Health-Related Quality of Life in Relation to Different Levels of Disease Severity in Patients with Chronic Heart Failure

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Abstract. The purpose of the present study was to compare differences in physiological outcomes and health-related quality of life (HRQOL) in relation to degree of illness in patients with chronic heart failure (CHF) and to compare HRQOL in CHF patients with that of a normal Japanese population. One hundred and twenty-five patients with stable CHF (93 men, 32 women, mean age 63.3 ± 12.4 years) with left ventricular ejection fraction (LVEF) of less than 40% were enrolled in the present study. We used New York Heart Association (NYHA) functional class as an index of degree of illness. In 64 of the 125 patients, physiological outcome measures included peak oxygen uptake (peak VO₂) and VE/VO₂ slope. HRQOL was assessed with the medical outcome study short form-36 (SF-36) Japanese version. In addition, SF-36 scores of CHF patients were compared against Japanese standard values. Age and LVEF did not differ according to NYHA functional class. The eight SF-36 subscale scores and peak VO₂ decreased with increases in the NYHA functional classes, whereas VE/VO₂ slope increased with increases in NYHA functional class (p<0.05). Of the 8 SF-36 subscales measured in CHF patients, only the bodily pain score attained that of the normal Japanese population. These findings suggest that HRQOL decreases as NYHA functional class increases and other physiological measures worsen. In addition, HRQOL values of CHF patients were low in comparison with standard values of a normal Japanese population.

Key words: health-related quality of life, physiological outcomes, chronic heart failure

Chronic heart failure (CHF) is the most common cardiovascular disease¹. It leads to frequent hospitalizations and is associated with functional incapacity². One of the important objectives of cardiac rehabilitation (CR) for CHF is improvement in exercise capacity associated with mortality and morbidity³. Some studies have shown that CR improves peak oxygen uptake (peak VO₂) and endothelial function in patients with CHF³⁴. Hambrecht et al.⁴ reported in patients with CHF that moderate-intensity aerobic exercise training significantly improved endothelium-mediated vasodilation of the peripheral vasculature after 24 weeks and that these changes were correlated with changes in peak VO₂.

Another important objective of CR is improvement in health-related quality of life (HRQOL)⁵. HRQOL is a relatively new scientific measure to evaluate effectiveness of treatment strategies and the course of a disease. Reports exist from many countries discussing HRQOL in CR⁶⁷. In CHF, several disease-specific instruments, such as the Minnesota living with heart failure questionnaire, have proved useful in clinical studies⁸⁹. However, the
disadvantage of these specific measures is that they are difficult to compare in the normal population.

Recently, HRQOL was shown to be decreased in patients with coronary artery bypass graft surgery in comparison with that in the general population according to the medical outcome study 36-item short form health survey (SF-36), a validated, reliable, and multidimensional generic measure of quality of life(9). Several studies have reported on HRQOL in patients with coexisting acute myocardial infarction (AMI) and cardiac surgery(10–12). We also previously reported that an 8-week program of exercise training has specific effects on improvement of HRQOL and physiological outcomes in Japanese patients(13). However, few studies have investigated the relation of HRQOL to cardiac disease. Particularly, the relation of different levels of disease severity to HRQOL in patients with CHF is unknown.

Although individual perceptions may differ regarding the value of exercise considered important in the design of strategies to improve exercise in CHF patients, only a few studies have reported on HRQOL in Japanese CHF patients, who may have a different cultural background from that of Caucasian populations. Therefore, the purpose of the present study was to compare differences in physiological outcomes and HRQOL in patients with different levels of CHF disease severity and to determine whether CHF patients would have reproducible HRQOL outcomes comparable to HRQOL of the normal Japanese population.

Methods

Study design and subjects

This was a cross-sectional study in which subjects were selected from among 127 outpatients who visited St. Marianna University School of Medicine Hospital for evaluation of CHF. The inclusion criterion was a left ventricular ejection fraction (LVEF) below 40%. Patients of New York Heart Association (NYHA) functional class IV were excluded as were those who had neurological, peripheral vascular, orthopedic, or pulmonary disease. In all patients, NYHA classification was determined by an independent investigator. Of the 127 patients, 125 were included in this study. Two patients were excluded due to their failure to complete the HRQOL questionnaire.

Ethics

The present study was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research. Informed consent was obtained from each patient.

Clinical characteristics of the patients

A cardiologist assessed LVEF as an index of cardiac function and brain natriuretic peptide (BNP) concentration as an objective index of the level of disease severity. We also evaluated several patient characteristics, including age, sex, etiology of heart failure, and medications.

