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Clinical importance of respiratory muscle fatigue in patients with cardiovascular disease

Masanobu Taya, RPT, MSc[a,b], Eisuke Amiya, MD, PhD[a,c,*], Masaru Hatano, MD, PhD[a,c], Akihito Saito, MD, PhD[a], Daisuke Nitta, MD, PhD[a], Hisataka Maki, MD, PhD[a], Yumiko Hosoya, MD, PhD[a,c], Shun Minatsuki, MD, PhD[a], Masaki Tsuji, MD, PhD[a], Tatsuyuki Sato, MD[a], Haruka Murakami, MD[a], Koichi Narita, MD[a], Yuto Konishi, RPT[a,b], Shogo Watanabe, PhD[d], Kazuhiko Yokota, RPT[b], Nobuhiko Haga, MD, PhD[b], Issei Komuro, MD, PhD[a]

Abstract

Patients with cardiovascular diseases frequently experience exertional dyspnea. However, the relationship between respiratory muscle strength including its fatigue and cardiovascular dysfunctions remains to be clarified.

The maximal inspiratory pressure/maximal expiratory pressure (MIP/MEP) before and after cardiopulmonary exercise testing (CPX) in 44 patients with heart failure and ischemic heart disease were measured. Respiratory muscle fatigue was evaluated by calculating MIP (MIPpost/MIPpre) and MEP (MEPpost/MEPpre) changes.

The mean MIPpre and MEPpre values were 67.5 ± 29.0 and 61.6 ± 23.8 cm H_2O, respectively. After CPX, MIP decreased in 25 patients, and MEP decreased in 22 patients. We evaluated the correlation relationship between respiratory muscle function including respiratory muscle fatigue and exercise capacity evaluated by CPX such as peak VO2 and VE/VCO2 slope. Among MIP, MEP, change in MIP, and change in MEP, only the value of change in MIP had an association with the value of VE/VCO2 slope ($R = -0.36$, $P = .017$). In addition, multivariate analysis for determining factor of change in MIP revealed that the association between the change in MIP and eGFR was independent from other confounding parameters (beta, 0.40, $P = .017$). The patients were divided into 2 groups, with (MIP change < 0.9) and without respiratory muscle fatigue (MIP change > 0.9), and a significant difference in peak VO2 (14.2 ± 3.4 [with fatigue] vs 17.4 ± 4.7 [without fatigue] mL/kg/min; $P = .020$) was observed between the groups.

Respiratory muscle fatigue demonstrated by the change of MIP before and after CPX significantly correlated with exercise capacity and renal function in patients with cardiovascular disease.

Abbreviations: CPX = cardiopulmonary exercise testing, CVDs = cardiovascular diseases, EF = ejection fraction, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure.

Keywords: cardiopulmonary exercise, heart failure, ischemic heart disease, renal function, respiratory muscle fatigue, ventilatory efficiency

1. Introduction

The major issue in cardiovascular diseases (CVDs) such as ischemic heart disease or heart failure is exercise capacity impairment.[1] Exercise capacity is mainly limited by cardiovascular dysfunctions; however, it is affected by various extracardiac factors, such as muscle strength or respiratory function.[2–4] Sarcopenia is one of the crucial factors that significantly impact exercise capacity.[5]

Respiratory function is another extracardiac determinant of exercise capacity and is known to be impaired in patients with CVD.[6,7] Previously reported mechanisms include ventilation and perfusion irregularity and pulmonary distensibility reduction.[8]

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[a] Department of Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, [b] Department of Rehabilitation Medicine, the University of Tokyo Hospital, [c] Department of Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, Tokyo, [d] Department of Medical Technology, Graduate School of Health Sciences, Okayama University, Okayama Prefecture, Japan.

[*] Correspondence: Eisuke Amiya, Department of Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan (e-mail: amiyae-tky@umin.ac.jp).

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Moreover, sarcopenia affects respiratory function through the dysfunction of the respiratory muscle.[9] Some reports have shown that decreased respiratory muscle power affects the clinical course in patients with CVD.[4] However, the clinical importance of respiratory muscle function in patients with CVDs has not been fully explained.

According to respiratory muscle function, the idea of respiratory muscle fatigue has been presented in pulmonology, and it also involves limiting exercise tolerance.[10] Fatigue is the loss in capacity of the muscle to develop force or velocity, resulting from muscle activity under load.[11] The relationship between respiratory muscle fatigue and CVDs is also unclear. Furthermore, there has been no standard method to evaluate respiratory muscle fatigue.

