Differential response to resistance training in CHF according to ACE genotype

DIFFERENTIAL RESPONSE TO RESISTANCE TRAINING IN CHF ACCORDING TO ACE GENOTYPE

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ABSTRACT

Background. The Angiotensin Converting Enzyme (ACE) gene may influence the risk of heart disease and the response to various forms of exercise training may be at least partly dependent on the ACE genotype. We aimed to determine the effect of ACE genotype on the response to moderate intensity circuit resistance training in chronic heart failure (CHF) patients

Methods. The relationship between ACE genotype and the response to 11 weeks of resistance exercise training was determined in 37 CHF patients (New York Heart Association Functional Class = 2.3 ± 0.5; left ventricular ejection fraction 28 ± 7%; age 64 ± 12 years; 32:5 male:female) who were randomized to either resistance exercise (n=19) or inactive control group (n=18). Outcome measures included VO_2 peak, peak power output and muscle strength and endurance. ACE genotype was determined using standard methods.

Results. At baseline, patients who were homozygous for the I allele had higher $\dot{V}O_{2peak}$ ($p = 0.02$) and peak power ($p = 0.003$) compared to patients who were homozygous for the D allele. Patients with the D allele, who were randomized to resistance training, compared to non-exercising controls, had greater peak power increases (ID $p < 0.001$; DD $p < 0.001$) when compared with patients homozygous for the I allele, who did not improve. No significant genotype-dependent changes were observed in $\dot{V}O_{2peak}$, muscle strength, muscle endurance or lactate threshold.

Conclusion. ACE genotype may have a role in exercise tolerance in CHF and could also influence the effectiveness of resistance training in this condition.

Key Words: heart failure, genes, exercise

INTRODUCTION

Of an evolving class of enzymes involving the renin-angiotensin system, the most studied is the first angiotensin converting enzyme (ACE), which catalyzes the production of angiotensin II and renders bradykinin inactive. A polymorphism in intron 16 of the ACE gene is characterized by the presence (insertion - I) or absence (deletion - D) of a 287-bp sequence, with the highest serum ACE activity in individuals carrying the DD genotype (1).

ACE DD genotype has been related to an increased incidence of myocardial infarction (2), and early onset of coronary heart disease (3), independent of conventional risk factors. Increased risk of secondary events following myocardial infarction (4), and heart failure severity (5) have been linked to the D allele.

The major symptoms of chronic heart failure (CHF) are exertional fatigue and breathlessness (6), with poor exercise capacity being a strong and independent prognostic indicator of morbidity in CHF (7). Aerobic exercise training improves $\dot{V}O_{2\,peak}$ and exercise tolerance (8) in these patients, while similar changes coupled with increases in muscular strength have been observed with resistance training (9).

The possibility that ACE genotype may have an important role in physical performance has been inferred in both observational and intervention studies. Cross-sectional studies have reported the ACE I allele to be associated with enhanced endurance exercise performance in endurance athletes (10, 11) and congestive heart failure patients (12). However, other studies have found no relationship (13) , or a lower endurance performance in individuals with the I allele (14). Few studies have

investigated the effect of ACE genotype on the response to exercise training over time. These have been conducted in healthy volunteers and have suggested that aerobic training may result in greater improvements in moderate intensity aerobic tolerance in those with the I allele (15). In healthy young males with the D allele, 6-9 weeks of resistance training resulted in greater strength increases (16, 17). To date only two studies have investigated the effect of ACE genotype on the response to exercise training in patients with cardiovascular disease with discordant findings (18, 19). DeFoor and colleagues (18) reported that three months of aerobic training resulted in greater benefits to peak oxygen uptake in coronary artery disease (CAD) patients who were homozygous for the I allele. In contrast, a similar study found no ACE genotype-dependent response to a 12 week cardiac rehabilitation program in patients following an acute myocardial infarction (19). However, the effect of ACE genotype on the response to exercise in CHF patients has never been examined.

Given the possible mechanisms by which ACE gene I/D polymorphism might influence the severity of CHF, exercise tolerance and potential consequent outcomes in CHF patients, we examined the effect of ACE genotype on the response to moderate intensity circuit resistance training in CHF patients.

MATERIALS AND METHODS

Participants.

