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Aerobic interval training improves oxygen uptake efficiency by enhancing cerebral and muscular hemodynamics in patients with heart failure

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ABSTRACT

Background: Abnormal ventilatory/hemodynamic responses to exercise contribute to functional impairment in patients with heart failure (HF). This study investigates how interval and continuous exercise regimens influence functional capacity by modulating ventilatory efficiency and hemodynamic function in HF patients.
Methods: Forty-five HF patients were randomized to perform either aerobic interval training (AIT; 3-minute intervals at 40% and 80% VO_{2peak}) or moderate continuous training (MCT; sustained 60% VO_{2peak}) for 30 min/day, 3 days/week for 12 weeks, or to a control group that received general healthcare (GHC). A noninvasive bio-reactance device was adopted to measure cardiac hemodynamics, whereas a near-infrared spectroscopy was employed to assess perfusion/O_2 extraction in frontal cerebral lobe ($\Delta[THb]_{FC}/\Delta[HHb]_{FC}$) and vastus lateralis ($\Delta[THb]_{VL}/\Delta[HHb]_{VL}$), respectively.
Results: Following the 12-week intervention, the AIT group exhibited higher oxygen uptake efficiency slope (OUES) and lower V_E-VCO_2 slope than the MCT and GHC groups. Furthermore, AIT, but not MCT, boosted cardiac output (CO) and increased $\Delta[THb]_{FC}$, $\Delta[THb]_{VL}$, and $\Delta[HHb]_{VL}$ during exercise. In multivariate analyses, CO was the dominant predictor of VO_{2peak}. $\Delta[THb]_{FC}$ and $\Delta[THb]_{VL}$, which modulated the correlation between CO and OUES, were significantly correlated with OUES. Simultaneously, $\Delta[THb]_{VL}$ was the only factor significantly associated with V_E-VCO_2 slope. Additionally, AIT reduced plasma brain natriuretic peptide, myeloperoxidase, and interleukin-6 levels and increased the Short Form-36 physical/mental component scores and decreased the Minnesota Living with Heart Failure questionnaire score.
Conclusions: AIT effectively improves oxygen uptake efficiency by enhancing cerebral/muscular hemodynamics and suppresses oxidative stress/inflammation associated with cardiac dysfunction, and also promotes generic/disease-specific qualities of life in patients with HF.

1. Introduction

Heart failure (HF) is a major cardiovascular syndrome with increasing incidence and prevalence [1]. This chronic cardiac condition oftentimes accelerates deconditioning and the consequent vicious cycle of numerous associated disorders [2]. Moreover, HF patients on optimal cardiovascular pharmacologic therapy frequently remain burdened by dyspnea and exercise intolerance [3]. Abnormal cerebral and muscular hemodynamic responses to exercise may contribute to impaired functional capacity in HF patients [4]. Recent investigations have suggested that depressed cardiac output (CO) and heightened ventilatory responses to exercise in patients with advanced HF reduced cerebral perfusion/oxygenation and considerably limited exercise performance [4–6]. Although cardiac rehabilitation is a valuable non-pharmacologic intervention for improving aerobic fitness and overall health status in patients with HF [1], controversy persists regarding the type and degree of exercise that optimally promotes beneficial adaptations in central and peripheral hemodynamics.

Aerobic interval training (AIT) is a more effective modality for improving aerobic fitness than traditional moderate continuous training (MCT) in patients with coronary artery disease or left ventricular dysfunction [7–9]. Furthermore, the AIT regimen has been demonstrated to rescue impaired contractility, attenuate hypertrophy, and reduce expression of atrial natriuretic peptide of cardiac myocytes in animal model of post-infarction HF [10–12]. However, few studies have investigated whether AIT influences peripheral (such as cerebral and skeletal muscular tissues) hemodynamics by modulating ventilatory efficiency and the distribution of blood flow from the heart [11,12]. Moreover,

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the relationship between changes in tissue perfusion/oxygenation and exercise performance caused by AIT has not yet been established.

This investigation thus attempts to clarify how interval and continuous exercise regimens influence central and peripheral hemodynamic responses to exercise in patients with HF. We hypothesize that AIT influences functional capacity by modulating ventilatory efficiency and cardiac-cerebral-muscular hemodynamic responses to exercise in patients with HF. We also anticipate that AIT improves efficiency in ventilation–perfusion matching during exercise more than does MCT.

2. Methods

2.1. Subjects

This study enrolled 45 patients diagnosed with HF from the Department of Cardiology, Chang Gung Memorial Hospital. HF was diagnosed if the patients had (i) a left ventricular ejection fraction (LVEF) ≤40% and belonged to New York Heart Association functional classes II to III despite receiving optimal treatment for at least 12 months according to American Heart Association/American College of Cardiology guidelines, or (ii) LVEF >40% with episodes of acute pulmonary edema after excluding other non-cardiogenic etiologies. Exclusion criteria included the presence of atrial fibrillation/flutter, second/third degree heart block, or anemia (hemoglobin concentration ≤12 g/dL in men and ≤11 g/dL in women), history of life-threatening ventricular arrhythmias, recent unstable angina, myocardial infarction or coronary revascularization (<4 weeks), uncontrolled diabetes mellitus, severe chronic obstructive pulmonary disease, or symptomatic cerebrovascular disease within 12 months, collagen vascular disease, alcohol or drug abuse during the previous 12 months or significant renal or hepatic disease. Subjects were randomly divided into aerobic interval training (AIT, n = 15), moderate continuous training (MCT, n = 15), and general healthcare (GHC, n = 15) groups. The investigation was performed according to the Helsinki declaration, and was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan. All subjects provided informed consent after the experimental procedures were explained.

2.2. Exercise training

AIT and MCT subjects performed supervised hospital-based training on a bicycle ergometer (Ergoselect 150P, Germany), completing three weekly sessions for 12 weeks, and GHC subjects only engaged in general home-based health care. The AIT group warmed up for 3 min at 30% of VO_{2peak} [≈30% heart rate reserve (HRR); $\approx 30\% \cdot (HR_{peak} - HR_{rest}) + HR_{rest}$] before exercise five 3-minute intervals at 80% of VO_{2peak} (≈80% HRR). Each interval was separated by 3-minute exercise at 40% of VO_{2peak} (≈40% HRR). The exercise session was terminated by 3-minute cool-down at 30% of VO_{2peak}. The exercise protocol in the MCT group comprised a warm-up at 30% of VO_{2peak} for 3 min, followed by continuous 60% of VO_{2peak} (≈60% HRR) for 30 min, then a cool-down at 30% of VO_{2peak} for 3 min. The two protocols were isocaloric at the same exercise duration. All subjects used a HR monitor (Tango, SunTech Medical, UK) to obtain the assigned intensity of exercise. Borg 6-to-20 scale was used to assess the rate of perceived exertion during and after each exercise session. The work-rate of bicycle ergometer was adjusted continuously to ensure that the intensity of exercise matched the target HR throughout the training period. The GHC patients followed advice from their rehabilitation physicians with regard to home-based physical activity. Patients were instructed to immediately stop exercise training if they had chest pain or other cardiac symptom/sign. The rates of compliance with the AIT, MCT, and GHC subjects were 93.3%, 86.7%, and 86.7%, respectively.

2.3. Graded exercise test

Subjects performed a graded exercise test on a bicycle ergometer (Ergoselect 150P, Germany) to assess their aerobic fitness and hemodynamic functions 2 days before and 2 days after the 12-week intervention. Each subject was instructed to fast for at least 8 h and to refrain from exercise for at least 24 h before the test. All subjects arrived at the testing center at 9:00 AM to eliminate diurnal effects. The exercise test comprised 2 min of unloaded pedaling followed by a continuous increase in work-rate of 10 W per minute until exhaustion (progressive exercise to peak oxygen consumption, VO_{2peak}) [4,13,14]. Minute ventilation (V_E), oxygen consumption (VO_2), and carbonic dioxide production (VCO_2) were measured breath by breath using a computer-based system (MasterScreen CPX, Cardinal-health Germany). Heart rate (HR) was determined from the R-R interval on a 12-lead electrocardiogram, mean arterial pressure (MAP) was measured using an automatic blood pressure system (Tango, SunTech Medical, UK), and arterial O_2 saturation was monitored by finger pulse-oximetry (model 9500, Nonin Onyx, Plymouth, Minnesota). The VO_{2peak} was defined by the following criteria: (i) VO_2 increased by less than 2 mL/kg/min over at least 2 min, (ii) HR exceeded 85% of its predicted maximum, (iii) the respiratory exchange ratio exceeded 1.15, or (iv) some other symptom/sign limitations, as described in the guidelines of the American College of Sports Medicine for exercise testing [15]. Ventilatory threshold was determined by two experienced, independent reviewers using the V-slope method and verified based on ventilatory criteria as follows: (i) the V_E/VO_2 ratio increased without a corresponding increase in the V_E/VCO_2 ratio, (ii) $P_{ET}O_2$ increased without a decrease in the $P_{ET}CO_2$, or (iii) departure from linearity for V_E [15].

