Physical Exercise and Antioxidant Defenses in the Heart[a]

MUSTAFA ATALAY[b] AND CHANDAN K. SEN[b,c,d]

[b]*Department of Physiology, University of Kuopio, 70211 Kuopio, Finland*
[c] *Biological Technologies Section, Environmental Energies Technologies Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720-3200, USA*

ABSTRACT: Cardiac muscle relies highly on aerobic metabolism. Heart muscle has a high oxygen uptake at resting conditions, which increases many fold during exhaustive physical exercise. Such a high rate of oxidative metabolism is often associated with enhanced production of reactive oxygen metabolites. A single bout of strenuous exercise has been demonstrated to induce oxidative damage in heart. Such oxidant insult may lead to adaptive responses and strengthen antioxidant defenses in the heart tissue. Endurance exercise training has indeed been shown to upregulate heart tissue antioxidant defenses. Recently, we have observed that even predominantly anaerobic sprint training regimens may enhance cardiac antioxidant defenses. Regular physical exercise may beneficially influence cardiac antioxidant defenses and promote overall cardiac function.

INTRODUCTION

Cardiac muscle has unique aerobic metabolism characteristics. The ability to provide energy through anaerobic glycolysis is limited in this tissue. At rest, oxygen uptake per gram of heart muscle is more than the oxygen consumption of skeletal muscle during heavy physical exercise. During physical exercise coronary blood flow increases up to fourfold and heart muscle has remarkable ability to extract oxygen from blood.[1] While oxygen is essential for aerobic metabolism in the heart tissue, a heavy load of oxygen metabolism in the heart during physical exercise has been shown to be associated with enhanced production of partially reduced forms of oxygen and their reactive derivatives, collectively known as reactive oxygen species. Elevated levels of oxidative damage markers, which may be caused by various mechanisms as listed in TABLE 1, have been shown in the post-exercise heart tissue.[2–5]

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[d]Address correspondence to: Chandan K. Sen, Ph.D., Life Sciences Addition, Building 20A, Room 251C, Mail Stop 3200, University of California, Berkeley, California 94720-3200; Telephone: (510) 642-4445; Fax: (510) 644-2341; E-mail: cksen@socrates.berkeley.edu

TABLE 1. Possible mechanisms inducing oxidative stress in the exercising heart

Organelle/Tissue	Process/Site	Mechanism	Reference
Mitochondria	electron transport chain	univalent reduction of oxygen	32
Mitochondria/cystosol	xanthine oxidase	O_2 acts as an electron acceptor	41
Activated neutrophils	NADPH oxidase/ phagosomes	oxidative burst, myeloperoxidase	33
Endothelial cells Cardiac muscle Macrophages Neuromuscular junction	nitric oxide synthesis	peroxynitrate formation	34
Cardiac muscle	myoglobin	metmyoglobin production	35
Cardiac muscle Erythrocytes	any site hosting Fe/Cu	transition metals Fenton reaction	36

ACUTE EXERCISE

Acute physical exercise increases cardiac contractility and heart rate. Strenuous exercise may be associated with a fourfold increase in blood flow through and oxygen consumption by the myocardium.[1] A single bout of exhaustive treadmill running has been shown to decrease total glutathione levels in the heart without causing significant increase of lipid peroxidation and glutathione oxidation (TABLE 2). In contrast, Ohkuwa and colleagues[6] reported increased cardiac levels of reduced glutathione after one short bout of exercise in young rats. This increase in heart glutathione level was thought to be caused by enhanced hepatic glutathione efflux during exercise.[6] In this study hydroxyl radical formation, however, markedly increased in the heart of young physically active rats despite the elevated cardiac glutathione content.[6] Benderitter and colleagues[7] reported that swim exercise until exhaustion did not increase lipid peroxidation, but decreased vitamin E levels in heart tissue of rats swim-trained for 9 weeks. In a comparable study Frankiewicz-Jozko and colleagues[3] reported a significant increase of levels of thiobarbituric acid–reactive substances in heart tissue of untrained rats 3 h after exhaustive treadmill exercise, but no change of post-exercise thiobarbituric acid–reactive substances content was detected in animals treadmill-trained for 4 weeks. These studies suggest that training and the acute exercise may cause oxidative damage to lipids in the heart. Levels of 8-hydroxydeoxyguanosine (8-OH-dG), a DNA oxidative damage marker, have been shown to be increased following both spontaneous and forced exercise in rats. 8-OH-dG levels were twofold higher in forced-exercise groups than in spontaneous-exercise groups, indicating the importance of exercise intensity on oxidative DNA damage in the heart tissue.[5]

