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ORIGINAL ARTICLE

Impact of sleep-disordered breathing on myocardial damage and metabolism in patients with chronic heart failure

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Abstract Sleep-disordered breathing (SDB) has a critical association with mortality and morbidity of patients with chronic heart failure (CHF). Troponin T is a marker of ongoing myocardial damage and predicts adverse clinical outcomes in patients with CHF. Carnitine plays an important role in the utilization of fatty acids in the myocardium. It has been reported that myocardial carnitine levels decrease in the failing heart. We hypothesized that plasma troponin T and carnitine are increased due to the leakage from damaged cardiomyocytes or the alteration of myocardial metabolism in CHF patients with SDB. We examined the relation of plasma troponin T and carnitine levels with severity of SDB in CHF. We used portable sleep monitor and measured the apnea–hypopnea index (AHI), plasma levels of high-sensitive troponin T and carnitine in 131 CHF patients. These patients were divided into three groups based on AHI: group A (None–mild SDB AHI < 15/h, $n = 45$), group B (Moderate SDB $15 \leq$ AHI < 30/h, $n = 32$) and group C (Severe SDB AHI ≥ 30/h, $n = 54$). Levels of high-sensitive troponin T and plasm total carnitine were significantly higher in group C than in groups A and B [high-sensitive troponin T; group A 0.009 (0.005–0.016), group B 0.012 (0.006–0.021), group C 0.021 (0.011–0.039) ng/ml, total carnitine; group A 61.0 ± 15.1, group B 65.0 ± 13.5, group C 73.3 ± 17.5 μmol/l, $P < 0.01$ vs. group A and $P < 0.05$ vs. group B, respectively]. Furthermore, in the multiple regression analysis, the independent factors to determine plasma levels of log (high-sensitive troponin T) were high-sensitive C-reactive protein and AHI, and the independent factors to determine plasma levels of carnitine were glomerular filtration rate and AHI. The present study suggests that SDB is associated with latent myocardial damage and alteration of myocardial carnitine metabolism in patients with CHF, presented by higher circulating troponin T and carnitine levels.

Keywords Chronic heart failure · Sleep-disordered breathing · Myocardium · Troponin T · Carnitine

Introduction

Chronic heart failure (CHF) is the major cause of death in elderly in many countries. Sleep-disordered breathing (SDB) mutually accelerates inflammation and sympathetic nervous activity in CHF, and is associated with adverse outcomes in patients with CHF [1–3]. Troponin T is a marker of ongoing myocardial damage and predicts adverse clinical outcomes in patients with CHF [4–7]. Carnitine is an essential cofactor for fatty acid oxidative metabolism, the predominant source of ATP in the normal aerobic heart [8]. Additionally, carnitine is the requisite carrier for the transport of fatty acids from the cytosol across the mitochondrial membrane for beta oxidation [9]. Previous studies have indicated that decreased myocardial free carnitine concentration, and increased plasma acylcarnitine and urinary free carnitine excretion were evident in patients with CHF [10]. These results suggest that myocardial damage and mechanical cardiac overload

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may affect on myocardial carnitine metabolism in patients with CHF.

However, ongoing myocardial damage and carnitine metabolism in CHF with SDB are not fully understood. Therefore, we sought to clarify the relationship of the severity of SDB with increased myocardial damage and alteration of myocardial carnitine metabolism in patients with CHF. We examined circulating levels of plasma high-sensitive troponin T, free carnitine, and acyl carnitine in CHF with SDB.

Methods

The study subjects consisted of 131 consecutive patients (95 men, mean age 61 ± 14 years) with CHF who were referred for overnight polygraphy at Fukushima Medical University between January 2012 and June 2012. Inclusion criteria were (1) the presence of symptomatic CHF, which was defined as New York Heart Association class > II; (2) prescribed with standard pharmacotherapy (including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers, diuretics, etc.); and (3) having a stable clinical status, defined as receiving medical therapy with no worsening of CHF for at least 3 months prior to study enrollment. The exclusion criteria were the presence of receiving hemodialysis and SDB therapy. Patients were divided into three groups based on the apnea–hypopnea index (AHI) value: group A (none-mild SDB $0 \leq$ AHI < 15/h, $n = 45$), group B (moderate SDB $15 \leq$ AHI < 30/h, $n = 52$), and group C (severe SDB AHI ≥ 30/h, $n = 34$). We compared clinical characteristics, echocardiographic parameters, and laboratory data, including plasma levels of high-sensitive troponin T and carnitine between the three groups. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethics committee of Fukushima Medical University.