This study investigated the impact of respiratory muscle strength including respiratory muscle fatigue on exercise capacity in patients with CVD. In addition, the method used to evaluate respiratory muscle fatigue in patients with CVD was assessed.

2. Methods

2.1. Study subjects

Study participants were selected from a group of patients who had a cardiopulmonary exercise test from November 2015 to January 2017 to evaluate the statuses of their ischemic heart disease or congestive heart failure. Ischemic heart disease was defined as the presence of at least 1 of the following: >50% luminal diameter narrowing of >1 epicardial coronary artery on angiography; history of coronary revascularization; or history of myocardial infarction. On the other hand, heart failure was defined as the presence of at least 2 of the following: heart failure symptoms and signs; elevated B-type natriuretic peptide (BNP) (>35 pg/mL); decreased left ventricular ejection fraction (EF < 40%). Exclusion criteria were history of heart transplant, severe illnesses other than heart disease, and the presence of any clinical comorbidity that may affect exercise performance. Patients were also excluded if they were unable to achieve an adequate pedal rotation speed, had a heart rate at rest of >110 bpm, or manifested presence of moderate valvular disease, thought to be the cause of the patient's symptoms. This study complied with the principles of the Declaration of Helsinki and was reviewed and approved by the University of Tokyo Institutional Review Board (approval number, 2650).

2.2. Cardiopulmonary exercise testing (CPX)

Symptom-limitedCPX was performed on an electromagnetically braked upright cycle ergometer (Corival, Lode, Holland) with a metabolic gas analyzer (AE-300S, Minato Medical Science, Osaka, Japan). After a 4-minute rest on the cycle ergometer, a 4-minute warm-up exercise was commenced at 20 W (or 15 W), and then the work rate was increased by 5 or 10 W every minute. CPX was discontinued

(i) if pedal rotations were delayed;
(ii) if the patient reached the maximum symptom-limited performance determined by a Borg score of ≥17;
(iii) when 85% of the age-predicted maximal HR was achieved; or
(iv) if there was evidence of ST-T wave changes in ECG or if any cardiac event, such as arrhythmia or chest pain, occurred; or
(v) peak respiratory exchange ratio was over 1.1.[12] For all the subjects, expired gases were continuously measured on a breath-by-breath basis.

2.3. Evaluation of respiratory muscle, handgrip, and knee extensor strength

The maximal inspiratory pressure/maximal expiratory pressure (MIP/MEP) before and after CPX were measured using a spirometer (HI-801, CHEST MI, Tokyo). In a sitting position, patients breathed into a scuba-type mouthpiece and were instructed to exhale the residual volume followed by a maximum inspiratory effort through the mouthpiece. The respiratory muscle fatigue was evaluated as presented in previous reports[13] by calculating MIP (MIPpost/MIPpre) and MEP (MEPpost/MEPpre) changes represented by percentile.

Moreover, handgrip and knee extensor strengths were evaluated during CPX. Handgrip strength was determined using a digital dynamometer (Takei Scientific Instruments Co., Ltd., Niigata, Japan), and isometric knee extensor strength was measured using μTas F-1 (ANIMA, Tokyo, Japan).[14] Knee extension was briefly measured in a sitting position (90° hip flexion with the pelvis fixed with 90° knee flexion), and handgrip strength was measured using a dynamometer placed at the level of the lateral malleolus. The test was performed at least twice by a trained personnel, with the highest value recorded.

2.4. Laboratory data

The echocardiogram and blood sample findings were obtained from the measurements performed close to the collection of the CPX data. Standard echocardiographic imaging was done to evaluate the left ventricular ejection fraction and left ventricle diameter. The presence or absence of valvular heart disease was also evaluated. For laboratory data, fasting blood samples were collected, and laboratory findings were analyzed using the standard laboratory methods at the University of Tokyo Hospital (Tokyo, Japan). The glomerular filtration rate was estimated using the following equation: $eGFR = 194 \times \text{serum creatinine}^{-1.094}\,(\text{mg/dL}) \times \text{age}^{-0.287} \times 0.739$ (if female).

