



Short-term isometric exercise reduces systolic blood pressure in hypertensive adults: Possible role of reactive oxygen species (R1)

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Abstract

Objective: A short-term isometric exercise protocol was tested in ten hypertensive individuals to determine its efficacy as a high blood pressure-reducing intervention.

Design: The study was a prospective case study of 10 hypertensive individuals (8 men, 2 woman, mean age=52+5 years) who underwent six weeks of isometric exercise training (three sessions/week).

Methods: Blood pressure, blood lipids and markers of oxidative stress were monitored before, during and following the isometric intervention. Electron spin resonance spectroscopy was used to directly measure radicals in the blood samples.

Results: After six weeks, systolic blood pressure decreased an average 13 mm Hg ($p < 0.05$) from a mean blood pressure of 146 to 133 mmHg, a level that is below the usual 140 mmHg hypertension threshold. Blood lipids were unchanged, but markers of oxidative stress were affected, with a dramatic decrease in exercise-induced oxygen centered radicals (-266%), ($p < 0.05$) and an increased resting whole blood glutathione:oxidized glutathione ($+61\%$) in hypertensive adults following six weeks of isometric exercise.

Conclusion: Six weeks of isometric exercise training was effective in lowering systolic but not diastolic blood pressure in pre-hypertensive and hypertensive individuals, and enhanced antioxidant protection is a likely underlying mechanism.

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1. Introduction

High blood pressure is one of the leading causes of death in developed countries [1]. Causes of hypertension include heart dysfunction resulting in abnormal systolic pressure (most frequent cause in younger patients), increased vascular resistance (predominant adult cause) or increased blood volume [2]. The cause of 90–95% of all hypertension

cases is unknown. Hypertension has traditionally been defined as systolic blood pressure (SBP) of 140 mm Hg and/or a diastolic pressure (DBP) of 90 mm Hg, or higher. Individuals with SBP=120–139 mm Hg or DBP=80–89 mm Hg are now considered to be pre-hypertensive and require a health intervention [3].

The majority of diagnosed hypertensive patients use medication, such as angiotensin II inhibitors, beta-blockers, or calcium channel blockers, to reduce blood pressure [4]. Although medications lower blood pressure, long-term medication regimens can lead to deleterious side effects. One widely studied alternative intervention found to be effective, is aerobic exercise (e.g. jogging, biking, swim-

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ming) [5,6]. Despite the success of aerobic exercise in reducing blood pressure, most studies show that 50% of adults who begin an aerobic exercise program drop out within 3–6 months and fewer than 20% continue exercising after 24 months [7].

This study investigates an isometric exercise intervention, which utilizes isometric exercise training (IET) to lower blood pressure. An IET protocol has been developed for the CardioGrip® handgrip dynamometer (MD Systems, Inc., Westerville, OH), which requires only 10 min per day, three days per week, for a minimum of six weeks [8]. Minimal time, ease of performance, and no known side effects may contribute to increased adherence to IET compared with dynamic aerobic exercise programs. While many studies have shown benefits of dynamic exercise in reducing hypertension, [9], not all studies concur [10] and point to individual variability, different starting blood pressure levels, and adherence problems to explain disparate findings in the blood pressure-lowering effects associated with dynamic exercise.

One of the first published studies that investigated blood pressure responses to isometric exercise found that whole body isometric contractions reduced blood pressure [11]. Over ten years later, Buck and Donner [12] described an inverse relation between the incidence of hypertension and the amount of isometric exercise associated with various occupations. In a controlled study, approximately ten years later, Wiley et al. [8] described a significant decrease in blood pressure in hypertensives following four 2-min handgrip contractions at 30% of one's maximum voluntary contraction, interspersed with 3-min rest intervals, performed 3 days per week for 8 weeks. When these subjects ceased performing isometric exercise, their blood pressures returned to the original hypertensive levels. Ten years after Wiley's study, another study by Taylor et al. [13] reported that isometric exercise lowered resting blood pressure in hypertensives. Taylor et al. reported that hypertensive adults who performed isometric handgrip training at moderate intensity, which was 30% of maximum voluntary contraction (MVC), reported a mean 13.8% decrease in SBP. This decrease in SBP was accompanied by an increase in vagal tone and decrease in sympathetic tone. The redox state is known to regulate blood vessel tone and pressure via thiol cycling that conveys a variety of vasodilatory and constrictive agents to the blood vessel wall. Pro and antioxidant activities associated with oxidative stress may be a mechanism by which isometric exercise influences blood pressure.

