10.1	31.7±5.0	NS

Data are mean±SD.
ET, exercise training; NYHA, New York Heart Association; NIsCM, non-ischemic cardiomyopathy; IsCM, ischemic cardiomyopathy; HT, hypertension; HL, hyperlipidemia; IGT, impaired glucose tolerance; DM, diabetes mellitus; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BB, β-blocker; Car, carvedilol; Meto, metoprolol; Biso, bisoprolol; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; $\dot{V}O_2$, oxygen uptake; $\dot{V}E$, ventilation; $\dot{V}CO_2$, carbon dioxide output.

Methods

Patients

Forty-five CHF patients with advanced LV dysfunction who fulfilled the following inclusion criteria were included in the present study: 15–80 years old, advanced LV systolic dysfunction (LVEF <25%), reduced exercise tolerance with normalized peak oxygen uptake <70%, a well-controlled body fluid level (euvolemic), and no signs of worsening HF over the preceding 2-week period. LVEF was determined during left ventriculography using contrast medium or radioisotope. Of the 45 patients, we retrospectively assigned 33 patients who participated in a 3-month cardiac rehabilitation program with ET to the ET group and the remaining 12 patients who did not undergo ET to the inactive control group. All patients were taking a β-blocker and were in a stable state.

The Cardiac Rehabilitation Program

The cardiac rehabilitation program with ET for CHF at our institute has been previously described.[16] Before entering the ET program, patients were confirmed not to have evidence of ischemia or severe arrhythmia during a level walking test. All patients gave written informed consent before entering the program.

The exercise program consisted of walking, bicycling on an ergometer, and calisthenics of 40–60 min/session 3–5 sessions/week for 3 months. Exercise intensity was determined individually at 30–50% of heart rate (HR) reserve (Karvonen's equation: k=0.3–0.5),[17] an anaerobic threshold (AT) level obtained in a maximal symptom-limited cardiopulmonary exercise test, or at levels 11–13 ("fairly light" to "somewhat hard") of the 6–20 scale rating of perceived exertion (the original Borg's score[18,19]). Care was taken to prescribe a slightly lower level of exercise intensity (30–40% of HR reserve or an AT level) and lower session frequency (3 sessions/week) to patients with very low LVEF (<20%). The exercise program usually began with supervised sessions for 2–4 weeks, followed by home exercise combined with once or twice weekly supervised sessions for the remaining 8–10 weeks. Home exercise consisted mainly of brisk walking at a prescribed HR for 30–50 min, 3–5 times a week.

Patients were encouraged to attend education classes, which were held 3 times each week with lectures given by physicians, nurses, dieticians, and pharmacists on coronary artery disease, secondary prevention, HF management, diet, smoking cessation, and medication. In addition, all ET group patients received individual counseling on exercise prescription, secondary prevention, and daily life activities by a physician and a nurse at the time of hospital discharge and at the end of the 3-month cardiac rehabilitation program.

The inactive control patients did not participate in any exercise program or perform regular home exercise.

Cardiopulmonary Exercise Testing

Patients were scheduled to undergo a symptom-limited cardiopulmonary exercise test at the beginning and end of the 3-month study period.[20] After a 2-min rest period on the bicycle ergometer in an upright position, patients pedaled at an intensity of 0 W for 1 min (warm-up), and were then subjected to an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. The 12-lead ECG was continuously monitored and blood pressure was measured every minute with a sphygmomanometer. Expired gases were collected and analyzed continuously with an AE-280S or AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak $\dot{V}O_2$) was defined as the highest $\dot{V}O_2$ value achieved at peak exercise. Ventilation ($\dot{V}E$) and carbon dioxide output ($\dot{V}CO_2$) were measured and the gradient of the $\dot{V}E$–$\dot{V}CO_2$ relationship ($\dot{V}E$ vs. $\dot{V}CO_2$ slope) was determined.

