中心とした心臓リハビリテーションの効果は既に確立されているといっても過言ではない．PCIや冠動脈バイパス術（coronary artery bypass grafting;CABG）はあくまでも冠動脈狭窄に対する局所治療であり，冠危険因子や生活習慣を改善しないかぎり，再発する可能性が極めて高いと言える．多くの医療者は感覚的にはそれに気づきながらも，実際の診療に運動療法や患者教育を導入できないでいるが，それを必須な治療であると真に考えていないからにほかならない．運動療法は導入や継続は必ずしも容易ではなく，また，不安定狭心症をはじめとする重症例では冠血行再建が明らかに優る．現代におけるCADに対する理想的な治療戦略は，「冠血行再建」＋「包括的介入」をセットとした心臓リハビリテーションである．

表3　心筋梗塞二次予防要約表より：運動療法（心臓リハビリテーション）

1．運動負荷試験に基づき，1回最低30分，週3～4回（できれば毎日），歩行・走行・サイクリングなどの有酸素運動を行う．（エビデンスA）
2．日常生活の中の身体活動（通勤時の歩行，家庭内外の仕事等）を増す．（エビデンスB）
3．10～15RM1＊1程度のリズミカルな抵抗運動を有酸素運動とほぼ同頻度に行う．（エビデンスA）
4．中等度ないし高リスク患者＊2は施設における運動療法が推奨される．（エビデンスB）

＊1：RM:Repetition Maximum（最大反復回数），10RMとは10回繰り返せる強さのこと．
＊2：高リスク患者：
・著しい左室機能不全（EF≦30%）．
・安静時ないし運動誘発性の危険な心室性不整脈．
・運動中の15 mmHg以上の収縮期血圧低下，負荷量を増加しても血圧が上昇しない．
・心肺蘇生からの生還者．
・うっ血性心不全，心原性ショック，危険な心室性不整脈を合併した心筋梗塞．
・重篤な冠動脈病変および運動療法誘発の著しい心筋虚血（0.2 mV以上のST低下）．

文献
1) Saltin B, et al.:Response to exercise after bed rest and after training. Circulation 38 (Suppl. 7) : VII 1-78, 1968
2) Franciosa JA, et al.:Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 47:33-39, 1981
3) Belardinelli R, et al.:Randomized, controlled trial of long-term moderate exercise training in chronic heart failure:effects on functional capacity, quality of life, and clinical outcome. Circulation 99:1173-1182, 1999
4) American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure:A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 107:1210-1225, 2003
5) 日本心臓リハビリテーション学会（監）：心臓リハビリテーション：AHCPRガイドライン．心臓リハビリテーション学会，協和企画，1996
6) 循環器病の診断と治療に関するガイドライン（2006年度合同研究班報告）（班長；野原隆司）：運動療法の有用性とその機序，心血管疾患におけるリハビリテーションに関するガイドライン（2007年改訂版），8-12，2007〔http://www.j-circ.or.jp/guideline/pdf/JCS2007_nohara_h.pdf〕
7) Taylor RS, et al.:Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med 116: 682-692, 2004
8) Witt BJ, et al.:Cardiac rehabilitation after myocardial infarction in the community. J Am Coll Cardiol 44:988-996, 2004
9) Suaya JA, et al.:Cardiac rehabilitation and survival in older coronary patients. J Am Coll Cardiol 54:25-33, 2009
10) Goel K, et al.:Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. Circulation 123:2344-2352, 2011
11) Ornish D, et al.:Can lifestyle changes reverse coronary heart disease? The Lifestyle Heart Trial. Lancet 336:129-133, 1990
12) Schuler G, et al.:Regular physical exercise and low-fat diet. Effects on progression of coronary artery disease. Circulation 86:1-11, 1992

13) Sdringola S, et al.:Combined intense lifestyle and pharmacologic lipid treatment further reduce coronary events and myocardial perfusion abnormalities compared with usual-care cholesterol-lowering drugs in coronary artery disease. J Am Coll Cardiol 41:263-272, 2003
14) 齋藤宗靖：厚生省循環器病研究　循環器疾患のリハビリテーションに関する研究（班長：齋藤宗靖）．平成5年度報告書，520，1994
15) Paul-Labrador M, et al.:Risk stratification for exercise training in cardiac patients:do the proposed guidelines work?. J Cardiopulm Rehabil 19:118-125, 1999
16) 循環器病の診断と治療に関するガイドライン（2010年度合同研究班報告）（班長：小川久雄）：運動療法．心筋梗塞二次予防に関するガイドライン（2011年改訂版），15-17，2011〔http://www.j-circ.or.jp/guideline/pdf/JCS2011_ogawah_h.pdf〕

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# Relation of the three-component model of short form-36 scores to disease severity in chronic heart failure outpatients

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Chronic heart failure (CHF) leads to frequent hospitalizations and is associated with functional incapacity and poor health-related quality of life (HRQOL) [1]. The medical outcome study 36-item short form health survey ShortForm-36 (SF-36), consisting of 36 items representing 8 subscales, is used worldwide to assess HRQOL [2]. However, the relation of the three-component model of SF-36 scores [3] to disease severity in CHF outpatients is unknown. We aimed to determine the relation of differences in scores from the three-component model of the SF-36 to disease severity in CHF outpatients and to compare these scores with those of the Japanese normal population in year 2007.

This cross-sectional study comprised 243 consecutive stable CHF outpatients beginning cardiac rehabilitation (CR). We evaluated patient characteristics including left ventricular ejection fraction and brain natriuretic peptide (BNP) concentration. New York Heart Association (NYHA) functional class IV patients, as determined by an independent investigator, were excluded as were patients with neurological, peripheral vascular, orthopedic, or pulmonary disease.

HRQOL was assessed with the SF-36, Japanese version, consisting of 36 items representing 8 subscales [2]. Multidimensional properties of HRQOL are measured with adequate reliability and validity [2,3] on a 0-to-100 scale with higher scores representing higher HRQOL [2]. Recently, the eight SF-36 subscales were combined into the physical component summary (PCS) score, mental component summary (MCS) score, and role component summary (RCS) score [2,3]. To compare these scores with those of the Japanese norm, SF-36 subscale scores were converted into a deviation score based on scores of the 2007 Japanese national norm [2,3]. A score $<50$ indicates that the specific health concept was below that of the Japanese national norm [2,3].

This study was approved by our university's Institutional Committee on Human Research. Informed consent was obtained from each patient. Results are expressed as mean ± standard error. One-way analysis of variance and chi-square tests were used to analyze differences such as clinical characteristics between the three scoring groups. Analysis of covariance was performed to adjust for the effect of clinical characteristics on PCS, MCS, and RCS scores between the three groups. Analysis with the Tukey post-hoc test was also performed on these values in the three groups. A $P$ value of $<0.05$ was considered significant. Statistical analyses were performed with SPSS 17.0J statistical software (Tokyo, Japan).

Clinical characteristics of age ($P=0.001$), sex ($P=0.006$), and BNP concentration ($P=0.001$) differed significantly between the three scoring groups (Table 1). After adjusting for these, we found that all PCS, MCS, and RCS scores decreased as NYHA class increased ($P=0.01$). All PCS, MCS, and RCS scores except for MCS in NYHA I patients were lower compared with the 2007 Japanese norm (Table 2).

The results show that in CHF patients, differences in SF-36 PCS, MCS, and RCS scores relate to degree of illness as classified by NYHA functional class. We previously suggested that physiological outcomes such as peak oxygen uptake and upper and lower muscle strength indices decrease with increase in NYHA class in CHF patients [4]. Therefore, not only physiological outcomes but all aspects of HRQOL dramatically decrease as the severity of disease worsens in CHF patients, reflecting the severe impact of CHF on daily life, even though the study patients were

**Table 1**
Clinical characteristics of the patients.

| Group | NYHA (I) | NYHA (II) | NYHA (III) | F or $\chi^2$ value | P value |
|---|---|---|---|---|---|
| No. of patients | 100 | 105 | 38 | | |
| Age (years) | 52.6 ± 1.3 | 59.2 ± 1.2 | 63.1 ± 1.7 | 11.9[a] | 0.001 |
| Sex (male/female) | 91/9 | 79/26 | 28/10 | 10.2 | 0.006 |
| Body mass index (kg/m$^2$) | 24.5 ± 0.5 | 23.4 ± 0.4 | 22.9 ± 0.6 | 2.4[a] | 0.090 |
| LVEF (%) | 37.7 ± 1.3 | 36.3 ± 1.4 | 32.2 ± 2.1 | 2.2[a] | 0.110 |
| BNP (pg/ml) | 97.1 ± 11.3 | 239.7 ± 26.5 | 411.0 ± 58.5 | 24.4[a] | 0.001 |
| Etiology (%) | | | | | |
| Cardiomyopathy | 48.0 | 47.6 | 42.1 | 0.41 | 0.810 |
| Previous myocardial infarction | 31.0 | 30.4 | 28.9 | 0.05 | 0.973 |
| Arrhythmia | 16.0 | 15.3 | 21.1 | 0.71 | 0.700 |
| CABG/VR | 5.0 | 6.7 | 7.9 | 0.47 | 0.788 |
| Medications (%) | | | | | |
| β-blockers | 87.7 | 86.6 | 86.8 | 0.05 | 0.972 |
| ARB | 40.8 | 43.8 | 47.3 | 0.72 | 0.693 |
| ACEI | 54.6 | 50.4 | 68.4 | 3.63 | 0.162 |
| Diuretic | 85.0 | 81.9 | 97.3 | 5.46 | 0.079 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker, BNP, brain natriuretic peptide, CABG, coronary artery bypass grafting, LVEF, left ventricular ejection fraction, NYHA, New York Heart Association, VR, valve replacement.
[a] F value.