The purpose of this study was to pilot the CardioGrip® handgrip dynamometer in a small, controlled case study, where pre-hypertensive and hypertensive individuals followed a standard IET protocol for 6 weeks to lower blood pressure. Known mediators of blood pressure: blood lipids and markers of oxidative stress, were evaluated before and after the IET intervention.

2. Methods

Ten hypertensive individuals were recruited from a local Midwestern (U.S.A.) community (Table 1). Miami University's Institutional Review Board approved the study design and all subjects provided informed consent. The subjects had elevated blood pressure for at least six months and were considering blood pressure intervention options. They had their physician's approval to participate in this exercise study.

No subjects were accepted that were currently taking prescribed heart or vasculature medication. During a three-week preliminary screening, blood pressure measurements were taken while subjects were seated, two or three times per week, between 0900 and 1100 to determine eligibility in the study. A 10-min quiet rest period was followed by two blood pressure readings with a 5-min rest in between. When a determination for inclusion was made, those subjects returned to the lab for two weeks of pre-exercise training blood pressure measurements at a similar time of day, in a seated position and with two measurements 5 min apart. A significant change in blood pressure in either direction prior to the exercise intervention was grounds for exclusion. No subjects were excluded due to changes in resting blood pressure prior to IET. During the five weeks prior to IET, blood pressure was monitored. This data served as a reference control for comparison with blood pressure measurements taken during and following six weeks of IET. All subjects were required to maintain regular food intake and not change their level of physical activity other than the IET for the six-week study. They were required to refrain from physical exercise for 24 h prior to coming the lab for blood pressure and exercise testing. No subjects indicated that they were highly trained, which was confirmed by a submaximal graded exercise test. One trained technician, who was blinded to the study, performed all measurements. Standard practices for blood pressure measurement, as reported by Kirkendall et al. [14], were followed. Rate of deflation of the cuff followed the recommended 2 mm Hg per second. Requirements for inclusion were three pre-training measurements of blood pressure falling within the range of 130/85–160/100 mm Hg, with a coefficient of variation <5%. This range places individuals in a pre-hypertensive to hypertensive range—both of which require a blood pressure-lowering intervention [3].

Body fat was estimated by bioelectrical impedance with a body fat analyzer (Body Logic Pro Omron Healthcare Inc., Vernon Hills, IL, Model HBF-300). Subjects served as their

Table 1
Description of subjects (Mean±SEM)

Gender (number)	Age (years)	Body weight (kg)	Body fat (%)	Body mass index	VO ₂ max (ml kg ⁻¹ min ⁻¹)	
Males						
Females						
8	2	52±5.0	79.4±5.0	29.6±2.5	26±1.0	27.8±2.8

own control in this six-week pre-test/post-test design. In previous studies [8,13] in our laboratory, no change in blood pressure occurred in a control group of hypertensives that did not follow an IET. Because of this and the high cost of the blood analyses, comparisons were made with the subjects' own baseline levels serving as the control. The YMCA 12-min graded exercise stress test [15] was administered pre-IET and following six weeks of IET. This protocol includes up to four consecutive 3-min workloads on a bicycle ergometer starting at 1 kg and increasing by either 0.5 or 1 kg depending on the exercise heart rate response. Subjects' heart rates were monitored by a Quinton ECG instrument using standard limb leads, and compared to workload. The slope of the line depicting the heart rate response to the last two workloads was used to estimate maximum oxygen uptake (VO_2 max). Mean estimated VO_2 max values were $27.8 \pm 2.8 \text{ ml kg}^{-1} \text{ min}^{-1}$ pre-IET and $30.7 \pm 3.9 \text{ ml kg}^{-1} \text{ min}^{-1}$ post-six weeks IET. The percent difference between the two tests was approximately 10%, but did not reach statistical significance, indicating a similar workload was performed both times and that six weeks of IET did not increase VO_2 max.

