Quantitative Assessment of Daily Physical Activity Levels in Patients With Chronic Heart Failure by Measuring Energy Expenditure — Effects of Converting Enzyme Inhibitor Therapy —

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Although a major goal in the treatment of chronic heart failure is to improve daily physical activity levels, this has not been assessed quantitatively. An increased daily activity level may be reflected by an increase in daily energy expenditure. In the present study, measurements of energy expenditure with a commercially available ambulatory calorimeter were first validated using cardiopulmonary exercise tests in 5 normal volunteers. The energy expenditure measured by the calorimeter correlated well with that estimated from oxygen uptake ($r=0.89$). Subsequently, the daily energy expenditure was serially measured with the calorimeter during long-term administration of the converting enzyme inhibitor ramipril for 24 weeks in 8 patients with chronic heart failure. Changes in echocardiographic parameters and exercise capacity were also studied. Peak oxygen uptake and anaerobic threshold assessed with symptom-limited maximal bicycle exercise were significantly increased 12 weeks or more after the initiation of treatment ($P<0.01$ and $P<0.01$, respectively). Left ventricular fractional shortening substantially, but not significantly, increased during this period ($P<0.1$). These results strongly suggest that an overall improvement in heart failure was achieved after long-term ramipril therapy. The energy expenditure during daily activities was also significantly increased after ramipril therapy for 24 weeks ($P<0.01$). Thus, the daily energy expenditure increased with improvement of heart failure, probably reflecting an increase in daily activity levels. We conclude that calorimetric measurement of daily energy expenditure is a novel and simple technique for quantitative evaluation of the effect of therapy on daily physical activity levels in patients with chronic heart failure.

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Since the daily lives of patients with chronic heart failure are limited due to symptoms of heart failure, a major goal in the treatment of chronic heart failure is to improve daily physical activity levels. Several clinical scales, including the New York Heart Association (NYHA) functional classification and the specific activity scale, have been proposed for the evaluation of daily physical activity levels in patients with chronic heart failure. However, these scales...

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are designed to identify the level of physical activity at which symptoms of heart failure develop, and, hence, depend primarily on the patient's subjective complaints and doctors' interviews. A more objective and quantitative measure is needed to evaluate the effect of therapy on daily activity levels.

Recently, Davies et al. reported that daily limb movements measured by movement sensors are decreased in patients with chronic heart failure, and depend on the severity of heart failure. Thus, measurements of daily energy expenditure may provide an objective assessment of the effect of therapy on daily physical activity levels in patients with chronic heart failure. A sophisticated ambulatory calorimeter is now commercially available.

The aim of the present study was two-fold; 1) to validate the ability of a commercially available calorimeter to measure energy expenditure during exercise, and 2) to examine the change in daily energy expenditure measured with this technique during long-term converting enzyme inhibitor therapy in patients with chronic heart failure.

METHODS

1. Validation of The Calorimeter

In the present study, a compact ambulatory calorimeter (Kenz Calorie Counter, Suzuken Co, Nagoya, Japan) equipped with an acceleration sensor was used. The apparatus weighs 70 g and measures $79 \times 64 \times 18$ mm. This apparatus was designed to detect the acceleration rate along the vertical axis at the waist during body movements and automatically calculate energy expenditure from the product of the acceleration rate and body weight. The calculated energy expenditure is integrated and stored internally.

A previous study demonstrated that the energy expenditure measured by this calorimeter well reflected the actual energy expenditure during treadmill exercise. In this study, we also tested the accuracy of the apparatus before beginning long-term converting enzyme inhibitor therapy. Five normal male volunteers performed seven-stage graded treadmill exercise to compare the calorimetric measurement of energy expenditure to that estimated from oxygen uptake. The exercise test was conducted with an initial walking speed of 1.2 km/h for 4 min, which was then increased at 1.0 km/h every 4 min without any change in the slope. At each exercise stage, total oxygen uptake for 4 min was measured using a respirometer system (RM-200, Minato Co, Tokyo, Japan) and energy expenditure was determined using the nomogram of energy equivalents for oxygen uptake. The energy expenditure during each exercise stage was simultaneously measured with the calorimeter attached to the waist.

