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REVIEW

Beneficial and harmful effects of exercise in hypertensive patients: the role of oxidative stress

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Oxidative stress has been implicated in the development and progression of hypertension. This review presents a comprehensive summary of original investigations focused on exercise-induced oxidative stress in hypertensive individuals. Single bouts of exercise can induce an acute state of oxidative stress. Chronic low-to-moderate exercise training improves the antioxidative defense and reduces the disease severity. However, the data that are currently available on the chronic intensive interval training-induced modification of the redox state in hypertensive patients are insufficient to draw adequate conclusions.
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INTRODUCTION

Under normal physiological conditions, oxidative stress (for example, an increased level of reactive oxygen species (ROS)) upregulates different signaling pathways and promotes cell survival. The generation of free radicals in the heart is needed for cellular responses such as myocardial growth and to maintain the smooth vascular tone.[1] One of the cellular adaptations associated with the generation of free radicals is mitochondrial biogenesis, where the improved efficiency of cardiac mitochondrial oxidative phosphorylation reduces the mitochondria permeability transition and increases the antioxidant capacity.[2] Over the last several years, evidence from both experimental and clinical studies has suggested that exercise training-mediated cardioprotection is due to improved intracellular redox signaling.[2–4] The physiological level of redox signaling (reversible oxidation processes) influences the vascular tone and both cardiac and skeletal muscle contractility.[4] In unbalanced redox systems, the variable roles of ROS may lead to various diseases, thus supporting the theory that exercise-induced oxidative stress can be damaging in the case of over-exercise syndrome, whereas oxidative stress can improve the oxidative defense and lead to cardiovascular protection[4,5]

Oxidative stress has been implicated not only in the development, but also in the progression of many cardiovascular diseases, including hypertension.[5–9] It is clearly documented that compared with healthy individuals, patients with cardiovascular diseases (CVD) have increased levels of biomarkers of oxidative stress and/or a decreased buffering capacity of the antioxidative protective systems (for example, superoxide dismutase (SOD); glutathione peroxidase (GPx); glutamyl-cysteine-synthase; catalase (CAT)).[7–9]

It has been shown that heart is highly susceptible to injury associated with ROS, which are generated by different mechanisms. Over 90% of the ATP required for the normal functioning of the heart is provided by the mitochondria via an efficient oxidative phosphorylation system.[7] Therefore, the overproduction of mitochondria-derived ROS, including increased NADPH oxidase and xanthine oxidase expression and activity, as well as elevated pro-inflammatory cytokine levels in the circulation (interleukin 1 and tumor necrosis factor) are associated with various cardiovascular conditions and diseases.[8,9]

Different CVD are associated with different target tissue of ROS and can thus be dominantly myocardial (post-infarction left ventricular remodeling, cardiomyopathy) or vascular (coronary artery disease, peripheral artery disease) or a combination of these (hypertension, heart failure).[6–8]

Physical activity and exercise, both aerobic and anaerobic, have favorable effects in the primary and secondary prevention of CVD.[10] Accordingly, the optimal levels of exercise capacity are associated with lower all-cause and cardiovascular mortality and morbidity.[10] However, acute exercise induces the overproduction of ROS and alters the delicate balance between free radical production and the antioxidant defense, thus representing a well-established model of oxidative stress.[11]

The purpose of the current review is to provide comprehensive data on the relationship between exercise and the ROS status in hypertensive individuals based on studies in animal models and on clinical trials (in hypertensive patients).

EXERCISE, OXIDATIVE STRESS AND HYPERTENSION: EXPERIMENTAL DATA

There is evidence that even acute bouts of exercise can ameliorate the endothelial function and lower the blood pressure (BP) in both

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healthy and hypertensive animals.[12–16] To date, the number of *in vivo* studies has been limited due to the complexity of exercise and the contributions of several organs and systems to ROS production.[17,18] Measurement of the tissue antioxidant capacity is providing more comprehensive insight into the biological effects of oxidative stress metabolites.[18–20] Another advantage of animal models is the more precise control of disease stages, which could be unstable in humans.

Numerous animal studies have shown significant improvements in the oxidative stress level after aerobic exercise training (Table 1).[19–26] Although the precise mechanism by which regular aerobic exercise improves the endothelial function is not yet clear, it is postulated that the enhancement of endothelium-dependent vasodilatation is mainly due to an increase in NO bioavailability.[19,20] In a study conducted by Sessa *et al.*[26] on the epicardial coronary arteries of dogs, the augmented shear stress after 10 days of exercise amplified the expression of the vascular endothelial constitutive NO synthase gene and led to acetylcholine (Ach)-stimulated NO release. Oxidized LDL has been shown to interfere with the formation of NO and to inactivate NO directly.[27]

Table 1 The influence of AET on biomarkers of oxidative stress in hypertension, experimental studies (trials)[19–25,27]