2.5. Statistical analysis

The results were presented as mean ± SD or as median (interquartile range). Using the Mann–Whitney *U* test and *t* test, the inter-group differences were evaluated. We also assessed the outliers with a Smirnov-Grubbs test and removed it. Potential relationships between the parameters were explored using Pearson correlation test. Variables with $P < .10$ in the univariate analysis were included in the multivariate analysis to identify the independent determinant for the MIP change. A *P*-value of $< .05$ was considered as statistically significant. PASW Statistics 18 (SPSS Inc., Chicago, IL) was used for statistical data analyses.

3. Results

3.1. Patient characteristics

Table 1 presents the patient characteristics: 81% patients were male and were diagnosed with heart failure or ischemic heart disease. The median brain natriuretic peptide value was 120 (80.2, 323) pg/mL, whereas the mean left ventricular EF value was 47.7 ± 20.8%.

Table 1

Patients characteristics.

N	44
Sex (M/F)	34/10
Age (yr)	61.3 ± 15.9
BMI (kg/m^2)	23.5 ± 3.7
eGFR (mL/min/1.73m^2)	59.6 ± 19.6
Hemoglobin (g/dL)	13.9 ± 1.5
Albumin (g/dL)	4.1 ± 0.3
Brain natriuretic peptide (pg/mL)	120 (80.2, 323.0)
Echocardiographic parameter	
Left ventricular Dd (mm)	53.9 ± 15.1
Ejection fraction (%)	47.7 ± 20.8
Etiology	
Heart failure	26 (59%)
Ischemic heart disease	24 (54%)
ACE/ARB	31 (70%)
Beta blocker	34 (77%)
Statin	29 (65%)
Cardiopulmonary exercise parameters	
Peak VO2 (mL/min/kg)	16.3 ± 4.5
VE/VCO2 slope ([L/min VE] / [mL/min CO2])	30.8 ± 7.5
Respiratory muscle strength	
Maximal inspiratory pressure (pre CPX) (mm Hg)	67.5 ± 29.0
Maximal inspiratory pressure (post CPX) (mm Hg)	65.4 ± 30.1
Maximal expiratory pressure (pre CPX) (mm Hg)	61.6 ± 23.8
Maximal expiratory pressure (post CPX) (mm Hg)	59.6 ± 25.8

ACE = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CPX = cardiopulmonary exercise test, Dd = diastolic diameter, eGFR = estimated glomerular filtration ratio, VCO2 = carbon dioxide output, VE = ventilatory equivalent, VO2 = oxygen uptake.

3.2. Respiratory muscle strength and association with other clinical parameters

The mean MIPpre and MEPpre values were 67.5 ± 29.0 and 61.6 ± 23.8 cm H_2O, respectively (Table 1, Fig. 1). The MEP and MIP values significantly correlated with each other ($R = 0.63$, $P < .001$) and with hemoglobin (MEP, $R = 0.53$, $P < .001$; MIP, $R = 0.30$, $P = .047$) (Supplementary table, http://links.lww.com/MD/E726). Handgrip strength was also correlated with MEP ($R = 0.47$, $P = .005$). Diabetes and the administration of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta blocker, or statin did not affect the MEP and MIP values. Additionally, the etiology of cardiovascular disorder did not affect the MIP and MEP values.

3.3. Clinical implication of respiratory muscle fatigue

Regarding the changes in MEP and MIP before and after CPX, MIP value increased after CPX in 19 patients, whereas it decreased in 25 patients (Fig. 1). In contrast, MEP value increased after CPX in 22 patients, whereas it decreased in 22 patients. Changes in MEP and MIP values showed no correlation ($R = 0.24$, $P = .12$). Among MIP, MEP, change in MIP and change in MEP, only the value of change in MIP had an association with parameters of exercise capacity (Table 2) and the MIP change value correlated with VE/VCO2 slope ($R = -0.36$, $P = .017$). In addition, it also had correlations with handgrip strength ($R = 0.36$, $P = .035$), and estimated glomerular filtration rate (eGFR) ($R = 0.42$, $P = .0043$) (Fig. 2, Table 3). Multivariate analysis for determining factor of change in MIP using VE/VCO2 slope, peak VO2, eGFR, hemoglobin, and handgrip strength revealed that the association between the ratio of change in MIP and eGFR was independent from other confounding parameters (beta, 0.40, $P = .017$).

