

Review

Oxidative stress and antioxidant defense mechanisms linked to exercise during cardiopulmonary and metabolic disorders

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Oxidative stress has been implicated in the pathophysiology of multiple human diseases, in addition to the aging process. Although various stimuli exist, acute exercise is known to induce a transient increase in reactive oxygen and nitrogen species (RONS), evident by several reports of increased oxidative damage following acute bouts of aerobic and anaerobic exercise. Although the results are somewhat mixed and appear disease dependent, individuals with chronic disease experience an exacerbation in oxidative stress following acute exercise when compared to healthy individuals. However, this increased oxidant stress may serve as a necessary “signal” for the upregulation in antioxidant defenses, thereby providing protection against subsequent exposure to prooxidant environments within susceptible individuals. Here we present studies related to both acute exercise-induced oxidative stress in those with disease, in addition to studies focused on adaptations resulting from increased RONS exposure associated with chronic exercise training in persons with disease.

Introduction

The production of reactive oxygen and nitrogen species (RONS) and the subsequent processing via the antioxidant defense system is a delicately balanced and continual process in vivo that serves several key roles in human physiology. RONS are very small molecules which are highly reactive due to their unpaired valence shell electrons, and are short-lived (e.g., 10^{-6} , 10^{-5} , 10^{-9} seconds for singlet oxygen, superoxide radical and hydroxyl radical, respectively). Hence, they often react with other molecules promoting either positive or negative effects. While RONS generation occurs in part as a consequence of normal cellular metabolism, they are also generated through exposure to a wide variety of environmental (e.g., cigarette smoke, ozone, dietary fat and carbohydrate) and physiological (e.g., physical and mental stress) challenges.¹ Specifically, RONS may be mediated by an increased activity of radical generating enzymes (e.g., xanthine

oxidase), activation of phagocytes, phospholipases, cyclooxygenases and lipoxygenases, as well as through disruption of the electron transport system leading to increased electron leakage and superoxide radical formation. Under optimal conditions, RONS regulate vital processes such as cellular signaling, immune function, apoptosis and gene transcription.¹ However, in response to a variety of stressors such as exposure to chemical pollutants,² cigarette smoke³, excess nutrient intake⁴ and physical exercise,⁵ RONS production increases. When in conjunction with poor antioxidant defense, a state of oxidative stress occurs, which may ultimately lead to oxidative damage to cellular DNA, proteins and lipids.²

Oxidative stress has been linked to the pathophysiology of a myriad (>100) of human diseases, as well as to the aging process.⁶ This relationship has been illustrated by several investigators reporting an increased production of RONS and/or an increased accumulation of oxidative stress biomarkers in diseased compared to healthy individuals.⁷⁻¹⁵ It is unclear as to whether the heightened oxidative stress observed in those with disease represents a causal relationship or whether increased RONS is simply a consequence of disease pathology.² However, it is plausible that chronic exposure to oxidative stress could represent a contributing factor to disease progression, as several mechanistic links have been recently described.¹⁶⁻²¹ Increased oxidative stress associated with disease is often related to a depletion in enzymatic and nonenzymatic antioxidants,⁶ thereby reducing the ability to protect against excess RONS exposure. This is particularly apparent when diseased individuals are exposed to RONS production in response to acute exercise (Tables 1–5), as heightened oxidative stress has been observed for such individuals as compared to healthy controls.^{7-12,22-31} While this has traditionally been viewed as a negative finding, based on the principle of hormesis, it is plausible to consider that such an acute increase in RONS may actually be a necessary stimulus to allow for an upregulation in antioxidant defense.³²

The purpose of this review is to first provide an account of the available literature pertaining to the effects of acute exercise on oxidative stress biomarkers in those with disease. It is comprised of >30 original human investigations focused on acute exercise and oxidative stress in a variety of disease conditions, separated by classification. Second, we provide a summary of work related to the impact of chronic exercise training on the antioxidant defense system and oxidative status of those with disease. Due to the relative paucity of data in this latter

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Table 1 Acute exercise-induced oxidative stress and COPD