	Subjects	*Training*	*Tissue*	*Markers*
de Andrade *et al.*[19]	SHR ($n=14$)	AET on treadmill (13 weeks, 5 per week)	Cardiac	Lipid hydroperoxidation↓ 4-HNE↓
Blanko-Rivero *et al.*[20]	SHR	AET (12 weeks)	Mesenteric arteries	nNOS↑ $O_2^{\cdot-}$↓ NO↑
Roque *et al.*[21]	SHR ($n=16$)	AET on treadmill (12 weeks, 5 days per week, 1 h, 55–65 mrs)	Coronary/ mesenteric arteries	$O_2^{\cdot-}$↓ SOD↑ NO↑
Fernandes *et al.*[22]	SHR ($n=14$)	Swimming, (10 weeks, 5 days per week, 1 h)	Skeletal muscle	eNOS↑ iNOS↓
Kimura *et al.*[23]	SHR ($n=10$)	Voluntary running (10 weeks)	Aorta	SOD↑ 4-HNE↓ 3-NT↓
Agarwal *et al.*[24]	SHR ($n=10$)	AET treadmill (16 weeks)	Myocardium, plasma	iNOS↓ $O_2^{\cdot-}$↓ $OONO^-$↓ Total ROS↓ SOD↑ GSH/GSSG↑ NO↑
Bertagnolli *et al.*[27]	SHR ($n=7$)	AET on treadmill, till 20 m min^{-1} (10 weeks, 5 days per week, 1 h)	Heart	SOD↑ Total nitrates/ nitrites↑ NE↓ Lipid peroxidation↑
Husain *et al.*[25]	Rats with ethanol induced HT ($n=7$)	Treadmill run (12 weeks, 1 h per day)	Plasma	NO↑ MDA↑ NADPH↓ GSH/GSSG↑ SOD↑ Catalase↑ Gpx↑

Abbreviations: 3- NT, nitrotyrosine; 4-HNE, hydroxynonenal; AET, aerobic exercise training; GSH/GSSG, endogenous reduced to oxidized glutathione ratio; MDA, malondialdehyde; mrs, maximal runnung speed; NE, norepinephine; $O_2^{\cdot-}$, superoxide anion; $OONO^-$, peroxynitrite; ROS, reactive oxygen species; SHR, spontaneously hypertensive rats; SOD, superoxide dismutase; TAC, total antioxidant capacity.

In addition to the heart and skeletal muscles, the lungs, brain and blood contribute to ROS generation. Recent experimental studies have suggested a potential role for circulating T cells (which express AT1 Rc) in the NADPH-induced generation of ROS, and that this could have an important role in the genesis of hypertension.[17] Furthermore, increased sympathetic activity and elevated levels of catecholamines, especially norepinephrine, induce the production of ROS both directly (via oxidation) and indirectly (by stimulating NAD(P)H via the α1-adrenergic receptor).[26] In the angiotensin II (Ang II)-induced hypertensive rat model, exercise decreased the BP, attenuated cardiac hypertrophy and decreased the levels of oxidative stress and pro-inflammatory cytokines in the paraventricular nucleus, which is an area of the brain that is important for the sympathetic regulation of BP.[28] Pro-inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-1β, act as neuromodulators that have key roles in the sympathetic control of BP. Anti-inflammatory cytokines such as interleukin-10 also have a significant impact on the BP and influence cardiac remodeling. Cytokines and the renin–angiotensin system interact, possibly via the production of ROS. Recently, investigators have identified NADPH oxidase and superoxide as key intermediates in Ang II intraneuronal signaling, and scavenging enzyme/cooper/zinc SOD (Cu/Zn SOD) has been recognized to inhibit the overexpression of superoxide.[29] These effects are transient, and after just 2 weeks of detraining, the exercise-induced attenuation of oxidative stress in the brain (as indicated by the increased level of NADPH oxidase and decreased level of Cu/Zn SOD) is abolished.[28]

Yang *et al.*[13] demonstrated that high-intensity exercise could improve the vasorelaxation in hypertensive rats.[13,14] It has also been shown that animals with decreased levels of antioxidant enzymes, and those deficient in NADPH have significantly higher BPs.[21] Furthermore, there is evidence suggesting that aerobic exercise training modulates the balance between vascular oxidants and antioxidants by reducing the vascular expression of NADPH oxidase.[19]

EXERCISE, OXIDATIVE STRESS AND HYPERTENSION: HUMAN STUDIES

There is little evidence for the effects of both acute and chronic exercise on biomarkers of oxidative stress in humans.[30,31] Direct measurement of the ROS level is technically complicated and expensive, and free radicals are extremely short-lived and participate in reactions close to the site of their generation. Therefore, ROS biology in humans is still not clearly defined, and standard methods are lacking for evaluating oxidative stress in the clinical setting.