IET occurred at the laboratory under supervision of a trained laboratory assistant so that the proper protocol was followed. It consisted of three brief (<20 min) sessions per week for six weeks using the CardioGrip[®] handgrip dynamometer. MVC was determined for both hands. Exercise consisted of four 45-s contractions, two with each hand, at 50% MVC, with 1-min rest between contractions. Effort was recorded by the exercise device, storing a score of accuracy of tracking on target, which provided a gauge of subject effort in pounds.

Each subject had a resting and post-submaximal dynamic exercise blood sample [8–10 ml] drawn from an antecubital vein before and after six weeks of IET. Whole blood glutathione (GSH) and oxidized glutathione (GSSG) were determined via spectrophotometric kinetic assays [16] using the GSH trap M2VP (Oxis International, Inc., Portland, Ore., USA). Blood lactate, a measure of relative exercise intensity, was determined via lactate dehydrogenase [17]. Whole blood samples (35 μl) were analyzed using solid-phase and enzymatic methods to measure total cholesterol, high-density lipoproteins (HDL), total triglycerides (TG) and glucose on a Cholestech LDX Analyzer (Cholestech Corporation, Model # 10-004, Hayward, CA). Low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) levels were calculated from the direct measurement of total cholesterol and HDL [18].

Plasma samples were analyzed for malonaldehyde using a kit from Calbiochem-Novabiochem Corp. (La Jolla, Calif., USA). Ascorbic acid was measured on the same day as the blood collection with reverse phase-high pressure liquid chromatography using Ultra Violet detection [19]. Plasma oxygen radical absorbance capacity (ORAC) was measured using a fluorescent protein (β -phycoerythrin) marker [20]. Nitrogen oxide levels in plasma were measured as nitrite,

after enzymatic conversion [21]. Reactive oxygen species (ROS) was measured by electron spin resonance spectroscopy (ESR) spectra collected in plasma obtained from whole blood samples treated with the spin trap α -phenyl-*tert*-butylnitron [22]. Bio-Rad (Hercules, Calif., USA) protein assay was used for total protein. InStat 2.02 was used to conduct paired analysis of variance (ANOVA) tests with Bonferroni multiple comparisons post hoc tests. A significance level of 95% was set (p -value<0.05).

3. Results

All ten individuals completed five weeks of preliminary blood pressure measurements and six weeks of IET and complied with instructions on maintaining their usual diet and level of physical activity (Table 1). Blood pressure measurements were stable in all subjects prior to IET, with a coefficient of variation <2%. Mean predicted VO_2 max did not change following 6 weeks of IET. Pre-IET mean SBP/DBP was $146 \pm 11/90 \pm 7$ mm Hg and mean post-IET SBP/DBP was $133 \pm 14/88 \pm 11$ mm Hg. Changes over six weeks were as follows: SBP: -9.7% ($p=.004$), DBP: -2.3% , mean arterial pressure: -5.5% (Figs. 1 and 2). Nine out of ten individuals had lower SBP after six weeks IET, with the reduction ranging between 2.8 and 14.5 mm Hg.

The intensity of aerobic exercise performed on the bicycle ergometer according to the YMCA protocol resulted in elevated blood lactate pre- (1.12 ± 0.14 to 2.67 ± 0.92 mMol) and post-IET (0.64 ± 0.08 to 5.52 ± 1.4 mMol). Aerobic exercise also induced prooxidant and antioxidant activities before and after six weeks of IET. Systolic ROS, as detected by ESR, increased 132% ($p<0.05$) following aerobic exercise in hypertensives. Following six weeks of