Reference	Subjects	Exercise	Tissue	Marker	Times	Effects
Vina (1996)	9 patients w/COPD	cycle ergometry at 40 W, 50–60 revolutions/min until dyspnea	blood	GSH GSSG	pre, post	↔ ↑
Heunks (1999)	16 patients w/COPD	GXT on cycle	blood	GSH GSSG MDA	pre, 0, 60 min post	↓ 0 post ↑ 0 post ↑ 0, 60 post
Couillard (2002)	11 patients w/COPD 12 controls	knee extension at loads ~40% MVC (12 per min) until exhaustion	blood	Phagocytic O ₂ ^{••} TBARS Vitamin E	pre, 0, 6 h post	↔ ↑ 6 h post in COPD ↔
Couillard (2003)	10 patients w/COPD 12 controls	knee extension at loads ~30% MVC (6 per min) until exhaustion	muscle	TBARS PC GPx	pre, 48 h post	↑ 48 h post in COPD ↑ 48 h post in COPD ↑ 48 h post in Control
Agacdiken (2004)	21 patients w/COPD 10 controls	GXT on TM	blood	MDA GSH Vitamin E	pre, 1, 3 h post	↑ 3 h post in COPD ↔ ↑ 1 h post in COPD
Koechlin (2004)	10 patients w/COPD 7 controls	knee extension at loads ~40% MVC (12 per min) until exhaustion	blood	Phagocytic O ₂ ^{••} TBARS PC Vitamin E TAS	pre, 0, 6, 24, 48 h post	↑ 6 h post in both ↑ 6 h post in COPD ↑ 6 h post in both ↔ ↔
Koechlin (2004)	9 patients w/COPD	Couillard 2002	blood	Phagocytic O ₂ ^{••} TBARS PC TEAC Vitamin E	pre, 0, 6 h post	↑ 6 h post ↑ 0, 6 h post ↑ 6 h post ↔ ↔
Mercken (2005)	11 patients w/COPD 11 controls	GXT on cycle and submax ride at 60% Wmax	blood urine breath	DNA damage (comet assay) MDA H ₂ O ₂	pre, 0, 4 h post	↑ 0, 4 h post in COPD ↑ 0, 4 h post in COPD 4 h post only in Control ↑ 4 h post in COPD 0 h post in Control
van Helvoort (2006)	20 patients w/COPD 10 controls	GXT on cycle and submax cycle ride at 50% Wmax	blood	Neutrophil O ₂ ^{••} TAS PC TBARS GSH GSSG	pre, during, post	↑ in COPD ↓ in both ↔ ↑ in COPD ↓ in both ↑ in COPD
Rabinovich (2006)	20 patients w/COPD 5 controls	11 min of cycling at 40% Wpeak	muscle	TGSH cis-parinaric acid	pre, post	↔ ↔
Pinho (2007)	15 patients w/COPD	GXT on cycle	blood	TBARS TRAP XO	pre, post	↔ ↔ ↓
van Helvoort (2007)	10 patients w/COPD	6 minute walk test GXT on cycle	blood	Neutrophil O ₂ ^{••} TAS PC TBARS	pre, post	↑ post both protocols ↓ post both protocols ↑ post 6 min walk ↑ post both protocols

Definitions: GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; O₂^{••}, superoxide radical; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GPx, glutathione peroxidase; TAS, total antioxidant status; TEAC, trolox equivalent antioxidant capacity; H₂O₂, Hydrogen Peroxide; TGSH, total glutathione; TRAP, total radical-trapping antioxidant parameter; XO, xanthine oxidase; SOD, superoxide dismutase; oxLDL, oxidized low density lipoprotein; GR, glutathione reductase; GST, glutathione transferase; CAT, catalase; LOOH, lipid hydroperoxides; 8-OHdG, 8-hydroxydeoxyguanosine; CD, conjugated dienes; ↑, significant increase from pre exercise value; ↓, significant decrease from pre exercise value; ↔, no significant change; numbers following ↑, ↓, ↔, represent respective time points where significant findings occurred.

Table 2 Acute exercise-induced oxidative stress and cardiovascular disease

Reference	Subjects	Exercise	Tissue	Marker	Times	Effects
Chen (1994)	30 hypercholesterolemic patients 30 controls	GXT	blood	MDA SOD	pre, 0, 10 min post	↑ 0 min post in both ↑ 0, 10 min post in both
Nishiyama (1998)	12 CHF patients 7 controls	GXT	blood	MDA SOD	pre, post	↑ in CHF ↔
Leaf (1998)	18 patients w/or w/out exercise-induced myo-cardial ischemia	GXT	blood	MDA	pre, post	↑ in ischemic group
Leaf (1999)	20 CAD patients (10 were tested post cardiac rehab)	GXT	blood	MDA Ethane Pentane	pre, 5 min post	↑ ↑ ↑
Jimenez (2000)	7 heart transplant patients 7 controls	GXT	blood	MDA GPX-plasma GPX-erythrocyte SOD Vitamin E	pre, 0, 30 min post pre, 24 h post (enzymes)	↔ ↔ ↔ ↑ 24 h post in HTR ↑ 30 min post in Control
Andican (2001)	12 CAD patients 8 w/out CAD	GXT	blood	TBARS GSH GPx SOD Vitamin E	pre, post	↔ ↓ in CAD ↓ in CAD ↓ in CAD ↔
Silvestro (2002)	30 w/intermittent claudication 10 controls	Group 1—exercise until claudication intollerable (max) Goup 2—exercise until claudication discomfort Controls—exercise to HR max	blood	TBARS	pre, post	↑ in group 1 only
Sayar (2007)	46 CHF patients 24 controls	GXT	blood	MDA	pre, post	↑ in CHF
Jorde (2007)	48 CHF patients 12 controls	GXT	blood	oxLDL	pre, post	↑ in CHF patients ↔ in controls
Lo Presti (2007)	15 CAD patients 13 controls	GXT	blood	TBARS TAS	pre, 0, 10 min post	↔ ↔

