Review Article

Update on the Mechanisms of Pulmonary Inflammation and Oxidative Imbalance Induced by Exercise

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Received 26 July 2015; Revised 2 November 2015; Accepted 8 November 2015

Academic Editor: Geraint D. Florida-James

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The mechanisms involved in the generation of oxidative damage and lung inflammation induced by physical exercise are described. Changes in lung function induced by exercise involve cooling of the airways, fluid evaporation of the epithelial surface, increased contact with polluting substances, and activation of the local and systemic inflammatory response. The present work includes evidence obtained from the different types of exercise in terms of duration and intensity, the effect of both acute performance and chronic performance, and the influence of special conditions such as cold weather, high altitude, and polluted environments. Levels of prooxidants, antioxidants, oxidative damage to biomolecules, and cellularity, as well as levels of soluble mediators of the inflammatory response and its effects on tissues, are described in samples of lung origin. These samples include tissue homogenates, induced sputum, bronchoalveolar lavage fluid, biopsies, and exhaled breath condensate obtained in experimental protocols conducted on animal and human models. Finally, the need to simultaneously explore the oxidative/inflammatory parameters to establish the interrelation between them is highlighted.

1. Introduction

When doing physical exercise, the usual levels of organic performance are exceeded. However, we are designed to execute the exercise, depending on its variety, duration, intensity, and the environmental conditions under which it is done. The physiological and pathological processes will be activated, which can lead to the generation of an oxidative imbalance and the establishment of an inflammatory process [1, 2]. The oxidative damage happens as an additional cost of using oxygen to obtain energy and can occur when there is an increase in the formation of prooxidants and/or when the antioxidant defense decreases, causing an alteration of tissue product functionality of the structural damage to all the cellular components that contain lipids, carbohydrates, proteins, and nucleic acids [3]. Another response mechanism to physical stress is inflammation, which is triggered as a reaction to the mechanical damage of structural components (connective tissue; muscle, tendon, and bone) and nonstructural components (erythrocytes, endothelium, and epithelia) of the body [4–8]. As a result, stress hormones are released, such as cortisol and catecholamines, which activates the immune system, causing a particular response profile based on the release of soluble mediators (cytokines) and arachidonic acid derivatives (prostaglandins and leukotrienes). The latter and the stress hormones will cause changes in the number and activation of leukocytes subpopulations to the point that intense exercise of long duration can induce immune suppression (increasing the susceptibility to infection) [9], in contrast to the exercise of moderate intensity, which boosts the immune response. Both the alteration of the redox system and the inflammatory reaction have multiple...
points of interaction that have been previously evidenced [10–12]. The study of inflammatory/oxidative damage at a pulmonary level has been a topic poorly addressed [13–15], particularly in healthy humans and even more so in athletes. Most of the information in this subject arises from pathophysiology of pulmonary diseases, such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease [16–27]. The lung has the crucial role of gas exchange and experiences great modifications of its activity during the exercise. This mobilizes larger volumes of air and modifies the breathing pattern from nasal to oral, increasing contact with a greater amount of pollutants that may be present in the environment. Also, the lung receives a greater amount of blood flow to increase the exchange in places that are well ventilated, which causes changes in the functioning of the vascular parenchyma [28, 29]. However, the anatomic-functional characteristics of the lungs make it very difficult to obtain information of the redox/inflammatory state in the different sectors of this organ. This work brings together the scientific papers that have addressed the phenomenon, as well as their potential explication on those who exercise.

2. Effects of Exercise on the Respiratory System and Its Relationship with the Generation of Oxidative/Inflammation Damage

When exercising, the mobilized air flow or pulmonary ventilation increases. This is explained by the increase of the respiratory rate, the tidal volume, and the appearance of bronchodilation. In addition to this, the pulmonary vascular bed will vasodilate to receive a greater blood flow. These changes, taken together, aim to increase gas exchange. Large air flows entering the lung during exercise will cause a modification of the breathing pattern towards one predominately oral, favoring the evaporation of the fluid covering the pulmonary epithelium and the decrease of temperature of the airways. As a result, the pulmonary passages will cool down and the osmolality of the epithelium will increase [30]. It should be noted that the cooling of the pulmonary passages as a result of the hyperventilation has been observed at comfortable environment temperature (±20°C) [31]. In this way, McFadden Jr. and Pichurko [31] showed a decrease of the tracheal temperature of 34°C at pulmonary ventilation of 15 L/min and of 31°C at 100 L/min. The cooling of the airway by hyperventilation produced by exercise is homologous to breathing cold air at rest. The latter is probably in the absence of air pollutants, the main irritive/proinflammatory factor of this region of our body. In cold environments, there is a greater amount of reports of respiratory symptoms [32] and chronic changes of epithelium similar to those of patients with chronically inflamed airways (e.g., asthmatics). Some authors observed, in humans, that the product of intense exercise appears to have similar symptoms to those observed in infection of upper airways [33–35]. However, with moderate training these symptoms decreased [36, 37]. It is probable that intense exercise of long duration, such as a marathon, will increase the susceptibility to infection of the airway by depression of the immune function, contrary to the effect caused by exercise of moderate intensity. Another factor involved in the oxidative/proinflammatory process of the airway is the greater contact with toxic particles and microorganisms present in the environment due to hyperventilation by exercise [38–40]. For example, the damaging effect on lung tissue of environmental substances such as chlorine, ozone, nitrogen oxides, particulate matter, and pollen is recognized [14, 41–43]. The entry of these substances by the pulmonary route can potentially generate systemic inflammation [44, 45] and this will affect the lungs. Finally, another factor of the recognized destabilizing effect of the oxidative balance and in favor of pulmonary inflammation is hypoxia [46, 47]. The general framework for the development of functional changes of the lung by exercise, the activation of the redox imbalance, and the inflammatory system are described in Figure 1.