The potential sources and activities of ROS during exercise are still unclear. It is generally assumed that most of the ROS are produced by the contracting skeletal and heart muscle rather than the vascular wall, except in the case of substantial muscle damage, where inflammatory processes may have a crucial role.[15] The family of NAD(P)H oxidases, which are expressed mostly in skeletal muscles and all vascular cell types (but also in the kidneys, brain, neutrophils and T cells), have a key role in the genesis of ROS. The mitochondrial electron transport chain in different tissues and cells (phagocytes and neutrophils are the important ROS generators in hypertensive individuals), uncoupled endothelial nitric oxide synthase and xanthine oxidase are the major sources of ROS during exercise.[10] Furthermore, the extent of ROS generation is related not only to the type of training (static, dynamic),

and the intensity and duration of exercise, but also to the dietary carbohydrate and fat intake, smoking status and exercise capacity.[32–34]

The fact that endothelial adaptations have been reported in both the vascular beds of skeletal muscles and in various other organs that are inactive or less active during exercise supports the systemic effects of exercise on the redox state of the whole body. Shear stress factors are involved in physical activity, and active muscles release several cytokines and other peptides (myokines) with anti-inflammatory actions, which, in turn, increase the bioavailability of NO and decrease the ROS production.[35]

Emerging evidence about the relationship between hypertension and oxidative stress has led to confusion regarding whether ROS represent the cause or the consequence of hypertension. Nonetheless, studies have shown that oxidative damage appears before the clinical manifestation of elevated BP.[6,35,36] The increased production of ROS and/or a decreased antioxidant capacity may not be direct causes of hypertension, but do have a role in its pathogenesis in susceptible individuals.[6] Endothelial dysfunction, which is characterized by enhanced vasoconstriction and impaired endothelium-dependent vasodilatation, is closely associated with the overproduction of vascular ROS, predominantly by high Ang II-stimulated redox signaling.[37] Circulating Ang II induces the activity of NADPH oxidase in the vascular wall (vasoconstriction), kidneys (sodium retention) and brain (central sympathetic activation).[6]

It appears that the exercise-induced increase in ROS production also serves as a signal for the upregulation of antioxidant defense mechanisms, such as increasing the level of antioxidant enzyme systems.[35] Therefore, repeated acute (for example, chronic) exercise has been proposed as the most representative model of the beneficial role of ROS because it leads to adaptive changes in antioxidative protection and alterations of the net redox status.[38,39] It was recently reported that the ROS that are generated during exercise indirectly induce elevated gene expression of major antioxidants (SOD, GPx, glutamyl-cysteine-synthase) through the indirect activation of the nuclear factor-κB transcription factor.[40] The underlying causes responsible for the genetic markers associated with hypertension have been reported in recent studies. The *cytochrome b-245 alpha polypeptide* (*CYBA*) gene is important in cellular redox homeostasis. A few genetic polymorphisms of *CYBA* are known to influence NADPH oxidase activation as well as the formation of free radicals and antioxidant reduction. Genotype-phenotype correlations of *CYBA* genetic variants in hypertensive patients have shown that the risk alleles are associated with decreased oxidant and increased antioxidant levels, suggesting probable mechanisms underlying the pathology of hypertension, and are potential targets for pharmacological intervention.[41]

In contrast, an inverse relationship was found between the BP level and activity of antioxidants (for example, SOD, GPx), which might indicate that an attenuated antioxidative capacity has a role in the pathogenesis of hypertension.[42] The levels of systolic BP and diastolic BP were found to be positively correlated with markers of oxidative stress and negatively correlated with the antioxidant capacity.[6] In addition, antioxidants and ROS scavenging enzymes are capable of reducing BP. The intracellular antioxidant defense enzyme, SOD, probably has an important protective role in the pathogenesis of hypertension. It affects vasodilatation and preserves the levels of NO by preventing its inactivation by superoxide, vascular remodeling, changes in the renal sodium balance, sympathetic activity and cardiac hypertrophy.[34] Compared with normotensive subjects, patients with long-term hypertension (>3 years) have a lower SOD level before and after exercise.[11] The expression of antioxidative defense molecules is probably also related to the severity of hypertension. In patients with essential hypertension, lower antioxidative protection (lower levels of SOD) was associated with significantly impaired diastolic function.[43]

The hypertensive response to exercise in hypertensive patients is closely associated with elevated left atrial pressure; therefore, the left atrial volume index is an independent predictor of hypertensive response to exercise in those patients.[44] Using more sensitive echocardiographic techniques, such as tissue imaging and validation of the deformation induced by strain, a positive impact of exercise training on the systolic and diastolic left and right ventricle functions was observed in pharmacologically treated hypertensive patients.[45]