Ventilation and VCO_2 responses, obtained during the period between the start of exercise and the peak, were used to calculate the V_E-VCO_2 slope using least squares linear regression ($y = m \cdot x + b$, m = slope) [16]. The OUES was derived from the slope of a common logarithm plot of V_E *versus* VO_2 ($VO_2 = a \log_{10} V_E \pm b$, a = OUES) [17–19]. Consequently, the OUES is an estimation of the ventilation efficiency with respect to VO_2, with steeper slopes indicating higher ventilatory efficiency [17–19]. Hematologic parameters (*i.e.*, erythrocyte count, hemoglobin, and hematocrit) were measured using an automatic blood cell counter (Sysmax SF-3000, GMI Inc.).

2.4. Cardiac hemodynamic measurements

NICOM (Cheetah Medical, Wilmington, Delaware) was used to evaluate cardiac hemodynamic response to exercise, which analyzes the phase shift ($\Delta\Phi$) created by alternating electrical current across the chest of the subject as described in our previous study [4,14]. Four dual surface electrodes were placed on the back of each subject to establish electrical contact with the body and avoid interference of upper body motion with the electrical cables during exercise testing. Stroke volume (SV) was estimated using the following equation: $SV = C \cdot VET \cdot d\Phi/dtmax$, where C is a constant of proportionality, and VET denotes the ventricular ejection time, as determined using the NICOM and electrocardiogram signals. The CO, MAP, total peripheral resistance (TPR), and arteriovenous O_2 difference (Da-vO_2) were then calculated using the following equation: $CO = SV \cdot HR$; $MAP = [(2 \times \text{diastolic blood pressure}) \pm \text{systolic blood pressure}]/3$; $TPR = MAP/CO$; and $Da\text{-}vO_2 = VO_2/CO$ [4,14].

2.5. Cerebral and muscular hemodynamic measurements

Two pairs of NIR probes (Oxymon, Artinis, The Netherland) were attached to each subject to monitor light absorption across the left frontal cortex region (FC) and vastus lateralis muscle (VL) during exercise testing, as described in our previous study [4,13,14]. The Beer–Lambert law was used to calculate micromolar changes in tissue oxygenation (Δ[O_2Hb] and Δ[HHb]) using received optical densities from the two NIR wavelengths of 780 and 850 nm. The differential pathlength factors of muscle and cerebral tissues were set to 4.95 and 5.93, respectively [20,21]. Total Hb concentration (Δ[THb]) was calculated as the sum of Δ[O_2Hb] and Δ[HHb] and used to indicate change in regional blood volume. Because Δ[HHb] is closely associated with changes in venous oxygen content and is less sensitive to Δ[THb] than is Δ[O_2Hb], the Δ[HHb] provides a highly sensitive measure of relative tissue de-oxygenation owing to oxygen extraction [22]. Data were recorded at 10 Hz and filtered using a Savitzky–Golay smoothing algorithm before analysis.

2.6. Inflammation-related biomarkers

An additional 5-mL blood sample was obtained from all subjects, placed in a cold centrifuge tube containing EDTA (final concentration, 4 mM), and immediately centrifuged at 3000 *g* for 10 min at 4 °C. The plasma samples were then stored at −80 °C until assay. Plasma brain natriuretic peptide (BNP) (USCN Life Science Inc., Burlington, NC), myeloperoxidase (MPO) (Immunology Consultants Laboratory, Newberg, OR), and interleukin-6 (IL-6) (eBioscience, San Diego, CA) concentrations were quantified by commercially available ELISA kids.

2.7. Health-related quality of life

Generic and disease-specific qualities of life (QoL) in the HF population were measured using the Short Form-36 Health Survey questionnaire (SF-36) and Minnesota Living with Heart Failure questionnaire (MLHFQ), respectively [23]. MLHFQ is developed as a self-assessment measure of therapeutic response to interventions for HF, whereas SF-36 is a generic measure and can help differentiate QoL issues related to co-morbidities from those related to HF [23].

2.8. Statistical analysis

Data were expressed as mean ± SEM, and were analyzed using the statistical software package StatView. Experimental results were analyzed by 3 (groups) × 2 (time sample points; *i.e.*, pre- and post-interventions) repeated measures ANOVA with Bonferroni's post hoc test to compare ventilatory and hemodynamic parameters and biomarkers at the beginning of this study and after 12 weeks in various groups. Additionally, the comparison of MLHFQ and SF-36 at the beginning of this study and 12 weeks later in various groups was analyzed using the Kruskal–Wallis test and post hoc test. Hierarchical regression models were used to demonstrate the relationships between ventilatory variables, which are VO_{2peak}, OUES, and V_E-VCO_2 slope, and hemodymanic variables by various regimens. The criterion for significance was $P < 0.05$.

3. Results

3.1. Physical fitness and ventilatory efficiency

The three groups did not differ significantly in anthropometric and clinical parameters or functional capacity at the start of the study (Table 1). Following 12 weeks of interventions, the AIT group displayed increased work-rate, V_E, VO_2 and VCO_2 at the ventilation threshold and peak exercise performance ($P<0.05$), but no significant changes in physical fitness occurred in either the MCT or GHC groups (Table 2). Moreover, the AIT regimen exhibited significantly elevated OUES (Fig. 1A, $P<0.05$) and lowered V_E-VCO_2 slope (Fig. 1B, $P<0.05$). Conversely, the MCT and GMC regimens did not influence the values of these indices of ventilatory efficiency (Fig. 1A and B). Additionally, there were no significant changes in hematologic parameters (*i.e.*, erythrocyte count, hemoglobin, and hematocrit) following AIT, MCT, or GHC for 12 weeks NE intervention (Table 1).

3.2. Cardiovascular hemodynamics

At the beginning of the intervention, the experiments evaluated the acute effects of aerobic interval exercise (AIE) and moderate continuous exercise (MCE) on hemodynamic functions. Alternating changes of CO and Da-vO_2 were observed during a bout of AIE, *i.e.*, periods of high intensity exercise had higher levels of CO (Figs. 2A and 3A) and Da-vO_2 (Figs. 2B and 3B) than did periods of low-intensity exercise. In contrast with AIE, a bout of MCE exhibited steady levels of CO (Fig. 2A) and Da-vO_2 (Fig. 2B) throughout the testing period. However, the average levels of CO (Fig. 3A) and Da-vO_2 (Fig. 3B) during AIE were similar to those during MCE.

Following 12 weeks of interventions, the AIT group revealed increased CO ($P\leq0.05$) and decreased TPR ($P\leq0.05$) at 25% to 75% or 100% of VO_{2peak} (Table 2 and Fig. 4A–C). These cardiovascular hemodynamic responses to exercise remained unchanged following 12-week MCT (Table 2 and Fig. 4D–F). However, the GHC patients displayed significantly decreased CO ($P\leq0.05$), accompanied by increased TPR ($P\leq0.05$) and MAP ($P\leq0.05$) at 25% to 75% or 100% of VO_{2peak} 12 weeks following the intervention (Table 2 and Fig. 4G–I).

AIT significantly increased LVEF as evaluated by echocardiography ($P<0.05$), whereas neither MCT nor GHC influenced the pumping efficiency of the heart (Table 1). Furthermore, AIT considerably reduced plasma levels of BNP (Fig. 5A, $P<0.05$), MPO (Fig. 5B, $P<0.05$), and IL-6 (Fig. 5C, $P<0.05$), and these oxidative stress/inflammatory biomarkers were unchanged following MCT and GHC (Fig. 5A–C).