3. Changes in Pulmonary Redox State and Exercise-Induced Inflammation

As mentioned previously, physical exercise induces changes in the redox/inflammatory state of the organism, at both systemic level and the different organs. In this regard, lung is one of the less studied organs in this context. In the following paragraphs, the most relevant results regarding pulmonary oxidative damage and inflammation caused by exercise are summarized. In this review, the work carried out in healthy subjects was privileged. Regarding the special conditions, hypoxia, water contaminants (chlorine), and cold have been included, leaving aside air pollutants, because there are several reviews regarding this subject [48, 49]. The details of the studies included in terms of goals, characteristics of the sample, the protocol used, and the results related to the pulmonary oxidative/inflammation damage by exercise are summarized in Tables 1 and 2 for human and animals, respectively.

4. Pulmonary Redox Balance and Acute Exercise

A direct relationship has also been reported during exercise, between the acute exercise intensity and the volume of exhaled nitric oxide (VNO), namely, volume minute (VE) multiplied by exhaled nitric oxide (eNO), for sedentary healthy [50, 60, 68, 69, 71, 82, 85–87, 90] and trained subjects [75, 89]. During exercise, eNO have been reported to be decreased when increasing VO2 [59, 75] and VE [75] in sedentary and active subjects [51, 60, 68, 69, 75, 82, 85, 86, 92]. In athletes, unlike Maroun et al. [75], Kippelen et al. [68] showed changes in eNO during exercise. In animal model, while exercising healthy horses, Mills et al. [112] observed a linear increase of the VNO as the oxygen consumption increased. After exercise, nitric oxide concentrations have
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AWs: airways; BALF: bronchoalveolar lavage fluid; CAD: coronary artery disease; CC16: Clara cell secretory protein; CHF: chronic heart failure; COPD: chronic obstructive pulmonary disease; Cys-Lts: cysteinyl leukotrienes; EB: exhaled breath; EBC: exhaled breath condensate; EIAH: exercise-induced arterial hypoxemia; EIB: exercise-induced bronchoconstriction; eNO: exhaled nitric oxide; FE(NO): fractional exhaled nitric oxide; HCO$_3^-$: bicarbonate; H$_2$O$_2$: hydrogen peroxide; HRmax: maximum heart rate; IFN-γ: interferon gamma; IFN-γ-induced protein-10: interferon-gamma-induced protein-10; IL-1αp70, IL-4, IL-8, and IL-10: interleukin-1αp70, interleukin-4, interleukin-8, and interleukin-10; IS: induced sputum; L-NMMA: N-monomethyl-L-arginine; L-lactate: lactate; LTB$_4$: leukotriene B$_4$; LTE$_{4}$: leukotriene E$_{4}$; MØ: macrophages; MAS: maximal aerobic speed; MS: mitral stenosis; MDA: malondialdehyde; MPO: myeloperoxidase; MASL: meters above sea level; NaCLO: sodium hypochlorite; NO$_2^-$: nitrite; NO output: nitric oxide output (eNO x VE); PGE$_2$: prostaglandin E$_2$; $P_{\text{max}}$: maximal power output; RANTES: regulated upon activation, normal T-cellexpressed, and secreted; TBARS: thiobarbituric acid reactive species; TNF(-α): tumor necrosis factor (alpha); TXB$_2$: thromboxane B$_2$; Se: selenium; VE: minute ventilation; VEGF: vascular endothelial growth factor; VNO: volume of nitric oxide; VO$_2$max: oxygen uptake (maximal); VT: tidal volume. In “Oxidative or inflammatory main results,” DE: during exercise and PE: postexercise. In “Aim,” *the effect of exercise was not the primary aim of the study. 