Clinical Data

Patients were scheduled to undergo echocardiography and plasma B-type natriuretic peptide (BNP) measurements at the beginning and end of the 3-month study period. LV internal diameters were acquired from the parasternal short-axis view, at the approximate mitral chordae level, using direct 2-dimensional measurements or targeted M-mode echocardiography if the M-mode cursor could be positioned perpendicular to the septum and LV posterior wall. Plasma BNP levels were measured with a specific immunoradiometric assay for human BNP using a commercial kit (Shionoria). The upper limit of normal plasma BNP level was 18.4 pg/ml. The minimal and maximal detectable levels of BNP were 4 and 2,000 pg/ml, respectively.

Statistical Analysis

Data are presented as the means±standard deviations. Significant differences were determined with paired or unpaired

Table 2. Results of ET in the Exercise and Control Groups

	ET group (n=24)			Inactive control group (n=12)		
	Pretraining	Posttraining	P value	Pretraining	Follow-up	P value
Plasma BNP (pg/ml)	432±451	214±232	<0.05	238±130	281±305	NS
LVEDD (mm)	73±6	66±11	<0.005	72±8	65±11	<0.01
LVFS (%)	12±4	16±6	0.065	10±3	19±9	<0.01
HR at rest (beats/min)	82±16	76±14	0.057	74±17	72±19	NS
Peak HR (beats/min)	129±28	134±22	NS	141±27	130±26	NS
Peak $\dot{V}O_2$ (ml/min)	1,005±295	1,167±397	<0.001	1,122±283	1,136±288	NS
Normalized peak $\dot{V}O_2$ (%)	50±11	58±14	<0.001	55±9	57±12	NS
Peak work rate (W)	96±28	111±30	<0.001	105±20	103±26	NS
AT (ml/min)	585±162	622±160	0.066	639±133	593±117	NS
$\dot{V}E$-$\dot{V}CO_2$ slope	34.8±11.0	32.9±10.9	NS	31.7±5.0	31.9±6.2	NS

Plasma BNP data were available for 21 patients in the ET group and 10 patients in the inactive control group.
LVEDD data were available for 18 patients in the ET group and 11 patients in the inactive control group.
LVFS data were available for 16 patients in the ET group and 11 patients in the inactive control group.
AT data were available for 19 patients in the ET group and 11 patients in the inactive control group.
LVFS, left ventricular fractional shortening; HR, heart rate; AT, anaerobic threshold. Other abbreviations as in Table 1.