All subjects underwent overnight polygraphy with the use of standard techniques, as previously reported in another literature [11]. Overnight polygraphy was performed using a portable sleep monitoring system (LS-300, Fukuda Denshi, Tokyo, Japan) that consisted of the monitoring of the electrocardiogram, thoracoabdominal motion, nasal airflow by an airflow pressure transducer, and arterial oxyhemoglobin saturation (SpO_2) by pulse oximetry. Apnea was defined as an absence of airflow for more than 10 s. Hypopnea was defined as a >30% reduction in monitored airflow for ≥10 s accompanied by a decrease in $SpO_2 > 3\%$. Obstructive apnea was defined as the absence of airflow for ≥10 s associated with ribcage and abdominal motion. Central apnea was defined as the absence of airflow for >10 s associated without ribcage and abdominal motion. The major polygraphic parameters investigated were AHI, central apnea index (CAI), obstructive apnea index (OAI), lowest pulse oxygen saturation (lowest SpO_2), and mean pulse oxygen saturation (mean SpO_2).

Blood samples were obtained the next morning after the polygraphy, while the patient was in a supine position under fasting state. We measured the plasma concentrations of high-sensitive troponin T, acyl carnitine, free carnitine, serum creatinine, high-sensitive C-reactive protein (CRP) and plasma B-type natriuretic peptide (BNP). The eGFRs were calculated by the Modification of Diet in Renal Disease formula. The Plasma BNP levels were measured using a specific immunoradiometric assay (Shionoria BNP kit, Shionogi, Osaka, Japan), and the high-sensitive troponin T levels were measured using electrochemiluminescence immunoassay (Elecsys Troponin T hs, Roche Diagnostics Ltd., Rotkreuz, Switzerland). Plasma carnitine profiles (free carnitine, acyl carnitine and total carnitine) were determined by an enzymatic cycling method with carnitine dehydrogenase (Kinos Co., Tokyo, Japan).

Echocardiography was performed using the standard techniques by an experienced echocardiographer at the echo laboratory in our hospital during daytime. Two-dimensional echocardiographic images were acquired from the parasternal long and short axis, and apical four chamber views. The major echocardiographic parameters investigated were left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), the ratio of left ventricular inflow E wave to A wave peak velocity (E/A), and the ratio of transmitral early left ventricular filling velocity to early diastolic Doppler tissue imaging of the mitral annulus (E/e'). All recordings were performed with ultrasound systems (Philips Medical Systems, Andover, MA, USA).

A Shapiro–Wilk test was used for assessment of the normal distribution. Normally distributed data are presented as mean ± SD, and non-normally distributed data are presented as median (inter-quartile range). Categorical variables are expressed as frequencies and relative frequencies. We used the one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Non-normally distributed data were analyzed by the Kruskal-Wallis test. Correlation between high-sensitive troponin T and total carnitine was assessed using Spearman correlation analysis. Multivariable regression analysis was used to determine plasma levels of high-sensitive troponin T and total carnitine. Because of non-normally distribution of high-sensitive troponin T value, we made log transformation for high-sensitive troponin T. To prepare for potential confounding, we introduced the following factors, known to affect the plasma high-sensitive troponin T and the