Definitions: GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; $O_2^{\cdot -}$, superoxide radical; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GPx, glutathione peroxidase; TAS, total antioxidant status; TEAC, trolox equivalent antioxidant capacity; H_2O_2 , Hydrogen Peroxide; TGSH, total glutathione; TRAP, total radical-trapping antioxidant parameter; XO, xanthine oxidase; SOD, superoxide dismutase; oxLDL, oxidized low density lipoprotein; GR, glutathione reductase; GST, glutathione transferase; CAT, catalase; LOOH, lipid hydroperoxides; 8-OHdG, 8-hydroxydeoxyguanosine; CD, conjugated dienes; ↑, significant increase from pre exercise value; ↓, significant decrease from pre exercise value; ↔, no significant change; numbers following ↑, ↓, ↔, represent respective time points where significant findings occurred.

area of investigation (11 original studies), this section is sparse in comparison to the initial section on acute exercise.

Acute Exercise-Induced Oxidative Stress and Disease

While multiple disease states have been reported to be associated with elevated oxidative stress, those categories that have been investigated in relation to exercise include chronic obstructive pulmonary disease, cardiovascular disease (e.g., heart failure, atherosclerosis, peripheral arterial disease), and metabolic disease (e.g., diabetes and obesity). Additionally, the impact of acute exercise on oxidative stress in cigarette smokers has been investigated. Because cigarette smoking is considered a major risk factor for most of the above mentioned disease states, these studies will be discussed.

Chronic obstructive pulmonary disease (COPD). Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible disease of the respiratory tract, characterized by limited or obstructed airflow, believed to be brought on by an abnormal and/or excessive inflammatory response in the lungs.³³ Cigarette smoking is suggested to be the primary etiological factor in the development of COPD, as more than 90% of patients with COPD are smokers.³⁴ Both inflammation and oxidative stress appear to play a critical role in the development and/or the progression of COPD (reviewed in ref. 33). Mechanistically, both RONS, as well as inflammatory cells likely exert both an independent, as well as an intricately connected impact on disease development, as both activate each other in a cyclical manner. This process has been reviewed recently,^{33,35,36} and

Table 3 Acute exercise-induced oxidative stress and diabetes

Reference	Subjects	Exercise	Tissue	Marker	Times	Effects
Laaksonen (1996)	9 type 1 diabetics 13 controls	cycle for 40 min @ 60% VO _{2max}	blood	TBARS	pre, post	↑ in both
				TGSH		↔
				GSSG		↑ in both
Atalay (1997)	9 type 1 diabetics 14 controls	cycle for 40 min @ 60% VO _{2peak}	blood	TBARS	pre, post	↑ in both
				TGSH		↔
				GPx		↑ in Control
				GR		↔
				GST		↔
				SOD		↔
				CAT		↔
Davison (2002)	12 type 1 13 controls	GXT on cycle	blood	PBN adducts (α-phenyl-tert-butyl nitron)	pre, post	↑ (pooled data)
				MDA		↔
				LOOH		↑ (pooled data)
				Vitamin C		↔
				Vitamin E		↓ in Control
				Beta-carotene		↔
Villa-Caballero (2007)	12 sedentary type 2 9 active type 2 12 controls	GXT on treadmill	blood	TBARS	pre, 5, 15, 30, 60 min post	↔
				GSH		↔

Definitions: GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; O₂^{•-}, superoxide radical; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GPx, glutathione peroxidase; TAS, total antioxidant status; TEAC, trolox equivalent antioxidant capacity; H₂O₂, Hydrogen Peroxide; TGSH, total glutathione; TRAP, total radical-trapping antioxidant parameter; XO, xanthine oxidase; SOD, superoxide dismutase; oxLDL, oxidized low density lipoprotein; GR, glutathione reductase; GST, glutathione transferase; CAT, catalase; LOOH, lipid hydroperoxides; 8-OHdG, 8-hydroxydeoxyguanosine; CD, conjugated dienes; ↑, significant increase from pre exercise value; ↓, significant decrease from pre exercise value; ↔, no significant change; numbers following ↑, ↓, ↔, represent respective time points where significant findings occurred.