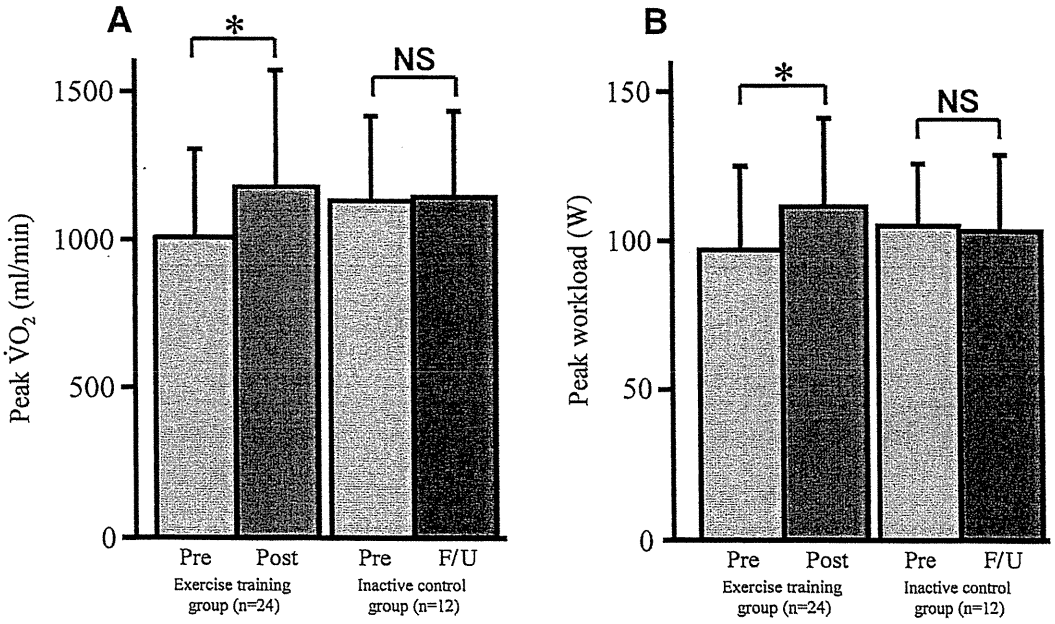

Figure 1. (**A**) Peak oxygen uptake (peak $\dot{V}O_2$) before and after the 3-month study period in the exercise training (ET) group (**Left**) and inactive control group (**Right**). (**B**) Peak workload before and after the 3-month study period in the ET group (**Left**) and inactive control group (**Right**). *P<0.001 compared with pretraining. Pre, pretraining; Post, posttraining; F/U, follow-up.

t-tests as appropriate. Considering the small number of inactive control patients, we also analyzed the differences between groups using a non-parametric Mann-Whitney U test, and the differences before and after ET in each group using Wilcoxon test. Differences in frequencies were analyzed with the Fisher exact probability test or the chi-square test. Pearson's correlation analysis was used to evaluate the correlation between the change in peak $\dot{V}O_2$ and the change in BNP. Statistical calculations were performed using Statview software. A P value less than 0.05 was considered statistically significant.

Results

Table 1 summarizes the clinical characteristics, baseline LV function and exercise tolerance in the ET and inactive control groups. There were no significant differences between the ET and control groups at baseline. The non-parametric Mann-Whitney U test yielded the same results (data not shown). All patients were already on β-blocker therapy at the time of study entry, but some patients were still being up-titrated. The proportion of patients taking β-blockers for more than 3 months was 24% (8/33 patients) in the ET group and 33% (4/12 patients) in the control group (NS). The doses of β-blockers were similar between the 2 groups at the time of