**Table 2**
Differences in PCS, MCS, and RCS adjusted for age, sex, and BNP.

| Group | NYHA (I) | NYHA (II) | NYHA (III) | F value | P value |
|---|---|---|---|---|---|
| No. of patients | 100 | 105 | 38 | | |
| PCS | 49.5 ± 0.8[a] (47.8–51.2) | 43.6 ± 0.7[b] (42.1–45.1) | 32.6 ± 1.3[c] (29.9–35.2) | 50.7 | 0.01 |
| MCS | 52.3 ± 1.1[a] (50.1–54.6) | 47.8 ± 1.0[b] (45.9–49.8) | 39.7 ± 1.7[c] (36.3–43.2) | 16.4 | 0.01 |
| RCS | 48.6 ± 1.5[a] (45.5–51.7) | 44.1 ± 1.4[b] (41.3–46.9) | 33.8 ± 2.4[c] (29.0–38.7) | 11.4 | 0.01 |

Values are shown as mean ± standard error (95% confidence interval). Independent variables of analysis of covariance: age, sex, and BNP. Abbreviations: BNP, brain natriuretic peptide, MCS, mental component summary, NYHA, New York Heart Association, PCS, physical component summary, RCS, role component summary.
[a] $P<0.05$, NYHA I vs. NYHA III.
[b] $P<0.05$, NYHA I vs. NYHA II.
[c] $P<0.05$, NYHA II vs. NYHA III.

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ambulatory and in a compensated stage. Compared with the Japanese norm, our CHF patients showed global reductions in SF-36 PCS, MCS, and RCS except for MCS in NYHA I patients. Although the most pronounced loss of HRQOL was observed in the domain of physical problems relating to symptoms of shortness of breath, SF-36 subscale scores relating to mental status (vitality and mental health) and role status (role-emotional and social functioning) were also low. Thus, both mental status and role status must be considered in CHF outpatients, and the effect of CR on these aspects must be evaluated in longitudinal settings and for longer periods in the future.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [5].

## References

[1] Arena R, Myers J, Williams MA, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation 2007;116:329–43.
[2] Fukuhara S, Suzukamo Y. Manual of SF-36 v2 Japanese version. Kyoto: Institute for Health Outcomes & Process Evaluation Research; 2004.
[3] Suzukamo Y, Fukuhara S, Green J, Kosinski M, Gandek B, Ware JE. Validation testing of a three-component model of Short Form-36 scores. J Clin Epidemiol 2011;64:301–8.
[4] Izawa KP, Watanabe S, Yokoyama H, et al. Muscle strength in relation to disease severity in patients with congestive heart failure. Am J Phys Med Rehabil 2007;86:893–900.
[5] Shewan LG, Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2011;153:239–40.


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# Relation between maximum phonation time and exercise capacity in chronic heart failure patients

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Background. **Patients with chronic heart failure (CHF) commonly fatigue easily due to low peak oxygen uptake (peak $VO_2$), an important index of exercise capacity. Maximum phonation time (MPT) is widely used to evaluate maximum vocal capabilities because it is non-invasive, quick, and inexpensive.**

Aim. **The aim of this study was to determine the relation between MPT and exercise capacity, and MPT required to attain an exercise capacity of ≥5 metabolic equivalents (METs) in CHF outpatients.**

Design. **Cross-sectional study.**

Setting. **Outpatient cardiac rehabilitation unit.**

Population. **We enrolled 111 CHF outpatients (mean age 54.2±10.1 years).**

Methods. **Peak $VO_2$ was assessed during cardiopulmonary exercise testing (CPX) as the index of exercise capacity. After CPX, we divided the patients into two groups according to exercise capacity: ≥5 METs group (N.=68) and <5 METs group (N.=43). Measurements of MPT were taken in the seated position. All patients were asked to produce a sustained vowel /a:/ for as long as possible and were verbally encouraged during respiratory effort.**

Results. **After adjustment for patient clinical characteristics, MPT in the CHF patients was found to be significantly higher in the ≥5 METs group than in the <5 METs group (22.1±8.4 vs. 17.0±11.6 s, F=13.5, P<0.001). Receiver-operating characteristic curve analysis of exercise capacity of ≥5 METs extracted a cutoff value for MPT of 18.27 s, with a sensitivity of 0.76, 1-specificity of 0.33, and AUC value of 0.81 (95% CI: 0.70-0.87, P<0.001).**

Conclusion. **There were differences in MPT in relation to an exercise capacity threshold of ≥5 METs in CHF outpatients. A MPT of 18.27 sec may be the best cutoff value to identify people with or without exercise capacity of ≥5 METs.**

Clinical rehabilitation impact. **Measurement of MPT may be a useful method for estimating exercise capacity in CHF outpatients.**

Key words: Chronic heart failure - Exercise test - Oxygen consumption.

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Patients with chronic heart failure (CHF) commonly fatigue easily due to low peak oxygen uptake (peak $VO_2$), an important index of exercise capacity.[1, 2] Low peak $VO_2$, a leading cause of hospitalization [2] and predictor of mortality in cardiac patients, has a major adverse impact on health status, including impairment of health-related quality of life.[3, 4] Peak $VO_2$ is one important criterion used worldwide to evaluate cardiac patients for heart transplantation.[1, 2] Moreover, an exercise capacity of <5 metabolic equivalents (METs) in apparently normal subjects and those with cardiovascular disease imparts a high risk for death and low ability to perform activities of daily living (ADL).[4, 5] Peak $VO_2$ is most strongly associated with self-reported physical functions such as stooping, crouching, kneeling, lifting, or performing ADL, and subjects with an exercise capacity of less than approximately 5 METs can experience significant difficulty in performing daily tasks.[6]

Maximum phonation time (MPT), which is related to pulmonary functions such as forced vital capacity (FVC) in myopathic patients [7] and forced expiratory volume in 1 second ($FEV_{1.0}$) after thyroplasty,[8] is widely used to evaluate maximum vocal capabilities because it is non-invasive, quick, and inexpensive. MPT has also been used to objectively assess the degree of severity of dysphonia and to determine effects of voice therapy.[9, 10]

Previous studies of CHF patients show positive correlations between respiratory functions such as inspiratory muscle pressure (MIP), expiratory muscle pressure (MEP), percent predicted FVC, percent predicted $FEV_{1.0}$, and exercise capacity.[11, 12] However, little is known about either the relation between peak $VO_2$ and MPT or that between baseline levels of MPT in CHF patients with an exercise capacity of ≥5 METs and mortality and ADL.

We hypothesized that positive correlations exist between MPT and peak $VO_2$ and in differences in MPT necessary to attain an exercise capacity of ≥5 METs in CHF patients. Thus, the purpose of the present study was to determine the relation between peak $VO_2$ and MPT, the differences in MPT in the performance of an exercise capacity of ≥5 METs, and the level of MPT required to attain an exercise capacity of ≥5 METs in outpatients with CHF.

## Materials and methods

### Study design and patient population

In this cross-sectional study, CHF outpatients were selected from 468 cardiac patients with myocardial infarction, coronary artery bypass grafting, and/or valve replacement who visited St. Marianna University School of Medicine Hospital from January 2009 to March 2011 for evaluation of exercise capacity by cardiopulmonary exercise testing (CPX). From these 468 patients, 111 stable CHF outpatients (mean age 54.2±10.1 years) just beginning a cardiac rehabilitation (CR) program were included in the present study. Inclusion criteria were left ventricular ejection fraction (LVEF) <45%, age >30 years old, prior completion of first-time CPX, and measurement of MPT. New York Heart Association (NYHA) functional class IV patients were excluded as were those with neurological, peripheral vascular, orthopedic, or pulmonary disease (percent predicted FVC <80% or percent predicted $FEV_{1.0}$ <70%). NYHA classification was determined in all patients by an independent physician.

We evaluated patient characteristics that included age, sex, body mass index (BMI), etiology of heart failure, and medications. A cardiologist assessed cardiac function by ultrasound measurement of LVEF and disease severity by brain natriuretic peptide (BNP) concentration.[13]

The present study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research (Approval no. 1480). Written informed consent was obtained from each patient.

### MPT

MPT was measured with a stopwatch with the patient in the seated position. Patients were asked to produce a sustained vowel /a:/ for as long as possible and were verbally encouraged during this effort. The method, variability, and reliability of this measurement were previously described.[10] Trials were assessed by a physical therapist. Three consecutive trials were performed with a 15-second break between each trial. The highest value measured was considered the index of MPT (s) in the present study.

### Respiratory function

Respiratory function [11, 12] was assessed before CPX with a spirometer (Multi-Functional Spirometer HI-801 (CHEST); Nipon Corp., Tokyo, Japan). Measurements were taken with the patient in the seated position, and all patients were verbally encouraged during respiratory effort. Inspiratory and expiratory muscle indices and spirometric indices were calculated as the highest of three trials and included MIP, MEP, percent predicted FVC, and percent predicted $FEV_{1.0}$, taking into account age, sex, height, and body weight. Measurements were performed by a physical therapist.