Next, we divided patients into 2 groups by the presence of absence of respiratory muscle fatigue, which was defined as change in MIP < 0.9 in accordance with previous report.[13] The clinical parameters of patients with (change in MIP < 0.9) and without respiratory muscle fatigue (change in MIP > 0.9) were

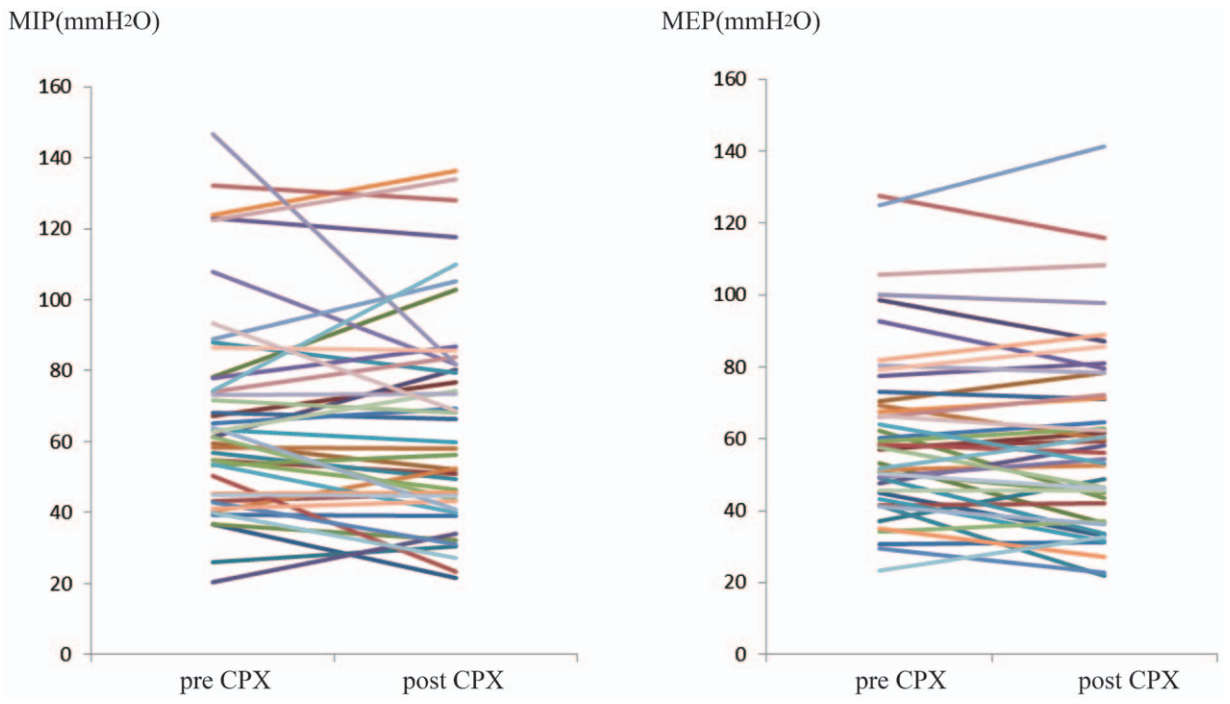

Figure 1. The changes in maximal inspiratory pressure and maximum expiratory pressure before (pre cardiopulmonary exercise testing [CPX]) and after (post CPX) CPX.

Table 2

Associations between respiratory muscle function and exercise capacity.

	Peak VO2		VE/VCO2 slope	
	R	*P* value	*R*	*P* value
MIPpre	0.007	.97	0.079	.61
MEPpre	0.20	.20	−0.27	.081
MIP change	0.28	.063	−0.36	.018*
MEP change	0.093	.55	−0.19	.22

* $P < .05$.

MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, VCO2 = carbon dioxide output, VE = ventilatory equivalent, VO2 = oxygen uptake.

compared to investigate the clinical implication of respiratory muscle fatigue. In background such as respiratory muscle strength and laboratory data, no significant difference was noted between patients with and without muscle fatigue other than renal function. However, exercise capacity exemplified by peak VO2 significantly differed between the 2 groups (14.2 ± 3.4 [with fatigue] vs 17.4 ± 4.7 [without fatigue] mL/kg/min; $P = .020$) (Table 4).