Hypertensive patients have a diminished capacity of the antioxidant defense system, and therefore experience an exacerbation of oxidative stress following exercise.[44,45] The lower levels and bioavailability of antioxidant enzyme systems (SOD, GPX and CAT) found in hypertensive subjects, both before and after acute exercise, resulted in excessive oxidative impairment. Furthermore, in patients with hypertension, blunted SOD production during exercise was associated with a lower exercise capacity.[11,43]

OXIDATIVE STRESS AND HYPERTENSION: THERAPEUTIC APPROACHES USING DIFFERENT TYPES OF TRAINING

A plethora of evidence suggests that regular aerobic physical activity is one of the most effective non-pharmacological approaches to prevent and treat hypertension. A prospective 4.7-year follow-up study with 6278 participants showed that moderate- and high-intensity fitness were associated with a 26 and 42% lower risk of hypertension, respectively.[46] Exercise, either dynamic or static, is capable of reducing the resting systolic BP and diastolic BP by 3.0 and 2.4 mm Hg, respectively, in healthy subjects and by 6.9 and 4.9 mm Hg, respectively, in hypertensive subjects.[47] In patients with hypertension, exercise may improve the endothelial function and decrease the BP.[7,48] In patients with mild hypertension, 6 months of aerobic exercise training (three times per week at 50–70% of the maximal oxygen consumption, VO_2max) led to improvements in the aerobic capacity that were accompanied by improvements in the redox state (for example, an increase in antioxidative capacity and a decrease in urinary NO metabolites).[16]

During acute exercise associated with a progressive increase in oxygen consumption, there is an acute state of oxidative stress that occurs with the overproduction of tissue and plasma free radicals.[38] This oxidative stress is the consequence of two parallel processes: an increase in the endothelial shear stress and the inefficiency of the mitochondrial respiratory chain. Both processes are followed by elevated antioxidant levels. Both aerobic and anaerobic exercises induce ROS production, which might lead to oxidative stress. The production of ROS depends on the exercise intensity, duration (protocol) and type and on the level of aerobic capacity (maximal oxygen consumption, training status), age, smoking and diet, as previously mentioned.[33,38,43] During low-intensity and short-duration exercise, the antioxidant defense is usually sufficient to counter the ROS production and prevent oxidative damage. Throughout exhaustive exercise, the metabolic rate in skeletal muscles may increase to almost 100 times the resting levels, and the consequent multiple-fold increase in oxygen consumption is associated with a higher production of ROS, followed by an upregulation of the antioxidant defense. However, newer trends in cardiac rehabilitation suggest that high-intensity interval training (HIIT) might be not only a more time-efficient alternative, but also beneficial in secondary prevention in terms of improving the exercise capacity, metabolic profile and BP.[46,47,49–51] Vigorous leisure-time physical activity is

associated with improved carotid arterial distensibility and a decreased resting heart rate in older healthy adults.[52,53]

However, there are limited data on the usefulness of high-intensity exercise in the treatment of hypertensive subjects in light of ROS modulations. In their recent meta-analysis, Weston *et al.*[53] observed that HIIT is not only more enjoyable, but also superior to the moderate-intensity continuous training in terms of increasing the aerobic capacity and NO availability, reducing the systolic BP and diastolic BP, reducing oxidative stress and inflammation, and improving the insulin sensitivity, β-cell function and lipid profile in patients with hypertension, obesity, metabolic syndrome, coronary artery disease and heart failure. They proposed a program comprising 3 days per week of a 40 min HIIT protocol consisting of the following: 10 min of warm-up at 60% of the maximal heart rate (HRmax), 4×4 min intervals at 85–95% of the HRmax with 3×3 min of active pauses between the exercise bouts at 70% of the HRmax, followed by a 5 min cool-down at 50% of the HRmax.[53] Several studies showed that high-intensity exercise is associated with a substantial induction of NADPH oxidase activity, through various mechanisms, including effects on neutrophils, which are the main sources of extracellular ROS production.[53,54] In well-trained individuals, HIIT also increases the VO_2max and upregulates the antioxidant status (increases SOD, GPx and CAT in erythrocytes). Braith *et al.*[55] showed the utility of both moderate and HIIT, with a more substantial impact on aerobic capacity found for HIIT.[55] Moreover, HIIT significantly reduces the BP level, improves the exercise capacity and lipid profile, and induces higher levels of antioxidant enzyme activity (SOD and CAT).[33,51,53,56] Those findings are in line with the previous evidence that high-intensity exercise is more valuable than moderate-intensity exercise in improving the aerobic capacity and lipid profile.[57]