### Exercise capacity

All 111 patients underwent symptom-limited CPX via a ramp protocol on a cycle ergometer (Strength

Ergo 8; Fukuda Denshi Co., Tokyo, Japan) during stable CHF. Testing consisted of an initial 3-minute rest on the cycle ergometer, 3 minutes of warm-up (20 watts load), and full exercise with linear load increased by 1 watt every 6 seconds. A 12-lead ECG was continuously monitored throughout CPX, and heart rate was determined from the ECG R-R interval. $VO_2$ was measured throughout the exercise period with an aero monitor (AE-300S; Minato Ikagaku Co., Tokyo, Japan) and calculated on a personal computer.[13]

Measurements made from expired gasses were used as indices of cardiovascular dynamics during exercise. Exercise capacity was calculated following measurement of peak $VO_2$. The exercise testing endpoint was determined according to guidance from the American Heart Association [14] and criteria of the American College of Sports Medicine[15] and included leg fatigue, shortness of breath, or respiratory exchange ratio >1.10. No patient had chest pain, ischemic ST changes, or serious arrhythmia during CPX. METs were calculated as METs = peak $VO_2$ ml/kg/min / 3.5 ml/kg/min. After CPX, we divided the patients into two groups according to exercise capacity attained: ≥5 METs group and <5 METs group).

### Statistical analysis

Results are expressed as mean ± standard deviation (SD). First, correlation of peak $VO_2$ with MPT and pulmonary function test results was performed with Pearson's correlation coefficient, and predictors of peak $VO_2$ were determined by multiple regression analysis in all patients. Second, parametric and chi-square tests were used to analyze differences between the ≥5 METs group and <5 METs group. The unpaired t-test was used to test for differences such as clinical characteristics between the two groups. One-way analysis of covariance (ANCOVA) was performed with the variables as covariates. Choice of covariates was guided by $\chi^2$ analyses and t-tests, which indicated significant differences between the two groups in the clinical characteristics of age, BNP, and NYHA class. Finally, receiver-operating characteristic (ROC) curves[16] were constructed by means of plotting true-positive rates (sensitivity) against false-positive rates (1-specificity) following calculation of the sensitivity of MPT for an exercise capacity of ≥5 METs to determine the best cutoff value for the whole sample. The area under the curve (AUC) was also calculated and is shown with 95% confidence interval (CI). A value of $P<0.05$ was considered significant. Statistical analyses were performed with IBM SPSS 17.0 J statistical software (SPSS Japan, Inc., Tokyo, Japan).

## Results

### Relation between peak $VO_2$ and MPT and respiratory functions

Relations between peak $VO_2$ and MPT and respiratory function test results for all CHF patients are shown in Table I. Peak $VO_2$, MPT, MIP, MEP, percent predicted FVC, and percent predicted $FEV_{1.0}$ in all patients were 19.8±6.3 mL/kg/min, 20±7.4 s, 80.9±32.6 $cmH_2O$, 107.0±41.1 $cmH_2O$, 96.7±21.1%, and 79.6±8.4%, respectively. Peak $VO_2$ correlated positively with MPT, MIP, and percent predicted FVC in all patients. However, multiple regression analysis revealed MPT to be the predictor of peak $VO_2$ in all patients ($R^2$=0.312, coefficient (β)=0.558, F=49.81, $P<0.001$). A scatter plot of peak $VO_2$ versus MPT values is shown in Figure 1.

### Patient clinical characteristics

After CPX, we divided patients into groups according to exercise capacity: ≥5 METs group,

Table I.—Correlation between peak $VO_2$ and MPT and respiratory function test results.

| Variables | r | P |
|---|---|---|
| MPT sec | 0.558 | <0.001 |
| MIP $cmH_2O$ | 0.340 | <0.001 |
| MEP $cmH_2O$ | 0.171 | 0.072 |
| Percent predicted FVC | 0.268 | 0.004 |
| Percent predicted $FEV_{1.0}$ | 0.143 | 0.134 |

$FEV_{1.0}$: forced expiratory volume in 1 second; FVC: forced vital capacity; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; MPT: maximum phonation time; peak $VO_2$: peak oxygen uptake.

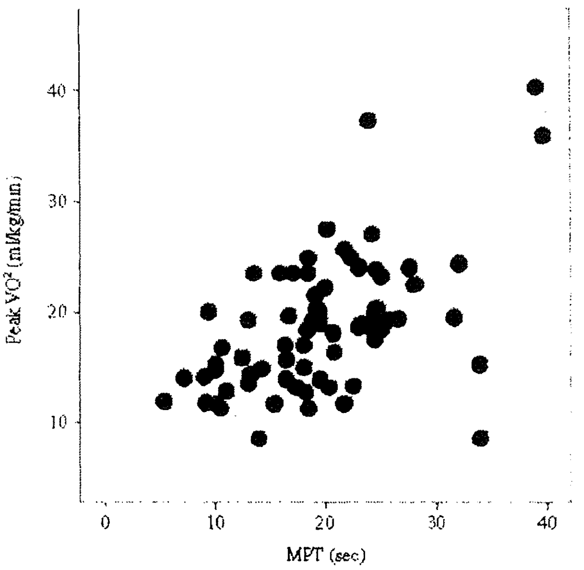


Figure 1.—Scatter plot of peak oxygen uptake (Peak $VO_2$) versus maximum phonation time (MPT) values

(N.=68) and <5 METs group, (N=43). Patient characteristics and functional variables of the two groups are summarized in Table II. Patient characteristics, including BMI, LVEF, etiology of CHF, and medications, were almost identical between the ≥5 METs and <5 METs groups. However, age, BNP, and NYHA class differed significantly between the two groups.

## Comparison of MPT between groups

Differences in MPT between groups according to exercise capacity in CHF outpatients are shown in Table III. MPT in the CHF outpatients was found to be significantly higher in the ≥5 METs group than in the <5 METs group. After adjustment for age, BNP, and NYHA class, MPT in the CHF outpatients was also found to be significantly higher in the ≥5 METs group than in the <5 METs group (22.1±8.4 vs. 17.0±11.6 s, F=13.5, P<0.001).

## Cutoff value of MPT necessary to attain an exercise capacity of ≥5 METs

The sensitivity of each cutoff value for the ≥5 METs group was calculated, and ROC curves were constructed for the CHF outpatients (Figure 2). ROC analysis of exercise capacity of ≥5 METs extracted a cut-off value for MPT of 18.27 s, with a sensitivity of 0.76, 1-specificity of 0.33, and AUC value of 0.81 (95% CI: 0.70-0.87, P<0.001).

Table II.—**Clinical characteristics of the patients by group.**

| Characteristics | ≥5 METs group | <5 METs group | t or $\chi^2$ value | P value |
|---|---|---|---|---|
| N of patients | 68 | 43 | | |
| Age (years) | 52.7±11.6 | 56.5±17.9 | 2.00* | 0.04 |
| Male (%) | 82.9 | 78.5 | 2.61 | 0.30 |
| BMI (kg/m²) | 23.2±4.2 | 22.9±7.4 | 1.04* | 0.30 |
| LVEF (%) | 31.1±15.8 | 30.6±18.9 | 0.84* | 0.40 |
| BNP (pg/mL) | 220.7±253.9 | 306.9±319.2 | -2.23* | 0.02 |
| NYHA class (I/II/III) | 26/42/0 | 4/24/16 | 33.4 | <0.001 |
| Etiology (%) | | | | |
| Cardiomyopathy | 51.2 | 46.1 | 2.01 | 0.46 |
| Previous MI | 26.4 | 23.6 | 0.49 | 0.71 |
| Arrhythmia | 14.9 | 17.8 | 0.56 | 0.27 |
| CABG/VR | 7.5 | 12.5 | 2.16 | 0.31 |
| Medications (%) | | | | |
| Beta-blockers | 81.0 | 79.9 | 0.71 | 0.24 |
| ARB | 41.7 | 47.9 | 0.43 | 0.33 |
| ACEI | 50.5 | 44.7 | 0.54 | 0.28 |
| Diuretic | 87.5 | 86.1 | 0.09 | 0.52 |

Values are shown as mean ± standard deviation where appropriate. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; LVEF: left ventricular ejection fraction; METs: metabolic equivalents; MI: myocardial infarction; NYHA: New York Heart Association; VR: valve replacement. *t value.

TABLE III.—Differences in maximum phonation time between groups.

| Variables | ≥5 METs group | <5 METs group | F value | P value |
|---|---|---|---|---|
| No of patients | 68 | 43 | | |
| Maximum phonation time (s) | 22.9±7.4 (21.5-24.3) | 15.4±9.5 (13.5-17.3) | 44.4 | <0.001 |
| Maximum phonation time (s) adjusted for age, BNP, and NYHA functional class | 22.1±8.4 (20.5-23.6) | 17.0±11.6 (14.9-19.0) | 13.5 | <0.001 |

Strength values are shown as mean ± standard deviation (95% confidence interval). Independent variables of analysis of covariance: age, BNP, and NYHA functional class. BNP: brain natriuretic peptide; METs: metabolic equivalents; NYHA: New York Heart Association.