Table 4 Acute exercise-induced oxidative stress and obesity

Reference	Subjects	Exercise	Tissue	Marker	Times	Effects
Vincent (2004)	14 obese 14 nonobese	resistance Rx (7 exercises, 3 sets, 45–80% 1RM) (RX) & aerobic exercise (same HR and duration w/RX) (AX)	blood	TBARS	pre, post	↑ post RX/AX in both
				LOOH		↑ post RX/AX in both
				TAS		↑ post RX in nonobese/ ↓ post AX in obese
Vincent (2005)	24 obese 8 nonobese	GXT on treadmill	blood	LOOH Total thiols	pre, post	↑ in obese ↔
Vincent (2006)	29 overweight/obese 20 control	GXT on treadmill	blood	LOOH TBARS	pre, post	↑ in both ↑ in both
Vincent (2006)	23 obese 25 nonobese	30 min constant load cycle test	blood	LOOH TAS	pre, post	↑ in both ↔
Lwow (2007)	200 overweight/obese	30 cycle test (30–50% VO _{2max})	blood	TBARS	pre, 0, 6 h post	↑0, 6 h post

Definitions: GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; O₂^{•-}, superoxide radical; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GPx, glutathione peroxidase; TAS, total antioxidant status; TEAC, trolox equivalent antioxidant capacity; H₂O₂, Hydrogen Peroxide; TGSH, total glutathione; TRAP, total radical-trapping antioxidant parameter; XO, xanthine oxidase; SOD, superoxide dismutase; oxLDL, oxidized low density lipoprotein; GR, glutathione reductase; GST, glutathione transferase; CAT, catalase; LOOH, lipid hydroperoxides; 8-OHdG, 8-hydroxydeoxyguanosine; CD, conjugated dienes; ↑, significant increase from pre exercise value; ↓, significant decrease from pre exercise value; ↔, no significant change; numbers following ↑, ↓, ↔, represent respective time points where significant findings occurred.

it has been suggested that intra and extracellular RONS production via mitochondrial respiration and/or membrane bound NADPH or xanthine oxidase gives rise to the increased gene transcription of certain inflammatory cytokines, as well as the increased circulation

of phagocytic cells.³⁷ This increase in inflammation and circulating phagocytes (particularly macrophages and neutrophils) gives rise to further RONS production via activation of certain radical generating enzymes and/or phagocytic respiratory burst, respectively.³³ Potential

Table 5 Acute exercise-induced oxidative stress and cigarette smokers

Reference	Subjects	Exercise	Tissue	Marker	Times	Effects
Surmen-Gur (1999)	19 smokers	20 maximal isokinetic knee extensions w/nondominant leg	blood	MDA	pre, post	↔
	17 non-smokers			SOD		↓ in nonsmokers
				GPx		↔
Bloomer (2007)	14 smokers	GXT	blood	Vitamin E	pre, post	↓ in both
	15 non-smokers			MDA		↑ in smokers
	(all untrained)			PC		↑ in both
Gochman (2007)	14 smokers	GXT	blood	8-OHdG	pre, post	↔
	14 non-smokers			PC		↑ in both
	(physically active)			LOOH		↔
				CD		↑ in smokers
				Vitamin A		↔
	Vitamin E	↔				

Definitions: GSH, reduced glutathione; GSSG, oxidized glutathione; MDA, malondialdehyde; $O_2^{\cdot-}$, superoxide radical; TBARS, thiobarbituric acid reactive substances; PC, protein carbonyls; GPx, glutathione peroxidase; TAS, total antioxidant status; TEAC, trolox equivalent antioxidant capacity; H_2O_2 , Hydrogen Peroxide; TGSH, total glutathione; TRAP, total radical-trapping antioxidant parameter; XO, xanthine oxidase; SOD, superoxide dismutase; oxLDL, oxidized low density lipoprotein; GR, glutathione reductase; GST, glutathione transferase; CAT, catalase; LOOH, lipid hydroperoxides; 8-OHdG, 8-hydroxydeoxyguanosine; CD, conjugated dienes; ↑, significant increase from pre exercise value; ↓, significant decrease from pre exercise value; ↔, no significant change; numbers following ↑, ↓, ↔, represent respective time points where significant findings occurred.

sources of increased RONS production and inflammation include exposure to cigarette smoke, other pollutants, ischemia/reperfusion injury to peripheral tissues resulting from inadequate lung function, as well as increased mitochondrial superoxide production.³³ Because the latter two events can be brought about during an acute exercise session, several studies have investigated the impact of acute exercise on the systemic oxidative stress response in COPD patients. These studies are discussed below and presented in Table 1.

The impact of acute exercise on oxidative stress in COPD patients was first investigated by Vina and colleagues,³⁸ who reported an increase in oxidized glutathione (GSSG) following cycle ergometry at an intensity comparable to normal activities of daily living (~3 METS). This post-exercise increase in GSSG was prevented following supplemental administration of oxygen at a flow rate of 2–3 L·min⁻¹, suggesting a role of alternate RONS generating pathways (e.g., NADPH oxidase, xanthine oxidase) other than increased mitochondrial superoxide production, in eliciting an oxidative insult post exercise.³⁸ In agreement with these findings, a similar study reported an increase in GSSG and malondialdehyde (MDA), as well as a decrease in reduced glutathione (GSH), following a graded exercise test (GXT) in COPD patients, which was prevented by infusion with 300 mg allopurinol 24 and one hour pre exercise.³⁹ Allopurinol is a known inhibitor of the radical generating enzyme xanthine oxidase,⁴⁰ which has been shown to be activated in response to periods of ischemia followed by reperfusion. Taken together, these results suggest that the impaired pulmonary function seen in COPD patients likely leads to an imbalance between oxygen supply and demand to the exercising musculature during acute exercise, potentially resulting in the increased production of RONS via xanthine oxidase. This increase in RONS appears evident even at low intensities comparable to activities of daily living, suggesting that patients with COPD may be under a chronic state of oxidative stress.³⁸