Goto *et al.*[30] showed that 12 weeks of high-intensity exercise increased the concentrations of biomarkers of oxidative stress more than moderate-intensity exercise did, leading to increases in the levels of 8-hydroxy-2-deoxyguanosine (in plasma) and malondialdehyde-modified LDL (in serum, indicator of oxidized LDL) in healthy subjects.[30] However, that study also showed that only moderate exercise (not mild- or high-intensity exercise) increased the endothelium-dependent vasodilatation through NO.[30] In normal subjects, long-term high-intensity exercise (70–80% VO_2max) might impair endothelium-dependent vasodilatation by depleting the antioxidative capacity (decreasing α-tocopherol and β-carotene). In hypertensive subjects, the potential of low-to-moderate- and high-intensity exercise programs to lower the BP was almost equal. At least 30 min of moderate-intensity dynamic aerobic exercise daily, preferably combined with dynamic resistant training 2–3 days per week, is generally recommended for hypertensive patients.[47]

A recent study showed that standard (moderate) exercise training, but not HIIT, prevents hypertension-induced fibrosis of the heart, stimulates cardiac angiogenesis and increases the endothelial nitric oxide synthase content. The same study also found that in the presence of hypertension, HIIT induced substantial cardiac hypertrophy, for example, pathological remodeling of the heart.[54] Given these somewhat conflicting results, future studies will be needed to elucidate methods to stratify patients to obtain the best therapeutic benefit of exercise. Compared with healthy individuals, patients with CVD show significant differences in the extent of exercise-induced ROS production and antioxidative protection, so the complex mechanisms underlying the detrimental and beneficial roles of ROS associated with exercise in this population are still unclear.

It has been reported that high-fat meals induce extensive mitochondrial ROS production, and that chronic exposure to postprandial lipemia-induced oxidative stress might be associated with endothelial dysfunction and an increased cardiovascular risk. Several studies have proven that HIIT is an effective intervention to reduce postprandial lipemia. Other promising strategies are fasted-state and prior (day) exercise, which substantially reduce postprandial glycemia and lipemia, respectively. It was recently reported that prior exercise diminished the adverse impact of postprandial lipemia on the intracellular ROS generation, consequently increasing the antioxidant gene expression and reducing the intracellular lipid uptake.[55] Accordingly, prior exercise might be effective in preventing the oxidative stress-mediated detrimental effects of high-fat consumption on the CVS.

Repeated exercise-induced alterations in laminar shear stress increase the levels and activity of SOD, CAT and GPx.[18,58] However, Xie *et al.*[59] showed that the use of a ROS scavenger (for example, PEG CAT, which eliminates H_2O_2) almost completely abolished the coronary arteriole vasodilatation induced by exercise training.[60] In addition, the diminished excitation–contraction coupling shown under conditions where ROS activity was depleted (after the administration of antioxidants) raises doubts about the rationale of using antioxidants immediately before moderate-intensity exercise.[34,61,62]

The widespread use of antioxidant supplementation, especially in the athletic population, is based on evidence that it could neutralize the detrimental effects of ROS and thereby diminish muscle damage and improve performance. However, because it was clearly demonstrated that the endogenous 'antioxidant' effects of exercise are generated primarily by ROS themselves, the use of antioxidant supplements has been questioned in circumstances in which the redox balance is preserved. Several studies have proven that antioxidant supplements could, in fact, hamper the favorable adaptation to exercise. For example, Gomez-Cabrera *et al.*[34] recently discussed this issue and proposed that antioxidants might be beneficial in situations where ROS overproduction could impact exhaustion (such as during competition), but not on an everyday basis, during training, where the ROS carry adaptive, physiological roles. Data about the impact of antioxidant supplementation on exercise adaptation in hypertensive patients are still lacking.

PERSPECTIVE

Future trials are needed to evaluate the effects of exercise on the cardiovascular system in hypertensive patients, particularly with regard to the ROS level and antioxidative defense, especially those focused on the adaptive upregulation of the mitochondrial redox balance and signaling in myocardial and vascular cells. Such data will be important because therapeutic exercise training programs, as well as antioxidant supplementation, could be useful in hypertensive patients.

CONCLUSION

In this review, we evaluated the role of oxidative stress in hypertensive individuals in terms of disease development and prognosis and regarding different types of provocative or therapeutic exercise (acute, chronic and intensive interval training). A handful of investigators have noted an exacerbation of oxidative stress in hypertensive patients compared to healthy controls and documented that ROS have an important role in the development and course of hypertension. However, all forms of exercise are related to higher ROS production in both humans and animal models. Several factors appear to be important for the exercise-induced oxidative stress response, including the form, duration and intensity of exercise as well as the training status and dietary intake. Chronic low-to-moderate-intensity exercise training has been documented to ameliorate the ROS levels, but the

available data regarding the redox changes that occur during HIIT are conflicting, and additional studies are needed.

