INTRODUCTION

In Japan, approximately 20% of all inpatients are diagnosed as having cardiovascular disease. Furthermore, the proportion of people over 65 years of age with cardiovascular disease is >25%. The proportion of patients with cardiovascular disease will likely increase further because of the progressive aging of the population. In Japan, it is anticipated that the incidence of left ventricular dysfunction will initially increase rapidly and then increase more slowly to reach a peak of 1.32 million patients by 2035, with the rapid phase of increase occurring by 2020.1 To understand the nature of heart failure (HF), it is necessary to understand the relationship between the heart and other organs, such as the brain, lung, kidney, and liver. With respect to the relationship between the heart and kidney, for example, some reports have shown that exercise therapy correlates with improvements in renal function in patients with both cardiovascular disease and chronic kidney disease. Exercise therapy could, therefore, be an effective clinical strategy to improve renal function.2,3

Furthermore, the relationship between the heart and the liver has recently drawn attention. It has been shown that bilirubin is independently associated with morbidity and mortality.4–8) Changes in total bilirubin levels may offer insight into the underlying pathophysiology of chronic HF.9) Furthermore, looking at the relationship between liver dysfunction and exercise capacity, the 6-minute walking distance (6MD) increased significantly after liver transplantation, compared with the pre-transplantation value.9)
Moreover, the 6MD was shorter in patients with chronic liver disease than in healthy subjects, and total bilirubin (T-bil) levels in cachectic patients of New York Heart Association (NYHA) class III were higher than those in NYHA class II patients. However, to date, there has been no report evaluating the relationship between liver dysfunction and exercise capacity in HF patients. Abnormal liver function findings have been observed in 46% of acute decompensated HF patients. Consequently, we conducted this study to examine the relationship between liver dysfunction and functional capacity in HF patients.

**METHODS**

**Study Population**

Between April 2015 and November 2016, we consecutively enrolled all 36 HF patients who underwent cardiopulmonary exercise testing (CPX) at Miyakonojo Medical Association Hospital (Table 1). The exclusion criteria were as follows: (1) contraindications of CPX, (2) patients who reached their anaerobic threshold (AT) during warming-up, (3) acute coronary syndrome, (4) acute myocarditis, (5) hepatobiliary diseases, and (6) drug-induced liver dysfunction.

**Data Processing Method**

All subjects performed symptom-limited, ramp-incremental CPX on a cycle ergometer (Fukuda Denshi; Strengthergo 8) to determine the peak oxygen uptake (VO₂). Peak VO₂ was determined when the subjects were no longer able to maintain cycling at 50 rpm. During exercise, we monitored electrocardiographic changes, such as heart rate (HR), arrhythmia, and ST-T changes using an exercise testing monitoring device (Fukuda Denshi; stress test system). Gas samples were collected on a breath-by-breath basis. The results obtained for VO₂, tidal volume, respiratory rate, and V̇E were sampled every 8 s as measurement indices of respiratory response using a respiratory metabolism monitoring system (Minato Ikagaku; AE-310S). Systolic blood pressure and diastolic blood pressure were measured every minute using an exercise testing blood pressure monitoring device (Sun Tech Medical; TangoM2). We obtained the patient data, i.e., sex, age, height, body weight (BW), medication, smoking status, NYHA class, HF etiology, comorbidities, and signs of right-side HF, including the presence of jugular venous distension (JVD) and peripheral edema, from medical charts. The standard body weight (SBW) was calculated as follows: height (cm) − 100 − (height (cm) − 150)/4 for men and height (cm) − 100 − (height (cm) − 150)/2.5 for women. Blood samples were collected for measurement of albumin (Alb), alkaline phosphatase, alanine transaminase, aspartate transaminase (AST), brain natriuretic peptide (BNP), C-reactive protein, hemoglobin, T-bil, total protein, white blood cell count, and γ glutamyl transferase. Furthermore, we calculated the geriatric nutrition risk index (GNRI) using Alb and SBW, as follows: 14.89 × Alb (g/dl) + (41.7 × BW (kg)/SBW (kg)). If the value of BW (kg)/SBW (kg) was less than 1, we calculated it as 1.4

The following medication groups were investigated: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics, and statins.