Physiological outcomes

Of the 125 patients, 64 underwent cardiopulmonary exercise testing (CPX) via a ramp cycle ergometer protocol during stable CHF. Peak VO$_2$ and the slope of the relation between ventilation and carbon dioxide production (VE/VO$_2$ slope) were measured as indices of physiological outcomes. Measurements made from expired gasses were used as indices of cardiovascular dynamics during exercise. Symptom-limited exercise testing was performed on a CORIVAL 400 the standard in ergometry (Lode Co., Groningen, Holland). Throughout the test, a 12-lead ECG was continuously monitored, and heart rate was measured from the R-R interval of the ECG (ML-5000, Fukuda Denshi Co., Tokyo, Japan). VO$_2$ was measured throughout the exercise period with an AE-300S aero monitor (Minato Ikagaku Co., Tokyo, Japan) and calculated with a personal computer (Pentium 98 SE, EPSON Co., Nagano, Japan). The endpoint of exercise testing was determined according to the criteria of the American College of Sports Medicine(14). Prescribed cardiac medications were continued on the day of the exercise test.

HRQOL

General HRQOL was measured with the Medical Outcome Study 36-item Short Form Health Survey (SF-36)(15). The SF-36 consists of 36 items representing 8 subscales that cover the domains of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 is a standardized, generic HRQOL measurement instrument that has been validated in the general normal Japanese population(16). It measures multidimensional properties of HRQOL on a scale ranging from 0 to 100, with lower scores representing a lower HRQOL and higher score indicating a superior HRQOL.

To compare scores to the normal Japanese population, SF-36 subscale scores were converted into a deviation score adjusted for sex and age based on scores of the Japanese national norm(16,17). This is a mean score of 50 with a standard deviation (SD) of ± 10. In the present study, a score <50 indicates that the score representing the specific health concept was below that of the Japanese national norm after adjusting for age and sex. The questionnaires were computer-scanned and scored by the Public Health Research Foundation (Tokyo, Japan)(18).

Statistical analysis

Results are expressed as mean ± SD. Non-parametric and chi-square tests were used to analyze differences in clinical factors. Because comparisons between groups were
performed for each NYHA class and the CHF sample across the eight SF-36 subscales, the Mann-Whitney U test was used to test for differences between two independent groups, and the Kruskal-Wallis test was used to test for differences between three groups in HRQOL and physiological outcomes. Statistical analyses were performed with SPSS 9.0J statistical software (SPSS Japan, Inc, Tokyo, Japan). A p value of <0.05 was considered significant.

**Results**

**Clinical factors**

Clinical factors and HRQOL scores of 125 patients were available for statistical analysis. Patient characteristics and functional variables in all patients are summarized in Table 1. The majority of patients (91.2%) were in NYHA functional class I or II, and almost all patients were being treated with diuretics. Patient characteristics, including age and sex, were almost identical between the three groups, which consisted of patients in NYHA functional class I, II, or III. LVEF did not differ significantly between NYHA classes I (28.6 ± 7.4%), II (28.5 ± 8.6%), and III (32.0 ± 8.1%), (p=0.501). However, BNP differed significantly between NYHA class I (163.1 ± 138.4 pg/ml), II (312.5 ± 259.6 pg/ml), and III (549.5 ± 353.7 pg/ml), (p=0.000). Oral dosages of drugs did not differ significantly between the three groups.

**Physiological outcomes**

The endpoint of the exercise test was leg fatigue, shortness of breath, or gas exchange ratio ≥1.20. No patient showed ischemic ST changes or experienced chest pain or serious arrhythmia during exercise testing. Comparisons performed after testing involved a total of 64 patients divided into three subgroups: NYHA functional class I (n=36), NYHA functional class II (n=22), and NYHA functional class III (n=6) (Table 2). Physiological outcomes were significantly different between NYHA functional classes (Table 2). Higher functional class was associated with poorer physiological outcomes.

**Difference in HRQOL subscale scores according to NYHA functional class**

Comparisons performed after SF-36 testing involved 125 patients divided into three subgroups: NYHA functional class I (n=54), NYHA functional class II (n=60), and NYHA functional class III (n=11). The data collected from the three groups are presented in Table 3. HRQOL as assessed by the SF-36 scores was lowest for patients in NYHA functional class III, and there were significant differences in scores between functional classes except for that of the bodily pain score (Table 3). The most significant decreases observed in the SF-36 scores were in patients of NYHA functional class III, and almost all patients were being treated with diuretics. Higher functional class was associated with poorer HRQOL.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (yrs.)</th>
<th>Sex (Male/Female)</th>
<th>BNP (pg/ml)</th>
<th>LVEF (%)</th>
<th>Etiology of heart failure N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (yrs.)</td>
<td>63.3 ± 12.4</td>
<td>92/33</td>
<td>266.8 ± 250.5</td>
<td>29.0 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Previous myocardial infarction 30 (24)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Valvular heart disease 23 (18.4)</td>
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<td></td>
<td></td>
<td></td>
<td>Hypertensive heart disease 10 (8)</td>
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<td>Atrial fibrillation 4 (3.2)</td>
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<td></td>
<td>Congenital heart disease 4 (3.2)</td>
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<td>Dilated cardiomyopathy 54 (43.2)</td>
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<tr>
<td>Medication</td>
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<td></td>
<td>Diuretics 119</td>
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<td>Digitalis 34</td>
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<td></td>
<td></td>
<td>ß-blockers 40</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ACEI or ARB 112</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