Increased oxidative stress has also been reported in COPD patients following both acute maximal^{7,8,10,41} and submaximal^{7,10} aerobic exercise. This has been the case with one exception,⁴² evident

by reported increases in MDA,^{8,10} thiobarbituric acid-reactive substances (TBARS),^{7,41} protein oxidation (protein carbonyls),⁴¹ DNA damage (comet assay),¹⁰ phagocytic superoxide production,^{7,41} as well as changes in glutathione redox status⁷ and other components of the antioxidant defense system (e.g., total antioxidant status).⁷ In those studies in which a healthy control group was utilized for comparison, exacerbated increases have been reported in COPD patients.^{7,8,10} These effects appear most pronounced in muscle-wasted COPD patients [fat-free mass <16 kg·m⁻² (men) or <15 kg·m⁻² (women)], as they have been shown to present with lower levels of GSH at rest, as well as experience greater increases in oxidative stress post exercise, compared to their non-muscle wasted counterparts.⁷ Hence, lower antioxidant defense may be a contributing factor to increased exercise-induced oxidative stress in those with COPD.

Although the majority of investigations using COPD patients have reported an increase in oxidative stress in response to exercise, significance has not been observed for all biomarkers studied (i.e., lipid, protein, DNA, antioxidant status). This is a common occurrence throughout the literature, as null findings for certain biomarkers may be related to the time to oxidation and “repair” of a given molecule. In this regard, inadequate sampling time may help to explain much of the variability in results,⁴³ as the majority of studies have only taken samples immediately pre and post exercise.^{7,42,44,45}

Aside from aerobic exercise, investigators have also measured the oxidative stress response in COPD patients following knee extension exercise performed at 30–40% maximal voluntary contraction until exhaustion.^{9,22,23,46} Findings have included increased lipid peroxidation,^{9,22,23,46} protein oxidation,^{9,23,46} and phagocytic superoxide production.^{9,46} Similar to aerobic exercise, exacerbated increases in oxidative stress biomarkers have been reported for COPD patients compared to healthy controls.^{9,23}

Clearly, acute exercise has the ability to result in increased RONS and subsequent oxidative damage in COPD patients. Inadequate oxygen likely leads to an acute state of ischemia followed by

reperfusion, resulting in the formation of RONS via radical generating enzymes (e.g., NADPH oxidase, xanthine oxidase). While two studies have successfully used antioxidants in patients with COPD to minimize the oxidative stress associated with acute exercise,^{8,46} exercise training has also been investigated and will be discussed in a later section.

Cardiovascular disease (CVD). Cardiovascular disease (CVD) is the leading cause of death in the United States.⁴⁷ Two common conditions that exist under the umbrella of CVD that contribute significantly to morbidity and mortality include congestive heart failure (CHF)¹⁷ and coronary artery disease (CAD).⁴⁸ Oxidative stress has been suggested to play a role in either the primary or secondary etiology of both CHF¹⁷ and CAD,⁴⁸ evident by increased oxidative stress biomarkers and/or decreased antioxidant defenses at rest in diseased compared to healthy controls.¹⁷ As with COPD, several mechanistic links related to increased RONS production in CVD have been identified, including increased NADPH and xanthine oxidase activity, increased mitochondrial superoxide production resulting from mitochondrial dysfunction, as well as enhanced circulating concentrations of inflammatory cytokines.⁴⁹ Increased RONS production leads to an exacerbation of disease severity, illustrated primarily by the role of RONS in promoting endothelial dysfunction¹⁹ and atherogenesis,¹⁶ as well as cardiomyocyte apoptosis, left ventricular remodeling and depressed myocardial contractility.⁴⁹ Exposure to excess RONS may lead to the increased accumulation of oxidized LDL (oxLDL) particles within the intima of arteries, thereby promoting atherogenesis and systemic inflammation.¹⁶ This increase in fatty lesion formation and a pro-inflammatory environment could lead to the development and/or progression of arterial disease, myocardial infarction or stroke.¹⁶ Myocardial infarction could in turn promote the development of CHF due to impaired ventricular performance, resulting in severely compromised functional capacity.