3.3. Cerebral and muscular hemodynamics

Alternating changes of Δ[THb] in FC (Fig. 2C), as well as, Δ[THb] (Fig. 2E) and Δ[HHb] (Fig. 2F) in VL were observed during a bout of

Table 1
Demographic and clinical characteristics in various regimens.

		AIT		MCT		GHC	
		Pre	Post	Pre	Post	Pre	Post
Anthropometrics/clinical characteristics							
Gender	n (M/F)	15 (10/5)	14 (9/5)	15 (9/6)	13 (8/5)	15 (10/5)	13 (9/4)
Age	year	67.5 ± 1.8	–	66.3 ± 2.1	–	67.8 ± 2.5	–
Height	cm	162.3 ± 1.4	–	163.1 ± 1.2	–	161.2 ± 1.8	–
Weight	kg	64.5 ± 1.3	64.3 ± 1.5	65.1 ± 1.4	64.9 ± 0.8	63.9 ± 0.9	64.2 ± 1.1
Systolic BP	mm Hg	141 ± 2	139 ± 3	142 ± 3	140 ± 3	142 ± 5	143 ± 4
Diastolic BP	mm Hg	83 ± 2	81 ± 4	82 ± 3	81 ± 4	83 ± 3	84 ± 3
Erythrocyte	$\times10^7$/μL	43.6 ± 0.1	43.7 ± 0.1	43.3 ± 0.2	43.1 ± 0.3	43.7 ± 0.2	43.4 ± 0.2
Hemoglobin	%	39.1 ± 0.8	39.3 ± 0.9	39.0 ± 0.5	38.9 ± 0.6	39.2 ± 0.7	39.1 ± 0.6
Hematocrit	g/dL	13.5 ± 0.3	13.6 ± 0.4	13.4 ± 0.2	13.3 ± 0.3	13.6 ± 0.3	13.7 ± 0.3
Etiology (primary cause)							
Ischemic heart disease	n (%)	10 (67)	–	9 (60)	–	10 (67)	–
Hypertension	n (%)	2 (13)	–	2 (13)	–	2 (13)	–
Cardiomyopathy	n (%)	3 (20)	–	4 (27)	–	3 (27)	–
Heart failure duration	year	4.2 ± 1.8	–	4.5 ± 2.0	–	4.3 ± 1.6	–
Functional capacity							
MET	unit	4.57 ± 0.3	5.52 ± 0.3*	4.54 ± 0.2	4.57 ± 0.5	5.0 ± 0.4	4.6 ± 0.4
Echocardiography							
LVEF	%	38.3 ± 3.5	48.6 ± 3.3*	38.6 ± 4.8	43.1 ± 5.9	38.0 ± 3.8	42.7 ± 3.2
Metabolic biomarkers							
Glucose	mg/dL	121 ± 5	118 ± 6	114 ± 6	116 ± 5	114 ± 6	117 ± 13
Hb_{A1C}	%	6.6 ± 0.4	6.6 ± 0.2	6.5 ± 0.3	6.6 ± 0.1	6.2 ± 0.3	6.1 ± 0.3
Cholesterol	mg/dL	175 ± 7	165 ± 9	185 ± 14	167 ± 5	182 ± 13	180 ± 11
Triglyceride	mg/dL	123 ± 8	120 ± 12	118 ± 13	114 ± 15	116 ± 15	115 ± 9
LDL-C	mg/dL	111 ± 7	99 ± 6	112 ± 13	116 ± 15	115 ± 9	109 ± 11
HDL-C	mg/dL	37 ± 2	36 ± 1	37 ± 2	36 ± 1	35 ± 3	38 ± 3
Uric acid	mg/dL	7.2 ± 0.5	7.6 ± 0.5	7.8 ± 0.6	6.7 ± 0.8	6.8 ± 0.5	6.6 ± 0.4
Albumin	g/dL	4.0 ± 0.2	4.1 ± 0.1	4.2 ± 0.1	3.9 ± 0.2	3.8 ± 0.1	4.3 ± 0.2
Renal function							
BUN	mg/dL	16.7 ± 1.3	17.8 ± 2.6	19.0 ± 1.1	16.4 ± 1.3	21.1 ± 1.3	19.5 ± 2.0
Creatinine	mg/dL	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Medications							
Digoxin	n (%)	3 (20)	2 (14)	4 (27)	3 (23)	3 (20)	2 (15)
β-Blocker	n (%)	14 (93)	13 (92)	14 (93)	12 (92)	15 (100)	12 (92)
ACE/ARB	n (%)	12 (80)	11 (79)	12 (80)	10 (77)	13 (87)	10 (77)
Ca^{2+}channel blocker	n (%)	10 (67)	9 (64)	9 (60)	8 (62)	11 (73)	9 (69)
Diuretics	n (%)	8 (53)	7 (50)	7 (47)	6 (46)	7 (47)	6 (46)

AIT, aerobic interval training; MCT, moderate continuous training; GHC, general healthcare; Pre, pre-intervention; Post, post-intervention; M, male; F, female; BP, blood pressure; MET, metabolic equivalences; LVEF, left ventricular ejection fraction; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; BUN, blood urine nitrogen; ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Values are mean ± SEM.

* $P<0.05$, Pre *vs.* Post.

Table 2
The effects of various interventions on cardiopulmonary fitness during exercise test.

		AIT		MCT		GHC	
		Pre	Post	Pre	Post	Pre	Post
Ventilatory threshold							
Work-rate	watt	42 ± 5	64 ± 4*	43 ± 3	42 ± 5	42 ± 5	39 ± 5
V_E	L/min	26.4 ± 1.5	32.4 ± 1.3*	25.6 ± 0.9	24.6 ± 0.9+	27.1 ± 1.6	24.4 ± 1.4+
VO_2	mL/min/kg	11.1 ± 0.6	14.1 ± 0.5*	11.9 ± 0.5	11.3 ± 0.5+	11.7 ± 0.5	10.8 ± 0.6+
VCO_2	mL/min/kg	10.8 ± 0.5	13.8 ± 0.4*	11.7 ± 0.4	11.0 ± 0.4+	11.8 ± 0.6	10.7 ± 0.5+
HR	bpm	109 ± 3	110 ± 5	110 ± 5	109 ± 5	106 ± 3	106 ± 2
SV	mL	65 ± 4	94 ± 9*	67 ± 5	70 ± 6+	74 ± 6	63 ± 1.4*,+
CO	L/min	7.0 ± 0.5	10.2 ± 1.2*	7.2 ± 0.4	7.1 ± 0.4+	7.5 ± 0.6	6.5 ± 0.6*,+
TPR	mm Hg/L/min	14.8 ± 1.3	10.1 ± 1.1*	14.7 ± 0.8	14.6 ± 0.8+	14.4 ± 1.2	19.0 ± 1.7*,+
MAP	mm Hg	103 ± 3	102 ± 4	105 ± 5	104 ± 6	107 ± 2	123 ± 4*,+
SaO_2	%	95 ± 1	96 ± 1	96 ± 1	95 ± 1	96 ± 1	97 ± 1
Da-vO_2	mL/dL	11.8 ± 0.5	11.2 ± 0.9	11.6 ± 0.7	11.4 ± 0.8	11.8 ± 0.8	11.4 ± 0.7
Peak performance							
Work-rate	watt	86 ± 7	111 ± 9*	83 ± 6	90 ± 11	89 ± 11	84 ± 11
V_E	L/min	50.1 ± 2.9	58.6 ± 4.2*	45.1 ± 3.5	44.0 ± 3.4+	53.1 ± 4.9	48.7 ± 4.2+
VO_2	mL/min/kg	16.0 ± 1.0	19.6 ± 1.2*	15.9 ± 0.7	16.0 ± 1.5+	17.5 ± 1.5	16.1 ± 1.4+
VCO_2	mL/min/kg	19.3 ± 1.6	23.8 ± 1.8*	19.0 ± 1.2	18.9 ± 1.3+	21.1 ± 1.3	19.4 ± 1.4+
HR	bpm	137 ± 6	143 ± 5	135 ± 10	138 ± 12	132 ± 11	135 ± 11
SV	mL	67 ± 4	87 ± 6*	70 ± 2	66 ± 2+	70 ± 4	56 ± 5*,+
CO	L/min	9.0 ± 0.4	11.8 ± 0.8*	9.4 ± 0.7	9.0 ± 1.1+	9.2 ± 0.6	7.6 ± 0.5*,+
TPR	mm Hg/L/min	13.1 ± 0.8	10.1 ± 0.8*	12.6 ± 1.3	13.0 ± 1.1+	13.2 ± 0.7	16.8 ± 1.6*,+
MAP	mm Hg	117 ± 3	119 ± 2	118 ± 2	117 ± 4	122 ± 3	126 ± 3
SaO_2	%	96 ± 1	95 ± 1	96 ± 1	96 ± 1	97 ± 1	96 ± 1
Da-vO_2	mL/dL	12.2 ± 0.6	12.9 ± 1.0	12.4 ± 1.2	12.5 ± 1.1	11.5 ± 1.4	11.3 ± 0.7