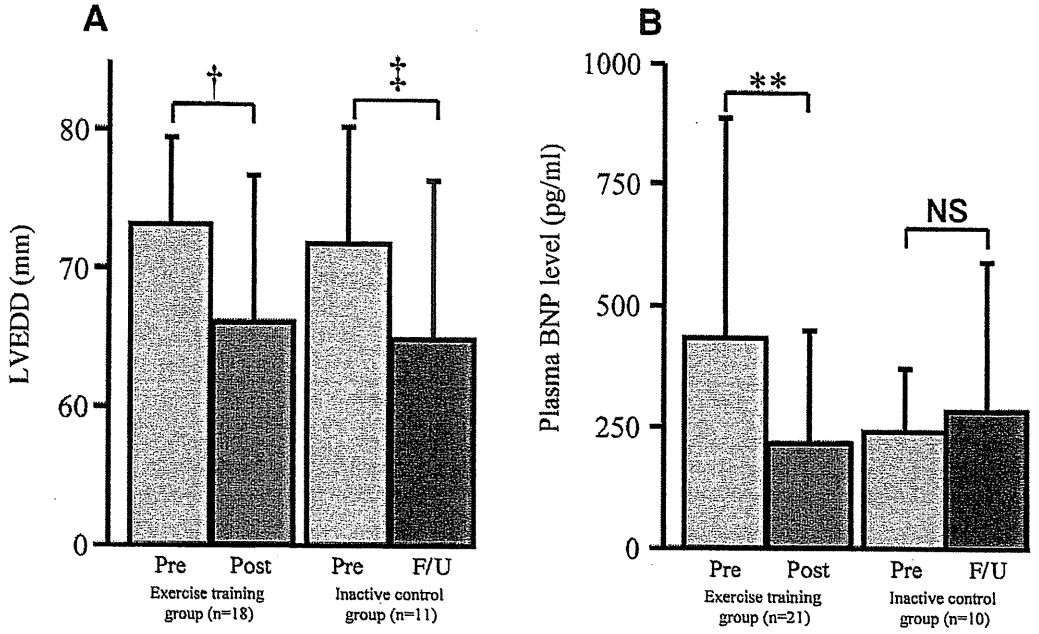

Figure 2. (**A**) Left ventricular end-diastolic diameter (LVEDD) before and after the 3-month study period in the exercise training (ET) group (**Left**) and inactive control group (**Right**). (**B**) Plasma B-type natriuretic peptide (BNP) before and after the 3-month study period in the ET group (**Left**) and inactive control group (**Right**). †P<0.005, ‡P<0.01, **P<0.05 compared with pretraining. Pre, pretraining; Post, posttraining; F/U, follow-up.

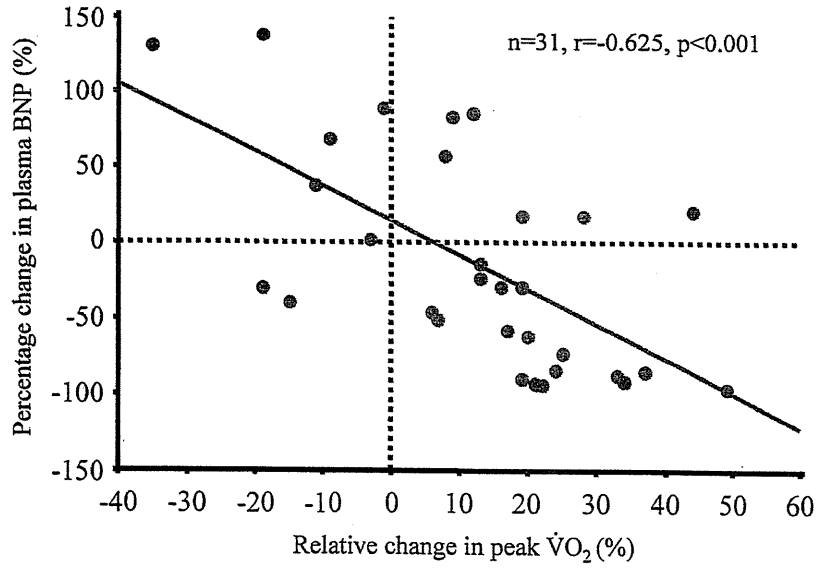

Figure 3. Significant inverse correlation between the relative change in peak oxygen uptake (peak $\dot{V}O_2$) [{(peak $\dot{V}O_2$ after the 3-month–peak $\dot{V}O_2$ at baseline)/peak $\dot{V}O_2$ at baseline}×100] and percentage change in plasma B-type natriuretic peptide (BNP) [{(plasma BNP after the 3-month–plasma BNP at baseline)/plasma BNP at baseline}×100] in all study patients.

study entry (for carvedilol, 11.3 mg/day in the ET group and 13.2 mg/day in the control group, NS). The schedule of up-titration and the final dose of β-blockers were left to the attending physicians.

Of the 33 patients in the ET group, 24 (73%) completed the 3-month ET program, and among the 9 patients who did not complete the study, one had an exacerbation of HF (3%), one withdrew for a non-cardiac medical reason (claudication) (3%) and the remaining 7 withdrew for social reasons (the distance to the institute was too far, return to work, etc) (21%). These 9 patients were excluded from the statistical analysis of ET effects. There were no significant differences in the baseline plasma BNP levels, LV end-diastolic dimensions (LVEDD), LVEF, or exercise capacity between the 24 patients who completed the 3-month ET program and the 9 patients who withdrew. No serious cardiac events, including death or cardiopulmonary arrest, occurred during the ET sessions. No patients developed new atrial fibrillation during

Table 3. Effect of Training in Heart Failure Patients With Advanced LV Dysfunction (Mean or Median LVEF <20%)