After written informed consent, 37 patients (32 men, 5 women) with stable CHF were enrolled in the study and underwent baseline testing. Descriptive characteristics of the participants are presented in Table 1. Using randomly generated

numbers with allocation being held by a third party, patients were randomised to either 11 weeks of moderate intensity resistance training exercise (n = 19; 16 male; 3 female) or a non-training control group (n = 18; 16 male; 2 female).

Inclusion and Exclusion Criteria

Patients were included if they were at least 18 years of age with stable left ventricular systolic heart failure characterised by typical clinical features, a left ventricular ejection fraction (LVEF) < 40% (by gated blood pool scan) and New York Heart Association functional class II or III. To ensure clinical stability prior to commencement in the study, all patients were required to have been on stable (> 2 weeks) pharmacological therapy prior to study entry, and not to have had any coronary event or revascularisation procedure within the previous six months.

Patients were excluded if cardiovascular limitations were deemed to be associated with a high risk of complications from exercise testing or training. These included current angina; cardiac arrest, symptomatic or sustained ventricular tachycardia within the previous six months; exercise-induced ventricular tachycardia or systolic blood pressure drop of > 20mmHg; or musculoskeletal or respiratory problems or other co-morbidity that would affect the ability to take part in an exercise training program or that were considered to be the limiting factor for exercise.

Written informed consent was obtained from all patients prior to their entry into this study that was approved by the Human Research Ethics Committees of Austin Health and Victoria University and complied with the Declaration of Helsinki.

Exercise Testing

Peak total body oxygen consumption ($\dot{V}O_{2\ peak}$) was determined during a symptom-limited graded exercise test on an electronically braked bicycle ergometer (Ergomed, Siemens, Erlangen, Germany), commencing at 10 W and increasing by 10 $W.min^{-1}$ to volitional fatigue or a level of 17 on the 6-20 point Borg scale of perceived exertion (20). Expired volume and expired oxygen and carbon dioxide concentrations were analysed and used to compute $\dot{V}O_2$, carbon dioxide production (VCO_2), and respiratory exchange ratio ($RER = VCO_2/\dot{V}O_2$) as previously described (9). Arterialised blood samples were obtained during the incremental exercise test from a dorsal hand vein via a 20-guage indwelling catheter. Oxygen saturation in the blood samples was consistently in excess of 95%, confirming arterialisation. Details of the exercise testing protocols and measurements have been reported previously (9). Plasma lactate levels were determined and lactate threshold calculated using a log-log transformation plot of plasma lactate concentration versus power output as previously described (21, 22).

Unilateral (right leg) skeletal muscle strength and endurance for knee extension were assessed using an isokinetic dynamometer (MERAC, Universal, Cedar Rapids, Iowa), with microprocessor, as described previously (9). Briefly, strength was measured as the peak angular torque (Nm) generated during 3 maximal continuous repetitions at an angular velocity of $60^{o}.sec^{-1}$. After 3 minutes of recovery, endurance was determined as the total angular work (joules) performed during the middle 16 of 20 consecutive maximal repetitions at an angular velocity of $180^{o}.sec^{-1}$.

Resistance Training

Training (3 sessions per week) was undertaken in the hospital gymnasium using a multi-station hydraulic resistance training system (HydraGym, Belton, USA), arm (Repco, Melbourne, Australia) and leg cycling (Repco, Melbourne, Australia) ergometers, and a set of stairs as previously described (9). Briefly, the graduated resistance training program used the following exercises, alternating between upper and lower body: leg cycling (0.5 - 2 min), elbow extension / flexion (30 s), stair climbing (0.5 - 2 min), arm cycling (0.5 - 2 min), knee extension / flexion (30 s), shoulder press / pull (30 s). Recovery intervals between exercises were determined as the period required to return heart rate to within 10 beats of the pre-exercise (rest) recording. For safety reasons workload intensities were reduced if the heart rate response to a station was within 5 $b.min^{-1}$ of peak heart rate. Participants began by performing a single set of each exercise at the lowest resistance on the hydraulic resistance training system while technique was trained and the safety of the patient was established. Exercise progressions were introduced by increasing resistance and the number of sets for a given exercise as has been described previously (9). Adherence was monitored as attendance. Adverse events were documented and patients were reviewed by their primary care physician before being permitted to continue in the study. Cardiac rate and rhythm were continuously monitored and recorded during exercise on a four channel (patient) telemetry system (prototype designed by Victoria University bioengineers, Melbourne, Australia). Patients randomized to the control group were requested not to alter their normal activities of daily living or physical activity during the 11 week experimental period. Descriptive characteristics of the training and control groups of patients are presented in Table 1.