Exercise induced oxidative stress has been studied within patients with various forms of CVD, as presented in Table 2. Increased oxidative stress in response to a GXT has been noted in patients with both CHF^{12,25,26} and CAD,^{27,50} evident by increased MDA,^{12,25,50} oxLDL²⁶ and expired breath pentane/ethane⁵⁰, as well as decreased GSH²⁷ and antioxidant enzyme activity.²⁷ Moreover, in those studies in which a healthy control group has been utilized for comparison, exacerbated oxidative stress has been evident in those with CVD.^{12,25-27} In opposition to the above, null findings for lipid peroxidation have also been reported following a GXT in CAD patients.^{27,51} However, lipid peroxidation was assessed via TBARS, which has been shown to lack sensitivity.⁵²

Similar to the above results for those with CHF or CAD, increased oxidative stress has been reported in subjects without diagnosed CAD but who presented with exercise-induced ischemia,⁵³ as well as in subjects with peripheral vascular disease.²⁸ It should be noted that infusion of vitamin C (50 mg/min) for 20 minutes pre exercise eliminated the post-exercise increase in TBARS,²⁸ indicating a benefit of antioxidant treatment. In hypercholesterolemic subjects, a post-exercise increase in MDA has been reported following a GXT,⁵⁴ a finding that may be partly explained by the increased superoxide production known to be present in hypercholesterolemic patients.⁵⁵ Finally, no increase in MDA has been reported in heart transplant recipients following a GXT.⁵⁶ However, the null findings may be due

to the training status of the subject population, as all were aerobically trained and may have had improved antioxidant defense.⁵⁶

Diabetes. Diabetes is a condition characterized by chronic elevations in blood glucose brought on either via the autoimmune destruction of pancreatic beta cells (type 1) or the development of insulin resistance in the peripheral tissues (type 2).⁵⁷ Both forms of diabetes are associated with an increased risk for developing microvascular (retinopathy, neuropathy) and macrovascular (atherosclerosis) complications, which have been linked to oxidative stress.⁵⁷ Increased oxidative stress biomarkers have been reported in diabetics compared to healthy controls, and the role of RONS in diabetes etiology has been the topic of numerous reviews.^{18,58} It appears that this chronic exposure to hyperglycemic conditions gives rise to increased superoxide production resulting from postprandial hyperglycemia,¹⁸ glucose autooxidation,⁵⁹ the formation of advanced glycation end products⁶⁰ and activation of the polyol pathway.⁶¹

As with COPD and CVD patients, diabetics (in particular type 1) have been the focus of exercise-induced oxidative stress research (Table 3). Increased TBARS^{13,14} and GSSG¹³ have been reported following submaximal aerobic exercise in type 1 diabetic subjects. In regards to maximal exercise, direct production of RONS via electron spin resonance spectroscopy has been reported following a GXT; however, it is important to note that significance was only achieved when data for both type 1 diabetic and healthy control subjects were pooled.¹⁵ Despite the observation of increased levels of exercise-induced oxidative stress biomarkers in studies involving type 1 diabetics, when compared to healthy individuals, the relative magnitude of increase does not differ; rather the group differences at rest are merely maintained during the post exercise period. Other investigators have reported no changes in MDA,¹⁵ total glutathione (TGSH), antioxidant enzyme activity,¹⁴ or circulating antioxidants¹⁵ in response to acute exercise in type 1 diabetics.

Only one study to our knowledge has been conducted addressing the impact of acute exercise (GXT) on measures of oxidative stress (TBARS, GSH) in type 2 diabetics.⁶² Unfortunately, findings proved difficult to interpret, as the authors failed to report if the post exercise values were statistically significant from the pre exercise values; thus these are presented as null findings in Table 3. Taken together, unlike findings for patients with COPD and CVD, diabetic subjects do not appear to experience any further increase in exercise-induced oxidative stress compared to healthy controls.

Obesity. Closely linked to the development of type 2 diabetes, obesity has been studied in relation to exercise and oxidative stress (Table 4). This association between these two disorders appears due to the increased circulating levels of tumor necrosis factor- α within obese individuals, which has been shown to be released from adipocytes⁶³ as well as impart an insulin resistant state.⁶⁴

Increased lipid peroxidation has been reported in obese individuals following acute submaximal^{29,31,65} and maximal^{30,66} aerobic exercise, as well as following a single session of resistance exercise.²⁹ Moreover, obese individuals (BMI > 30 kg•m⁻²) have been noted to experience a greater magnitude of increase in selected biomarkers when compared to normal weight controls.^{29,30} However, these results appear mixed in overweight (BMI > 25 kg•m⁻²) populations, with studies reporting conflicting results.^{31,66}

Cigarette smoking. Although not a disease itself, cigarette smoking has consistently been shown to increase the susceptibility for