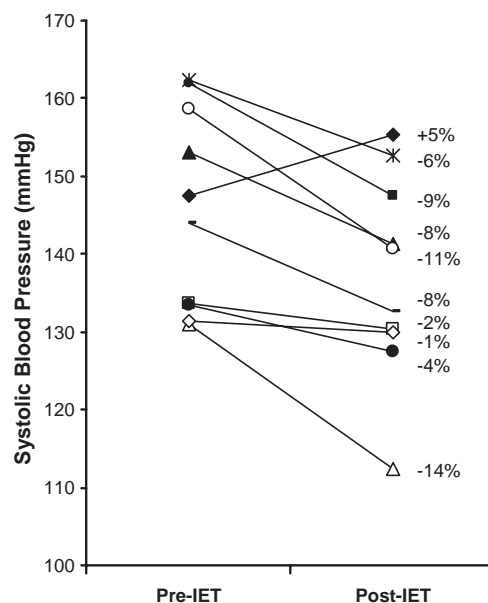


Fig. 1. Individual resting systolic blood pressure values before and after 6 weeks of IET.

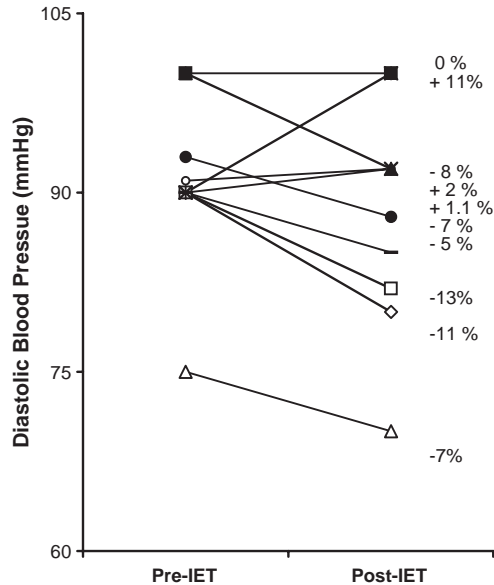


Fig. 2. Individual resting diastolic blood pressure values before and after 6 weeks of IET.

IET, resting ROS levels were similar, but the post-exercise ROS were only 36% higher than resting levels ($p=0.25$) (Fig. 3). Hyperfine coupling constants recorded from the ESR spectra were: a_N 13.80 G and a_H 2.76 G, which are in agreement with previously published results indicating the presence of secondary lipid-derived oxygen-centered radicals such as alkoxy radicals [22]. Additionally a secondary two-line signal was observed in 10% of the samples with a splitting factor of almost 80 G. This signal is attributed to a copper-containing molecule such as caeruloplasmin, which might be released due to muscular contraction during exercise. Resting GSH:GSSG levels increased 61%

($p<0.05$) following IET indicating a shift towards more antioxidant protection. Shifts in other oxidative stress biomarkers and in blood lipids did not reach statistical significance (Tables 2 and 3). Systolic but not diastolic blood pressure increased in a similar way following aerobic and isometric exercise (Fig. 4). Heart rate response to exercise was also similar following aerobic and isometric exercise (Fig. 5).

4. Discussion

Nine of ten pre-hypertensive and hypertensive individuals lowered their resting SBP following six weeks of IET. It is noteworthy that pre-IET mean SBP was 146 mm Hg and post-IET mean SBP was 133 mm Hg, which is below the hypertensive benchmark of 140 mm Hg and close to recent goals of 130 mm Hg or less [3]. This change occurred only following IET. Prior to IET, individual blood pressure measurements varied less than 2%, indicating reliability and confirming that the subsequent decrease in blood pressure was likely due to the IET and not other aspects involved with the study (e.g. visits to the laboratory, regular monitoring, etc.). Changes observed in mean SBP in hypertensives in this study are similar to those reported previously [8,13]. Since elevated markers of oxidative stress have been associated with ventricular function [23] and described in hypertensive patients [6,14], we investigated oxidative stress as a potential mediator in blood pressure change in hypertensives as a result of IET.