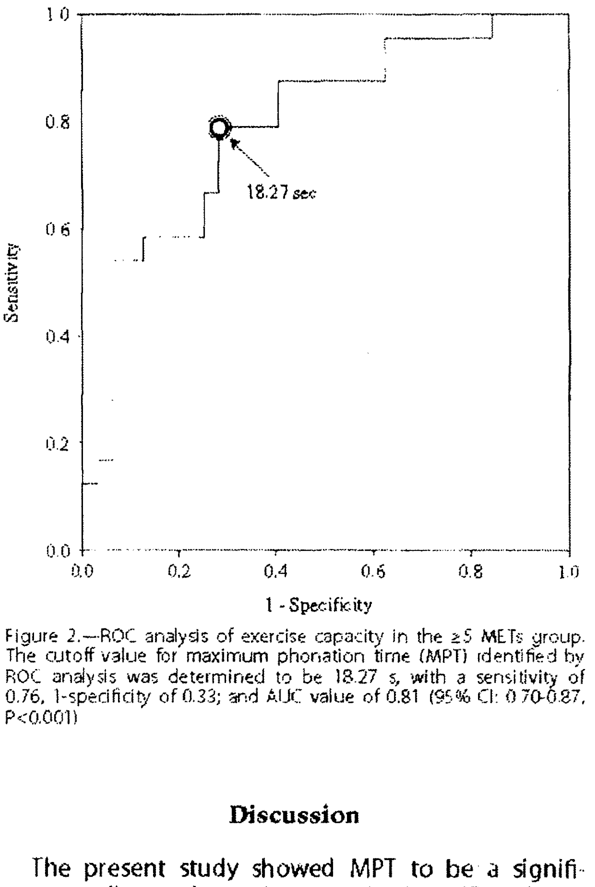


Figure 2.—ROC analysis of exercise capacity in the ≥5 METs group. The cutoff value for maximum phonation time (MPT) identified by ROC analysis was determined to be 18.27 s, with a sensitivity of 0.76, 1-specificity of 0.33; and AUC value of 0.81 (95% CI: 0.70-0.87, P<0.001)

## Discussion

The present study showed MPT to be a significant predictor of exercise capacity in CHF patients. After adjusting for age, BNP, and NYHA class, MPT was significantly higher in patients with an exercise capacity of ≥5 METs versus those with an exercise capacity of <5 METs. The cutoff value for MPT in CHF patients having an exercise capacity of ≥5METs was approximately 18.27 s.

Peak $VO_2$ assessed by CPX correlated significantly with MPT, MIP, and percent predicted FVC, and tended to relate to MEP. Faggiano et al.[11] reported that variables such as MIP, MEP, FVC, $FEV_{1.0}$, and alveolar-capillary membrane diffusing capacity were related to peak $VO_2$ in 161 male patients (mean age 59 years) with heart failure. In particular, lung diffusing capacity and respiratory muscle function appear to affect exercise capacity during heart failure. Our results are agreement with previous investigators who have emphasized the importance of respiratory muscle strength, particularly as indicated by MIP, in CHF patients.[12] MIP is also an independent prognostic predictor in heart failure.[17] Improved MIP results in improvement of dyspnea, walking distance, and peak $VO_2$.[12] However, multiple regression analysis in the present study showed MPT to be the only significant predictor of peak $VO_2$ in all CHF outpatients.

Phonation requires close coordinated movement of the vocal cords and supralaryngeal muscles and the movement of the respiratory bellows, which provide the subglottic pressure and global air flow needed to drive continuous sound generation.[18] It is clear that oxygen uptake increases during phonation due to the energy expenditure required.[18] Performance of the MPT test has a direct effect on peak $VO_2$ because it requires active changes in heart rate, stroke volume, and arterio-venous $O_2$ difference (the components of peak $VO_2$) to create the force needed to generate the sound required of the MPT test, and thus, MPT can be directly associated with peak $VO_2$. Of the factors analyzed in the present study, only the MPT test requires continuous work by the patient, and this may be the reason why MPT was the only predictor of peak $VO_2$ in all of the CHF outpatients. Therefore, we believe that MPT, in addition to other pulmonary function measurements, may useful for predicting and estimating exercise capacity in CHF outpatients.

Both BNP and NYHA class increase as CHF severity increases,[19] and these three factors correlate negatively with exercise capacity.[19] Thus, we believe that an exercise capacity threshold of ≥5 METs reflects the degree of seriousness of CHF equally as well as do age, BNP, or NYHA class. After adjusting for these three variables, MPT in the CHF patients was found to be significantly higher in the ≥5 METs group than in the <5 METs group (22.1±8.4 vs. 17±11.5 s, F=13.5, P<0.001, Table III).

Yanagihara et al.[20] reported that in normal subjects, average MPT was 30.2 sec in men and 22.5 s in women, and Hirano et al.[21] also studied normal subjects and reported an average MPT of 34.6 s in men and 25.7 s in women. Moreover, Maslan et al.[22] recently reported that 69 older healthy adults in the seventh (N.=15), eighth (N.=26), and ninth (N.=28) decades of life had mean MPTs of 22.27, 22.97, and 21.14 s, respectively. These values were superior to those in both of our CHF patient groups. Although MPT was significantly higher in the ≥5 METs versus <5 METs group, it was lower than that measured in normal subjects.

ROC analysis indicated an exercise capacity of ≥5 METs in our CHF patients to be equivalent to a MPT of approximately 18.27 s (Figure 1). An AUC of 0.7-0.9 for a test can be interpreted to indicate moderate accuracy.[23, 24] Thus, the AUC of 0.81 in the present study indicates moderate accuracy, and the cut-off value of 18.27 s for MPT in the present study could possibly be used to estimate the exercise capacity of CHF patients.

The present study is the first, to our knowledge, to evaluate a relation between MPT and an exercise capacity of ≥5 METs in CHF outpatients beginning a CR program. Further study is required to evaluate the effect of training methods to improve MPT in a CR program for CHF outpatients that would result in an exercise capacity of >5 METs. The present study had several limitations. First, the sample size was small, and the study was of cross-sectional design. We investigated differences in MPT in relation to peak $VO_2$ assessed at a particular time; however, it would be highly desirable to document longitudinal changes in peak $VO_2$ and MPT in CHF patients. Second, few female CHF patients were studied, and sex related differences in MPT could not be determined. Third, MPT can be influenced by various factors such as vocal cord function and anatomic abnormalities of the upper airway, voice dexterity, cigarette smoking, and other factors. However, we did not perform a preliminary assessment of these specific factors in the study patients. Finally, we did not directly measure the relation between risk factors and differences in MPT associated with exercise capacity, nor did we assess mortality, morbidity, or occurrence of events such as hypotension, syncope, or severe arrhythmia during CR. Future trials are needed to evaluate the relation between MPT levels and these factors in CHF patients.

The number of older patients in heart failure who have become severely disabled has increased,[25] and evaluation of exercise capacity by CPX in these patients may not easy. However, evaluation of MPT can be performed quickly and easily. Thus, MPT could potentially be a useful method to estimate exercise capacity in these CHF patients and in those with varying degrees of symptom severity.

## Conclusions

The present study showed positive correlations between peak $VO_2$ and MPT and respiratory function test results in CHF outpatients, and MPT was found to be a significant predictor of peak $VO_2$. There were differences in MPT in relation to an exercise capacity threshold of ≥5 METs in CHF outpatients. An exercise capacity of ≥5 METs was equivalent to a MPT of approximately 18.27 s. This value may be the best cutoff value with which to identify people with or without exercise capacity of ≥5 METs and may be a useful target for estimating exercise capacity in CHF patients. We suggest that an exercise capacity threshold of ≥5 METs might have some influence on the length of MPT.

## References


1. Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail 2011;13:347-57.
2. Metra M, Ponikowski P, Dickstein K, McMurray JJ, Gavazzi A, Bergh CH et al. Advanced chronic heart failure: A position statement from the Study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2007;9:684-94
3. Jeng C, Yang MH, Chen PL, Ho CH. The influence of exercise tolerance on quality of life among patients with heart failure. Qual Life Res 2004;13:925-32

4. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.
5. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554-9.
6. Morey MC, Pieper CF, Cornoni-Huntley J. Is there a threshold between peak oxygen uptake and self-reported physical functioning in older adults? Med Sci Sports Exerc 1998;30:1223-9.
7. Toyoda C, Ogawa M, Oya Y, Kawai M. Maximum phonation time as a tool of screening respiratory muscle weakness in myopathic patients. No To Shinkei 2004;56:873-6 [In Japanese]
8. Yumoto E, Minoda R, Toya Y, Miyamaru S, Sanuki T. Changes in respiratory function after thyroplastic surgery. Acta Otolaryngol 2010;130:132-7.
9. Speyer R, Heijnen BJ, Baijens LW, Vrijenhoef FH, Otters EF, Roodenburg N et al. Quality of life in oncological patients with oropharyngeal dysphagia: validity and reliability of the Dutch version of the MD Anderson Dysphagia Inventory and the Deglutition Handicap Index. Dysphagia 2011;26:407-14.
10. Speyer R, Bogaardt HC, Passos VL, Roodenburg NP, Zumach A, Heijnen MA et al. Maximum phonation time: variability and reliability. J Voice 2010;24:281-4.
11. Faggiano P, D'Aloia A, Gualeni A, Giordano A. Relative contribution of resting haemodynamic profile and lung function to exercise tolerance in male patients with chronic heart failure. Heart 2001;85:179-84.
12. Ribeiro JP, Chiappa GR, Neder JA, Frankenstein L. Respiratory muscle function and exercise intolerance in heart failure. Curr Heart Fail Rep 2009;6:95-101.
13. Izawa KP, Watanabe S, Osada N, Kasahara Y, Yokoyama H, Hiraki K et al. Handgrip strength as a predictor of prognosis in Japanese patients with congestive heart failure. Eur J Cardiovasc Prev Rehabil 2009;16:21-7.
14. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF et al. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 2010;122:191-25.
15. Hanson P. Clinical exercise testing. In: Blair SN, Painter P, Pate RR, Smith LK, Taylor CB, editors. Resource manual for guidelines for exercise testing and prescription. Philadelphia: Lea & Febiger; 1988. p. 205-22.
16. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med 2000;45:23-41.
17. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kubler W et al. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. Circulation 2001;103:2153-8.
18. Miyamura M, Ishida K, Katayama K, Sato Y, Morotome Y, Shima N et al. Cardiorespiratory responses to hypoxia and hypercapnia at rest in vocalists. Jpn J Physiol 2003;53:17-24.
19. Izawa KP, Watanabe S, Yokoyama H, Hiraki K, Morio Y, Oka K et al. Muscle strength in relation to disease severity in patients with congestive heart failure. Am J Phys Med Rehabil 2007;86:893-900.
20. Yanagihara N, Koike Y, Von Leden H. Phonation and respiration. Function study in normal subjects. Folia Phoniatr (Basel) 1966;18:323-40.
21. Hirano M, Koike Y, Von Leden H. Maximum phonation time and air usage during phonation. Clinical study. Folia Phoniatr (Basel) 1968;20:185-201.
22. Maslan J, Leng X, Rees C, Blalock D, Butler SG. Maximum phonation time in healthy older adults. J Voice 2011;25:709-13.
23. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med 2003;29:1043-51.
24. Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr 2007;96:644-7.
25. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1893-900.


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# Upper and Lower Extremity Muscle Strength Levels Associated With an Exercise Capacity of 5 Metabolic Equivalents in Male Patients With Heart Failure

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■ **PURPOSE:** Exercise capacity of fewer than 5 metabolic equivalents (METs) has been associated with high risk of death and poor physical functioning in male patients with heart failure (HF). Therefore, we aimed to determine upper and lower extremity muscle strength levels required to attain an exercise capacity of 5 or more METs in male outpatients with HF.

■ **METHODS:** We enrolled 148 male HF patients (age 60.1 ± 1.0 years). Peak oxygen uptake (peak $\dot{V}O_2$) was assessed by cardiopulmonary exercise testing (CPX). After CPX, we further divided the patients into groups according to exercise capacity: 5 or more METs (group A, n = 85) and fewer than 5 METs (group B, n = 63). Handgrip strength and knee extensor and flexor muscle strengths were assessed as indices of upper and lower extremity muscle strength, respectively. Receiver operating characteristic curves were used to select cutoff values for upper and lower extremity muscle strength resulting in an exercise capacity of 5 or more METs in these patients.

■ **RESULTS:** Exercise capacity of 5 or more METs in male HF patients was equivalent to approximately 35.2 kgf of handgrip strength and 1.70 Nm/kg of knee extensor and 0.90 Nm/kg of knee flexor muscle strengths.

■ **CONCLUSIONS:** These upper and lower extremity muscle strength values may be useful target goals for improvement of exercise capacity, risk management, and activities of daily living in male HF patients.

K E Y W O R D S

exercise capacity

heart failure

lower extremity muscle strength

upper extremity muscle strength

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Patients with heart failure (HF) commonly fatigue because of poor skeletal muscle function and low peak oxygen uptake (peak $\dot{V}O_2$).[1-3] Low peak $\dot{V}O_2$ is a leading cause of hospitalization and predictor of mortality in cardiac patients and has a major adverse impact on health status, including impairment of health-related quality of life (HRQOL).[4-6] Burns et al[1] previously reported that 35% of HF patients experienced dyspnea immediately after walking less than 1 block, 62% were in poor physical condition, and 46% were readmitted to hospital within 1 year. These findings are explained by the skeletal muscle atrophy, impaired muscle function, and altered metabolism seen in HF patients.[2,3] We previously reported that peak $\dot{V}O_2$ correlates positively with upper and lower extremity muscle strength in HF patients[7] and suggested that peak $\dot{V}O_2$ and upper and lower extremity muscle strength indices decrease in HF patients as New York Heart Association (NYHA) functional class increases. Since 2000, several reports have suggested that not only peak $\dot{V}O_2$ but also upper and lower extremity muscle strength is a predictor of survival in HF patients.[8,9] Moreover, both apparently normal subjects and those with cardiovascular disease who have an exercise capacity of fewer than 5 metabolic equivalents (METs) are considered to be at high risk for death and to have low ability to perform activities of daily living (ADL).[10,11] A previous study suggested that peak $\dot{V}O_2$ was most strongly associated with self-reported physical functions such as stooping, crouching, kneeling, lifting, or performing ADL in community-dwelling adults, and subjects with an exercise capacity of less than approximately 5 METs experienced significant difficulty in the performance of daily tasks.[11] Jeng et al[5] also suggested that patients whose exercise intensity tolerance was 5 or more METs had better physical functioning as assessed by 36-Item Short Form Health Survey (SF-36).

One important objective of cardiac rehabilitation (CR) in HF patients is improvement in exercise capacity and muscle strength, which is associated with mortality, morbidity, and measured HRQOL.[12,13] Cardiac rehabilitation improves peak $\dot{V}O_2$, muscle strength, endothelial function, and HRQOL in HF patients.[12,13] Although individual perceptions may differ regarding the value of exercise when designing strategies to improve muscle strength in HF patients, few studies have reported on upper and lower extremity muscle strength in HF patients.[8,9,12,13] Little is known about baseline levels of upper and lower extremity muscle strength in HF patients with an exercise capacity of 5 or more METs at entry into a phase II CR program.

We hypothesized that there are differences in upper and lower extremity muscle strength levels necessary to attain an exercise capacity of 5 or more METs in male HF patients. Therefore, the purpose of the present study was to determine (1) differences between upper and lower extremity muscle strength in the performance of exercise capacity of 5 or more METs and (2) the levels of upper and lower extremity muscle strength associated with an exercise capacity of 5 or more METs in male outpatients with HF.

## METHODS

This cross-sectional study comprised consecutive chronic HF outpatients selected from 1016 cardiac patients with myocardial infarction, coronary artery bypass grafting, and/or valve replacement, who visited St. Marianna University School of Medicine Hospital from November 2004 to October 2009 for evaluation of exercise capacity by cardiopulmonary exercise testing (CPX). From these 1016 patients, 148 stable HF outpatients, who were beginning a CR program at the request of their physician or by their own wish, were included in the present study. Inclusion criteria were male sex, left ventricular ejection fraction (LVEF) less than 45%, completion of first-time CPX, and repeat measurement of upper and lower extremity muscle strength. NYHA functional class IV patients were excluded as were those with neurological, peripheral vascular, orthopedic, or pulmonary disease. NYHA classification was determined in all patients by an independent investigator. The present study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research (Approval No. 340). Informed consent was obtained from each patient.

### Clinical Characteristics of Patients

We evaluated several patient characteristics, including age, etiology of HF, and medications. A cardiologist assessed cardiac function by ultrasound measurement of LVEF and disease severity by brain natriuretic peptide (BNP) concentration. A blood sample for measurement of BNP was drawn from a cubital vein of each patient after 15 minutes of rest in the supine position before CPX. Blood samples were immediately immersed in ice and centrifuged at 3000 revolutions per minute for 10 minutes at 4°C. The plasma was stored at −70°C, and BNP was measured by radioimmunoassay within 1 week of sampling.[7,9]

### Exercise Capacity

All 148 outpatients underwent CPX via a ramp cycle ergometer protocol. A CORIVAL 400 ergometer (Lode Co, Groningen, the Netherlands) was used for symptom-limited exercise testing, which consisted of an initial 3 minutes of rest on the cycle ergometer, 3 minutes of warm-up (20-W load), and full exercise with a linear increase in load by 1 W every 6 seconds. A 12-lead electrocardiogram (ECG) was continuously monitored throughout CPX, with heart rate determined from the R-R interval of the ECG (ML-5000, Fukuda Denshi Co, Tokyo, Japan). $\dot{V}O_2$, the relation between minute ventilation and carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope), and respiratory exchange ratio (RER) were measured throughout the exercise period with an AE-300S aero monitor (Minato Ikagaku Co, Tokyo, Japan) and calculated on a personal computer.[7-9] Peak work rate was also measured at the end of CPX.

Measurements made from expired gasses were used as indices of cardiovascular dynamics during exercise. Exercise capacity was calculated following measurement of peak $\dot{V}O_2$. The endpoint of exercise testing as determined by the criteria of the American College of Sports Medicine[14] included leg fatigue, shortness of breath, or RER > 1.15. Metabolic equivalents for each patient were calculated as follows: METs = peak $\dot{V}O_2$ $mL \cdot kg^{-1} \cdot min^{-1}$/ 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$. After CPX, we divided the patients into 2 groups according to exercise capacity: ≥5 METs (group A, n = 85) and <5 METs (group B, n = 63).