Blood Sampling

Blood samples for ACE genotype analysis were collected from the antecubital vein using a direct needle puncture technique. The blood was collected in heparin coated tubes and stored on ice for transport to the laboratory where the DNA extraction technique was performed. DNA was extracted from the white blood cells by the standard salting-out methods (23). Briefly, each genotype was identified by polymerase chain reaction amplification of a sequence from intron 16 of the ACE gene (24). Subsequently alleles (490 bp: I and 190 bp: D) were differentiated on an agarose gel by ethidium bromide staining (24). All genotyping was performed by an experienced researcher who was blinded to subject data. The study was double blind with respect to the participants' genotype.

Statistical Analysis

A χ^2 test was used to determine whether the observed genotype frequency was in Hardy Weinberg equilibrium [expected frequency of alleles: ($p^2 + 2pq + q^2 = 1$), where p is the more common allele and q is the less common allele]. One way analysis of variance (ANOVA) via general linear modelling was used to test for baseline associations between $\dot{V}O_{2\ peak}$, peak power output, lactate threshold and quadriceps muscle strength and endurance. Repeated measures ANOVA (treatment x genotype) was performed to test for baseline differences in exercise tolerance between treatment groups. In order to account for differences in the dependent variables over the intervention period, the change in $\dot{V}O_{2\ peak}$, peak power output, lactate threshold and quadriceps muscle strength and endurance following each treatment was calculated for each subject. The mean change in those values was calculated for each exercise treatment in each genotype, and compared using repeated measures ANOVA with treatment/genotype interactions, adjusted for initial values. All analysis was

performed using Stata 9.2 (Statistical Data Analysis, StataCorp, College Station, Texas USA). Where significant interactions were identified for any of the measures, post hoc analyses were conducted using Holms test to locate the means that were significantly different. Data are expressed as means ± SD. A p value of less than 0.05 was considered significant. P values of less than 0.10 were considered to constitute a trend.

RESULTS

Participant Characteristics

Baseline characteristics of the participants are presented in Table 1. A χ^2 analysis indicated the genotype frequencies of the CHF patients were in Hardy-Weinberg equilibrium (p = 0.42). When separated according to genotype the three groups did not vary significantly in age, height, weight or body mass index (BMI). LVEF was different in patients randomized to the control group (p = 0.035) but not the training group. When separated according to the treatment group into which they had been randomised, there were no significant differences in any descriptive characteristic (Table 1).

Baseline Results

There was a strong correlation between peak power attained during the symptom-limited graded exercise test (PP; W) and peak aerobic power ($\dot{V}O_{2\ peak}$; $ml.kg.^{-1}min^{-1}$) in the participants at baseline (r = 0.854; p < 0.0001). There was a significant association between baseline PP and ACE genotype (Table 2) with higher PP in II than DD (p = 0.003) patients and a trend towards higher PP in II than ID (p = 0.07) patients. Associated with this, there was also a higher baseline $\dot{V}O_{2\ peak}$ in II

than DD patients (p = 0.02), with only a trend towards higher $\dot{V}O_{2\ peak}$ in II than ID genotype patients (p = 0.09). There were no differences in either PP (p = 0.28) or $\dot{V}O_{2\ peak}$ (p = 0.44) in ID compared to DD genotype patients. No differences between the genotypes were observed in peak RER or the workloads at which lactate threshold occurred (Table 2). There was no relationship between ACE genotype and either quadriceps muscle strength or endurance in the CHF patients at baseline. Post hoc testing revealed no differences between groups randomised to either exercise or the control protocol in any measure of exercise tolerance.