Many studies have reported reduced blood pressure following 8–12 weeks of dynamic exercise [9]. The mechanisms of blood pressure-lowering effects associated with dynamic exercise include weight loss, a post-exercise

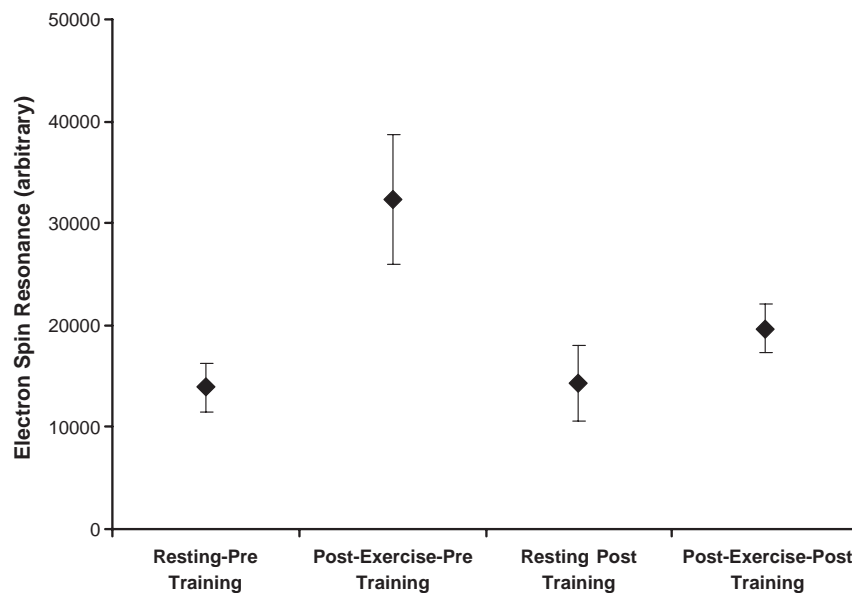


Fig. 3. ESR signal before and after isometric exercise training and aerobic exercise. The spin trapped radical species in whole blood were quantitated by determining the double integral of the signal in arbitrary units. Bars indicate means with SEM for 10 individuals.

Table 2

Biomarkers of oxidative stress in hypertensive subjects pre- and post-isometric exercise training (IET) at rest and after exercise

Biomarker	Pre-IET	Pre-IET	Post-IET	Post-IET
	Rest	Exercise	Rest	Exercise
Ascorbic acid (μM)	24.8 \pm 3.0	24.8 \pm 3.3	26.0 \pm 2.5	26.1 \pm 2.6
Orac (μM)	1150.5 \pm 127.2	1321.7 \pm 135.8	1271.4 \pm 131.5	1241.9 \pm 129.9
GSH/GSSG	19.1 \pm 5.6	24.4 \pm 4.3	30.7 \pm 5.0*	23.44 \pm 2.3
Nitrate/nitrite (μM)	4.63 \pm 0.5	4.05 \pm 0.4	4.04 \pm 0.7	3.77 \pm 0.7
Lipox/protein ($\mu\text{M}/\text{mg}/\text{ml}$)	0.208 \pm 0.04	0.152 \pm 0.04	0.253 \pm 0.06	0.268 \pm 0.08

Mean values \pm SEM.* $p < 0.05$ between pre and post-resting samples.

decrease in stroke volume and cardiac output, total peripheral resistance, muscle sympathetic nerve discharge, altered baroreceptor reflex circulatory control, reduced vascular responsiveness to alpha-adrenergic receptor-mediated stimulation, and activation of endogenous opioid and serotonergic systems [24]. Decreased tonic sympathetic nerve activity produced by exercise training is also considered as a possible mechanism involved in the attenuation of hypertension induced by exercise [25]. While many studies have shown benefits of dynamic exercise in reducing hypertension, not all studies concur [10] and point to individual variability, different starting and ending blood pressures, and adherence problems to explain disparate findings in blood pressure-lowering effects associated with dynamic exercise.

The underlying mechanisms for how IET lowers blood pressure are not well understood. Taylor et al. [13] elucidated a mechanism that may have contributed to the hypotensive effect of isometric exercise training related to changes in autonomic nervous system activity. They reported a decreased sympathetic and an increased vagal activity based upon power spectral analyses of low and high frequency components of heart rate variability. They concluded that changes in autonomic function towards vagal control explain part of the isometric exercise-blood pressure link.