## Handgrip Strength

To assess upper limb muscle power, we measured handgrip strength with a standard adjustable-handle JAMAR dynamometer (Bissell Healthcare Co, Grand Rapids, Michigan) set at the second grip position for all subjects. This method provides reliable and valid output data.[7,9,15] Three measurements were made on each hand, and attention was paid to a possible Valsalva effect. We calculated the average of the highest value of the right- plus left-side handgrip strength/2 (kgf). This value was considered the index of handgrip strength.

## Knee Extensor and Flexor Muscle Strength

We assessed lower limb muscular strength by measuring knee extensor and flexor muscle strengths with a Biodex System 2 isokinetic dynamometer (Biodex Medical Systems, Inc, New York). This method also provides reliable and valid output data.[7,9,16] A maximum of 5 repetitions was performed for knee extensors and flexors at isokinetic speeds of 60° per second. Isokinetic test results were analyzed with Biodex System 2 software. After measurement, we calculated the average of the highest value of the right- plus left-side knee extensor strength/2 (Nm/kg) and that of the flexor muscular strength/2 (Nm/kg). These values were considered the indices of knee extensor and flexor muscle strength.

## Statistical Analysis

Results are expressed as $M \pm SE$. Parametric and $\chi^2$ tests were used to analyze differences between groups A and B. Because comparisons were performed between groups A and B, the unpaired $t$ test was used to test for differences in variables related to clinical characteristics and exercise capacity. To compare handgrip and knee extensor and flexor muscle strength variables between the 2 groups, one-way analysis of covariance with the variables as covariates was performed. Choice of covariates was guided by $\chi^2$ analyses and $t$ tests, which indicated significant differences between groups A and B in the clinical characteristics of age, BNP, and NYHA class.

Receiver operating characteristic (ROC)[17-19] analysis was performed for the different tests, and ROC curves were plotted to examine the trade-off between sensitivity and specificity and to determine the statistically best cutoff point by maximizing the difference between the number of true-positive test results (sensitivity) and the number of false-positive results (1 − specificity). To compare the diagnostic accuracy of the tests, the area under the curve (AUC) with 95% CI was calculated. Diagnostic sensitivity and specificity are reported for the selected cutoff points, and likelihood ratios for a positive test result are provided as measures of diagnostic accuracy. Receiver operating characteristic curves were constructed by means of plotting true-positive rates (sensitivity) against false-positive rates (1 − specificity) following calculation of the sensitivity for handgrip and knee extensor and flexor muscle strengths of an exercise capacity of 5 or more METs to determine the best cutoff value for each group. A $P$ value of less than .05 was considered significant. Statistical analyses were performed with IBM SPSS 17 statistical software (IBM SPSS Japan, Inc, Tokyo, Japan).

# RESULTS

Patient characteristics and functional variables in all patients are summarized in Table 1. Patient characteristics, including body mass index, LVEF, etiology of HF, and medications, were almost identical between groups A and B. However, age, BNP concentration, and NYHA functional class differed significantly between the 2 groups.

## CPX Values

Cardiopulmonary exercise testing values of the 2 patient groups are summarized in Table 2. No patient experienced chest pain, abnormal blood pressure response, ischemic ST changes, or serious arrhythmia during CPX. All patients achieved an RER > 1.15. Peak $\dot{V}O_2$ and peak work rate were significantly higher, and $\dot{V}E/\dot{V}CO_2$ slope was significantly lower in group A than in group B. Respiratory exchange ratio did not differ significantly between the 2 groups.

**Table 1 • Clinical Characteristics of Patients**

| Characteristic | Group A (≥5 METs) | Group B (<5 METs) | $t$ or $\chi^2$ | $P$ Value |
|---|---|---|---|---|
| Patients, n | 85 | 63 | | |
| Age, y | 56.9 ± 1.2 | 65.4 ± 1.4 | −5.82[a] | .01 |
| BMI, kg/m$^2$ | 23.6 ± 0.4 | 22.8 ± 0.4 | 1.09[a] | .27 |
| LVEF, % | 32.2 ± 1.3 | 30.2 ± 1.2 | 0.90 | .36 |
| BNP, pg/mL | 93.1 ± 10.2 | 419.3 ± 48.1 | −6.71[a] | .01 |
| NYHA class, I/II/III | 54/31/0 | 3/35/25 | 21.8 | .01 |
| Etiology, % | | | | |
| Cardiomyopathy | 42.2 | 45.9 | 5.86 | .11 |
| Previous MI | 32.9 | 28.3 | | |
| Arrhythmia | 19.5 | 15.2 | | |
| CABG/VR | 5.4 | 11.5 | | |
| Medications, % | | | | |
| β-Blockers | 82 | 78.5 | 0.68 | .26 |
| ARB | 42.5 | 46.8 | 0.42 | .31 |
| ACEI | 50.7 | 44.9 | 0.50 | .29 |
| Diuretic | 87.7 | 87.3 | 0.08 | .55 |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MI, myocardial infarction; NYHA, New York Heart Association; VR, valve replacement.

[a]$t$ value.

## Comparison of Handgrip and Knee Extensor and Flexor Muscle Strengths

Differences in handgrip and knee extensor and flexor muscle strengths between groups according to exercise capacity in the male HF patients are shown in Table 3. After adjustment for age, BNP concentration, and NYHA class, handgrip and knee extensor and flexor muscle strengths in the study patients were all significantly higher in group A than in group B.

## Cutoff Values of Muscle Strengths Associated With an Exercise Capacity of 5 or More METs

The sensitivities of each cutoff value for group A (≥5 METs) were calculated and used to construct ROC curves for the male HF patients (Figure 1). Using ROC analysis of exercise capacity of 5 or more METs, we identified a cutoff value for handgrip strength of 35.2 kgf, with a sensitivity of 0.78, 1 − specificity of 0.32, and AUC value of 0.815 (95% CI: 0.747-0.884, $P$ = .00001). The cutoff value identified for knee extensor muscle strength was 1.70 Nm/kg, with a sensitivity of 0.77, 1 − specificity of 0.31, and AUC value of 0.807 (95% CI: 0.739-0.875, $P$ = .00001), and that for knee flexor muscle strength was 0.90 Nm/kg, with a sensitivity of 0.78, 1 − specificity of 0.39, and AUC value of 0.789 (95% CI: 0.717-0.861, $P$ = .00001).

# DISCUSSION

The present study shows that for male patients with HF, there are differences in upper and lower extremity muscle strength associated with an exercise capacity threshold of 5 or more METs, and the cutoff points for handgrip strength and knee extensor and flexor muscle strengths in these patients at an exercise capacity of 5 or more METs were 35.2 kgf, 1.70 Nm/kg, and 0.90 Nm/kg, respectively.

Age and BNP concentration were significantly lower in group A than in group B in the present study, and NYHA functional class also differed significantly between the groups. Both BNP concentration and NYHA functional class have been shown to increase as HF becomes more severe,[7,9,20] and age, BNP concentration, and NYHA functional class correlate negatively with exercise capacity.[7,20] Thus, we believe that the inability to attain an exercise capacity threshold of 5 or more METS reflects the degree of severity of HF

**Table 2 • CPX Values of Patients, *M* ± SE (Range)**

| Variables | Group A (≥5 METs) | Group B (<5 METs) | *t* | *P* Value |
|---|---|---|---|---|
| Patients, n | 85 | 63 | | |
| Peak $\dot{V}O_2$, mL·kg$^{-1}$·min$^{-1}$ | 23.19 ± 0.48 (18.00-40.20) | 14.48 ± 0.29 (8.60-17.40) | 13.61 | .001 |
| $\dot{V}E/\dot{V}CO_2$ slope | 28.91 ± 0.55 (21.00-50.20) | 38.58 ± 0.93 (24.20-55.10) | −9.49 | .001 |
| Peak work rate, W | 127.30 ± 4.50 (69.00-258.00) | 76.63 ± 2.17 (43.00-120.00) | 8.76 | .001 |
| RER | 1.22 ± 0.09 (1.15-1.49) | 1.21 ± 0.08 (1.15-1.52) | 0.45 | .652 |

Abbreviations: CPX, cardiopulmonary exercise testing; METs, metabolic equivalents; $\dot{V}O_2$, oxygen uptake; $\dot{V}E/\dot{V}CO_2$ slope, relation between minute ventilation and carbon dioxide production; RER, respiratory exchange ratio.

equally as well as do age, BNP concentration, or NYHA functional class.

We previously reported that peak $\dot{V}O_2$ and handgrip and knee extensor and flexor muscle strength indices decreased with increases in NYHA class and that peak $\dot{V}O_2$ correlated positively with all muscle strengths.[7] In the present study, handgrip and knee extensor and flexor muscle strengths adjusted for age, BNP concentration, and NYHA class in group A were significantly higher than those in group B (Table 3), suggesting an association between the attainment of an exercise capacity threshold of 5 or more METs and the amount of handgrip and knee extensor and flexor muscle strength that can be generated.