Echocardiographic parameters were measured according to the current guidelines of the European Society of Cardiology. Systolic left ventricular function was assessed by calculating the left ventricular ejection fraction (LVEF) using Simpson’s biplane method. Moreover, to determine the presence of right-side HF, we confirmed whether the patients had tricuspid regurgitation (TR).

The blood sample data and echocardiographic parameters recorded on the date closest to the CPX were adopted. Non-measured echocardiographic data were treated as missing values. This study was conducted as a retrospective observation study. The study protocol was approved by the Ethics Committee of Miyakonojo Medical Association Hospital.

**Statistical Analysis**

All data are expressed as the mean ± SD. All parameters except for sex, medication, smoking, NYHA class, HF etiology, comorbidities, JVD, peripheral edema, and TR were initially tested to determine whether they were distributed normally. If the distribution was normal, we determined the relationship between peak VO₂ and the parameter using Pearson’s correlation coefficient. If the data were not normally distributed, Spearman’s rank correlation coefficient was used. To extract the factors that influenced peak VO₂, multivariate regression analysis was performed. However, the number of adjustment variables was limited because of the small sample size of this study. The appropriate number of adjustable variables was calculated as the “sample size/15”. Therefore, we initially used the stepwise method based upon Akaike’s Information Criterion (AIC) to reduce the number of adjustable variables. From the AIC results, we determined the final number of adjustable variables, the value determined by “sample size/15” from the P-value <0.05. Ultimately, we performed the final multiple regression analysis using the extracted value. The significance
Table 1. Baseline patient characteristics

| Characteristic                  | Value               |
|--------------------------------|---------------------|
| Age (years)                    | 60.3 ± 12.8         |
| Sex (male/female)              | 26/3                |
| Height (cm)                    | 167.2 ± 7.9         |
| Weight (kg)                    | 64.2 ± 13.1         |
| BMI                            | 23.1 ± 4.7          |
| Smoking (%)                    | 55.2                |
| Peak VO$_2$ (ml/kg/min)        | 10.7 ± 2.9          |

Blood samples

| Parameter       | Value               |
|-----------------|---------------------|
| Alb (g/dL)      | 3.6 ± 0.7           |
| ALP (IU/L)      | 223.3 ± 57.9        |
| ALT (IU/L)      | 29.5 ± 15.2         |
| AST (IU/L)      | 27.6 ± 10.6         |
| BNP (pg/ml)     | 606.6 ± 505.6       |
| CRP (mg/dL)     | 0.7 ± 1.1           |
| Hb (g/dL)       | 13.4 ± 2.1          |
| T-bil (mg/dL)   | 0.8 ± 0.5           |
| TP (g/dL)       | 6.5 ± 0.7           |
| WBC (/μL)       | 5.8 ± 7.9           |
| GNRI            | 99.0 ± 7.9          |
| γGTP (IU/L)     | 55.9 ± 42.6         |

Medication

| Medication       | Value               |
|------------------|---------------------|
| ACE inhibitor (%)| 65.5                |
| ARB (%)          | 58.6                |
| β blocker (%)    | 86.2                |
| Ca blocker (%)   | 34.5                |
| Diuretics (%)    | 65.5                |
| Statin (%)       | 44.8                |

Echocardiographic parameters

| Parameter       | Value               |
|-----------------|---------------------|
| LV EF (%)       | 37.2 ± 7.9          |
| TR (%)          | 100                 |

Signs of right side HF

| Parameter       | Value               |
|-----------------|---------------------|
| Jugular venous distention (%) | 0                |
| Peripheral edema (%)      | 13.8               |

Basic clinical characteristics of HF

| Parameter       | Value               |
|-----------------|---------------------|
| HFReF (%)       | 75.9                |
| NYHA (I/II/III/IV) (n) | 0/14/14/1         |

HF etiology

| Parameter       | Value               |
|-----------------|---------------------|
| Hypertension (%)| 27.6                |
| Ischemic heart disease (%) | 6.9             |
| Dilated cardiomyopathy (%) | 34.5            |
| Arrhythmia (%)  | 20.7                |
| Other cardiomyopathy (%) | 3.4             |
| Others (%)      | 6.9                 |