**Table 2.** Comparison of peak VO₂ and VE/VO₂ slope among different NYHA classes in patients with CHF

<table>
<thead>
<tr>
<th>Variable</th>
<th>NYHA I (n=36)</th>
<th>NYHA II (n=22)</th>
<th>NYHA III (n=6)</th>
<th>Kruskal-Wallis p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>22.3 ± 5.0ab</td>
<td>17.9 ± 4.4c</td>
<td>14.9 ± 5.0</td>
<td>0.001</td>
</tr>
<tr>
<td>VE/VO₂ slope</td>
<td>30.8 ± 5.7ab</td>
<td>35.7 ± 7.4c</td>
<td>39.1 ± 10.8</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Significant differences were noted in measurements of peak VO₂ and VE/VO₂ slope in the three groups.

- **a** Significantly different when compared with NYHA II group.
- **b** Significantly different when compared with NYHA III group.
- **c** Significantly different when compared with NYHA III group.

Data are expressed as mean ± SD. CHF, chronic heart failure; NYHA, New York Heart Association.
The present study, an SF-36 score <50 indicated that the score representing the specific health concept was below that of the normal Japanese population after adjusting for age and sex. In our total CHF patient sample, no SF-36 score except that for the bodily pain subscale attained the level of scores of normal Japanese populations (Fig. 1). The lowest scores were obtained for role limitation because of patient physical problems. SF-36 subscale scores that grade mental status, such as social functioning and role-emotional, were also low.

### Discussion

This study shows a difference in cardiac function as related to degree of illness, HRQOL, and physiological outcomes such as peak VO$_2$ and VE/VECO$_2$ slope in Japanese CHF patients. We chose to evaluate HRQOL with the SF-36 instrument because it is well validated, scores for the general population have been published, and an increasing number of researchers are using this test.$^{18}$

As an objective index of disease severity, we measured BNP concentration. BNP concentration increases as CHF becomes more severe, and BNP is a known, independent factor of mortality of CHF.$^{19}$ Because BNP concentration in our study increased as NYHA functional class increased,
we thought that BNP reflected the degree of seriousness of CHF as well as NYHA functional class did.

With regard to physiological outcomes, it was previously reported that peak VO₂ and VE/VCO₂ slope vary inversely, and both are related to symptom scores and prognosis. Itoh et al. previously reported that peak VO₂ is expressed as a percentage of predicted values determined. As a result, % peak VO₂ decreases significantly with increasing severity of disease, or, in other words, peak VO₂ decreases as NYHA functional class increases. In the present study, although LVEF of patients did not differ between NYHA functional class groups, peak VO₂ decreased as NYHA functional class increased. This finding from our study is consistent with those of earlier studies.

A recent study also reported that patients with CHF breathe more often during exercise than do controls, resulting in an increase in VE/VCO₂ slope. In the present study, the VE/VCO₂ slope increased as NYHA functional class increased. The increased VE/VCO₂ slope must therefore be a result of other mechanisms. Ventilation perfusion mismatch, impaired diffusion of metabolic gases, respiratory muscle weakness, and heightened sensitivity of peripheral receptors have all been postulated as possible causes. In this way, physiological outcomes such as peak VO₂ and VE/VCO₂ slope appeared to differentiate clearly between different grades of disease severity, as measured by NYHA functional class.

With regard to another important outcome, indices of HRQOL also decreased with NYHA functional class. All aspects of HRQOL were dramatically reduced in NYHA class I, II, and III patients, reflecting the severe impact of CHF on daily life, even though the patients were in a compensated stage and in an ambulatory setting. This also applied to another HRQOL instrument, the Nottingham Health Profile (NHP), and suggested that when using the aforementioned measures, improvements in HRQOL may also reflect improved NYHA functional class. Indeed, quality of life, as reflected by the NHP, has been shown to improve, as has NYHA functional class, after heart transplantation. These data imply that HRQOL may be especially relevant in CHF, in which NYHA functional class is of prime importance.