Myers et al[10] suggested that there are age-adjusted relative risks of death for each of the major risk factors in male subjects who achieve a peak exercise capacity of fewer than 5 METs as compared with the fittest subjects. For subjects with any of these risk factors, the relative risk of death from any cause increased significantly as exercise capacity decreased. They also suggested that in subjects with cardiovascular disease, who have an exercise capacity of fewer than 5 METs, exercise capacity is a significantly better predictor of mortality than are the other major risk factors. Each 1-MET increase in exercise capacity improved survival by 12%.[10]

ROC analysis in the present study showed that an exercise capacity of 5 or more METs in male HF patients was equivalent to approximately 35.2 kgf of handgrip strength (AUC value, 0.815) and 1.70 Nm/kg of knee extensor (AUC value, 0.807) and 0.90 Nm/kg of flexor (AUC value, 0.789) muscle strengths (Figure 1). Because an AUC value of 0.7 to 0.9 for a test can be interpreted to indicate moderate accuracy,[18,19] the AUC values in the present study indicate moderate accuracy.

We previously found by ROC analysis that a cutoff value of 32.2 kgf for handgrip strength was a predictor

**Table 3 • Comparison of Handgrip and Knee Extensor and Flexor Muscle Strengths Between Groups, M ± SE (95% CI)**

| Factors | Group A (≥5 METs) | Group B (<5 METs) | *F* | *P* Value |
|---|---|---|---|---|
| Patients, n | 85 | 63 | | |
| Handgrip strength, kgf | 40.90 ± 0.73 (39.45-42.35) | 33.97 ± 0.94 (32.10-35.83) | 35.2 | .001 |
| Knee extensor muscle strength, Nm/kg | 1.95 ± 0.45 (1.86-2.04) | 1.58 ± 0.57 (1.46-1.69) | 26.6 | .001 |
| Knee flexor muscle strength, Nm/kg | 1.09 ± 0.27 (1.03-1.14) | 0.85 ± 0.35 (0.78-0.92) | 19.4 | .001 |

Abbreviation: METs, metabolic equivalents.

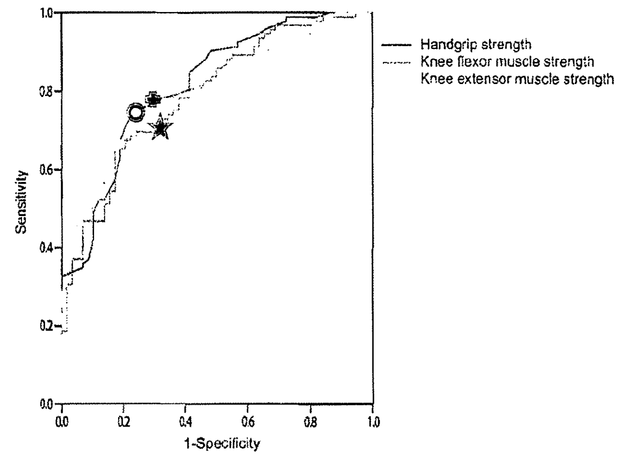


**Figure 1.** Cutoff values for handgrip and knee extensor and flexor muscle strength identified by ROC analysis of exercise capacity of 5 or more metabolic equivalents (METs) in group A. Circle: Cutoff value of handgrip strength = 35.2 kgf, with a sensitivity of 0.78, 1 − specificity of 0.32; and AUC value of 0.815 (95% CI): 0.747-0.884, *P* = .00001. Plus: Cutoff value of knee extensor muscle strength = 1.70 Nm/kg, with a sensitivity of 0.77, 1 − specificity of 0.31, and AUC value of 0.807 (95% CI: 0.739-0.875, *P* = .00001). Star: Cutoff value of knee flexor muscle strength = 0.90 Nm=kg, with a sensitivity of 0.78, 1 − specificity of 0.39, and AUC value of 0.789 (95% CI: 0.717-0.861, *P* = .00001).

of mortality in male HF patients.[7] Another study also suggested that a cutoff value of 0.68 Nm/kg for knee flexor muscle strength was related to mortality in individuals with severe HF and that this variable is superior to others such as peak $\dot{V}O_2$ and workload.[8] Although we did not investigate mortality *per se* in the present study, results imply that as a predictor of mortality in male HF patients, handgrip and knee flexor muscle strengths may be similar to other variables related to mortality.

Several previous reports suggested a positive correlation between knee extensor muscle strength and gait speed, and when knee extensor muscle strength was less than 1.20 Nm/kg, correlation between these values was even stronger.[21,22] When knee extensor muscle strength was less than 1.17 Nm/kg, gait was impossible in cardiac patients. Moreover, Manini et al[23] examined the relation between knee extensor muscle strength and severe mobility limitation (SML), which was defined as 2 consecutive reports of great difficulty or inability to walk one-quarter mile or climb 10 steps. They reported that in 1355 apparently healthy men aged 70 to 79 years, cut points defining high and low risks of SML corresponded to less than 1.13 Nm/kg and more than 1.71 Nm/kg of knee extensor muscle strength, respectively. The average knee extensor muscle strength of 1.70 Nm/kg in the present study was superior or similar to target variables related to ADL and low risk of SML. This index could possibly be used not only as an indicator of improvement in exercise capacity but also as an index to gauge both the risk of SML and the improvement in ADL of HF patients.

Evaluation of both handgrip and knee extensor muscle strength may be useful to estimate exercise capacity in male HF patients. As an evaluation of muscle strength, particularly handgrip strength can be performed quickly and easily, so determination of an exercise capacity of 5 METs might be done by handgrip strength alone. However, because lower extremity muscle strength is also related to ADL such as gait speed and degree of gait independence in male cardiac patients,[21,22] evaluation of both upper and lower extremity muscle strengths may be a more useful method to estimate true exercise capacity in these HF patients and in those with varying degrees of symptom severity.

To our knowledge, this study is the first to evaluate a relation between an exercise capacity of 5 or more METs and handgrip and knee extensor and flexor muscle strength in male HF patients beginning a CR program. Several recent reports suggested that combining resistance training with aerobic exercise may be an effective intervention to increase exercise capacity and muscle strength and improve HRQOL in cardiac patients.[24,25] Further study is required to evaluate the effect of resistance training in a CR program for HF outpatients that would result in an exercise capacity of 5 or more METs.

This study has several limitations. First, sample size was small, and the study was of cross-sectional design. The main aim of this study was to assess differences in muscle strength in relation to peak $\dot{V}O_2$ assessed at a particular time. Nevertheless, it would be highly desirable to document longitudinal changes in peak $\dot{V}O_2$ and muscle strength in patients with HF. Second, only male HF patients were studied; thus, we did not determine gender related differences in muscle strength. Further studies are needed in terms of investigating gender related differences. Finally, we neither directly measured the relation between risk factors, mortality, and differences in muscle strength associated with exercise capacity, nor did we assess morbidity or occurrence of events such as hypotension, syncope, or severe arrhythmia during CR. Therefore, future trials are needed to evaluate the relation between muscle strength levels and these factors in male HF patients.

## CONCLUSION

We found differences in handgrip and knee extensor and flexor muscle strength adjusted for age, BNP concentration, and NYHA class in relation to an exercise capacity threshold of 5 or more METs in male outpatients with HF. An exercise capacity of 5 or more METs in these patients was equivalent to approximately 35.2 kgf of handgrip strength and 1.70 Nm/kg and 0.90 Nm/kg of knee extensor and flexor muscle strengths, respectively. These values may be useful target goals for improvement of exercise capacity, risk management and ADL in male HF patients.