AIT, aerobic interval training; MCT, moderate continuous training; GHC, general healthcare; Pre, pre-intervention; Post, post-intervention; V_E, minute ventilation; VO_2, O_2 consumption; VCO_2, CO_2 production; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; MAP, mean arterial pressure; SaO_2, arterial O_2 saturation; Da-VO_2, arteriovenous O_2 difference. Values are mean ± SEM.

* $P<0.05$, Pre *vs.* Post.

\+ $P<0.05$, AIT *vs.* MCT or GHC.

AIE but not MCE. During AIE, periods of high intensity exercise had higher levels of Δ[THb] in FC (Fig. 3C) and VL (Fig. 3E) and Δ[HHb] in VL (Fig. 3F) than did periods of low-intensity exercise. Furthermore, AIE also elicited higher average levels of Δ[THb] in FC (Fig. 3C) and VL (Fig. 3E) than did MCT.

The AIT regimen for 12 weeks further increased Δ[THb] (Fig. 6A, $P<0.05$) in FC and Δ[THb] (Fig. 7A, $P<0.05$) and Δ[HHb] (Fig. 7B, $P<0.05$) in VL at 25% or 50% to 100% of VO_{2peak}. However, no significant changes in cerebral and muscular vascular/metabolic responses to the graded exercise test occurred after 12-week interventions with MCT (Fig. 6C and D and Fig. 7C and D) and GHC (Fig. 6E and F and Fig. 7E and F).

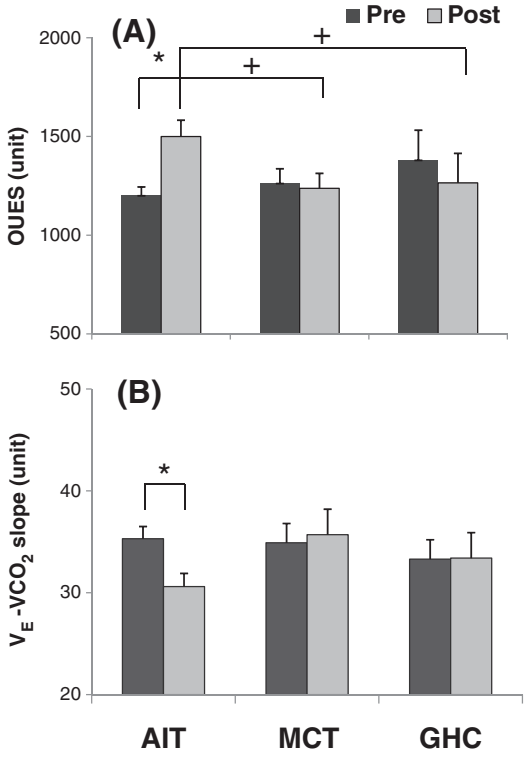

Fig. 1. The effects of aerobic interval training (AIT), moderate continuous training (MCT), and general healthcare (GHC) on ventilatory efficiency [oxygen uptake efficiency slope (OUES) (A) and V_E-VCO_2 slope (B)] in patients with heart failure. Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post; +$P<0.05$, AIT *vs.* MCT or GHC.

3.4. Relationships between ventilatory and hemodynamic adaptations

Table 3 shows Pearson correlation coefficients of the main ventilatory and hemodynamic variables changed by various regimens in patients with HF. Levels of peak CO, Δ[THb] and Δ[THb] in FC, and Δ[HHb] in VL were positively correlated with VO_{2peak} or OUES and negatively correlated with V_E-VCO_2 slope.

Furthermore, under the assumptions that changes of ventilatory efficiency are associated with changes in central (cardiac) or peripheral (cerebral and muscular) hemodynamic responses to exercise after 12 weeks of intervention, hierarchical regression models were performed to demonstrate the relationships between ventilatory and hemodymanic adaptations.

In Table 4, the first hierarchical multiple regression analysis used VO_{2peak} as the outcome variable. When peak CO was entered at the first step, it explained 54.5% of the variance in exercise capacity (VO_{2peak}) ($\Delta R^2 = 0.545$, $F = 51.498$, $P \leq 0.001$). Variables represented for perfusion including peak Δ[THb] levels in FC and VL entered in the second step increased the explained variance by 17.1% ($\Delta R^2 = 0.171$, $F = 12.299$, $P \leq 0.001$). Peak Δ[THb] level in FC was positively associated with VO_{2peak} ($\beta = 0.316$, $P \leq 0.05$), while peak Δ[THb] levels in VL not significantly correlated with VO_{2peak} ($\beta = 0.259$, $P \geq 0.05$). Variables peak Δ[HHb] levels in FC and VL, entered in the third step, were not significantly associated with VO_{2peak} and only increased explained variance by 0.5% ($\Delta R^2 = 0.005$, $F = 0.330$, $P \geq 0.05$).