Table 1 Clinical characteristics and polygraphic data in HF patients

	Group A ($n = 45$)	Group B ($n = 52$)	Group C ($n = 34$)
Age (years)	57.5 ± 14.6	59.6 ± 12.2	66.4 ± 12.7**
Gender, male (%)	27 (60)	40 (77)	28 (82)
BMI (kg/m^2)	22.87 ± 3.82	25.04 ± 3.36*	25.61 ± 5.39*
Comorbidity			
Hypertension (*n*, %)	22 (49)	24 (46)	23 (68)
Diabetes mellitus (*n*, %)	4 (9)	6 (12)	7 (21)
Smoking history (*n*, %)	21 (47)	29 (56)	18 (53)
Etiology			
Cardiomyopathy (*n*, %)	15 (33)	13 (25)	11 (32)
Ischemic (*n*, %)	10 (22)	19 (37)	15 (44)
Valvular (*n*, %)	6 (14)	5 (9)	4 (12)
Other (*n*, %)	14 (31)	15 (29)	4 (12)
Polygraphic data			
AHI (times/h)	9.4 ± 3.8	21.5 ± 4.3**	41.9 ± 9.1**††
CAI (times/h)	1.1 ± 0.9	3.7 ± 2.5**	12.2 ± 2.1**††
OAI (times/h)	3.3 ± 2.1	7.5 ± 4.1**	7.5 ± 5.1**
Lowest SPO_2 (%)	84.7 ± 8.3	82.9 ± 5.4	80.2 ± 8.1*
Mean SPO_2 (%)	95.9 ± 2.7	95.7 ± 1.8	93.9 ± 3.1**††

BMI body mass index, *AHI* apnea–hypopnea index, *CAI* central apnea index, *OAI* obstructive apnea index, *lowest* SpO_2 lowest oxyhemoglobin saturation, *mean* SpO_2 mean oxyhemoglobin saturation

* $P < 0.05$ and ** $P < 0.01$ vs. group A

†† $P < 0.01$ vs. group B

plasma carnitine levels, and variables which were significantly different among three groups into models: age, gender, body mass index, BNP, eGFR, high-sensitive CRP, LVEF, and AHI. Parameters with statistical significance in the univariable analysis ($P < 0.10$) were included in the multivariable analysis. A value of $P < 0.05$ was considered significant for all comparisons. All analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY, USA).

Results

The clinical characteristics and polygraphic data of the study subjects are shown in Table 1. Age and body mass index were significantly higher in group C than in groups A and B. There were no significant differences in comorbidity and etiology. AHI, CAI and OAI were significantly higher in group C than in groups A and B. In addition, AHI, CAI and OAI were significantly higher in group B than in group A. The laboratory and echocardiographic data are shown in Table 2. There were no significant differences in BNP, high-sensitive CRP, PaO_2 and $PaCO_2$ among the 3 groups. Estimated GFR was significantly lower in group C than in groups A and B. There were no significant differences in any echocardiographic parameters. Moreover, there was a positive correlation between high-sensitive troponin T and total carnitine ($R = 0.255$, $P < 0.05$).

Figure 1 demonstrates comparisons of plasma levels of high-sensitive troponin T. Plasma levels of high-sensitive troponin T were significantly higher in group C than in groups A and B. Figure 2a–c demonstrates comparisons of plasma levels of free carnitine, acylcarnitine and total carnitine among 3 groups, respectively. Plasma levels of free and acyl carnitine were significantly higher in group C than in group A. Moreover, plasma levels of total carnitine were significantly higher in group C than in groups A and B.

In the multiple regression analysis (Tables 3 and 4), the independent factors to determine the plasma levels of log (high-sensitive troponin T) were high-sensitive CRP and AHI. In addition, the independent factors to determine the plasma levels of carnitine were eGFR and AHI.

From the receiver operating characteristic curve (ROC) analysis, high-sensitive troponin T (a cut-off value of 0.011 ng/ml) identified severe SDB with sensitivity 78 %, specificity 51 %, and area under the curve 0.72. Similarly, total carnitine (a cut-off value of 62.9 μmol/l) identified severe SDB with sensitivity 67%, specificity 52 %, and area under the curve 0.65.