First author	Year	Number of patients	Age (years)	NYHA (II/III)	LVEF (%)	ACEI/ARB (%)	BB (%)	Duration	Increments of peak $\dot{V}O_2$ ($ml \cdot min^{-1} \cdot kg^{-1}$)
Coats AJS	1990	11	63	7/4	19	82	–	8 weeks	14.3→16.7 (17%↑)
Coats AJS	1992	17	61.8	10/7	19.6	88	0	8 weeks	13.2→15.6 (18%↑)
Adamopoulos S	1995	12	62.4	6/6	18.9	92	0	8 weeks	12.4→–
Sturm B	1999	13	55	6/7	17	92	23	12 weeks	15.9→18.5 (16%↑)
Quittan M	1999	12	57	7/5	17	100	25	3 months	15.9→18.5 (16%↑)
Van Berendoncks AM	2010	46	57.5	34/12	17	100	70	4 months	19→21 (11%↑)
Nishi I	2011	24	51	11/13	17	88	100	3 months	16.3→18.7 (15%↑)

Abbreviations as in Table 1.

the rehabilitation program.

Exercise Variables

After the 3-month study period, resting HR was unchanged in the control group, but tended to decrease in the ET group (P=0.057, **Table 2**), and peak HR did not change in both groups (**Table 2**). The ET group showed significant improvements in peak $\dot{V}O_2$ (1,005±295 to 1,167±397 ml/min, 16±15%; 16.3±4.3 to 18.7±5.1 $ml \cdot min^{-1} \cdot kg^{-1}$, 15±14%, both P<0.001) and its normalized value (P<0.001) after the study period, whereas the inactive control group did not (**Table 2, Figure 1A**). In addition, only the ET group achieved a significant increase in peak work rate after the 3-month ET (96±28 to 111±30 W, P<0.001) (**Table 2, Figure 1B**). $\dot{V}E$ vs. $\dot{V}CO_2$ slope did not significantly change in either group after the 3-month study period (**Table 2**).

The non-parametric Wilcoxon test yielded the same results, except that $\dot{V}E$ vs. $\dot{V}CO_2$ slope significantly decreased only in the ET group after the 3-month study period (median 31.1 to 29.4, P<0.05).

LV Function and BNP

LVEDD significantly decreased in both the ET group (P< 0.005) and the inactive control group (P<0.01) (**Table 2, Figure 2A**), and the relative decrease in LVEDD was similar between the 2 groups (ET group –10±11% vs. inactive control group –10±10%, NS). LV fractional shortening (FS) increased in both groups, but the change reached a statistical significance only in the inactive control group (P<0.01) and not in the ET group (P=0.065) (**Table 2**).

Compared to their baseline levels, plasma BNP concentrations significantly decreased (P<0.05) after the ET program, but did not change in the inactive control group (n=10) (**Table 2, Figure 2B**).

When the percentage change in BNP [{(BNP after 3 months–BNP at baseline)/BNP at baseline}×100] was plotted against the relative change in peak $\dot{V}O_2$ [{(peak $\dot{V}O_2$ after 3 months–peak $\dot{V}O_2$ at baseline)/peak $\dot{V}O_2$ at baseline}×100] in the entire patient population, there was a significant inverse correlation (r=–0.625, P<0.001, n=31), indicating that a greater increase in peak $\dot{V}O_2$ was associated with a greater decrease in plasma BNP (**Figure 3**).

Discussion

ET has been shown to favorably affect the outcomes and quality of life of many patients with CHF, but it has remained unclear whether ET is safe and beneficial for those CHF patients with advanced LV dysfunction and on β-blocker therapy. We set out to examine that question, and our data indicate that, in this subset of CHF patients, an appropriate ET program safely increased exercise capacity and decreased plasma BNP levels without promoting deleterious LV remodeling. Additionally, there was a significant inverse correlation between plasma BNP and peak $\dot{V}O_2$ during the study period, suggesting that improvements in exercise capacity are associated with amelioration of elevated LV load. Finally, the prescribed ET program was very well tolerated; the withdrawal rate from the exercise program due to cardiac reasons was only 3%.