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## References

1. Piepoli MF, Corrà U, Benzer W, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* 2010;17:1-17.
2. Massie BM, Simonini A, Sahgal P, Wells L, Dudley GA. Relation of systemic and local muscle exercise capacity to skeletal muscle characteristics in men with congestive heart failure. *J Am Coll Cardiol.* 1996;27:140-145.
3. Osada N, Chaitman BR, Miller LW, et al. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *J Am Coll Cardiol.* 1998;31:577-582.
4. Burns RB, McCarthy EP, Moskowitz MA, Ash A, Kane RL, Finch M. Outcomes for older men and women with congestive heart failure. *J Am Geriatr Soc.* 1997;45:276-280.
5. Jeng C, Yang MH, Chen PL, Ho CH. The influence of exercise tolerance on quality of life among patients with heart failure. *Qual Life Res.* 2004;13:925-932.
6. Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation.* 2003;108:1554-1559.
7. Izawa KP, Watanabe S, Yokoyama H, et al. Muscle strength in relation to disease severity in patients with congestive heart failure. *Am J Phys Med Rehabil.* 2007;86:893-900.
8. Hülsmann M, Quittan M, Berger R, et al. Muscle strength as a predictor of long-term survival in severe congestive heart failure. *Eur J Heart Fail.* 2004;6:101-107.
9. Izawa KP, Watanabe S, Osada N, et al. Handgrip strength as a predictor of prognosis in Japanese patients with congestive heart failure. *Eur J Cardiovasc Prev Rehabil.* 2009;16:21-27.
10. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002;346:793-801.
11. Morey MC, Pieper CF, Cornoni-Huntley J. Is there a threshold between peak oxygen uptake and self-reported physical functioning in older adults? *Med Sci Sports Exerc.* 1998;30:1223-1229.
12. Sbruzzi G, Ribeiro RA, Schaan BD, et al. Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomized controlled trials. *Eur J Cardiovasc Prev Rehabil.* 2010;17:254-260.
13. Piepoli MF, Guazzi M, Boriani G, et al. Exercise intolerance in chronic heart failure: mechanisms and therapies. Part II. *Eur J Cardiovasc Prev Rehabil.* 2010;17:643-648.
14. Hanson P. Clinical exercise testing. In: Blair SN, Painter P, Pate RR, Smith LK, Taylor CB, eds. *Resource Manual for Guidelines for Exercise Testing and Prescription.* Philadelphia, PA: Lea & Febiger; 1988:205-222.
15. Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. *J Rehabil Med.* 2001;33:36-41.
16. Feiring DC, Ellenbecker TS, Derscheid GL. Test-retest reliability of the biodex isokinetic dynamometer. *J Orthop Sports Phys Ther.* 1990;11:298-300.
17. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med.* 2000;45:23-41.
18. Fischer JE, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. *Intensive Care Med.* 2003;29:1043-1051.
19. Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. *Acta Paediatr.* 2007;96:644-647.
20. Stanek B, Frey B, Hülsmann M, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. *J Am Coll Cardiol.* 2001;38:436-442.
21. Yamasaki H, Yamada S, Tanabe K, et al. Effects of weight training on muscle strength and exercise capacity in patients after myocardial infarction [in Japanese]. *J Cardiol.* 1995;26:341-347.
22. Yamasaki H, Yokoyama H, Aoki U, et al. Relationship between muscle strength in knee extensors and gait speed, independent gait in the elderly patients [in Japanese]. *Sogo Rehabil.* 1998;26:689-692.
23. Manini TM, Visser M, Won-Park S, et al. Knee extension strength cutpoints for maintaining mobility. *J Am Geriatr Soc.* 2007;5:451-457.
24. Puetz TW, Beasman KM, O'Connor PJ. The effect of cardiac rehabilitation exercise programs on feelings of energy and fatigue: a meta-analysis of research from 1945 to 2005. *Eur J Cardiovasc Prev Rehabil.* 2006;13:886-893.
25. Keteyian SJ, Fleg JL, Brawner CA, Piña IL. Role and benefits of exercise in the management of patients with heart failure. *Heart Fail Rev.* 2010;15:523-530.

# Association between heart rate at rest and myocardial perfusion in patients with acute myocardial infarction undergoing cardiac rehabilitation – a pilot study

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## Abstract

**Introduction:** This study was conducted to determine if there was a link among heart rate at rest (rHR), muscle volume changes, and single photon emission computed tomography (SPECT) parameters after 6-month cardiac rehabilitation in patients with acute myocardial infarction (AMI).
**Material and methods:** Twenty-nine consecutive AMI patients (mean age: 63.0 ±9.1 years) who received appropriate percutaneous coronary intervention on admission were enrolled. $^{99m}$Tc-Sestamibi myocardial SPECT images were obtained at the early (30 min) and delayed (4 h) phases after tracer injection at 2 weeks (0M) and 6 months (6M) after the onset of AMI. Within a few days of SPECT, all patients underwent cardiopulmonary exercise test for evaluation of cardiac rehabilitation effects. Before the initiation of exercise test, leg muscle volume was measured. All patients were stratified into the ≥ 70 beats per minute (bpm) ($n$ = 15) or < 70 bpm ($n$ = 14) group based on rHR at 6M.
**Results:** There were no significant differences in the recanalization time, peak cardiac enzyme, or initial left ventricular ejection fraction between the two groups. After the 6-month training, the muscle volume changes in the lower limbs (< 70 bpm, 0.23 ±0.22; ≥ 70 bpm, –0.07 ±0.26, $p$ < 0.05) were significantly greater in the < 70 bpm group than the ≥ 70 bpm group. The decreased rate of rHR had a significant correlation with the improved global severity ($r$ = 0.62, $p$ = 0.001) and extent ($r$ = 0.48, $p$ = 0.017) of left ventricle evaluated by $^{99m}$Tc-Sestamibi myocardial SPECT delayed phase.
**Conclusions:** The result of this preliminary study demonstrated that improved myocardial perfusion was closely related to decreased rHR after cardiac rehabilitation.

**Key words:** cardiac rehabilitation, exercise capacity, myocardial infarction, skeletal muscle, single photon emission computed tomography.

## Introduction

Since 1990, single-photon emission computed tomography (SPECT) with technetium-99m hexakis 2-methoxy-isobutyl-isonitrile ($^{99m}$Tc-sestamibi) has been used to assess the extent of myocardial damage at rest in patients with acute myocardial infarction (AMI) [1, 2]. $^{99m}$Tc-sestamibi SPECT, which measures the extent and severity of ischemia, is commonly used for risk stratification of patients with coronary artery disease (CAD)

[3]. Repeated myocardial imaging with $^{99m}$Tc-sestamibi performed in the acute phase and days after primary reperfusion treatment allows reliable assessment of the area at risk, the final infarct size, and the volume of salvaged myocardium by reperfusion therapy [4-6]. In addition, the infarct size (i.e., the number of residual cardiac segments with perfusion defects), as measured with SPECT, is strongly associated with the mortality risk [7].

Most AMI patients receive cardiac rehabilitation, as well as statin administration, for improvement of their prognoses [8-11]. Since the close association between the heart rate at rest (rHR) and coronary mortality was first described by Dyer *et al.* [12], rHR has gained broad attention among physicians [13, 14]. VanHees *et al.* [15] reported that physical training after AMI decreased the rHR. To date, only a handful of studies have reported the association between the findings on myocardial nuclear imaging and the effects of cardiac rehabilitation [16], and no studies have demonstrated an association between the findings of myocardial SPECT and the rHR after cardiac rehabilitation in AMI patients. The present study was aimed at clarifying the aforementioned association in AMI patients after successful percutaneous coronary intervention (PCI) and cardiac rehabilitation.

## Material and methods

### Subjects

The study subjects were 29 consecutive patients (mean age: 63.0 ±9.1 years) with *de novo* AMI due to single coronary arterial disease diagnosed between October 2009 and June 2011. On arrival at the emergency department, venous blood samples were collected from the cubital vein. The diagnosis of AMI was made by cardiologists, based on electrocardiographic changes, echocardiographic findings, presence of human heart fatty acid binding protein in the serum as detected by immunochromatography, and hematological findings, including the blood levels of MB isoenzyme of creatinine kinase (CK-MB). In order to determine the actual onset time of the AMI, the patients and their family members were interviewed. In primary PCI, a thrombus aspiration catheter was employed to negotiate the occluded lesions; coronary angiography was performed during the PCI. The PCI procedure was considered successful when the residual stenosis was less than 25%, in the absence of dissection, as previously described [17]. Blood samples were collected every 3 h after the PCI to determine the peak levels of the cardiac enzymes. All patients were treated with conventional medications after PCI, and none showed exacerbation of the symptoms or needed hospitalization for AMI-related complications before or after the scintigraphic examinations. Patients with previous myocardial infarction, left main trunk lesion, cardiogenic shock, cardiomyopathies, atrial fibrillation, active infectious disease, hematological disease, end-stage renal and hepatic disease, and patients who were not able to undergo the cardiac rehabilitation program, were completely excluded from the study subjects.

The study protocol included blood tests, PCI, $^{99m}$Tc-sestamibi radionuclide examination, and cardiac rehabilitation. This study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki, and was approved by the Human Investigation Committee of St. Marianna University School of Medicine (study protocol No. 1604). The nature and purpose of this study were thoroughly explained to all patients prior to their enrollment in this study, and written informed consent was obtained from each of the patients.

### Radionuclide studies

All study patients underwent myocardial SPECT 2 weeks (0M) and 6 months (6M) after the onset of AMI. $^{99m}$Tc-sestamibi (740 MBq; Fuji Film RI Pharma Co. Ltd., Tokyo, Japan) was injected into the left antecubital vein, followed by acquisition of SPECT images in two phases: initially at 30 min after the radionuclide injection (early $^{99m}$Tc-sestamibi uptake), and subsequently, at 4 h after the radionuclide injection (delayed uptake) as previously reported [18].

Before performing the SPECT, anterior and lateral planar images were acquired for 300 s using a gamma camera equipped with a low-/medium-energy general-purpose collimator and a 512 × 512 matrix. $^{99m}$Tc-sestamibi images were obtained using a double-headed gamma camera (Symbia E; Siemens-Asahi Medical Technologies Ltd., Tokyo, Japan) equipped with a low-/medium-energy general-purpose collimator. Two detectors (2 × 180°) were used to acquire 64 views for 25 s in 5.6° steps using a 64 × 64 matrix. The energy window of $^{99m}$Tc was centered at 140 keV ± 15%.

Raw imaging data were reconstructed using Butterworth-filtered back-projection (order, 8; cutoff frequency, 0.37 cycles/cm). Transaxial slices were reconstructed and reoriented to represent coronal slices, and then horizontal long- and short-axis slices were acquired by axis shift.

Standard electrocardiographically gated images were acquired in 64 steps at 19 s per step, using the step acquisition mode in the time duration between two consecutive R waves of the electrocardiogram (RR) interval, and divided into 16 frames. Tracer uptake was assessed by non-gated early images created from the sums of all of the gated images obtained in the standard acquisition mode.