Response to Training

The resistance training protocol resulted in significant improvements in $\dot{V}O_{2\ peak}$ and in muscle strength and endurance when the effect of training was examined regardless of genotype (9). However, significant differences were noted between genotypes in the response to 11 weeks of resistance training and the control intervention. After accounting for differences between the genotypes at baseline, resistance training was observed to result in significantly greater increases in PP in patients with the D allele (ID and DD), compared to those who were homozygous for the I allele (Table 3). Resistance training also resulted in significantly greater increases in peak RER in heterozygotes (ID) compared to either homozygote (II and DD) group (Table3). No effect of genotype was observed for changes in $\dot{V}O_{2\ peak,}$ lactate threshold or muscular strength or endurance. In those randomised to the resistance training protocol there were significantly greater PP increases in patients with the D allele who were randomised to resistance training compared to those randomised to the non-training control group (ID p = 0.007; DD p = 0.001). In

contrast, patients in the resistance training group with the II genotype actually had a reduction in PP over the intervention, compared to the control group (p = 0.023; Table 3). No statistically significant genotype-dependent responses to either resistance training or the control protocol were observed in peak RER, quadriceps strength or endurance, or the power output at which lactate threshold occurred (Table 3). Due to a phenotypic distribution consistent with a dominant effect of the D allele, the data for all variables was reanalysed after accounting for baseline differences on the basis of the presence (ID and DD) or absence (II) of the D allele. In this analysis the changes observed in PP remained significant (p<0.001), however there was no significant effect for $\dot{V}O_{2\ peak}$ (p=0.146), peak RER (p=0.316), lactate threshold (p=0.585) or muscular strength (p=0.649) or endurance (p=0.215).

DISCUSSION

Major Findings

The main findings of the present study were that heart failure patients with the D allele have significantly lower peak power, measured on a graded exercise test, and that this can be reversed by a programme of resistance training. Moderate intensity resistance training resulted in greater improvements in PP in patients with the ID and DD genotypes compared to those with the II genotype, after controlling for the baseline PP level, indicating that the resistance training intervention preferentially improved physical function in patients with the D allele. While peak RER was significantly increased following training in the heterozygote group compared to both homozygote groups there was no trend for RER to change in response to training across the genotypes. However despite the changes that were observed in PP following the training intervention, no significant genotype dependent response to the

training intervention was seen in any of the other measured indicators of cardiovascular ($\dot{V}O_{2\ peak}$ and lactate threshold) or muscle (strength and endurance) function.

Effect of training on physical function

The genotype dependent changes in PP in response to the resistance training intervention that we observed in heart failure patients is in keeping with those of previous studies of healthy volunteers, which indicate that individuals with the D allele may be better suited to resistance or power type exercise than those homozygous for the I allele (16, 17). It might be tempting to suggest that the changes in peak RER were responsible for the changes in PP. However while peak RER was significantly increased following training in the heterozygote ID group compared to both homozygote (II & DD) groups there was no trend for RER to change in response to training across the genotypes and thus this does not provide a feasible rationale for the changes in PP. When baseline values were taken into account there were no genotype dependent differences in the response of $\dot{V}O_{2\ peak,}$ lactate threshold, or muscle strength or endurance to this resistance training protocol. Despite the lack of significant changes in these variables, the mean results indicate that there was a tendency for those with the D allele to demonstrate greater relative improvements in $\dot{V}O_{2\ peak}$ and quadriceps muscle endurance than patients with the I allele (Table 3) which provides a potential explanation for the increases observed in PP in patients with the D allele following the training intervention. Several potential mechanisms may assist in explaining these results.

One mechanism of potential relevance in CHF is the role of hormonal activation in increasing peripheral resistance, resulting in worsening ventricular function and further hormonal activation. Patients with the D allele may be subject to a higher degree of hormonally-induced increases in peripheral resistance due to elevated levels of ACE. This might explain the lower baseline $\dot{V}O_{2\ peak}$ and PP that was observed in patients with the D allele. Exercise training, which can reduce the neurohormonal upregulation in CHF patients (25), could thus be of greater benefit in patients with the D allele.