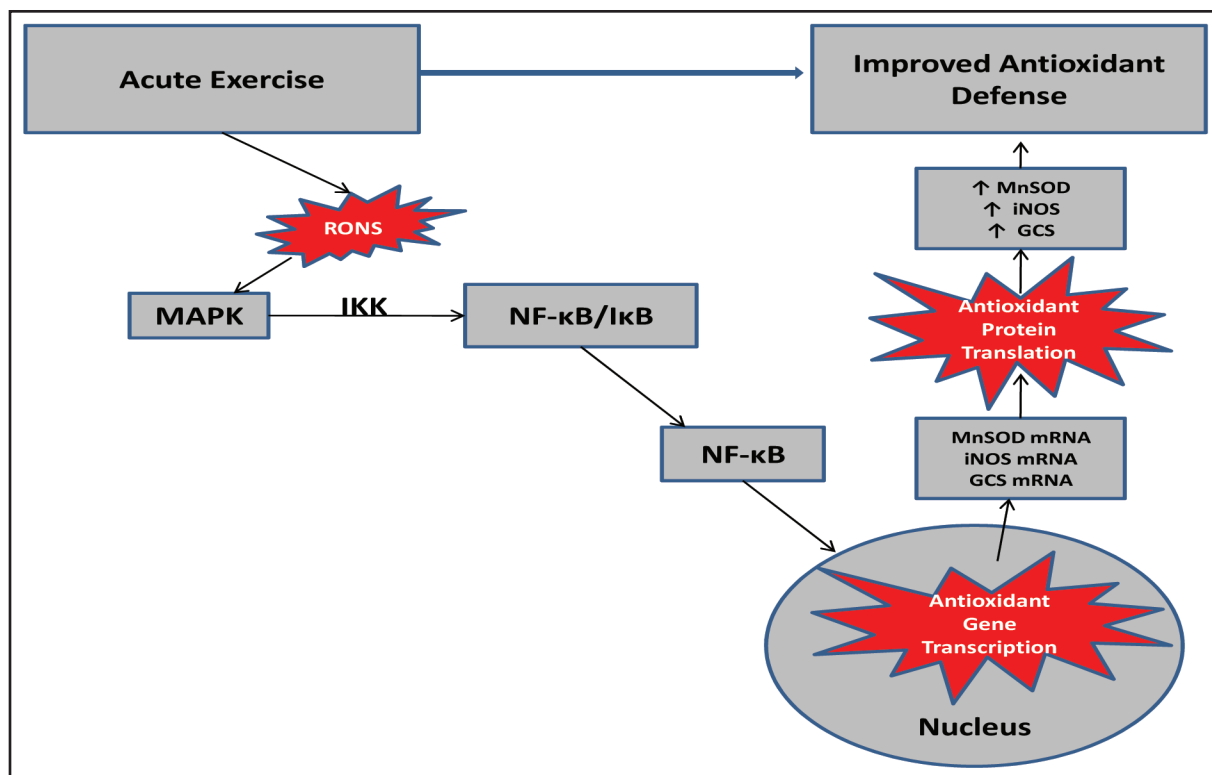


Figure 1. Potential changes in antioxidant defense as a result of chronic exercise training. Exercise-induced RONS production results in the activation of IκB kinase (IKK), secondary to the activation of mitogen activated protein kinases (MAPK). IKK then phosphorylates the inhibitory subunit of nuclear transcription factor-κB (NFκB), thus releasing it to migrate to the nucleus. Once inside the nucleus, NFκB promotes the transcription of several antioxidant enzymes [manganese superoxide dismutase (MnSOD), inducible nitric oxide synthase (iNOS), glutamylcysteine synthetase (GCS)]. Messenger RNA (mRNA) is then synthesized for each enzyme, exits the nucleus and undergoes translation, ultimately resulting in an upregulation in antioxidant protein expression and improved antioxidant defense.

the development of several disease conditions, including COPD,³⁴ CVD⁶⁷ and diabetes.⁶⁸ Much of the detrimental effects of cigarette smoking have been attributed to their role in inducing a state of oxidative stress,⁶⁹ as a single puff of a cigarette exposes an individual to more than 10^{15} free radicals in the gas phase alone, coupled with additional exposure in the tar phase equal to 10^{17} free radicals per gram.³ Elevated resting levels of oxidative stress biomarkers have been reported in smokers compared to nonsmokers.^{67,70-72} In regards to acute exercise-induced oxidative stress, three studies have been conducted to date (Table 5).