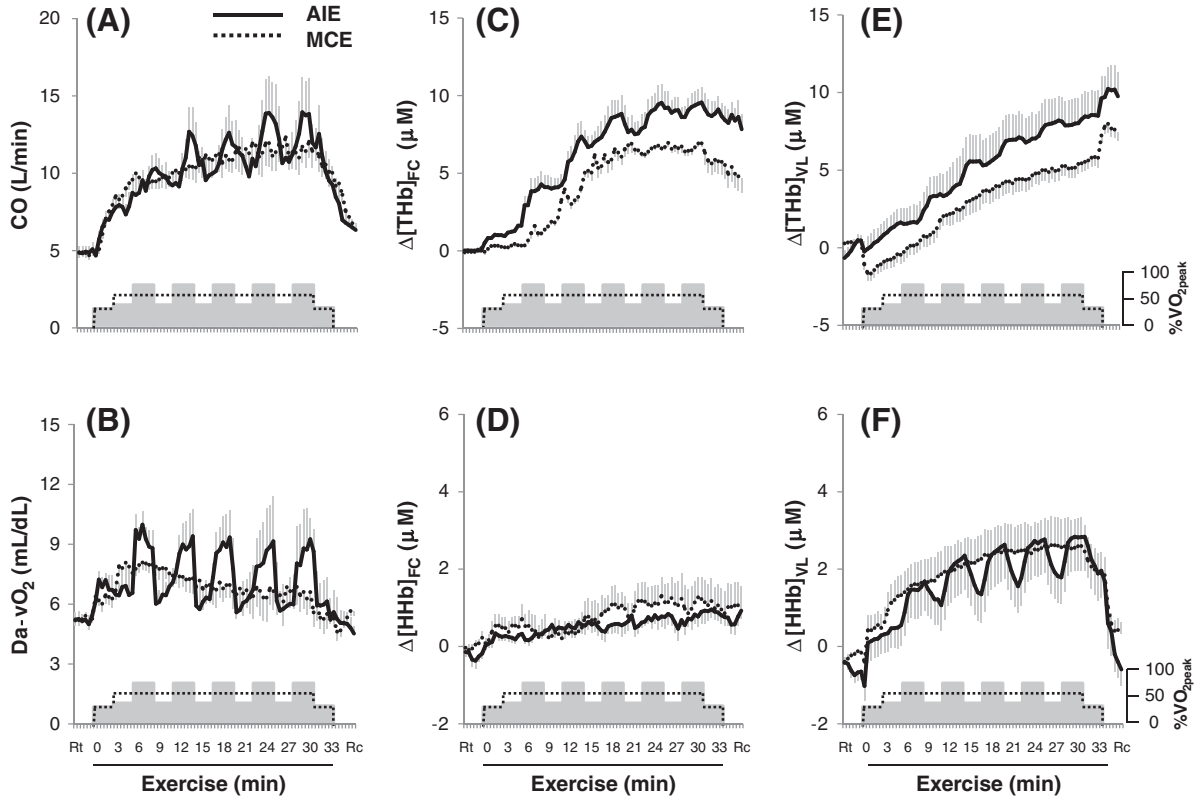

Fig. 2. Graphs show cardiac-cerebral-muscle hemodynamic responses to interval aerobic exercise (AIE) or moderate continuous exercise (MCE) in patients with heart failure (n = 6). CO, cardiac output (A); Da-vO_2, arteriovenous O_2 difference (B); $\Delta[THb]_{FC}$, perfusion in frontal cerebral lobe (C); $\Delta[HHb]_{FC}$, O_2 extraction in frontal cerebral lobe (D); $\Delta[THb]_{VL}$, perfusion in vastus lateralis muscle (E); $\Delta[HHb]_{VL}$, O_2 extraction in vastus lateralis muscle (F). Values are mean ± SEM.

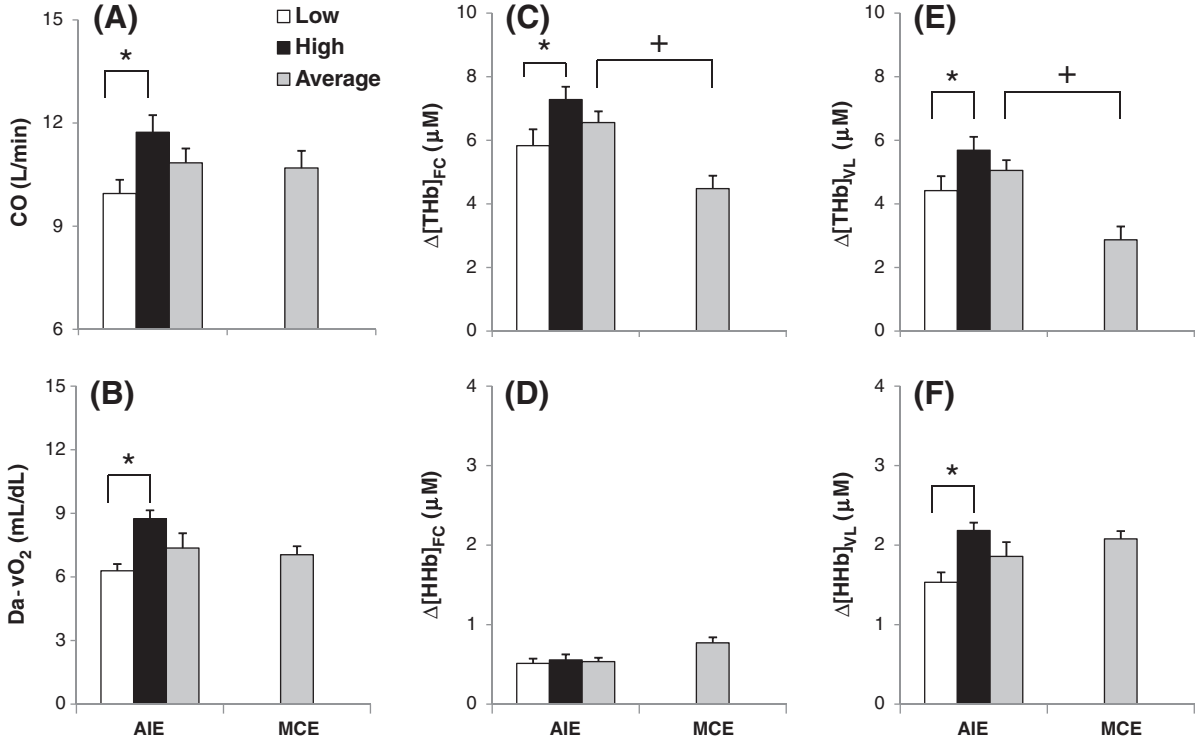

Fig. 3. The acute effects of aerobic interval exercise (AIE) and moderate continuous exercise on cardiac output (CO, A), arteriovenous O_2 difference (Da-vO_2, B), perfusion ($\Delta[THb]_{FC}$, C) and O_2 extraction ($\Delta[HHb]_{FC}$, D) of frontal cerebral lobe, and perfusion ($\Delta[THb]_{VL}$, E) and O_2 extraction ($\Delta[HHb]_{VL}$, F) of vastus lateralis muscle in patients with heart failure (n = 6). Low, the hemodynamic response to low-intensity exercise (40% VO_{2peak}) in AIE; High, the hemodynamic response to high-intensity exercise (80% VO_{2peak}) in AIE; Average, the average hemodynamic response throughout AIE or MCE period. Values are mean ± SEM. *$P \leq 0.05$, Low *vs.* High; +$P \leq 0.05$, AIE *vs.* MCE.

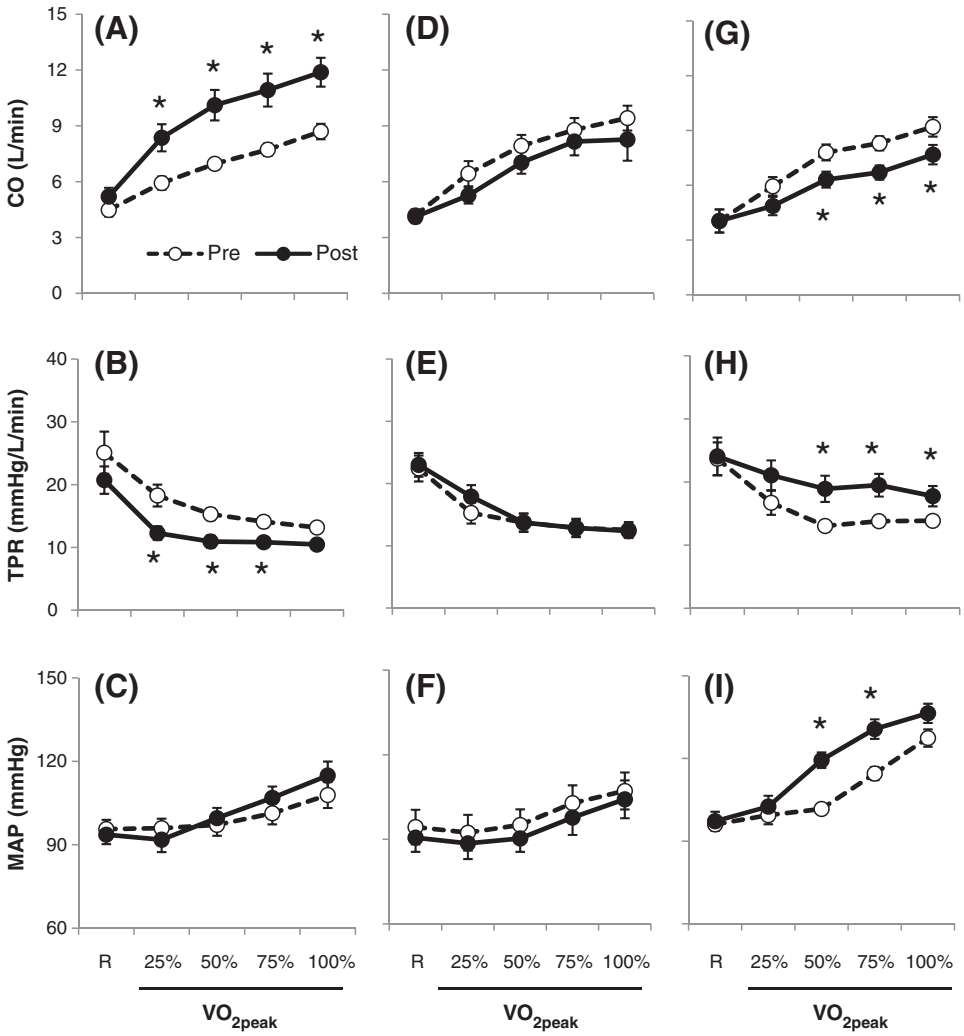

Fig. 4. The effects of aerobic interval training (A, B, C), moderate continuous training (D, E, F), and general healthcare (G, H, I) on cardiovascular hemodynamic responses during the graded exercise test in patients with heart failure. Cardiac output, CO (A, D, G); total peripheral resistance, TPR (B, E, H); mean arterial pressure, MAP (C, F, I); Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post.