In addition to NYHA functional class, more objective indices of functional capacity such as the 6-minute walk test also showed some relation to quality of life. However, Steptoe et al. found no univariate association between exercise capacity and quality of life in patients with mild to moderate CHF. In the present study, we also were not able to clarify this point. This raises the question as to which other predictors besides the most obvious prognostic somatic variables in CHF patients are important. Future trials are needed to evaluate the predictors of prognosis and/or mortality in patients with CHF.

Compared with the normal Japanese population, our CHF patients showed a global reduction in HRQOL as measured in 7 of the SF-36 subscales. Although the most pronounced loss of HRQOL was observed in the domain of role limitation because of physical problems, SF-36 subscales scores related to mental status such as social functioning and role-emotional were also low.

In apparently asymptomatic patients with left ventricular dysfunction, the SF-36 scores revealed significant decreases in the scales representing somatic physiological and mental status. In other words, poor HRQOL might be indicated not only by scores relating to physical but also mental state. The lack of association between LVEF and HRQOL is in total agreement with findings of previous studies.

In addition to decrease in physiological outcomes such as peak VO₂, one could speculate that these results reflect the effect of CHF on the central nervous system. Changes in central neurohumoral regulation systems or diminished central perfusion might impair cognitive capacity and trigger a latent vulnerability to depressive disorders.

Interestingly, with regard to the SF-36 bodily pain subscale score, we felt that improvement in this score was unrelated to bodily pain per se because CHF patients were not experiencing chest pain. For example, after the onset of AMI, patients may interpret the SF-36 bodily pain subscales as referring to chest pain. However, only 24% of patients in the present study had a previous MI. The possibility exists in the present study that CHF patients did not influence the SF-36 bodily pain subscale score. Therefore, we surmised that the bodily pain subscale may not be appropriate for the evaluation of patients with CHF.

To the best of our knowledge, Mitani et al. are the only other group to have evaluated HRQOL in Japanese CHF patients with the SF-36 health survey. In their study, although 91 patients with CHF had very poor HRQOL and overall reported bodily pain, their patients’ bodily pain scores were lower than those of the patients in our study. This discrepancy may be related to differences in patient characteristics. A possible reason may be that a higher percentage of CHF patients in their study had ischemic heart disease. Although our study patients included mainly those with cardiomyopathy, valvular heart disease, hypertensive heart disease, and atrial fibrillation, only 24% of patients had a previous myocardial infarction. In their study, 57% of CHF patients had ischemic heart disease. This may account for the difference in HRQOL-related findings between the present study and those of Mitani et al.

Recently, Tamura et al. developed a disease-specific quality of life measure in patients with CHF. They suggested that a disease-specific quality of life questionnaire is applicable to the evaluation of HRQOL in patients with CHF. We believe that both the SF-36 and
disease-specific quality of life questionnaires may be needed to evaluate HRQOL in future trials.

There were several limitations in the present study. First, the present study comprised a small sample, and thus it was not possible to determine what factors might predict reduced HRQOL. We did not ascertain the reasons for impaired HRQOL. Other conditions, such as hip pain, cancer, or depression, for example, may also result in lower HRQOL scores. Therefore, further studies are needed to investigate the relation between HRQOL and other factors.

Second might be the cross-sectional design of the study. The main thrust of the present study was to assess the differences in degree of illness in relation to physiological outcome and HRQOL assessed at a particular time. Nevertheless, it would be highly desirable to document longitudinal change in physiological outcome and HRQOL in patients with CHF. HRQOL and disease-specific quality of life questionnaires should be used in future studies to evaluate not only the effect of exercise performance but mental status as it relates to HRQOL over the long term after CR.

Finally, in the present study, although differences in physiological outcomes associate with NYHA functional classes were determined, we did not directly measure leisure-time physical activity. A previous study has shown that leisure-time physical activity influences HRQOL positively\(^\text{30}\). A recent review also indicated that an increased level of physical activity generally, although not always, favorably affects quality of life\(^\text{31}\). Therefore, future trials are needed to evaluate the relation between physical activity and HRQOL in patients with CHF.

**Conclusion**

We found in patients with CHF that as NYHA functional class increased, peak VO\(_2\) and almost all SF-36 subscale scores decreased, whereas VE/VCO\(_2\) slope increased. NYHA functional class, but not LVEF, appears to be related to HRQOL. Thus, in patients with CHF, not only objective physiological outcomes but also HRQOL decreased as NYHA functional class increased. In addition, all SF-36 subscale scores except that for bodily pain were greatly lower when compared to those of the normal Japanese population. Future trials will need to evaluate the effect of CR for longitudinal settings and for longer periods; long-term follow-up will be required to evaluate whether these benefits continue over time.

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