Maximal exercise in the form of a GXT has been shown to elicit an increase in lipid peroxidation (MDA,¹¹ conjugated dienes²⁴) and protein carbonyls¹¹ in smokers despite no change in 8-hydroxydeoxyguanosine,¹¹ lipid hydroperoxides or circulating antioxidants.²⁴ Two studies noted an exacerbated increase in lipid peroxidation in smokers compared to nonsmokers.^{11,24} In opposition to the above results, one study noted no change in MDA, glutathione peroxidase (GPx) or superoxide dismutase (SOD), despite a decrease in vitamin E in smokers following 20 maximal knee extensions.⁷³ However, it is possible that the exercise stress was insufficient to induce any significant increase in RONS.⁷³

Summary: acute exercise-induced oxidative stress and disease. It is clear that acute exercise has the ability to result in increased RONS formation leading to an acute state of oxidative stress. Although null findings are present in a few investigations, increased oxidative stress biomarkers have been noted following acute exercise in both

healthy individuals and those with COPD, CVD, type 1 diabetes and obesity, as well as for cigarette smokers. What is not entirely clear is whether or not those with disease are at increased risk for further macromolecule oxidation as compared to otherwise healthy individuals. In this regard the available results are mixed, as shown in Tables 1–5. How this oxidative stress response and subsequent adaptation to the antioxidant defense system ultimately translates into long term prognosis remains to be determined. Perhaps a more pronounced increase in RONS due to acute exercise is necessary in certain disease conditions in order to allow for further beneficial adaptations within the antioxidant defense system. The following section discusses studies focused on antioxidant upregulation as an adaptation to regular exercise training.

Chronic Exercise, Antioxidant Defense and Disease

A heightened oxidative stress response to acute exercise may serve as a critical “signaling” mechanism for the upregulation in antioxidant defenses, similar to what is commonly observed in healthy populations.^{74,75} Please see Figure 1 for an overview of such adaptations. Although data are relatively scarce, a few studies have investigated the impact of regular aerobic and anaerobic exercise training in diseased populations on the attenuation of oxidative stress biomarkers and/or the upregulation of antioxidant defenses.

With respect to CHF^{76,77} and CAD,⁷⁸⁻⁸⁰ regular exercise training (12 weeks of moderate intensity aerobic exercise performed three days a week) has been shown to decrease lipid peroxidation^{76,78-80}

and nitrotyrosine formation,⁷⁶ as well promote an upregulation in antioxidant defense, evident by an increase in the activity of superoxide dismutase,^{77,79} glutathione peroxidase^{76,77} and catalase.⁷⁶ In agreement with the above results, six months of moderate intensity (50–70% HR_{max}) aerobic exercise resulted in a decrease in lipid peroxidation,^{81,82} as well as an increase in GSH and catalase activity in type 2 diabetics⁸¹ and obese individuals.⁸² A similar study in obese individuals reported an attenuation in exercise-induced lipid peroxidation following 24 weeks of a moderate intensity, total body, resistance training protocol.⁸³

In opposition to the above results, null findings with respect to DNA oxidation have been noted following regular resistance exercise training in patients with rheumatoid arthritis.⁸⁴ Moreover, negative findings have been noted in a few exercise training studies using COPD patients, evident by decreases in GSH,⁸⁵ and increases in GSSG⁴² and lipid peroxidation.⁸⁶ Explanations for these effects appear to be related to the muscle wasting commonly observed in these individuals.⁷ It has been suggested that muscle wasted COPD patients may be more susceptible to RONS-mediated attack due to decreases in GSH and other antioxidant defenses present within the musculature.⁸⁷ It may be that the exercise-induced increase in RONS production serves to overwhelm the already compromised antioxidant defense system present in such a way that impairs the bodies ability to adapt, thereby preventing any upregulation in antioxidant defenses, as well as promoting additional muscle wasting.

Considering the above, although the majority of work indicates beneficial effects of regular exercise training on the antioxidant defense system and oxidative status of individuals with known disease, there are discrepancies in the literature. This may be partly due to the disease state being investigated, characteristics of the subjects enrolled (e.g., age, sex, stage of disease), the exercise training protocol used, and the biomarkers measured. Related to the latter, it should be noted that biomarkers do not react the same way in many cases, as studies incorporating multiple biomarkers have commonly observed differing effects depending on the measure.^{42,76,78,80,82,86} In this way, it is certainly possible that a portion of the null findings may be attributed to an insufficient variety of biomarkers utilized, in particular as related to enzymatic and nonenzymatic antioxidants. Future investigations should consider the incorporation of a variety of oxidative stress and antioxidant biomarkers in their research design. Clearly, more research is needed in this area to more fully understand the role of regular exercise training in the upregulation in antioxidant defense and the attenuation of oxidative stress within diseased populations.

Conclusion

Although the results are disease dependent and appear somewhat mixed, individuals with known disease often experience an exacerbation in oxidative stress following acute exercise when compared to healthy controls. This increase may serve as a necessary “signal” for the upregulation in antioxidant defenses, thereby providing protection against subsequent exposure to prooxidant environments. Because diseased individuals appear chronically exposed to higher levels of RONS, any increase in antioxidant defense may prove to attenuate the oxidant stress, potentially resulting in a delay in disease progression. It is possible that chronic exercise may prove beneficial in this regard. If so, and in accordance with the recent

joint initiative of the American College of Sports Medicine and the American Medical Association, exercise may be viewed as “medicine” for individuals who are at increased risk for oxidative stress related illness and disease.

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