Somani and colleagues[8] studied the response of cardiac antioxidant enzymes in untrained rats and in rats endurance-trained for 10 weeks. Acute exercise induced activities of Mn-superoxide dismutase, catalase, and glutathione peroxidase in untrained rats. The potential protective role of glutathione against exercise-induced oxidative stress has been tested using a glutathione-deficient rat model.[9,10] In con-

TABLE 2. Effects of acute exercise on heart antioxidant defenses and lipid peroxidation

Investigator/ Reference	Model	Type of Exercise	Effect
Benderitter *et al.*[7]	Swim-trained rats	Exhaustive swim	MDA→
			Vit E↓
Frankiewicz *et al.*[3]	Untrained rats	Exhaustive run	MDA ↑(3 h after ex)
	Treadmill-trained rats		MDA →(0–48 h after ex)
Ji [38]	Untrained rats	Exhaustive run	SOD ↑(immediately after)
			CAT →
			GSHPx C
			GRD→
			SOD →(30 min after)
			CAT →
			GSHPx →
			GRD →
Leeuwenburgh *et al.*[11]	Untrained mice	Exhaustive swim	GSH ↓, GSSG ↓
			GSH/GSSG →
			SOD ↑, GGT →, CAT →
			GSHPx →, GRD →, GST →
Ohkuwa *et al.*[6]	Young, physically active rats	Short run	GSH ↑, GSSG →
			GSH/TGSH ↑
			$OH^{\bullet}$ formation ↑
	Old, physically active rats		GSH ↓, GSSG ↓
			GSH/TGSH ↑
			$OH^{\bullet -}$ formation ↑
Sen *et al.* [9]	Untrained rats	Exhaustive run	TGSH ↓
			GSSG/TGSH →
			MDA →
Somani *et al.*[8]	Untrained rats	Exhaustive run	Mn-SOD ↑↑
			CAT ↑↑
			GSHPx ↑↑
	Endurance-trained rats		Mn-SOD ↑
			CAT ↑
			GSHPx ↑
Venditti & Di Meo[4]	Untrained rats	Exhaustive swim	MDA ↑
			LHP ↑
	Trained rats		MDA ↑
			LHP ↑

NOTATION: ↑, increased; ↓, decreased; →, no change; SOD, total superoxide dismutase activity; CAT, catalase activity; GSHPx, glutathione peroxidase activity; GRD, glutathione disulfide reductase activity; GST, glutathione S-transferases activity; GGT, γ-glutamyl transpeptidase, activity; GCS, γ-glutamylcysteine synthetase activity; TGSH, total glutathione content; GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; LHP, lipid hydroperoxide; Vit E, vitamin E content; T. antioxidant capacity, total antioxidant capacity; EPR, electron paramagnetic resonance spectroscopy; C, cytosolic; M, mitochondrial; I-R, ischemia-reperfusion.

trast to the response in the glutathione-adequate control group, exercise did not cause any further significant decrease of cardiac total glutathione levels, but increased significantly oxidized glutathione/total glutathione ratio in the heart of glutathione-deficient rats.[9] Glutathione deficiency also increased basal lipid peroxidation levels.[9] Leeuwenburgh and colleagues[11] also tested the effects of endogenous glutathione in glutathione-deficient mice subjected to swim exercise. In this study, which had a different exercise regimen, acute exercise did not influence oxidized glutathione/total glutathione ratio in heart.[11] The role of exogenous glutathione as well as N-acetyl-L-cysteine, a pro-glutathione drug, in cardiac antioxidant defenses at rest and after exercise has been also tested. Supplemented glutathione was observed to be not readily available to the heart.[9] In another supplementation study Kumar and colleagues[12] reported that swim training for 2 months resulted in elevated levels of lipid peroxidation byproducts in the heart. Vitamin E supplementation was effective in decreasing training-induced lipid peroxidation perhaps by inhibiting lipoxygenase activity. In a more recent study we observed that 8 weeks of α-lipoic acid supplementation (150 mg/kg/day) protected against exercise-induced GSH depletion in heart tissue in rats.[13] Furthermore, compared to non-supplemented control rats, α-lipoic acid supplementation markedly decreased overall heart lipid peroxidation measured as thiobarbituric acid–reactive substances.[13]

TRAINING

Most studies investigating the influence of physical training on tissue antioxidant status have tested the effect of endurance training, which enhances oxidative capacity of several tissues (TABLE 3).[14–18] Information on the effect of sprint training, which relies primarily on anaerobic metabolism, on tissue antioxidant defenses is limited.[19] We have recently observed that a predominantly anaerobic 6-wk sprint training program upregulates the activities of redox cycle enzymes, such as glutathione peroxidase and glutathione disulfide reductase, in rat heart tissue.[20] However sprint training did not affect the activities of glutathione S-transferases and total glutathione content in rat heart tissue.[20] Sprint-type exercise utilizes anaerobic energy pathways followed by oxidative metabolism during the recovery phase. In many ways the situation may be considered to be analogous to ischemia-reperfusion and has been shown to activate the xanthine oxidase pathway for superoxide production.[21]