Table 2 Data for blood examinations and echocardiography in HF

	Group A ($n = 45$)	Group B ($n = 52$)	Group C ($n = 34$)
Laboratory variables			
Free carnitine (μmol/l)	50.3 ± 12.9	53.9 ± 12.2	59.6 ± 14.3**
Acyl carnitine (μmol/l)	10.7 ± 4.0	11.2 ± 3.6	13.7 ± 7.1*
Total carnitine (μmol/l)	61.0 ± 15.1	65.0 ± 13.5	73.3 ± 17.5**†
High-sensitive troponin T (ng/ml)§	0.009 (0.005–0.016)	0.012 (0.006–0.021)	0.021 (0.011–0.039) **††
BNP (pg/ml)§	97.1 (37.7–236.0)	60.7 (25.8–173.7)	116.5 (32.9–334.7)
eGFR (ml/min/1.73/m^2)	75.1 ± 21.4	72.3 ± 22.9	58.3 ± 26.2**†
High-sensitive CRP§	0.12 (0.06–0.54)	0.21 (0.08–0.80)	0.21 (0.11–0.88)
PaO_2 (mmHg)	91.5 ± 28.4	93.1 ± 25.5	100.6 ± 55.5
$PaCO_2$ (mmHg)	41.3 ± 9.3	37.9 ± 6.9	38.7 ± 5.6
Echocardiographic data			
LVEF (%)	46.7 ± 16.9	50.1 ± 16.1	46.6 ± 12.4
LVMI (g/m^2)	133.9 ± 88.4	131.9 ± 49.6	132.9 ± 44.9
E/A	1.0 ± 0.5	1.0 ± 0.5	0.9 ± 0.5
E/E′	12.4 ± 6.7	12.0 ± 4.9	13.4 ± 8.2

BNP B-type natriuretic peptide, *eGFR* estimated GFR, *LVEF* left ventricular ejection fraction, *LVMI* left ventricular mass index, *E/A* a ratio of LV inflow *E* wave to *A* wave peak velocity, *E/E′* a ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole

** $P < 0.01$, * $P < 0.05$ vs. group A

†† $P < 0.01$, † $P < 0.05$ vs. group B

§ Non-normally distributed data are presented as median (interquartile range)

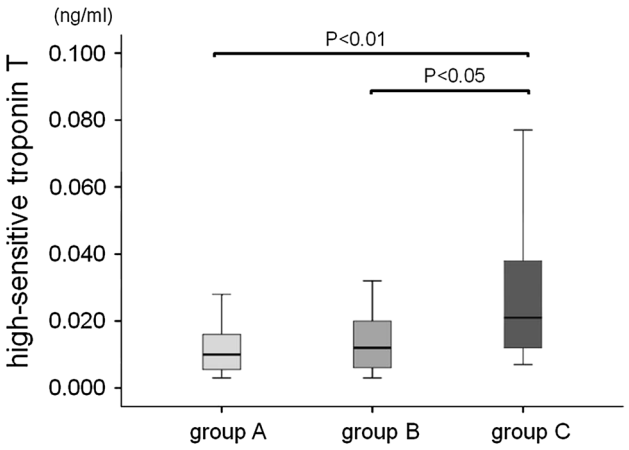

Fig. 1 Comparisons of plasma levels of high-sensitive troponin T in CHF patients

Discussion

In this study, plasma high-sensitive troponin T and total carnitine levels were significantly higher in CHF patients with severe SDB than in CHF without severe SDB. Furthermore, AHI is an independent factor to determine plasma levels of high-sensitive troponin T and carnitine. To the best of our knowledge, this is the first study to show the relationship of the severity of SDB in patients with CHF and increased ongoing myocardial damage and impact on myocardial carnitine metabolism.

Persistent release of myocardial troponins might reflect ongoing cardiac myocyte cell death. In the case of very low troponin levels, cardiac damage is assumed to be independent of an ischemic origin of the myocardium. The mechanism possibly responsible for releasing myocardial troponin is considered to be stretch of cardio myocytes and transient loss of cell membrane integrity. This reversible damage may contribute to the increase of circulating troponin T caused by irreversible injury of cardiomyocytes [4–7]. Several factors, including ischemic myocardial damage, activation of sympathetic nerve function, inflammatory processes, and autophagic degeneration, have been implicated in myocyte injury and death. All these pathways converge on myocardial damage and death by progressive necrosis or apoptosis. It has been reported that patients with ongoing myocardial damage showed higher reaction of CRP than those without ongoing myocardial damage, and there were significant correlations between the serum levels of troponin T and monocyte proinflammatory cytokine, such as tumor necrosis factor-alpha and interleukin 6 [12]. Indeed, elevated troponin T levels have been found to predict adverse outcomes in patients with CHF [4–7]. Recently, it has been reported that severity of SDB is associated with increased CRP [13] and troponin T [14] levels in patients without cardiovascular disease.