Comorbidities

| Parameter       | Value               |
|-----------------|---------------------|
| Cerebrovascular disorder (%) | 13.8          |
| Diabetes mellitus (%) | 41.4            |
| Hyperlipidemia (%) | 31                |
| COPD (%)         | 13.8                |

Values are expressed as mean ± SD. Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; CRP, C-reactive protein; Hb, hemoglobin; TP, total protein; WBC, white blood cell; γGTP, glutamyl-transpeptidase; ARB, angiotensin receptor blocker; Ca, calcium channel; COPD, chronic obstructive pulmonary disease.
RESULTS

Baseline Characteristics

The baseline characteristics of the study population are presented in Table 1.

A total of 36 patients were enrolled in this study. Five patients were excluded because of the emergence of AT during the warm-up period. Furthermore, two patients were excluded because the CPX values were abnormal due to an air leak. Ultimately, we examined 29 patients. The mean peak VO₂ in this study was 10.7 ± 2.9 ml/kg/min. Twenty-two of the 29 patients exhibited heart failure with reduced ejection fraction (HFrEF). None of the patients exhibited JVD, 4 of 29 patients exhibited peripheral edema, and all patients exhibited TR.

Correlations Between Peak VO₂ and the Measured Parameters

Table 2 presents the correlations between peak VO₂ and all parameters except for sex, medication, smoking history, NYHA class, HF etiology, comorbidities, JVD, peripheral edema, and TR. T-bil \( r = -0.379, 95\% \text{ CI: } -0.654 \text{ to } -0.014, P = 0.043 \) and AST \( r = -0.426, 95\% \text{ CI: } -0.685 \text{ to } -0.07, P = 0.021 \) correlated negatively with peak VO₂, whereas peak HR \( r = 0.391, 95\% \text{ CI: } 0.029 \text{ to } 0.663, P = 0.036 \) correlated positively with peak VO₂. None of the other parameters correlated with peak VO₂.

Multiple Logistic Regression Model

We initially calculated the “sample size (=29)/15” to determine the appropriate number of adjustable variables. Consequently, we used two factors for the final multiple regression analysis. As a result of the AIC, ACE (\( \beta = -1.82, P = 0.089 \)), treatment with statin (\( \beta = -2.79, P = 0.029 \)), and T-bil (\( \beta = -3.42, P = 0.013 \)) were extracted (multiple R-squared=0.4, P=0.004). Finally, we performed the multiple regression analysis using statin and T-bil. Table 3 presents the findings of the multiple logistic regression model. Treatment with statin (\( \beta = -3.19, P = 0.015 \)) and T-bil levels (\( \beta = -4.27, P = 0.002 \)) were
found to be predictors associated with peak VO$_2$ (multiple R-squared=0.32, P<0.006).

**DISCUSSION**

We studied 29 HF patients to determine whether liver dysfunction correlated with peak VO$_2$. Initially, we determined the safety of CPX to ensure that none of the patients experienced lethality, arrhythmia, vertigo, or dyspnea. We found that T-bil and AST correlated inversely with peak VO$_2$, whereas peak HR correlated positively with peak VO$_2$. Furthermore, statin treatment and T-bil levels were predictors associated with peak VO$_2$. These results suggested that HF patients with worse liver dysfunction tended to have reduced functional capacity.