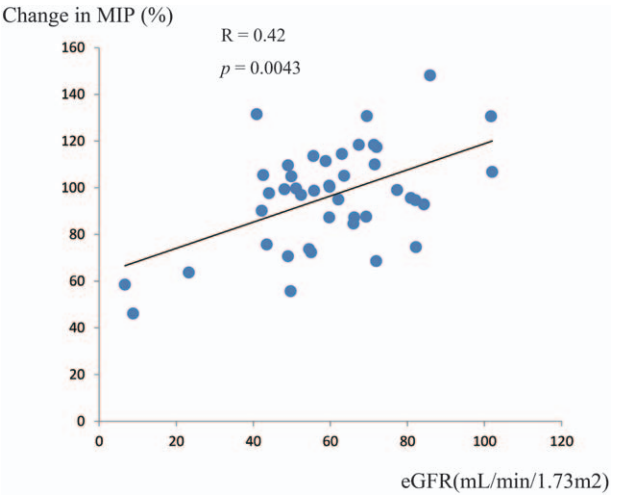

Figure 2. Correlation between the change in maximal inspiratory pressure (MIP) before and after a cardiopulmonary exercise test and estimated glomerular filtration rate. The change in MIP was calculated by MIP after cardiopulmonary exercise/MIP before cardiopulmonary exercise.

4. Discussion

This study investigated the relationship between respiratory muscle function including respiratory muscle fatigue and exercise capacity in patients with CVDs. Our results show that respiratory muscle fatigue, not respiratory muscle strength, significantly affects exercise capacity. In addition, the link between respiratory muscle fatigue and exercise capacity evaluated in this study also validated the method evaluating respiratory muscle fatigue.

Fatigue can be defined as a reduction in the force-generating capacity of the muscle from pre- to post-exercise. In this study, respiratory muscle fatigue was assessed by measuring changes in MEP and MIP before and after submaximal exercise. Generally, respiratory muscle fatigue can limit exercise capacity through an inadequate ventilator response.[10,15] In particular, inspiratory muscle fatigue was reported to relate with exercise capacity in patients with CVD.[16] In this study, the correlation between the change in MIP and VE/VCO2 slope (ventilatory cost of carbon dioxide elimination),[17] which denotes ventilatory efficiency, demonstrated the correlation between respiratory muscle fatigue and exercise capacity. Indeed, VE/VCO2 slope reflects physiological dead space ventilation and mismatching between perfusion and ventilation and it is 1 parameter of exercise capacity.[18] In addition, the feeling of fatigue might lead to an increase of respiratory drive, which could be also explained by the VE/VCO2 slope.[19] A mechanism of the association between respiratory muscle fatigue and exercise capacity is metaboreflex, wherein respiratory muscle fatigue increases sympathetic vasoconstrictions and leads to decreased perfusion to the extremities, resulting in limited exercise capacity.[20] It is important to evaluate the characteristics of respiratory muscle fatigue and formulate appropriate strategies to counteract this fatigue, particularly in CVD cases.

Another interesting finding of the present study was the association between renal dysfunction and respiratory muscle fatigue. The relationship between the change in MIP and VE/VCO2 slope suggested that the change in MIP is derived from a systemic pathway such as metaboreflex or the autonomic nervous system, and it also significantly correlated with renal function. Skeletal muscle abnormalities have been reported in renal

Table 3

Determinant factor for the change of maximal inspiratory pressure.

	monovariate		multivariate	
	R	*P* value	beta	*P* value
Age	−0.11	.45		
Hemoglobin (g/dL)	0.26	.093	-0.15	.47
eGFR (mL/min/1.73m^2)	0.42	.0043*	0.4	.017*
Albumin (g/dL)	0.093	.58		
Brain natriuretic peptide (pg/mL)	−0.17	.32		
Left ventricular Dd (mm)	0.019	.94		
Ejection fraction (%)	0.15	.34		
Hand grip strength (kg)	0.36	.035*	0.32	.1
Knee extensor strength (N)	0.28	.1		
Peak VO2 (mL/min/kg)	0.29	.06	0.16	.42
VE/VCO2 slope ([L/min VE] / [mL/min CO2])	−0.36	.017*	-0.62	.54

* $P < 0.05$.

Dd = diastolic diameter, MIP = maximal inspiratory pressure, VCO2 = carbon dioxide output, VE = ventilatory equivalent, VO2 = oxygen uptake.

Table 4

Characteristics in patients with and without respiratory muscle fatigue.