A similar procedure was applied with OUES as the outcome variable. In the first step, peak CO explained 30.9% of the variance of the OUES ($\Delta R^2 = 0.309$, $F = 19.216$, $P \leq 0.001$) but its significance disappeared when the variables peak Δ[THb] levels in FC and VL were entered as the second step. Peak Δ[THb] levels in FC ($\beta = 0.314$, $P \leq 0.01$) and in VL ($\beta = 0.967$, $P \leq 0.001$) were significantly positive associated with OUES and jointly explained 48.9% of its variance ($\Delta R^2 = 0.489$, $F = 49.481$, $P \leq 0.001$). The third step explained 3.2% of the variance of OUES ($\Delta R^2 = 0.032$, $F = 3.677$, $P \leq 0.05$) with only Δ[HHb] level in VL showed significantly positive correlation with OUES ($\beta = 0.368$, $P = 0.01$).

In the hierarchical multiple regression model of V_E-VCO_2 slope, the 3 steps explained 20.2%, 56.5% and 1.7% of its variance respectively (1st step, $\Delta R^2 = 0.202$, $F = 10.903$, $P \leq 0.01$; 2nd step, $\Delta R^2 = 0.565$, $F = 49.912$, $P \leq 0.001$; $\Delta R^2 = 0.017$, $F = 1.497$, $P \geq 0.05$). However, only peak Δ[THb] levels in VL demonstrated significantly negative association with V_E-VCO_2 slope ($\beta = -0.971$, $P \leq 0.001$) in this model. Again, the significance of peak CO correlated with V_E-VCO_2 slope was modulated when the 2nd step's variables were entered.

3.5. Health-related QoL

AIT substantially reduced MLHFQ score from 34.3 to 21.3 (Fig. 8A, $P<0.01$), whereas MCT modestly reduced the disease-specific QoL score from 34.8 to 28.3 (Fig. 8A, $P<0.05$). Additionally, AIT also significantly increased the subclass scores of the physical (Fig. 8B, 46.4 to 52.2) and mental (Fig. 8C, 43.3 to 51.3) dimensions in SF-36, respectively. However, GHC remained unchanged the scores of MLHFQ and SF-36 physical/mental components (Fig. 8A–C).

4. Discussion

This investigation clearly demonstrates that the AIT regimen significantly improves the aerobic fitness of HF patients by increasing their ventilatory efficiency and cardiac-cerebral-muscular hemodynamic responses to exercise. However, MCT for 12 weeks did not influence the values of the ventilatory and hemodynamic responses to exercise, and only maintained the ability to perform ventilation–perfusion matching during exercise as a pre-interventional status. Notably, AIT effectively (i) elevates OUES and lowers V_E-VCO_2 slope, (ii) increases CO and decreases TPR, (iii) enhances cerebral/muscular blood flow and muscular O_2 utilization during exercise, (iv) depresses oxidative stress/inflammation associated with cardiac dysfunction, and (v) promotes generic/disease-specific qualities of life in patients with HF. Despite no alterations in cerebral/muscular perfusion and oxygenation, GHC depresses cardiovascular hemodynamic response to exercise to below pre-interventional level.

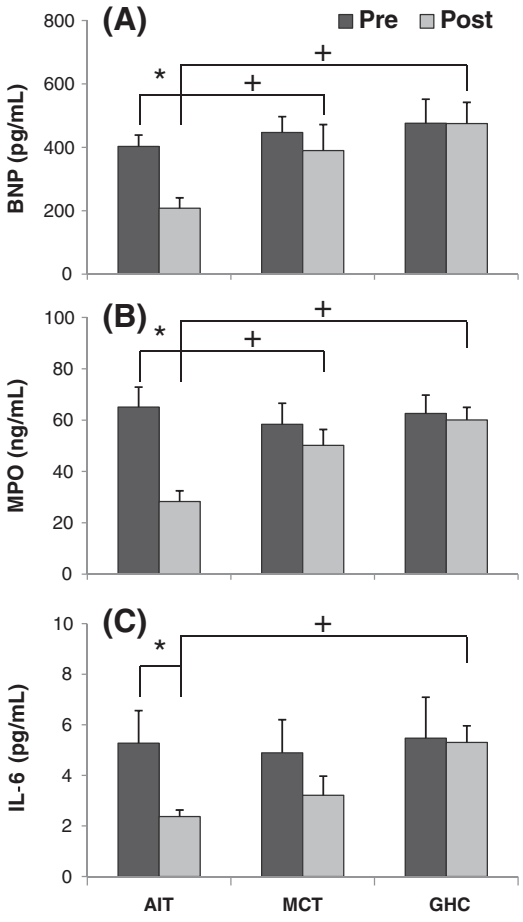

Fig. 5. The effects of aerobic interval training (AIT), moderate continuous training (MCT), and general healthcare (GHC) on inflammation-related biomarkers [brain natriuretic peptide (BNP) (A), myeloperoxidase (MPO) (B), and interleukin-6 (IL-6) (C)] in patients with heart failure. Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post; +$P<0.05$, AIT *vs.* MCT or GHC.

4.1. Central hemodynamic adaptation

This study found that regular AIE for 12 weeks increased cardiac SV by decreasing after-load (as TPR) at ventilatory threshold and peak performance, implying that the AIT regimen improves the pumping efficiency of the heart throughout aerobic and anaerobic exercise periods. Left ventricular function also improves significantly in AIT patients by observing the result of elevated LVEF. Additionally, reduced plasma BNP levels clearly demonstrate the effectiveness of AIT in modifying cardiac remodeling caused by HF [11,12].

Under isocaloric conditions, a bout of AIE causes alternating changes in CO and Da-vO_2, whereas acute MCE elicits steady state responses in these physiological variables. Previous investigations have shown that patients with ischemic heart disease developed a warm-up phenomenon during repeated exercise testing, characterized by delayed onset of angina pain and reduced electrocardiographic evidence of myocardial ischemia, an effect that comprised a form of preconditioning [24,25]. Animal studies have indicated that exercise preconditioning improved myocardial tolerance to ischemia by activating nitric oxide synthase and mitochondrial ATP-sensitive K^+ channel [11,12]. Additionally, the protective effects of exercise training on cardiovascular systems are likely associated with increasing coronary blood flow and cardiomyoglobin content as well as up-regulated expression of antioxidant enzymes and stress-related proteins [11,12]. This investigation further indicates that the levels of MPO and IL-6 in plasma decrease significantly following AIT. Accordingly, we posit that these AIT-induced adaptations protect against oxidative stress and inflammation associated with cardiac dysfunctional processes.

4.2. Peripheral hemodynamic adaptation

Although AIT enhances VL or FC perfusion during exercise, the enhancement of tissue to O_2 utilization is observed in VL rather than FC following this regimen. The difference in AIT effects in terms of perfusion and O_2 utilization between cerebral and muscular tissues may be associated with the different adaptations of various tissues to shear flow and/or metabolic stress.

The measurement results indicate that AIE induces higher levels of VL and FC perfusions than does MCE. Increased flow and correspondingly increased shear stress to the vessel walls during AIE may promote the release of nitric oxide from vascular endothelial cells [11,12], contributing to the regulation of vascular tone and subsequent increase in blood distribution to the cerebral and muscular tissues. Additionally, a phenomenon of repeated episodes of deoxygenation, indicated by an alternating change of Δ[HHb], in VL is presented at performing AIE but not MCE. A previous study using healthy subjects found that mitochondrial oxidative capacities in skeletal muscle were only enhanced after AIT, while increasing capillary densities following both AIT and MCT [26]. Recently, a clinical investigation of HF patients further demonstrated that AIT but not MCT improves mitochondrial biogenesis, as reflected by increased peroxisome proliferative activated receptor-γ coactivator-1α level, in skeletal muscle [9]. These results, together with those presented here, clearly demonstrate that AIT induces a metabolic adaptation in skeletal muscle. However, a bout of AIE does not cause an alternating change of Δ[HHb] in FC, suggesting that a long-term AIT regimen is insufficient to trigger a metabolic adaptation to cerebral tissues.