To suggest an optimal therapeutic modality of exercise, we summarized the available data regarding the beneficial and harmful effects of ROS in hypertensive individuals. Although excessive ROS production and oxidative stress during exercise can certainly result in physiological damage, occasionally even including irreparable oxygen injuries, an optimal level of pro-oxidant production may actually serve as a necessary stimulus for the upregulation of antioxidant defense mechanisms, thereby providing protection against future ROS attacks and disease development. In humans, the role of oxidative stress in exercise-induced adaptation is already well known. However, the critical level of ROS production required for optimal cardiovascular adaptation for different modes of exercise training in healthy subjects and in hypertensive patients is still undefined.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Lim HY, Wang W, Chen J, Ocorr K, Bodmer R. ROS regulate cardiac function via a distinct paracrine mechanism. *Cell Rep* 2014; **7**: 35–44.
2 Campos JC, Queliconi BB, Dourado PM, Cunha TF, Zambelli VO, Bechara LR, Kowaltowski AJ, Brum PC, Mochly-Rosen D, Ferreira JC. Exercise training restores cardiac protein quality control in heart failure. *PLoS ONE* 2012; **7**: e52764.
3 Bezzerides V, Rosenzweig A. Saying yes to exercise and NO to cardiac injury. *Circ Res* 2011; **108**: 1414–1416.
4 Campos JC, Gomes KM, Ferreira JC. Impact of exercise training on redox signalling in cardiovascular diseases. *Food Chem Toxicol* 2013; **62**: 107–119.
5 Majzunova M, Dovinova I, Barancik M, Chan JY. Redox signalling in pathophysiology of hypertension. *J Biomed Sci* 2013; **20**: 69.
6 Montezano AC, Dulak-Lis M, Tsiropoulou S, Harvey A, Briones AM, Touyz RM. Oxidative stress and human hypertension: vascular mechanisms, biomarkers, and novel therapies. *Can J Cardiol* 2015; **31**: 631–641.
7 Tsutsui H, Ide T, Kinugawa S. Mitochondrial oxidative stress, DNA damage, and heart failure. *Antioxid Redox Signal* 2006; **8**: 1737–1744.
8 Hori M, Nishida K. Oxidative stress and left ventricular remodelling after myocardial infarction. *Cardiovasc Res* 2009; **81**: 457–464.
9 Tsutsui H, Kinugawa S, Matsushima S. Mitochondrial oxidative stress and dysfunction in myocardial remodelling. *Cardiovasc Res* 2009; **81**: 449–456.
10 Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation* 2010; **122**: 1637–1648.
11 Dekleva M, Lazic JS, Pavlovic-Kleut M, Mazic S, Stevanovic A, Soldatovic I, Markovic-Nikolic N, Beleslin B. Cardiopulmonary exercise testing and its relation to oxidative stress in patients with hypertension. *Hypertens Res* 2012; **35**: 1145–1151.
12 Cheng L, Yang C, Hsu L, Lin MT, Jen CJ, Chen HI. Acute exercise enhances receptor-mediated endothelium-dependent vasodilation by receptor upregulation. *J Biomed Sci* 1999; **6**: 22–27.
13 Yang AL, Lo CW, Lee JT, Su CT. Enhancement of vasorelaxation in hypertension following high-intensity exercise. *Chin J Physiol* 2011; **54**: 87–95.
14 Yang AL, Su CT, Lin KL, Lee SD. Enhancement of vascular function mediated by insulin and insulin-like growth factor-1 following single exercise session. *Chin J Physiol* 2008; **51**: 71–77.
15 Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. *Physiol Rev* 2008; **88**: 1243–1276.
16 Feairheller DL, Brown MD, Park JY, Brinkley TE, Basu S, Hagberg JM, Ferrell RE, Fenty-Stewart NM. Exercise training, NADPH oxidase p22phox gene polymorphisms, and hypertension. *Med Sci Sports Exerc* 2009; **41**: 1421–1428.
17 Trott DW, Harrison DG. The immune system in hypertension. *Adv Physiol Educ* 2014; **38**: 20–24.
18 Rush JW, Turk JR, Laughlin MH. Exercise training regulates SOD-1 and oxidative stress in porcine aortic endothelium. *Am J Physiol Heart Circ Physiol* 2003; **284**: H1378–H1387.
19 de Andrade LH, de Moraes WM, Matsuo EH Jr, de Orleans Carvalho de Moura E, Antunes HK, Montemor J, Antonio EL, Bocalini DS, Serra AJ, Tucci PJ, Brum PC, Medeiros A. Aerobic exercise training improves oxidative stress and ubiquitin proteasome system activity in heart of spontaneously hypertensive rats. *Mol Cell Biochem* 2015; **402**: 193–202.
20 Blanco-Rivero J, Roque FR, Sastre E, Caracuel L, Couto GK, Avendaño MS, Paula SM, Rossoni LV, Salaices M, Balfagón G. Aerobic exercise training increases neuronal nitric oxide release and bioavailability and decreases noradrenaline release in mesenteric artery from spontaneously hypertensive rats. *J Hypertens* 2013; **31**: 916–926.
21 Roque FR, Briones AM, García-Redondo AB, Galán M, Martínez-Revelles S, Avendaño MS, Cachofeiro V, Fernandes T, Vassallo DV, Oliveira EM, Salaices M. Aerobic exercise reduces oxidative stress and improves vascular changes of small mesenteric and coronary arteries in hypertension. *Br J Pharmacol* 2013; **168**: 686–703.