With respect to the relationship between liver function and functional capacity, Alameri et al. reported differences in the 6MWD for 250 subjects who were categorized into four groups. The 6MWD was shorter as the severity of liver dysfunction progressed. Furthermore, the 6WMD became shorter as bilirubin levels increased. Some retrospective cohort studies have reported that physical capacity could be expected to improve after liver transplantation. They sought to describe the influence of orthotopic liver transplantation on the physical fitness of the recipient after transplantation. In this manner, improvements in liver function could influence the relationship with functional capacity. In our study, T-bil and AST correlated inversely with peak VO$_2$. Furthermore, T-bil, which indicates liver dysfunction, was a predictor that was associated with peak VO$_2$. Therefore, the results of these studies were consistent with our study findings. However, these studies did not reveal a role for liver dysfunction in HF patients. In heart failure, it is known that congestion of the liver may reduce hepatic clearance of endotoxins originating in the gut. In addition, the inflammatory status might be further accelerated by local hepatic secretion of pro-inflammatory cytokines, contributing to the catabolism and wasting processes. Therefore, decreasing liver function may lead to the worsening of HF. Shinagawa et al. also reported that increased T-Bil coincident with cardiac decompensation predicts a worse long-term prognosis of congestive heart failure, presumably through the propensity to manifest both congestion and tissue hypoperfusion simultaneously when the HF deteriorates. Furthermore, Valentova et al. reported that T-bil levels in NYHA class III cachectic patients were higher than those in NYHA class II patients. Functional capacity in NYHA class II patients is higher than that in NYHA class III patients. The NYHA classification system is known to indicate the severity of heart failure, and it has been reported that NYHA class and %peak VO$_2$ are correlated. These reports and our present findings suggest that evaluating liver function when considering functional capacity is important for HF patients. It is possible that worsening liver function may lead to low functional capacity because of low cardiac output and inflammation of skeletal muscles. However, we did not examine muscle strength, muscle mass, or the cardiac index, which is a limitation of this study. In contrast to our findings, Zheng reported that T-bil levels correlated negatively with left ventricular diastolic dysfunction in HF patients with preserved left ventricular ejection fraction (HFpEF). However, our study participants included both HFP EF and HFrEF patients. Furthermore, our study found that there was no correlation between peak VO$_2$ and LVEF, which is consistent with our results. For these reasons, our findings were distinct from those of the Zheng report.

In the current study, statin treatment was extracted as an independent factor associated with peak VO$_2$. A recent retrospective cohort study reported that significant correlations were observed between skeletal muscle index (SMI) and peak VO$_2$/BW in patients both with and without statin treatment. Furthermore, the ratio of peak VO$_2$/BW and the SMI significantly higher in patients with statin treatment than in those without statin treatment. Statin inhibits enhanced neutrophil function after reperfusion. As a result, statin treatment can improve liver function. Therefore, statin treatment might influence liver function and inhibit inflammation. For these reasons, statin treatment inhibits decreasing muscle mass and may contribute to high peak VO$_2$ levels.

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**Table 3.** Multivariate linear regression analysis

|        | Estimate | Error | P value |
|--------|----------|-------|---------|
| (Intercept) | 16.03 | 1.53 | <0.001 |
| Statin | −3.19 | 1.22 | 0.015 |
| T-bil | −4.27 | 1.23 | 0.002 |

Multiple R-squared, 0.32; P value, 0.006.
Study Limitations

Although this study suggested that peak VO₂ may be strongly influenced by T-bil and statin treatment, there are potential limitations to this study. First, the sample size was relatively small (analyzed sample: n=29). Second, peak oxygen consumption in HF is affected by many factors, including age, gender, cardiac function, lung function, and skeletal muscles. However, we were not able to analyze the effects of lung function and skeletal muscle because we did not perform pulmonary function testing or assess skeletal muscle strength. Third, our findings did not indicate a relationship between BNP and peak VO₂. We suggest that this may be due to the timing of the hematologic tests. The values for T-bil and other hematologic parameters were taken from the tests performed on the date closest to CPX testing. Consequently, the timing of the BNP measurement and the other hematologic measurements was different, because BNP is tested once per month in our hospital. Fourth, several studies have shown that T-bil correlates with various hemodynamic parameters, such as right atrial pressure, pulmonary artery wedge pressure, cardiac index, and central venous pressure. However, we were not able to measure these parameters because the pulmonary artery catheter could not be fitted to the study participants when they underwent CPX. We would address the detail of hemodynamics and effects of cardiac rehabilitation in the future.

CONCLUSION

In summary, we investigated the relationship between liver function in HF patients and functional capacity using CPX. Peak VO₂ was found to be correlated with T-bil, AST, and peak HR. Furthermore, statin treatment and T-bil were extracted as independent factors associated with peak VO₂. Our findings suggest that it is important for clinicians and physical therapists to evaluate liver function during cardiac rehabilitation.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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