Long-chain fatty acids constitute a basic substrate for oxidative energy metabolism in the myocardium. The primary function of carnitine is to permit the entry of esterified fatty acids (the source of ATP synthesis) into the mitochondrial matrix, where β oxidation occurs. The intracellular homeostasis of carnitine is controlled by different membrane transporters—the organic cation transporters (OCTNs), which operate on the intestinal absorption and renal reabsorption of carnitine, and play a

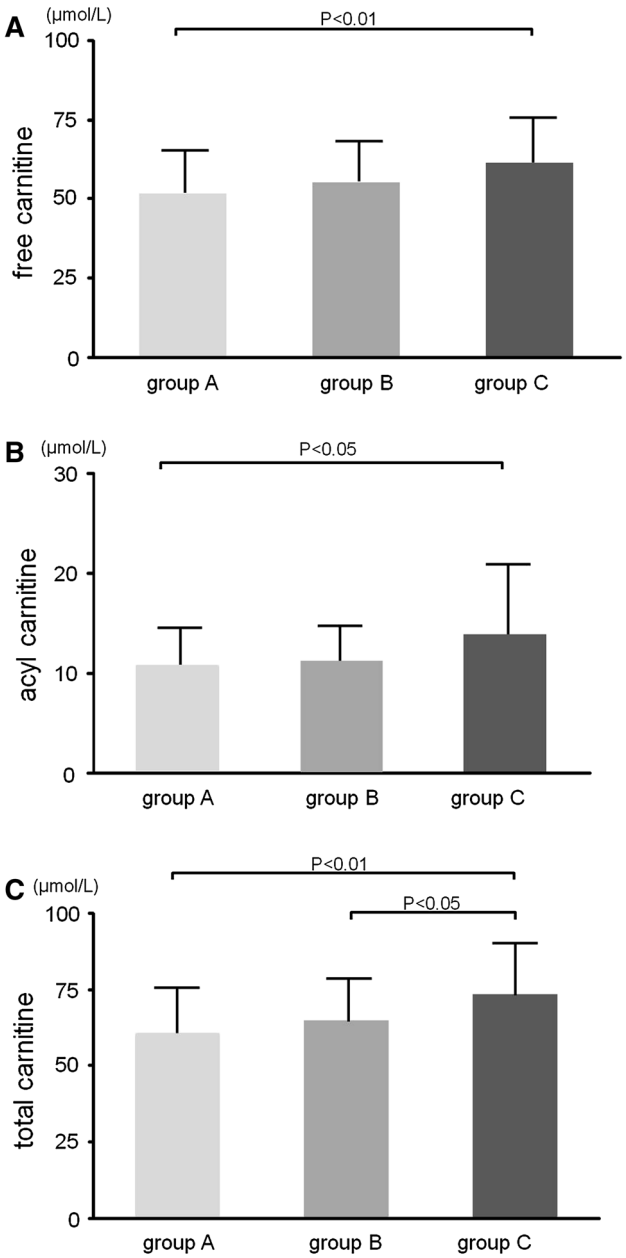

Fig. 2 Comparisons of plasma levels of free carnitine (**a**), acylcarnitine (**b**), and total carnitine (**c**) in CHF patients

Table 3 Multiple regression analysis to determine factors related to log (plasma high-sensitive troponin T)

Factors	Univariable analysis		Multivariable analysis	
	β coefficient	P value	β coefficient	P value
Age	0.102	0.311		
Male	0.145	0.148		
BMI	0.051	0.613		
BNP	0.336	0.001**	0.182	0.124
eGFR	−0.343	<0.001**	−0.196	0.082
High-sensitive CRP	0.336	0.002**	0.348	0.001**
LVEF	−0.354	<0.001**	−0.974	0.333
AHI	0.357	<0.001**	0.270	0.015*