22 Fernandes T, Nakamuta JS, Magalhães FC, Roque FR, Lavini-Ramos C, Schettert IT, Coelho V, Krieger JE, Oliveira EM. Exercise training restores the endothelial progenitor cells number and function in hypertension: implications for angiogenesis. *J Hypertens* 2012; **30**: 2133–2143.
23 Kimura H, Kon N, Furukawa S, Mukaida M, Yamakura F, Matsumoto K, Sone H, Murakami-Murofushi K. Effect of endurance exercise training on oxidative stress in spontaneously hypertensive rats (SHR) after emergence of hypertension. *Clin Exp Hypertens* 2010; **32**: 407–415.
24 Agarwal D, Haque M, Sriramula S, Mariappan N, Pariaut R, Francis J. Role of proinflammatory cytokines and redox homeostasis in exercise-induced delayed progression of hypertension in spontaneously hypertensive rats. *Hypertension* 2009; **54**: 1393–1400.
25 Husain K, Mejia J, Lalla J. Physiological basis for effect of physical conditioning on chronic ethanol-induced hypertension in a rat model. *Mol Cell Biochem* 2006; **289**: 175–183.
26 Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. *Circ Res* 1994; **74**: 349–353.
27 Bertagnolli M, Schenkel PC, Campos C, Mostarda CT, Casarini DE, Belló-Klein A, Irigoyen MC, Rigatto K. Exercise training reduces sympathetic modulation on cardiovascular system and cardiac oxidative stress in spontaneously hypertensive rats. *Am J Hypertens* 2008; **21**: 1188–1193.
28 Agarwal D, Dange RB, Vila J, Otamendi AJ, Francis J. Detraining differentially preserved beneficial effects of exercise on hypertension: effects on blood pressure, cardiac function, brain inflammatory cytokines and oxidative stress. *PLoS ONE* 2012; **7**: e52569.
29 Zimmerman MC, Lazartigues E, Sharma RV, Davisson RL. Hypertension caused by angiotensin II infusion involves increased superoxide production in the central nervous system. *Circ Res* 2004; **95**: 210–216.
30 Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, Kawamura M, Chayama K, Yoshizumi M, Nara I. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation* 2003; **108**: 530–535.
31 DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, Seals DR. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* 2000; **102**: 1351–1357.
32 Park JY, Ferrell RE, Park JJ, Hagberg JM, Phares DA, Jones JM, Brown MD. NADPH oxidase p22phox gene variants are associated with systemic oxidative stress biomarker responses to exercise training. *J Appl Physiol* 2005; **99**: 1905–1911.
33 Fukai T, Ushio-Fukai M. Superoxide dismutases: role in redox signaling, vascular function, and diseases. *Antioxid Redox Signal* 2011; **15**: 1583–1606.
34 Gomez-Cabrera MC, Domenech E, Viña J. Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. *Free Radic Biol Med* 2008; **44**: 126–131.
35 Korsager Larsen M, Matchkov VV. Hypertension and physical exercise: The role of oxidative stress. *Medicina* 2016; **52**: 19–27.
36 Nambiar S, Viswanathan S, Zachariah B, Hanumanthappa N, Magadi SG. Oxidative stress in prehypertension: rationale for antioxidant clinical trials. *Angiology* 2009; **60**: 221–234.
37 Touyz RM. Intracellular mechanisms involved in vascular remodelling of resistance arteries in hypertension: role of angiotensin II. *Exp Physiol* 2005; **90**: 449–455.
38 Fisher-Wellman K, Bell HK, Bloomer RJ. Oxidative stress and antioxidant defence mechanisms linked to exercise during cardiopulmonary and metabolic disorders. *Oxid Med Cell Longev* 2009; **2**: 43–51.
39 Mrakic-Sposta S, Gussoni M, Porcelli S, Pugliese L, Pavei G, Bellistri G, Montorsi M, Tacchini P, Vezzoli A. Training effects on ROS production determined by electron paramagnetic resonance in master swimmers. *Oxid Med Cell Longev* 2015; **2015**: 804794.
40 Gomez-Cabrera MC, Salvador-Pascual A, Cabo H, Ferrando B, Viña J. Redox modulation of mitochondriogenesis in exercise. Does antioxidant supplementation blunt the benefits of exercise training? *Free Radic Biol Med* 2015; **86**: 37–46.
41 Kumar R, Kohli S, Ali Z, Duhan K, Ram R, Gupta M, Tyagi S, Mohammad G, Pasha MQ. CYBA (p22phox) variants associate with blood pressure and oxidative stress markers in hypertension: a replication study in populations of diverse altitudes. *Hypertens Res* 2015; **38**: 498–506.
42 Dalle-Donne I, Rossi R, Colombo R, Giustarini D, Milzani A. Biomarkers of oxidative damage in human disease. *Clin Chem* 2006; **52**: 601–623.
43 Dekleva M, Celic V, Kostic N, Pencic B, Ivanovic AM, Caparevic Z. Left ventricular diastolic dysfunction is related to oxidative stress and exercise capacity in hypertensive patients with preserved systolic function. *Cardiology* 2007; **108**: 62–70.
44 Lee SE, Youn JC, Lee HS, Park S, Lee SH, Cho IJ, Shim CY, Hong GR, Choi D, Kang SM. Left atrial volume index is an independent predictor of hypertensive response to exercise in patients with hypertension. *Hypertens Res* 2015; **38**: 137–142.