4.3. Relationships between ventilatory and hemodynamic adaptations

Reduced cardiac output caused by HF may decrease pulmonary perfusion and CO_2 exchange, leading to hyperpnea upon exertion that represents a steeped V_E-VCO_2 slope [16,27]. Exertional hyperventilation reduces alveolar PCO_2 and subsequent $PaCO_2$, which responses may further induce cerebral vasoconstriction during exercise [16,28]. Furthermore, the reduction in FC perfusion/oxygenation inhibits cortical activation of efferent motor neurons, resulting in decreased muscle force-generating capacity and consequence of exercise intolerance [29,30]. The results of this study show that the AIT regimen lowers the V_E-VCO_2 slope, which may relieve the symptom of exertional hyperpnea in patients with HF. Regarding the relationships between changes in ventilation and perfusion under various regimens, variables CO, $\Delta[THb]_{FC}$, and $\Delta[THb]_{VL}$ are negatively correlated with the V_E-VCO_2 slope in the univariate analysis. However, after controlling for other factors in the hierarchical regression model, only variable $\Delta[THb]_{VL}$ is significantly associated with the V_E-VCO_2 slope. Moreover, variable $\Delta[THb]_{VL}$ is an effect modifier, which modulates the significant correlation status between CO or $\Delta[THb]_{FC}$ and V_E-VCO_2 slope. Accordingly, the present results suggest that AIT enhances skeletal muscular blood flow and thus accelerates clearance of metabolic products generated by exercise, ameliorating exertional hyperpnea and subsequently increasing cerebral perfusion, thus improving exercise tolerance in patients with HF.

On the other hand, AIT promotes HF patient aerobic capacity and efficiency through increasing VO_{2peak} and OUES levels, respectively. Moreover, the results analyzed by the hierarchical regression reveal that only variable CO is directly related to VO_{2peak}, whereas both variables $\Delta[THb]_{FC}$ and $\Delta[THb]_{VL}$ are closely associated with OUES.

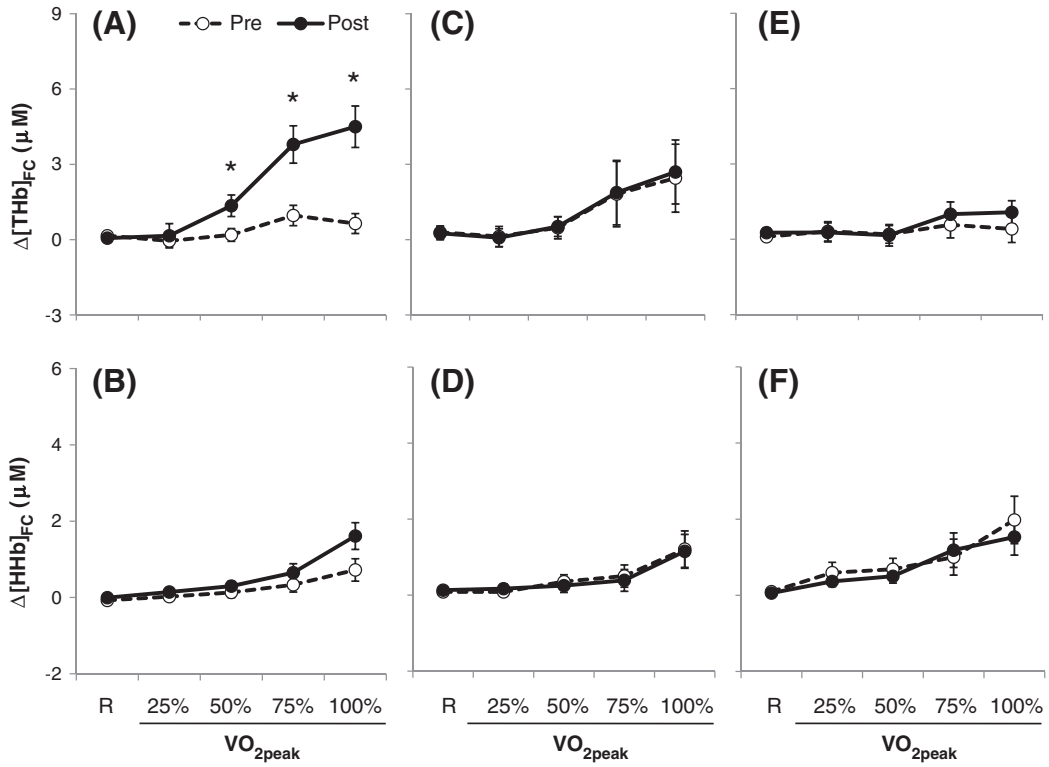

Fig. 6. The effects of aerobic interval training (A, B), moderate continuous training (C, D), and general healthcare (E, F) on perfusion ($\Delta[THb]_{FC}$) and O_2 extraction ($\Delta[HHb]_{FC}$) in frontal cerebral lobe during the graded exercise test in patients with heart failure. Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post.

These results imply that central (cardiac) and peripheral (cerebral and muscular) hemodynamic variables are independent influencing factors for aerobic capacity and efficiency in patients with HF, respectively.

4.4. Health-related QoL

Previous investigations strongly recommend that both generic and disease-specific measures should be included in the evaluation

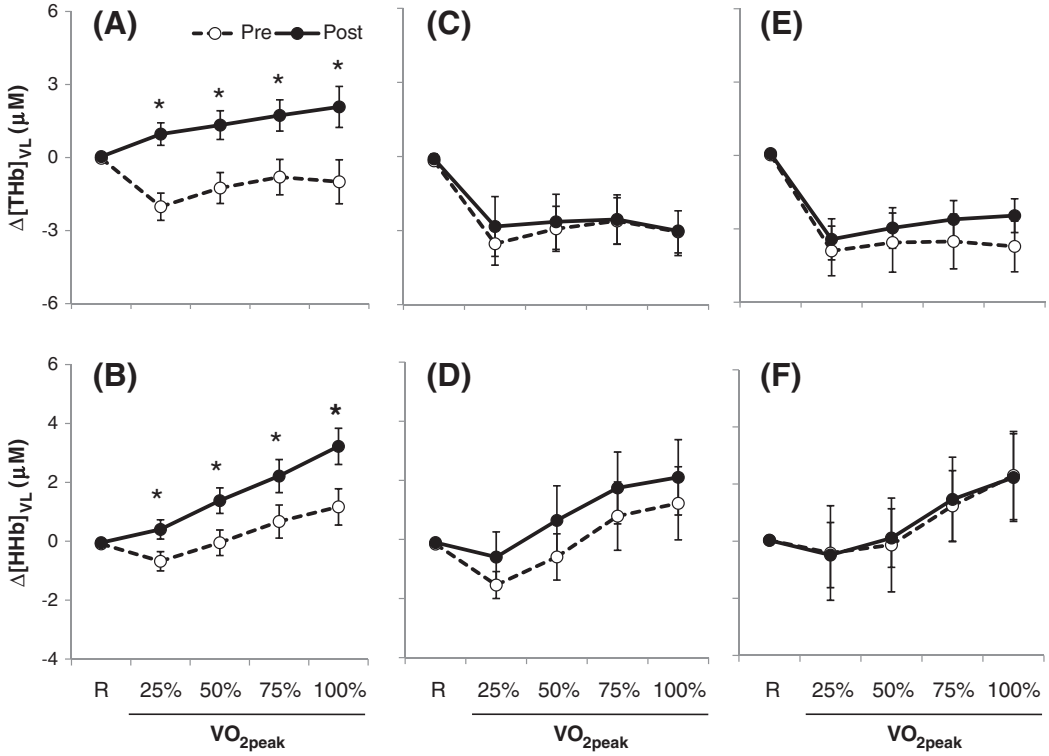

Fig. 7. The effects of aerobic interval training (A, B), moderate continuous training (C, D), and general healthcare (E, F) on perfusion ($\Delta[THb]_{VL}$) and O_2 extraction ($\Delta[HHb]_{VL}$) in vastus lateralis muscle during the graded exercise test in patients with heart failure. Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post.