Changes in the regulation of bradykinin may also have a role in the genotype-dependent changes in PP. D allele incidence has been linked to a higher rate of bradykinin degradation (26) while chronic exercise training has been observed to result in increases in sensitivity to bradykinin in the brachial arteries of swine *in vitro* (27). If this phenomenon were to occur in human vasculature in response to exercise training, it may partially account for the difference in PP noted in patients with the D allele compared to those homozygous for the I allele. The expected functional result of an elevation in circulating bradykinin after training would be increased skeletal muscle perfusion during exercise, and hence a delayed onset of lactic acidosis and fatigue. CHF patients display elevated peak lactates during exercise following a resistance training intervention compared to baseline results (21). This result in itself may be indicative of increased muscle blood flow, allowing a greater flux of lactate from the cells into the bloodstream for full removal. However, while the mean power output at which lactate threshold occurred changed by more in the training group than the control group in the current study, the changes were not significant, nor were they genotype-dependent (Table 3).

A possible mechanism for greater improvements in muscle strength in those with the D allele involves the potential role of angiotensin II. Angiotensin II is a mediator of the hypertrophic response to mechanical loading in rodent muscle (28, 29) . The potential synergistic actions of angiotensin II in combination with mechanical loading provides a mechanism by which the previously observed (16, 17) greater increases in strength following resistance training in subjects with the D allele may have occurred.

Study Limitations.

A limitation of the current study and possible reason for the lack of genotype-dependent changes in strength or $\dot{V}O_{2\ peak}$ is that all patients were taking ACE inhibitors (ACEi) or Angiotensin II receptor blockade (ARB) medications or both, these being equally spread between the randomised groups and between ACE genotypes for each group (Table 1). Recently McNamara and colleagues (30) have reported that heart failure patients who are homozygous for the D allele appear to benefit more from high doses of ACEi than those from either the II or ID genotypes. Any such dose related issues in the current study would likely have further reduced circulating angiotensin II potentially attenuating muscle hypertrophy and limiting ACE genotype initiated vasodilatation during exercise. Consequently it is possible that the medications taken by patients in the current study and the doses of these medications were responsible for the lack of genotype-dependent changes in muscle strength and $\dot{V}O_{2\ peak}$ in response to training. Nevertheless the genotype dependent changes in peak power with training indicate a potential role for genotype dependent exercise prescription.

Another potential limitation is that only five females participated in the current study (3 in the training group and 2 in the control group) therefore the relevance of the findings of the current study to females needs to be investigated further. Finally, whilst the genotype-dependent difference in PP in response to the exercise training needs to be interpreted with caution due to the small number of participants, the relationships that have been identified support the need for further investigation.

CONCLUSION

This study investigated the effect of ACE genotype on the response to moderate intensity resistance training in a group of CHF patients. The main finding was that patients with the D allele displayed greater improvements in peak power as a result of the training. This suggests a possible physiological role for the renin-angiotensin system in the training of CHF patients. If similar results are observed in future studies, determination of ACE genotype might allow CHF patients to be prescribed forms of exercise that more specifically rectify their particular functional limitation.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (31).

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Table 1. Descriptive statistics of subjects who underwent 11-weeks of resistance training (A) or continued normal daily activities (B) according to ACE genotype (Mean ± SD).

	ACE Genotype		
	II	**ID**	**DD**
A			
N	4 (21.1%)	10 (52.6%)	5 (26.3%)
Gender (M,F)	4,0	8,2	4,1
Age (yr)	66 ± 10	64 ± 13	63 ± 4
Height (m)	1.75 ± 0.06	1.70 ± 0.09	1.68 ± 0.09
Weight (kg)	75.4 ± 15.6	86.0 ± 15.8	74.2 ± 6.3
BMI ($kg.m^{-2}$)	24.7 ± 5.4	29.8 ± 5.4	26.4 ± 3.8
NYHA Functional Class 2/3	2/2	7/3	4/1
Etiology (Ischemic/Dilated Cardiomyopathy)	4/0	6/4	2/3
LVEF (%)	30 ± 8	28 ± 9	27 ± 7
ACE_i	3	9	4
ARB	2	1	1
β-Blockers	0	6	2
B			
N	4 (22.2%)	8 (44.4%)	6 (33.3%)
Gender (M,F)	4,0	8,0	4,2

Age (yr)	70 ± 6	61 ± 8	67 ± 12
Height (m)	1.71± 0.08	1.72 ± 0.08	1.70 ± 0.05
Weight (kg)	75.8 ± 7.8	82.4 ± 7.6	86.2 ± 21.6
BMI ($kg.m^{-2}$)	26.1 ± 3.2	27.8 ± 2.5	29.8 ± 7.8
NYHA Functional Class 2/3	3/1	5/3	6/0
Etiology (Ischemic/Dilated Cardiomyopathy)	2/2	7/1	5/1
LVEF (%)	27 ± 8	24 ± 6	33 ± 7*
ACE_i	4	8	4
ARB	0	0	4
β-Blockers	2	3	2

* P<0.05 compared to ID. BMI = Body mass index; NYHA = New York Heart Association; LVEF = Left ventricular ejection fraction; ACE_i = Angiotensin Converting Enzyme Inhibitors; ARB = Angiotensin Receptor Blockaders.