Endurance-exercise training may provide added antioxidant protection to the heart tissue. Ji and colleagues[22] have shown that post-training hypertrophied myocardium is more resistant to ischemia-reperfusion–induced glutathione depletion and hemodynamic dysfunction. Consistently, Somani and colleagues[8] reported increased levels of cytosolic GSH levels in the myocardium of 10-wk endurance-trained rats. Leichtweis and colleagues[23] studied the protective effect of 8–9 wk of vigorous swimming on the hearts of rats subjected to ischemia-reperfusion. Training decreased cytosolic reduced glutathione and oxidized glutathione/total glutathione ratio but increased the ability of the tissue to import extracellular glutathione by increasing the activity of γ-glutamyl transpeptidase. This study also showed that vigorous exercise training regimens might have detrimental effects on the heart by depressing mitochondrial function and downregulating tissue antioxidant defenses.

TABLE 3. Effects of chronic exercise on cardiac antioxidant defenses and exercise performance

Investigator	Model	Type of Training	Effect
Atalay *et al.*[20]	Rats	Spint run 6 wk	SOD →
			GSHPx ↑
			GRD ↑
			TGSH →
Gohil *et al.*[37]	Rats	Run 12 wk	Ubiquinone →
			Vit E →
			Cytochrome *c* reductase→
Higuchi *et al.*[31]	Rats	Run 3 months	Cu,Zn SOD →
			Mn SOD →
Hong & Johnson[27]	Normo/hyperten-sive rats	Run + 10 wk + Detraining 1 wk	CAT ↓ GSHPx ↓
Husain & Somani[24]	Rats	Training 6.5 wk	SOD ↑
			GSHPx ↑
			GSH ↑
Ji [38]	Rats	Run 12 wk	Cu,Zn SOD →
			Mn SOD →
			CAT →
			GSHPx (C-M) →
			GST →
Kanter *et al.*[30]	Mice	Swim 7 wk	SOD →
			CAT →
			GSHPx →
		Swim 21 wk	SOD →
			CAT ↑
			GSHPx →
Kihlstrom *et al.*[15]	Rats	Swim 3 months	CAT ↓
			Cu,ZnSOD ↓
			Thioredoxin reductase ↓
			GRD ↓
			Vit E ↓
Kim *et al.*26	Rats	Run 18.5 months	CAT ↑
			MDA ↓
Kumar *et al.*[12]	Rats	Swim 2 months	SOD ↑, xanthine oxidase ↑
		+ Vit E suppl.	Catalase ↓, GSHPx ↓, GST ↑
			MDA ↑, EPR signals ↑
			MDA ↓, EPR signals ↓
Leeuwenburgh *et al.*[18]	Rats	Run 10 wk	GSH / GSSG ↓
			SOD →, Mn-SOD →
			GSHPx → , GRD →
			GST ↓, GGT →, GCS →

(*Continued*)

TABLE 3. Effects of chronic exercise on cardiac antioxidant defenses and exercise performance

Investigator	Model	Type of Training	Effect
Leichtweis *et al.*[23]	Rats	Vigorous swim 8–9 wk + I-R	GSH →(mitochondrial) TGSH→, GSSG → GSH ↓, (cytosolic) GSSG /TGSH ↓ GGT ↑ MDA ↓
Lew & Quintanilha[16]	Rats	Run 10 wk	CAT ↑ GSHPx↑ GRD →
Powers *et al.*[17]	Rats	Run 10 wk/30, 60, 90 min	
		Low intensity	SOD → ↑, CAT →, GSHPx →
		Moderate intensity	SOD →↑, CAT →, GSHPx →
		High intensity	SOD ↑ ↑, CAT →, GSHPx →
Reznick *et al.*[39]	6-month-old mice	Run 5 wk	SOD ↑
	22-month-old mice		SOD →
	27-month-old mice		SOD ↓
Somani *et al.*[8]	Rats	Run 10 wk	Cytosolic GSH ↑
Tiidus & Houston[40]	Rats	Run 8 wk	SOD →
		Vit E suppl.	CAT →
		Vit E deprivation	GSHPx →
Venditti & Di Meo[4]	52-week-old rats	Swim 10 wk	GSHPx ↑ GRD ↑ T. antioxidant capacity ↑ Mitochondrial integrity →

[a]See TABLE 2 footnote for abbreviations.