45 Leggio M, Mazza A, Cruciani G, Sgorbini L, Pugliese M, Bendini MG, Severi P, Jesi AP. Effects of exercise training on systo-diastolic ventricular dysfunction in patients with hypertension: an echocardiographic study with tissue velocity and strain imaging evaluation. *Hypertens Res* 2014; **37**: 649–654.
46 Shook RP, Lee DC, Sui X, Prasad V, Hooker SP, Church TS, Blair SN. Cardiorespiratory fitness reduces the risk of incident hypertension associated with a parental history of hypertension. *Hypertension* 2012; **59**: 1220–1224.
47 Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2013; **2**: e004473.
48 Briones AM, Touyz RM. Oxidative stress and hypertension: current concepts. *Curr Hypertens Rep* 2010; **12**: 135–142.
49 Harris DA, Das AM. Control of mitochondrial ATP synthesis in the heart. *Biochem J* 1991; **280**(Pt 3): 561–573.
50 Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology* 2013; **28**: 330–358.
51 Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol* 2015; **119**: 753–758.
52 Bergholm R, Mäkimattila S, Valkonen M, Liu ML, Lahdenperä S, Taskinen MR, Sovijärvi A, Malmberg P, Yki-Järvinen H. Intense physical training decreases circulating antioxidants and endothelium-dependent vasodilation *in vivo*. *Atherosclerosis* 1999; **145**: 341–349.
53 Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med* 2014; **48**: 1227–1234.
54 O'Donovan G, Owen A, Bird SR, Kearney EM, Nevill AM, Jones DW, Woolf-May K. Changes in cardiorespiratory fitness and coronary heart disease risk factors following 24 wk of moderate- or high-intensity exercise of equal energy cost. *J Appl Physiol* 2005; **98**: 1619–1625.
55 Braith RW, Pollock ML, Lowenthal DT, Graves JE, Limacher MC. Moderate- and high-intensity exercise lowers blood pressure in normotensive subjects 60 to 79 years of age. *Am J Cardiol* 1994; **73**: 1124–1128.
56 Paoli A, Pacelli QF, Moro T, Marcolin G, Neri M, Battaglia G, Sergi G, Bolzetta F, Bianco A. Effects of high-intensity circuit training, low-intensity circuit training and endurance training on blood pressure and lipoproteins in middle-aged overweight men. *Lipids Health Dis* 2013; **12**: 131.
57 Huynh QL, Blizzard CL, Raitakari O, Sharman JE, Magnussen CG, Dwyer T, Juonala M, Kähönen M, Venn AJ. Vigorous physical activity and carotid distensibility in young and mid-aged adults. *Hypertens Res* 2015; **38**: 355–360.
58 Holloway TM, Bloemberg D, da Silva ML, Simpson JA, Quadrilatero J, Spriet LL. High intensity interval and endurance training have opposing effects on markers of heart failure and cardiac remodeling in hypertensive rats. *PLoS ONE* 2015; **10**: e0121138.
59 Xie W, Parker JL, Heaps CL. Effect of exercise training on nitric oxide and superoxide/H_2O_2 signalling pathways in collateral-dependent porcine coronary arterioles. *J Appl Physiol* 2012; **112**: 1546–1555.
60 Jenkins NT, Landers RQ, Thakkar SR, Fan X, Brown MD, Prior SJ, Spangenburg EE, Hagberg JM. Prior endurance exercise prevents postprandial lipaemia-induced increases in reactive oxygen species in circulating CD31+ cells. *J Physiol* 2011; **589** (Pt 22): 5539–5553.
61 Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, Kajiyama G, Oshima T. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. *Circulation* 1999; **100**: 1194–1202.
62 Khawli FA, Reid MB. N-acetyl cysteine depresses contractile function and inhibits fatigue of diaphragm *in vitro*. *J Appl Physiol* 1994; **77**: 317–324.