	MIP change < 0.9	MIP change >0.9	*P* value
N	14	30	
Age (yr)	64.8 ± 12.7	59.7 ± 17.1	NS
Hight (m)	1.64 ± 0.11	1.67 ± 0.72	NS
Weight (kg)	63.7 ± 16.1	65.4 ± 10.0	NS
Ejection fraction (%)	46.8 ± 16.8	48.2 ± 22.8	NS
Left ventricular Dd (mm)	51.9 ± 12.2	54.9 ± 16.6	NS
Peak VO2 (mL/min/kg)	14.2 ± 3.4	17.4 ± 4.7	.020*
VE/VCO2 slope ([L/min VE]/[mL/min CO2])	34.0 ± 7.7	29.5 ± 7.0	.019*
Hand grip (kg)	25.2 ± 6.9	32.1 ± 7.6	.019*
Knee extensor strength (N)	250.2 ± 55.7	307.2 ± 110.0	NS
Laboratory data			
Hemoglobin (g/dL)	13.3 ± 1.7	14.2 ± 1.4	NS
Albumin (g/dL)	4.08 ± 0.25	4.16 ± 0.38	NS
eGFR (mL/min/1.73m^2)	50.4 ± 23.0	63.8 ± 16.6	.033*
Brain natriuretic peptide (pg/mL)	155.5 (69.5, 406.5)	108.6 (48.5, 209.7)	NS
Respiratory muscle strength			
MIP pre (mm Hg)	64.6 ± 31.1	68.9 ± 28.4	NS
MEP pre (mm Hg)	55.2 ± 19.8	65.4 ± 24.9	NS

Dd = diastolic diameter, eGFR = estimated glomerular filtration ratio, MEP = maximal expiratory pressure, MIP = maximal inspiratory pressure, VCO2 = carbon dioxide output, VE = ventilatory equivalent, VO2 = oxygen uptake.

dysfunction.[21] Cupsti et al noted that the skeletal muscle of patients with chronic renal failure manifests unchanged sarcolemma excitability but abnormal oxidative metabolism and reduced segmental strength. A possible mechanism bridging muscle fatigue and renal dysfunction is oxidative stress. Indeed, the reactive oxygen species was reported to increase with renal dysfunction.[22] Muscle fatigue is associated with reactive oxygen, and mitochondrial dysfunction derived from renal impairment may also contribute to increased reactive oxygen, resulting in skeletal muscle fatigue.[23,24]

This study had the following limitations: small sample size, absence of control subjects, and the retrospective nature. The values of MIP and MEP were slightly low as compared with previous reports of subjects without clinical CVD.[25] However, Nanas demonstrated in similar way that there was no control subjects whose MIP decreased after CPX.[13] Therefore, respiratory muscle fatigue presented in the current study seems to be specific to patients with CVDs. Also, the patient population was limited to those receiving CPX, which may imply referral bias resulting in the possibility of the study population not being representative of the general population. Indeed, CPX was performed for the purpose of the evaluation of exercise capacity and the identification of appropriate load of exercise training in cardiac rehabilitation. The study design on the evaluation of the effect of medications was limited. Furthermore, a more robust study is warranted to verify the predictive value of respiratory muscle fatigue in cardiovascular disorders.

It is possible that the degree of load by cardiopulmonary exercise is not consistent. However, if the degree of load has some effects in this study, the low respiratory muscle fatigue level would correspond to the decrease of VO2 or decrease of VE/VCO2 slope, which is contrary to our results.

In conclusion, respiratory muscle fatigue demonstrated by the degree of MIP before and after CPX significantly correlated with exercise capacity and renal function in patients with CVD.

Author contributions

Conceptualization: Masanobu Taya, Eisuke Amiya.
Data curation: Masanobu Taya.
Formal analysis: Masanobu Taya, Eisuke Amiya.
Funding acquisition: Eisuke Amiya.
Investigation: Masanobu Taya, Akihito Saito, Tatsuyuki Sato, Haruka Murakami, Yuto Konishi, Koichi Narita, Tatsuyuki Sato.
Methodology: Masanobu Taya, Eisuke Amiya, Shogo Watanabe.
Resources: Masanobu Taya, Shogo Watanabe.
Supervision: Masaru Hatano, Nobuhiko Haga, Kazuhiko Yokota, Issei Komuro.
Writing – original draft: Masanobu Taya, Eisuke Amiya.
Writing – review & editing: Daisuke Nitta, Hisataka Maki, Yumiko Hosoya, Shun Minatsuki, Masaki Tsuji.

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