These factors are based on a linear regression analysis

BMI body mass index, *BNP* B-type natriuretic peptide, *eGFR* estimated GFR, *LVEF* left ventricular ejection fraction, *CRP* C-reactive protein, *AHI* apnea–hypopnea index

** $P < 0.01$, * $P < 0.05$

Table 4 Multiple regression analysis to determine factors related to plasma total carnitine

Factors	Univariable analysis		Multivariable analysis	
	β coefficient	P value	β coefficient	P value
Age	0.095	0.286		
Male	0.045	0.613		
BMI	0.028	0.757		
BNP	0.153	0.096	0.029	0.754
eGFR	−0.385	<0.001**	−0.287	0.003**
High-sensitive CRP	0.064	0.516		
LVEF	−0.167	0.058	−0.070	0.437
AHI	0.228	0.009**	0.203	0.026*

These factors are based on a linear regression analysis

BMI body mass index, *BNP* B-type natriuretic peptide, *eGFR* estimated GFR, *LVEF* left ventricular ejection fraction, *CRP* C-reactive protein, *AHI* apnea–hypopnea index

** $P < 0.01$, * $P < 0.05$

major role in tissue distribution and variations in transport rates [15]. The downregulated left ventricular OCTN2 expression may be associated with decreased left ventricular free carnitine levels [16]. Recent experimental studies have demonstrated that carnitine protects the myocardium against ischemic injury, angina, diastolic dysfunction and heart failure [15, 17, 18]. It has been reported that plasma concentrations of carnitine are (1) increased in patients with cardiomyopathy, [19] (2) have negative correlations with LVEF, [19] and (3) associated with increase of urinary carnitine excretion [20]. Furthermore, levels of plasma carnitine are thought to be affected by dietary intake, renal reabsorption and liver synthesis [21].

SDB accelerates inflammation, sympathetic nervous activity, the renin angiotensin aldosterone system [22], intermittent hypoxia [23], transient hypertension [24], and glomerular over-filtration [25], and causes renal dysfunction [26], left ventricular hypertrophy [27], as well as cardiac biventricular systolic and diastolic dysfunction. These mechanisms may cause ongoing myocardial damage expressed by troponin T. Furthermore, focusing on

carnitine, the OCTN2 expression was strongly reduced in the myocardium with significant inflammation (52 % compared with no inflammation), whereas the expression in the presence of a minor inflammation was unaltered compared to the myocardium with no inflammation [28]. Inflammation and subsequent myocardial damage may increase the levels of plasma carnitine. Recently, plasma acylcarnitine has been proposed to be a biomarker of insulin resistance and metabolic inflexibility in adults [29, 30]. The severity of SDB (as measured by AHI) was reportedly associated with insulin resistance. These findings, therefore, support our hypothesis that SDB may increase the risk for cardio-metabolic disease [31]. It has been reported that the leakage from damaged cardiomyocytes or deficient carnitine transport into cells may influence on increasing levels of plasma carnitine [21]. The mechanism behind higher carnitine levels in CHF patients with severe SDB still remains unclear; however, it may be due to increased cardiomyocyte damage and decreased carnitine transport into cardiac cells, or other reasons.

In the present study, we demonstrated that latent low-grade myocardial damage and altered carnitine metabolism were present among severe SDB patients in CHF, and these data may provide us novel mechanistic and therapeutic insights to understand the clinical impacts of SDB on CHF patients. Thus, cardiomyocyte protective approach by treatment of SDB has clinically important implications to improve prognosis of patients with CHF.

Study limitations

In our study, there were some study limitations. First, the gold standard for the diagnostic test of SDB is a full-channel polysomnography, which provides detailed information on the complete differentiation of the types of apnea [32]. In this study, our differentiation of SDB by portable sleep monitor might be less reliable than that by full polysomnography. Second, the number of study subjects was small, since this study was performed in a single institution. Hence, further investigation by full polysomnography may lead to the entire clarification of the mechanisms of myocardial damage and myocardial metabolism in CHF patients with SDB.

Conclusions

In conclusion, the present study suggests that SDB is associated with myocardial damage and alteration of myocardial carnitine metabolism in CHF patients.

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Conflict of interest None.

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