2. Long-Term Administration of Ramipril Subjects

To investigate the effect of an improvement in heart failure on daily physical activity levels, the calorimetric energy expenditure was serially measured during long-term administration of the converting enzyme inhibitor ramipril. Eight male patients with stable chronic heart failure, ranging in age from 44 to 77 years (mean, 59.6 years), were studied. The underlying diseases were dilated cardiomyopathy in 6 patients and old myocardial infarction without angina pectoris in the other 2. All of the patients showed sinus rhythm and all were classified into NYHA functional class II. Left ventricular end-diastolic dimension and fractional shortening determined with M-mode echocardiography under the guide of 2-dimensional images ranged from 46 to 64 mm (mean, 60.4 mm) and from 6 to 16% (mean, 10.9%), respectively. All of the patients had been treated with digitalis and/or diuretics for more than 2 months before the trial. None had been treated with other inotropic agents, beta-adrenoceptor blockers or converting enzyme inhibitors. However, 3 patients had received other vasodilators, including nitrates and calcium antagonists. These concomitant drugs were continued during the study.

Prior to entering the study, written informed consent was obtained from each patient.

Protocol of The Ramipril Study

During the run-in period for 4 weeks, the patients' conditions were confirmed to be stable through interviews, echocardiographic examinations, and cardiopulmonary exercise tests performed twice at an interval of 2
weeks. During the last 2 weeks of the run-in period, the energy expenditure was measured every day, using the calorimeter. On the last day of the run-in period, chest X-rays were also obtained.

During the treatment period, ramipril therapy was begun with an initial dose of 2.5 mg once a day, which was increased by 2.5 mg/day every 2 weeks until the resting systolic pressure was decreased by 10 mmHg or more. The final dose was 2.5 mg/day in 6 patients, 5 mg/day in one patient, and 10 mg/day in the remaining patient. Treatment was continued for 24 weeks at these final doses. Symptomatic, radiographic, echocardiographic, and exercise examinations were performed 6, 12, and 24 weeks after beginning treatment. During the 2 weeks preceding these measurements, the corresponding energy expenditure was measured every day, using the calorimeter.

Measurement of Energy Expenditure

The energy expenditure during daily activities was measured with continuous application of the calorimeter at the wrist from the time it was put on in the morning (wear-on) to the time it was taken off at night (wear-off). To minimize day-to-day variation in energy expenditure, the cumulative energy expenditure for 14 consecutive days was obtained in this study. During the measurement period, patients were instructed to continue their ordinary daily lives and record the wear-on and wear-off times are likely to be influenced by factors independent of improvement or exacerbation of heart failure, the energy expenditure per hour was calculated as an index of daily physical activity levels: i.e., (total energy expenditure for 14 day)/(summed application time for 14 days).

Cardiopulmonary Exercise Test

A ramp maximal bicycle exercise test was conducted with one-minute unloading pedaling, followed by 15-W incremental loading each minute until the patient was nearly exhausted. Gas exchange data were collected continuously during exercise using a breath-by-breath respiromonitor system. The system was calibrated immediately prior to each study using a 2-L calibration syringe and a gas mixture of 14.93% oxygen, 5.00% carbon dioxide, and 80.07% nitrogen. Oxygen uptake, carbon dioxide output, and minute ventilation were obtained every 10 sec. Exercise time, peak oxygen uptake, and oxygen uptake at the anaerobic threshold were obtained as indicators of exercise capacity. The anaerobic threshold was defined as the time point when the ratio of minute ventilation to oxygen uptake began to increase rapidly without a concomitant increase in the ratio of minute ventilation to carbon dioxide output?

Echocardiograms

Resting M-mode echocardiograms were recorded at the tip of the mitral valve under the guide of two-dimensional imaging. Left
TABLE I  EFFECTS OF RAMIPRIL ON HEMODYNAMIC PARAMETERS, CARDIAC FUNCTION, EXERCISE CAPACITY, AND ENERGY EXPENDITURE