Previous Studies

Several other studies over the past 20 years have studied the role of ET in patients with advanced LV dysfunction (mean LVEF <20%) (**Table 3**), and demonstrated a significant improvement in peak $\dot{V}O_2$ by 16–18% following ET.[6,11,13,21] However, β-blockers were prescribed to only 0–25% of enrolled patients in most of those studies,[6,11–13] and to 70% of the patients in one study.[14] In contrast, in the present study, all patients were prescribed β-blockers. Thus, our results are more relevant in the current era when β-blocker therapy is the standard of care.

β-blocker therapy does not improve peak $\dot{V}O_2$ in patients with CHF, despite the symptom amelioration, improvements in NYHA functional class, and increased LVEF associated with β-blocker therapy.[22,23] In contrast, ET can increase peak $\dot{V}O_2$ in patients with moderate to severe HF who are taking a β-blocker.[24–27] However, most of the previous studies examining ET in patients using β-blockers recruited only patients with LVEF in the range of 23–35%. The study population of the recent HF-ACTION trial, in which β-blockers were prescribed to 95% of patients, did not contain more than 50% of patients with an LVEF <25%.[15] Thus, to our knowledge, the present study is the first to examine the effects of ET in CHF patients with advanced LV dysfunction (LVEF <25%) and concurrent β-blocker therapy.

Exercise Capacity

There was concern that β-blockers could abrogate the benefits of ET in patients with CHF, but one study reported that β-blocker therapy did not affect ET-associated increases in exercise capacity.[24] Additionally, there were no differences in the effects of ET between patients receiving β-1 selective and non-selective α-β blockers.[28] The increase in peak $\dot{V}O_2$ in the ET group in the present study (15%) was less than that seen in the study of Demopoulos et al (24–27%),[24] but was comparable to the increase reported by Forissier et al (14–17%).[28]

In the HF-ACTION trial,[15] the ET group had a significant

improvement in peak $\dot{V}O_2$ at 3 months compared to the usual care group (0.6 vs. 0.2 ml·min^{-1}·kg^{-1}; P<0.001), but this increase was relatively small (median 4%). The authors attributed the relatively small improvement to low adherence to the exercise protocol. Thus, baseline patient characteristics, the specific exercise program prescribed, and adherence to that program likely all contribute to the magnitude of change in exercise capacity observed in the different studies.

LV Remodeling

In the present study, both study groups showed a decrease in LVEDD (ie, there was reverse LV remodeling). This result differs from those of Giannuzzi et al who found that LV remodeling was reversed by ET, but worsened in a control non-ET group with moderate CHF (average LVEF 25%).[29] These conflicting results may be due to the low rate of prescription of β-blockers in the study by Giannuzzi et al (20%).

In addition, experimental studies using a rat model showed that excessive exercise after a large myocardial infarction aggravated LV remodeling,[30,31] but moderate exercise had either no effect[32] or attenuated adverse LV remodeling.[33] Although the myocardial infarction models in the rat differ from human CHF, these findings suggest that exercise intensity in an ET program can affect LV remodeling. Based on this, exercise intensity was adjusted according to the severity of LV dysfunction in each patient in the present study. In addition to β-blocker therapy, this appropriate adjustment of exercise prescription may also have contributed to reverse LV remodeling.

Plasma BNP

Passino et al reported that ET decreases plasma BNP levels in patients with moderate CHF.[34] The present results are consistent with that study, but we extended these findings to a patient population with more severe LV dysfunction (mean LVEF 18%) and higher baseline BNP (365 pg/ml) than Passino's study (mean LVEF of 35% and baseline BNP of 187 pg/ml).