Table 3
Pearson correlation coefficients of ventilatory and hemodymanic variables changed by various interventions.

	VO_{2peak}	OUES	V_E-VCO_2 slope	CO	$\Delta[THb]_{FC}$	$\Delta[THb]_{VL}$	$\Delta[HHb]_{FC}$	$\Delta[HHb]_{VL}$
VO_{2peak}	–	0.742*	−0.467*	0.627*	0.586*	0.551*	−0.035	0.580*
OUES	0.742*	–	−0.726*	0.534*	0.755*	0.776*	0.016	0.619*
V_E-VCO_2 slope	−0.467*	−0.726*	–	−0.471*	−0.542*	−0.759*	−0.148	−0.689*
CO	0.627*	0.534*	−0.471*	–	0.488*	0.510*	−0.210	0.517*
$\Delta[THb]_{FC}$	0.586*	0.755*	−0.542*	0.488*	–	0.539*	−0.023	0.543*
$\Delta[THb]_{VL}$	0.551*	0.776*	−0.759*	0.510*	0.539*	–	0.008	0.863*
$\Delta[HHb]_{FC}$	−0.035	0.016	−0.148	−0.210	−0.023	0.008	–	−0.081
$\Delta[HHb]_{VL}$	0.580*	0.619*	−0.689*	0.517*	0.543*	0.863*	−0.081	–

VO_{2peak}, peak O_2 consumption; OUES, oxygen uptake efficiency slope; CO, cardiac output; $\Delta[THb]_{FC}$, perfusion in frontal cerebral lobe; $\Delta[THb]_{VL}$, perfusion in vastus lateralis muscle; $\Delta[HHb]_{FC}$, O_2 extraction in frontal cerebral lobe; $\Delta[HHb]_{VL}$, O_2 extraction in vastus lateralis muscle.
* Means significantly correlated at $P<0.05$ level.

of QoL in HF [23,31,32]. The analytical results presented in this study indicate that although both AIT and MCT decrease the score of MLHFQ, only AIT significantly increases the scores of the SF-36 physical and mental dimensions. These findings imply that AIT rather than MCT simultaneously improves generic and disease-specific QoL in patients with HF. A possible explanation of the superior effects of AIT on these health-related QoL issues, *i.e.*, AIT effectively enhances aerobic capacity and efficiency and relieves exercise intolerance, thus increasing the ability of patients to cope with the physical demands of daily activity and subsequently improving psychosocial status in HF patients. Furthermore, the better health-related QoL might exhibit less potential for mortality in HF patients [33] and simultaneously reduce the financial burden in their health care system [34].

4.5. Limitations of the study

Our small size in each group (n = 15) is a major limitation of this study. However, the hemodynamics-related results obtained from this investigation have high values of statistical power from 0.884 to 1.000. On the other hand, the exercise volume of MCT in this study might be too low to exert any positive effects on central and peripheral hemodynamic disturbances in patients with HF. The majority of the positive MCT studies applied the exercise training at least 5 days a week up to 6 times daily for a period of at least 12 weeks. Additionally, it is surprising to observe a fast deterioration of cardiovascular hemodynamic parameters in the GHC group. A possible reason is that poor functional capacity (≤5 METs) with advanced age (≥65 years old) in most tested subjects progressively decreases cardiopulmonary fitness and further debilitation while they do not engage in appropriate exercise training.

5. Conclusions

The AIT regimen designed in this study can enhance central and peripheral hemodynamic responses to exercise, apparently by increasing heart pumping efficiency and the delivery/utilization of O_2 to exercising skeletal muscles or cerebral tissues. Furthermore, the improvement of ventilatory efficiency by AIT may contribute to beneficial adaptations in central and peripheral hemodynamics, which effects are accompanied by the better global and disease-specific QoL in patients with HF. However, the traditional MCT regimen can only maintain these physiologic responses to exercise as pre-interventional status. These findings provide a new insight into the superior effects of AIT on ventilation–perfusion matching during exercise, and may have important implications for exercise training in HF rehabilitation.

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Table 4
The hierarchical regression models revealed relationships between ventilatory and hemodynamic adaptations.

Variables	VO_{2peak}					OUES					V_E-VCO_2 slope				
	β	t	*P*	F	ΔR^2	β	t	*P*	F	ΔR^2	β	t	*P*	F	ΔR^2
1st step															
Central hemodynamics				51.498***	0.545				19.216***	0.309				10.903**	0.202
CO	0.458	3.911	0.000			−0.032	−.0347	0.730			0.154	1.500	0.142		
2nd step															
Peripheral hemodynamics				12.299***	0.171				49.481***	0.489				49.912***	0.565
CTHb	0.316	2.527	0.016			0.314	3.222	0.003			−0.145	−1.320	0.194		
MTHb	0.259	1.120	0.270			0.967	5.349	0.000			−0.971	−4.773	0.000		
3rd step															
Tissue O_2 extraction				0.330	0.005				3.677*	0.032				1.497	0.017
CHHb	0.063	0.691	0.494			−0.022	−0.305	0.762			−0.099	−1.247	0.220		
MHHb	−0.046	−0.263	0.794			0.368	2.695	0.010			0.137	0.891	0.379		

VO_{2peak}, peak O_2 consumption; OUES, oxygen uptake efficiency slope; CO, cardiac output; $\Delta[THb]_{FC}$, perfusion in frontal cerebral lobe; $\Delta[THb]_{VL}$, perfusion in vastus lateralis muscle; $\Delta[HHb]_{FC}$, O_2 extraction in frontal cerebral lobe; $\Delta[HHb]_{VL}$, O_2 extraction in vastus lateralis muscle.
* $P<0.05$.
** $P<0.01$.
*** $P<0.001$.

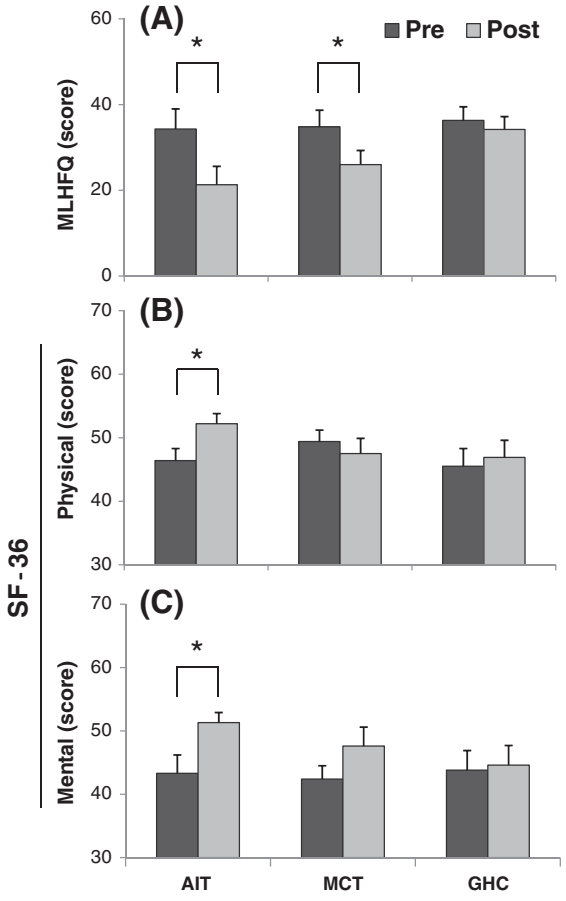

Fig. 8. The effects of aerobic interval training (AIT), moderate continuous training (MCT), and general healthcare (GHC) on health-related quality of life [Minnesota Living with Heart Failure questionnaire (MLHFQ) and Short Form-36 Health Survey questionnaire (SF-36) physical (B) and mental components (C)] in patients with heart failure. Pre, pre-intervention; Post, post-intervention. Values are mean ± SEM. *$P<0.05$, Pre *vs.* Post.

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