<table>
<thead>
<tr>
<th></th>
<th>Run-in period</th>
<th>Treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>first</td>
<td>final</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>120.3±20.2</td>
<td>118.3±21.2</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.5±8.0</td>
<td>78.5±9.4</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>88.1±12.4</td>
<td>87.9±9.0</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>56.4±8.1</td>
<td>55.1±5.1</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>60.4±7.7</td>
<td>61.0±7.7</td>
</tr>
<tr>
<td>ESD (mm)</td>
<td>54.0±8.2</td>
<td>54.4±8.4</td>
</tr>
<tr>
<td>FS (%)</td>
<td>10.9±3.4</td>
<td>11.5±3.5</td>
</tr>
<tr>
<td>ET (sec)</td>
<td>539±311</td>
<td>564±299</td>
</tr>
<tr>
<td>Peak VO2 (ml/min per kg)</td>
<td>18.3±4.6</td>
<td>18.8±4.2</td>
</tr>
<tr>
<td>AT (ml/min per kg)</td>
<td>12.1±3.0</td>
<td>12.5±3.8</td>
</tr>
<tr>
<td>Energy expenditure (kcal/h)</td>
<td>10.8±4.7</td>
<td>12.3±7.0</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; CTR, cardiothoracic ratio; EDD, left ventricular end-diastolic dimension; ESD, left ventricular end-systolic pressure; FS, left ventricular fractional shortening; ET, exercise time; VO2, oxygen uptake; AT, oxygen uptake at anaerobic threshold. Values are mean±SD. *p<0.05 vs the final evaluation of the run-in period, **p<0.01 vs the final evaluation of the run-in period.

ventricular end-diastolic and end-systolic dimensions were measured in a standard fashion as the mean value of three consecutive cardiac cycles. Fractional shortening was calculated as 100×(end-diastolic dimension—end-systolic dimension)/end-diastolic dimension.

Data Analysis
Data are expressed as the mean±SD. Data from the final evaluation of the run-in period and those from the treatment period were compared with ANOVA for repeated analysis. A p value of less than 0.05 was considered statistically significant.

RESULTS
1. Validation of The Calorimeter
The energy expenditure measured with the calorimeter increased in proportion to increases in the walking speed in individual subjects (Fig. 1A). Moreover, a close linear correlation was observed between the energy expenditure measured with the calorimeter and that estimated from oxygen uptake in individual subjects (r=0.93 to 0.98, mean, 0.96) and pooled data (r=0.89) (Fig. 1B). These results indicate that during level walking the calorimetric energy expenditure well reflects the actual energy expenditure.

2. Long-Term Administration of Ramipril (Table I)
Effects on Hemodynamics and Cardiac Function
All 8 of the patients completed the study without exacerbation of heart failure or changes in the dose or regimen of concomitant drugs. During the run-in period, significant changes were not observed in any parameter (Table I). Compared with the final baseline values, systolic and diastolic blood pressures significantly decreased 6 weeks after the initiation of ramipril therapy, although the decrease in systolic blood pressure was insignificant during the later period of the study. Heart rate remained unchanged during the study, suggesting the absence of reflex tachycardia. The cardiothoracic ratio and left ventricular dimensions gradually, but not significantly, decreased during the treatment period. Left ventricular fractional shortening substantially, but again not significantly, increased after 24 weeks of treatment (P<0.1).

Effects on Exercise Capacity
Compared with baseline values, the peak oxygen uptake and oxygen uptake at the anaerobic threshold were significantly increased after ramipril therapy for 12 weeks. A similar trend was observed on the exercise time. These improvements in exercise

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capacity, together with a favorable trend in left ventricular fractional shortening, suggest that an overall improvement of heart failure was achieved after long-term administration of ramipril for 12 weeks or more.

Effects on Energy Expenditure

The hourly energy expenditure measured by the calorimeter remained unchanged for the initial 12 weeks of the study. However, a significant increase was observed 24 weeks after the initiation of treatment (Table I and Fig. 2B). When individual responses were examined, the values after 24 weeks of treatment were consistently greater than baseline values (Fig. 2A). Thus, the hourly energy expenditure during daily activities increased after long-term ramipril therapy for 24 weeks.

DISCUSSION

Converting enzyme inhibitors, including ramipril, have been shown to have long-term beneficial effects in patients with chronic heart failure. In the present study, significant improvements in exercise capacity with a favorable trend in left ventricular fractional shortening were also observed after long-term administration of ramipril for 12 weeks or more. Since this study was not a controlled trial, it is unclear whether these improvements were due solely to the effect of ramipril or to some other mechanisms. However, we evaluated only quantitative endpoints in this study, and did not consider subjective symptoms. Thus, our results strongly suggest that whatever the mechanism, an overall improvement in heart failure was achieved during the treatment period.