The significant inverse correlation that we found between changes in BNP and exercise capacity is also consistent with the previous report,[34] which is somewhat counterintuitive because one could hypothesize that a greater increase in exercise capacity requiring a greater amount of ET would result in sustained LV wall stress and an associated increase in plasma BNP. However, the available data suggests that ET of an appropriate intensity and duration ameliorates the increased LV wall stress that stimulates BNP production. This hypothesis is consistent with the observation in a canine model of HF that regular ET lowers LV end-diastolic pressure at rest through enhanced nitric oxide production.[35] One remaining question is whether the observed decrease in BNP is attributable to ET alone or to the combination of ET and β-blocker therapy.

Etiology of CHF

It is intriguing whether the response to ET differs between CHF due to ischemic and non-ischemic cardiomyopathies. Because the total number of patients was not sufficient, such subgroup analyses were beyond the scope of the present study. However, a tentative analysis of 26 patients with a non-ischemic etiology showed a consistent result with the main results: After the 3-month study period, the non-ischemic ET group (n=16) showed significant increases in peak $\dot{V}O_2$ (1,019 to 1,210 ml/min, P<0.001) and peak work rate (100 to 116 W, P<0.001), whereas the non-ischemic inactive control group (n=10) did not (1,177 to 1,154 ml/min and 107 to 103 W, both NS), while having significant reductions in LVEDD in both groups (74 to 66 mm and 71 to 65 mm, both P<0.05). A larger study is necessary to explore the potential difference, if any, in response to ET between ischemic and non-ischemic CHF.

Safety of ET in HF

Among the study patients undergoing ET, 1 (3%) had worsening of HF in the 3-month study period. The ELVD-CHF trial followed patients with a mean LVEF of 25% for 6 months, and clinical events (death, HF hospitalization, temporary worsening of symptoms not requiring hospitalization) occurred in 9% of patients in the exercise group, but in 18% of patients in the usual care group.[29] Additionally, HF-ACTION followed patients with a median LVEF of 25% for 30 months, and worsening HF occurred in 26% of the ET group and 29% of the patients in the usual care group.[15] Thus, the incidence of cardiac events observed in the present study for patients with severe LV dysfunction is comparable to that seen in patients undergoing conventional care in previous studies, suggesting that ET for HF patients with severe LV dysfunction on β-blockers may be safe.

Clinical Implications

Our results extend previous findings[11,12,21,24,28] of the favorable effects of ET in CHF patients with moderate LV dysfunction[24,28] or not receiving β-blockers[11,12,21] to those with advanced LV dysfunction receiving β-blockers. Physicians are often reluctant to recommend ET to patients with HF, especially when the LVEF is markedly reduced. Our data suggest that, even in such patients with advanced LV dysfunction, appropriate ET/cardiac rehabilitation based on careful medical evaluation can lead to a significant improvement in exercise capacity and favorably affect LV remodeling and biomarkers of CHF progression.

Study Limitations

Our data provide a good rationale for future studies of ET for patients with advanced LV dysfunction in CHF, but our study is limited because it is retrospective and from a single center with a relatively small number of patients. Therefore, a large controlled randomized study should be performed to confirm these results.

An additional confounding factor in our study is the exclusion from the analysis of the 9 patients who dropped out of the study. However, an additional comparison between the completion group (n=24) and dropout group (n=9) yielded similar backgrounds, and we expect little bias from the exclusion of these patients.

All the patients in the present study were clinically stable on β-blockers and the proportion of patients taking β-blockers for more than 3 months was similar between the 2 groups, but the time from the initiation of β-blocker therapy to the start of ET varied. Additionally, β-blocker therapy was not standardized across the study participants. Therefore, we cannot draw any conclusions regarding the optimal time to initiate ET after the start of β-blocker therapy or which β-blocker is best[36] combined with ET. Further studies are necessary to address these issues.

Conclusion

In patients with CHF, advanced LV dysfunction and on β-blockers, ET can safely increases exercise capacity with favorable effects on LV remodeling and plasma BNP with a low incidence of cardiac complications (3%).