Several studies have examined the influence of exercise training on the activity of specific antioxidant enzymes. Because of the variations in experimental design, model, and analytical procedures, much of these studies may not be directly compared to each other. Overall, the results show that endurance training may enhance the activity of certain antioxidant enzymes in the heart. Lew and Quintanilha[16] reported that 10-wk treadmill training may enhance catalase and glutathione peroxidase activities in rat heart without affecting glutathione disulfide reductase activity. Husain and Somani[24] reported a significant increase of cardiac superoxide dismutase and glutathione peroxidase activities and glutathione content of 6.5-wk treadmill-trained rats. Somani and colleagues[8] showed that exercise-induced increases in the activities of Mn-superoxide dismutase, Cu,Zn-superoxide dismutase, catalase, and glutathione peroxidase were higher than respective increases in mRNA content of the respective enzymes. These results suggest that upregulation of enzyme activity may not be wholly accounted for by increased protein expression and that other factors contributing to the catalytic activity of these proteins may have been influenced by exercise.

One of the most comprehensive studies investigating the role of exercise training in regulating endogenous cardiac antioxidant defenses was reported by Powers and colleagues.[17] In this work, rats were treadmill-trained for 10 weeks at three different durations of daily run time (30, 60, and 90 min). Also, three different relative intensities of daily exercise (low, moderate, and high) were studied. None of these nine training groups showed any effects in cardiac citrate synthase, catalase, or glutathione peroxidase activities. In all duration groups of moderate and high intensity–trained animals, right ventricular superoxide dismutase activity increased in response to training. Left ventricular superoxide dismutase activity also increased after short-duration intensive training and long-duration training with low or moderate intensities. These data show that daily exercise intensity may influence training-dependent upregulation of the activity of cardiac antioxidant enzymes. Studies from our and Ji's laboratories have shown that endurance training does not affect rat skeletal muscle and heart glutathione S-transferases activities.[14,20,25] In other studies, endurance-type treadmill training was observed to decrease glutathione S-transferases activity in the heart.[18]

Endurance training of rats on treadmill enhances the ability to perform endurance exercise.[3] Despite longer exercise-duration in trained animals, exercise-induced elevation of tissue thiobarbituric acid–reactive substances levels was higher in the liver but not in heart suggesting that the trained heart was able to cope more efficiently with exercise-induced oxidative stress.[3] These results are consistent with the finding of another study by Kim and colleagues.[26] Direct evidence showing that indeed exercise training may strengthen cardiac antioxidant defenses was also obtained in a 10-wk swim-training study. Exercise training enhanced glutathione peroxidase, glutathione reductase enzyme activities, and total antioxidant scavenging capacity without changing mitochondrial integrity and resting lipid peroxidation in rats.[4] Hong and Johnson[27] have studied the effects of 10-wk treadmill training and 1-wk detraining on antioxidant enzyme activity in normotensive and hypertensive rats. Sedentary hypertensive rats had higher glutathione peroxidase activity in the left ventricles. Exercise training, however, decreased left ventricular glutathione peroxidase activity both in normotensive as well as in hypertensive rats. Another potential source of oxidative stress in the heart is a diet rich in fish oil.[28,29] We observed that a regimen of 8 weeks of 1 g/kg body weight/day fish oil supplementation increases cardiac glutathione peroxidase activity, which was normalized in the rats that were co-supplemented with fish oil and 500 mg/kg/day vitamin E (Atalay and colleagues, unpublished results).

Some other studies investigating the efficacy of endurance exercise training programs to enhance cardiac antioxidant defenses have shown mixed results. Kanter and colleagues[30] have tested the effects of 7-wk and 21-wk swim-training program on superoxide dismutase, catalase, and glutathione peroxidase enzyme activities in mice. After 21 weeks of training only catalase activity was upregulated in the heart tissue while activities of other antioxidant enzymes were increased only in blood and liver.[30] Similarly, Higuchi and colleagues[31] did not observe any increase of Cu,Zn-superoxide dismutase and Mn-superoxide dismutase activity in the heart after 3-month treadmill training. In another study, 3-month swim-training decreased the activities of catalase, Cu,Zn-superoxide dismutase, thioredoxin reductase, glutathione reductase, and vitamin E content mainly in the right ventricle and subendomyocardium, despite significant increase in the cardiac weight.[15]

In summary, an acute bout of strenuous physical exercise may pose oxidant insult to the heart. Despite some discrepancies in the literature, there is a general trend showing that chronic regular physical exercise may beneficially influence cardiac antioxidant defenses and promote overall cardiac function.

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