Table 2. The effects of ACE genotype on indices of physical performance in all participants at baseline (Mean ± SD)

Performance Results	**ACE Genotype**		
	II (n = 8)	**ID (n = 18)**	**DD (n = 11)**
Peak Power (W)	84 ± 14	69 ± 28	60 ± 20*
$\dot{V}O_{2\ peak}$ (ml.kg^{-1}.min^{-1})	19.4 ± 4.3	16.2 ± 5.5	14.9 ± 3.4*
Peak RER	1.25 ± 0.15	1.12 ± 0.13	1.16 ± 0.16
Lactate Threshold (W)	30.8 ± 6.6	30.7 ± 9.9	26.9 + 7.2
Quadriceps Strength (Nm)	107 ± 33	113 ± 34	114 ± 33
Quadriceps Endurance (J)	955 ± 400	1150 ± 442	1167 ± 426

RER denotes Respiratory Exchange Ratio (VCO_2/VO_2); *P < 0.05 compared to II.

Table 3. Comparison of mean change in parameters of exercise capacity and muscle strength following 11 weeks of resistance training (Exercise) or continued normal activity (Control)

	Exercise	Control	Comparison[1]		
Genotype	Mean ± SD	Mean ± SD	Difference	95% CI	P-value[2]
	Peak Power (W)				
II	-14 ± 4*	2 ± 8	16	(3.9 to 27.9)	
ID	18 ± 8*	- 5 ± 22	- 23	(-43.1 to -3.8)	<0.001
DD	18 ± 5*	- 1 ± 14	- 19	(-35.4 to -3.2)	<0.001
	$\dot{V}O_{2\ peak}$ (ml/kg/min)				
II	-1.0 ± 1.3	-2.4 ± 1.3	-1.4	(-3.30 to 0.62)	
ID	1.3 ± 2.3	-2.1 ± 2.9	-3.4	(-6.55 to -0.24)	0.202
DD	1.6 ± 0.7	-1.9 ± 3.2	-3.5	(-6.43 to -0.49)	0.322
	Peak RER				
II	-0.05 ± 0.08	0.12 ± 0.16	0.17	(0.02 to 0.32)	
ID	0.11 ± 0.13	0.05 ± 0.15	-0.07	(-0.25 to 0.12)	0.027
DD	-0.02 ± 0.13	0.05 ± 0.15	0.08	(-0.15 to 0.31)	0.426
	Lactate Threshold (W)				
II	8.0 ± 1.8	2.0 ± 0.8	-6.0	(-17.9 to 6.0)	
ID	12.4 ± 10.1	3.9 ± 6.2	-8.5	(-23.8 to 6.7)	0.736
DD	10.3 ± 3.7	-0.5 ± 2.2	-10.8	(-25.3 to 3.7)	1.000
	Quadriceps Strength (Nm)				

II	12 ± 12	- 1 ± 7	-13	(-29.2 to 3.3)	
ID	5 ± 16	3 ± 18	- 2	(-23.2 to 18.9)	0.630
DD	20 ± 19	- 2 ± 13	- 22	(-47.4 to 3.4)	0.485
	Quadriceps Endurance (J)				
II	68 ± 195	58 ± 205	- 10	(-275 to 255)	
ID	113 ± 175	- 52 ± 212	- 165	(-476 to 146)	0.330
DD	159 ± 323	- 94 ± 143	- 253	(-621 to 115)	0.393

[1] Estimated by repeated measures ANOVA, adjusted for initial exercise performance parameter values

[2] P-values corrected for multiple comparisons by the Holm method

RER denotes Respiratory Exchange Ratio (VCO_2/VO_2); * $p < 0.05$ for exercise training compared to control