Another possible underlying mechanism for reducing blood pressure following isometric exercise is that ischemia-reperfusion, which occurs during isometric contractions, may mediate oxidative stress related to the dramatic change from low oxygen levels during ischemia to high oxygen levels during reperfusion. Santangelo et al. [26] reported elevated antioxidant activity in response to ischemia-

reperfusion and antioxidants were thought to prevent or limit damage to blood vessels from the combined pressure changes and oxygen exposure. Markers of oxidative stress in blood measured in the present study include prooxidants: ROS using ESR, oxidized glutathione, and malonaldehyde (marker of lipid peroxidation). Markers of antioxidants include: glutathione, ascorbic acid, and oxygen radical absorbance capacity. Finally, another possible mechanism for IET-lowering of blood pressure is increased shear stress during the isometric effort due to increased blood pressure and cardiac output [27], which would result in an increased systemic shear stress. In addition there would be an increased shear stress with enormous reactive hyperemia following release of the handgrip contraction. This may activate endothelial nitric oxide release, causing vaso-relaxation [6]. In this study, blood nitrate and nitrite levels ranged from 3.77 to 4.60 μM pre- and post-IET and did not differ due to either exercise training or acute exercise.

Prior to and following six weeks of IET, all subjects completed a submaximal graded exercise test on a bicycle ergometer. Test–retest comparison showed similar efforts and no change in endurance capacity following IET. During the first aerobic exercise test ROS significantly increased (+132%), indicating a significant exercise-induced oxidative stress. When the same test was administered after six weeks of IET, exercise-induced ROS was dramatically attenuated and not significantly different (+36%) than resting ROS. This demonstrates an adaptation, possibly an upregulation of antioxidant activity or a reduced production of ROS following IET. This adaptation may contribute to prevention

Table 3

Blood lipids stress in hypertensive subjects pre- and post-isometric exercise training (IET) at rest and after exercise

Biomarker	Pre-IET	Post-IET
	Rest	Rest
Triglycerides (mg/dL)	131.0 \pm 16.8	153.5 \pm 26.9
Total cholesterol (mg/dL)	241.2 \pm 9.9	228.1 \pm 17.3
HDL (mg/dL)	62.8 \pm 5.5	54.6 \pm 4.5
LDL (mg/dL)	152.1 \pm 11.0	142.4 \pm 18.2
TC/HDL	4.2 \pm 0.4	4.5 \pm 0.5

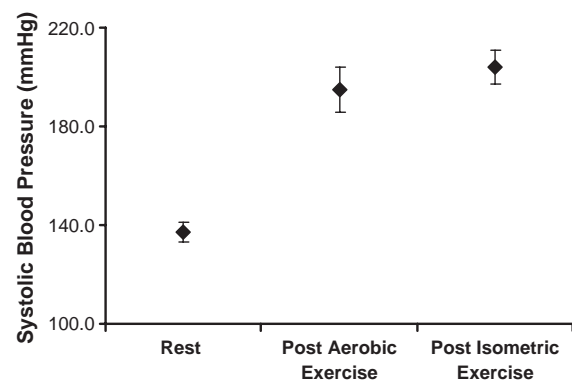
Mean values \pm SEM.

Fig. 4. Systolic blood pressure at rest and following aerobic and isometric exercise.

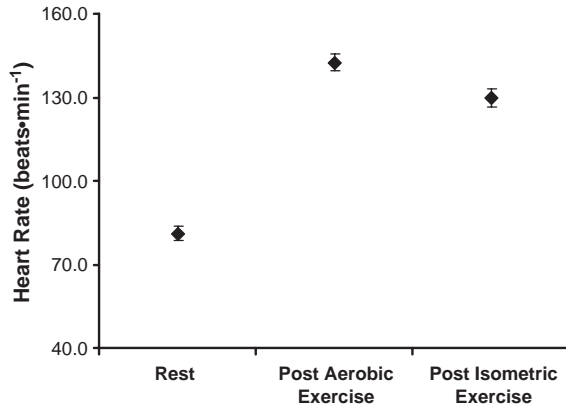


Fig. 5. Heart rate at rest and following aerobic and isometric exercise.

of oxidative stress and possibly play a mediating role in blood pressure regulation by decreasing the potential for oxidized lipids, proteins, and other molecules by superoxide radicals and ROS.