Using the calorimetric measurement, we further demonstrated that the hourly energy expenditure during daily activities significantly increased after long-term ramipril therapy, along with improvements in heart failure. Since this was an uncontrolled trial, it remains possible that the increase in energy expenditure was due to a placebo effect. However, this is unlikely because the hourly energy expenditure was almost unchanged over the initial 12 weeks of the study, despite ramipril administration (Fig. 2B). Thus, our findings suggest that body movements per unit time during daily life increase with an effective heart failure therapy, which may reflect an increase in daily physical activity levels. The calorimetric measurement of daily energy expenditure appears to be a novel and practical technique for evaluating the effect of therapy on daily physical activity levels in patients with chronic heart failure.

In the present study, the hourly energy expenditure was significantly increased after the administration of ramipril for 24 weeks, whereas improvements in exercise capacity were noted after only 12 weeks of treatment. Thus, although the precise mechanisms are unclear, increases in daily physical activity levels may be delayed for several weeks or months after an improvement in exercise capacity. Moreover, despite significant increases in exercise capacity and physical

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Fig. 2. (A) The hourly energy expenditure measured by the calorimeter before and during ramipril treatment in individual patients with chronic heart failure. (B) The averaged data for eight patients. Data are mean ± SD. *p<0.01 vs the run-in period.
activity levels, significant hemodynamic improvements were not observed in this study; although left ventricular fractional shortening substantially increased after 24 weeks of treatment, this change was not significant. The precise mechanisms underlying this discrepancy are also unclear. However, exercise capacity primarily depends on exercise hemodynamics in patients with chronic heart failure, and is independent of resting hemodynamics.\textsuperscript{14,15} Thus, it is possible that cardiac function reserve was restored with ramipril therapy and, hence, the cardiac output response to exercise was improved in our patients. The vasodilating capacity in exercising legs might also be improved by converting enzyme inhibitor therapy, which would contribute to an increase in exercise capacity.\textsuperscript{16}

The heart failure patients we studied were classified into NYHA class II. Therefore, our results also suggest that daily physical activity levels are limited even in mildly symptomatic patients with chronic heart failure. In these patients, it is usually difficult to evaluate the effect of therapy based on changes in subjective symptoms of heart failure. Thus, the calorimetric measurement of daily energy expenditure may be useful for assessing heart failure therapy, particularly in patients with mild chronic heart failure.

\textit{Limitations in Measuring Energy Expenditure}

There are several limitations in the measurement of daily energy expenditure with ambulatory calorimeters. The calorimeter used in this study was designed to detect the acceleration rate along the vertical axis at the waist during body movements, and to calculate the energy expenditure from the product of the acceleration rate and body weight? Indeed, during level walking, the calorimetric energy expenditure well reflects the actual energy expenditure (Fig. 1). However, body movement with a fixed waist position, such as in bicycle exercise, cannot be detected by this apparatus. Moreover, additional energy expenditure, such as that going up a slope or stairs, is also not detected by the calorimeter. Thus, the calorimetric measurement of daily energy expenditure may not be appropriate for comparing daily physical activity levels among subjects with different life styles or in different environments. However, in an individual subject, serial changes in calorimetric energy expenditure are likely to reflect changes in daily physical activity levels.

The day-to-day variation in energy expenditure has been reported to be fairly large, even in the same subject, because of weekly living cycles.\textsuperscript{7,18} Therefore, energy expenditure should be measured daily for a week or more to account for this variation. The daily energy expenditure was measured for 2 weeks in the present study. Although further studies are needed, this length of time appears to be adequate because the hourly energy expenditure was fairly constant during the initial phase of the study (Fig. 2).

In patients with heart failure, the severity of heart failure is most likely to determine daily physical activity levels. However, daily activity levels may also be influenced by a doctor’s advice to avoid excessive exertion. In the present study, this influence may have been minimized because the patients were instructed to continue their ordinary daily lives while wearing the calorimeter.

\textit{Conclusions}

Several clinical scales based on subjective symptoms have been used to evaluate the effects of therapy on daily activity levels in patients with chronic heart failure. Although this was a preliminary study with a small study population, the results strongly suggest that the calorimetric measurement of daily energy expenditure provides a quantitative and objective evaluation. However, further large controlled clinical trials are needed to validate this novel technique.

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