The importance of oxidative chemistry in the response to IET was also suggested by the changes noted in GSH and GSSG (Table 2). Resting GSH:GSSG levels were elevated following six weeks of IET ($p < 0.05$). There was no change in GSH:GSSG following exercise when the subjects were hypertensive (i.e. before IET). However, following six weeks of IET resting GSH:GSSG ratio increased 61%. GSH:GSSG decreased 24% following acute exercise indicating that basal levels of GSH were adequate to reduce ROS and implying that GSH was effectively oxidized to GSSG following exercise. Increased resting GSH:GSSG ratio suggests elevated antioxidant protection, which may have contributed to the lower exercise-induced ROS following IET. That resting levels of GSH:GSSG increased following IET despite no change in resting radical signals, implies a low level of radical activity involved in normal cell signaling. Nevertheless, not all markers of oxidative stress changed as a result of either aerobic exercise or IET. For example, specific measures of oxidative stress such as ascorbic acid, nitrate/nitrite, and malonaldehyde did not change over all four measurements.

A general index of antioxidant action, ORAC, also was not affected by either acute aerobic exercise or IET. The thiol ratio, GSH:GSSG, for rested individuals increased 61% following six weeks of IET, potentially providing more protection for exercise-induced oxidative stress. Following exercise, GSH:GSSG decreased 24%. The source of the extremely high ESR radical signal that appeared following aerobic exercise prior to the six week IET protocol is not clear. We do not know whether the signal resulted from increased prooxidant or attenuated antioxidant activity in the hypertensive group before the IET. There is a general agreement that regardless of the mechanism, oxidative stress is associated with cardiovascular complications. One mechanism by which oxidative stress may affect blood pressure is by the delivery or impediment of vasodilatory and vaso-

constrictive substances (e.g. oxidized low density lipoproteins and nitric oxide) to the blood vessel wall. Six weeks of IET appeared to reduce oxidative stress as indicated by the remarkably lower ESR signal immediately following aerobic exercise.

Our study is similar to previous studies [8,11] in which control groups showed no change in blood pressure while a group that performed IET had improved blood pressure. We ruled out the likelihood that a placebo effect may have contributed to lower blood pressure by having subjects serve as their own control and monitoring their blood pressure for five weeks prior to IET. No differences in SBP or DBP occurred prior to IET while six weeks of IET resulted in a mean decrease of nearly 10% in SBP and no significant change in DBP. There was more variability in DBP compared with SBP following IET. It is not clear why SBP but not DBP decreased in virtually all subjects following six weeks of IET or why a change in the redox environment would affect one but not the other. DBP has a smaller range compared with SBP and it is possible that changes in DBP are difficult to quantify by standard non-invasive blood pressure cuff measurements, and that small changes in DBP may have a notable impact on overall mean arterial pressure. The small number of subjects may limit the ability to generalize our results and a larger subject pool may show significant differences in DBP if the variability stays low and small changes are seen in most subjects. Results of the current study show that the reduced systolic blood pressure was accompanied by increased GSH:GSSG and dramatically lower exercise-induced ROS which suggest that six weeks of IET protected against oxidative stress both at rest and following exercise.

The influence of IET on lipid profile is not clearly understood [28,29,30]. In the present study, total cholesterol and LDL levels tended to decrease, triglycerides tended to increase (+17%), but none reached significance, supporting others studies [29,31] (Table 3).

In summary, our results indicate that six weeks of IET was associated with a significant reduction in systolic but not diastolic blood pressure, putting the average SBP of hypertensive and pre-hypertensive individuals (mean=146 mm Hg) below the traditional hypertensive systolic threshold of 140 to 133 mm Hg. IET also was associated with an up-regulation of resting whole blood GSH:GSSG, and attenuated levels of exercise-induced ROS. We conclude that the IET protocol followed with the CardioGrip® handgrip dynamometer reduces SBP in hypertensives and one of the underlying mechanisms is a favorable change in oxidative stress.

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