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</tr>
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AWs: airways; BALF: bronchoalveolar lavage fluid; EB: exhaled breath; EBC: exhaled breath condensate; EPO: eosinophil peroxidase; H₂O₂: hydrogen peroxide; IS: induced sputum; 8-isoprostane PGF₂α: 8-isoprostane prostaglandin F₂ alpha; MØ: macrophages; MPO: myeloperoxidase; NO: nitric oxide; PMNs: polymorphonuclear neutrophils; T: training volume; TNF-α: tumor necrosis factor-alpha. In “Aim,”* the effect of exercise was not the primary aim of the study.
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<td>Huang et al. 2008 [110]</td>
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<td>Kirschvink et al. 2002 [13]</td>
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<td>BALF</td>
<td>PE: ↑ [UA] in healthy horses</td>
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### Author, year | Aim | Sample characteristics | Exercise protocols | Samples obtained | Oxidative or inflammatory main results
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Lin et al. 2005 [111] | Oxidative stress and antioxidant defenses in animals supplemented or not with L-Arg* | Sprague-Dawley rats grouped as exercised (E) or sedentary (S) with L-Arg (+L-Arg) or control rats without L-Arg (C) | Race on treadmill for E groups at 20 m/min for 15 min and 25 m/min for 30 min; then they run at 30 m/min and 10% of inclination (70–75% VO2 max) until exhaustion (EC ~81 min and E+L-Arg ~87 min) | Lung tissue | PE: ↑ activity XO and MPO in EC in comparison to SC; ↑ [UA]; ↑ [NO], and ↑ [MDA] in EC in comparison to SC; ↑ activity SOD and GR in EC in comparison to SC
Mills et al. 1996 [112] | eNO and VNO during acute exercise | Healthy horses | Maximal incremental race until 9 m/s | EB | PE: positive correlation of eNO and VNO with the race intensity
Radák et al. 1998 [113] | Acute anaerobic exercise and oxidative modification of pulmonary proteins | Exercised Wistar rats (E) and sedentary control rats (C) | Two races on treadmills at 30 m/min for 5 min; after 5 min of recovery, a 3rd race to exhaustion was performed | Lung tissue | PE: > [SOD] and < [GSH-Px] in rats deficient in VitE and in comparison to control rats
Reddy et al. 1998 [114] | Pulmonary oxidative damage by acute strenuous exercise in rats deficient in Se and VitE | Female Wistar albino rats deficient in Se and VitE and control rats | Intense swimming to exhaustion | Lung tissue | PE: > [SOD] and < [GSH-Px] and < [GST] in rats deficient in VitE and in comparison to control rats
Prigol et al. 2009 [115] | Supplementation with (PhSe)2 and pulmonary oxidative damage caused by the exercise | Adult Swiss albino mice supplemented with (PhSe)2 and not supplemented control mice | Swimming exercise (20 min) for both groups after 7 d of supplementation | Lung tissue | PE: ↑ [MDA] and ↑ of CAT activity in mice not supplemented with (PhSe)2
Terblanche 1999 [116] | Exhaustive swimming and CAT activity in the lungs of male and female rats* | Sprague-Dawley rats | 1 h swimming | Lung tissue | PE: ↑ CAT activity in males and females

B: bronchoalveolar lavage fluid; CAT: catalase; (PhSe)2: diphenyl diselenide; GR: glutathione reductase; GSH: glutathione reduced; GSH-Px: glutathione peroxidase; GST: glutathione S-transferase; L-Arg: L-arginine; MASL: meters above sea level; MDA: malondialdehyde; MPO: myeloperoxidase; NO: nitric oxide; Se: selenium; SOD: superoxide dismutase; CuZn-SOD: copper-zinc-superoxide dismutase; Mn-SOD: manganese-superoxide dismutase; TBARS: thiobarbituric acid reactive substances; UA: uric acid; VNO: volume of nitric oxide; XO: xanthine oxidase; VitE: vitamin E; VitC: vitamin C. In "Oxidative or inflammatory main results," DE: during exercise and PE: postexercise. In "Aim," * the effect of exercise was not the primary aim of study.

### Author, year | Aim | Sample characteristics | Exercise protocols | Samples obtained | Oxidative or inflammatory main results
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Altan et al. 2009 [117] | SOD activity and [TBARs] postadaptation by training in altitude* | Wistar albino rats divided into trained in hypobaria (THb) and normobaria (TNb) and nontrained in hypobaria (Hb) and normobaria (Nb) | Comparison of baseline samples between groups trained with swimming (T: 5 at 30 min/day/or 4 days/week for 9 weeks) or nontrained and exposed or not to simulated altitude of 3000 MASL (E: 120 min/day for 4 days/week for 9 weeks) | Lung tissue | PT: >SOD activity in TNb in comparison to Nb; no differences in [TBARs] for the same groups
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<td>Epithelial remodeling, inflammatory cells, and apoptosis in the AWs after chronic exercise</td>
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<td>Gündüz et al. 2004 [122]</td>
<td>Oxidant and antioxidant systems in rats organs after a year of training*</td>
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<td>Administration of a ginseng intestinal metabolite (IH901) and exercise-induced oxidative stress in trained rat*</td>
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<td>PT: ↑ TBARs and ↑ protein carbonyl in EC versus RC</td>
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<td>PT: ↑ CuZn-SOD and ↑ Mn-SOD expression in lung parenchyma of ATU versus SU after an individual maximal exercise capacity test</td>
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Reis Gonçalves et al. 2012 [15] | Chronic aerobic exercise on pulmonary inflammation, cytokine, and antioxidant enzymes in animal model of acute pulmonary damage* | Trained BALB/c mice | Comparison of samples before and after a low intensity training on treadmill (T: 50% of MS for 60 min/d, 3 d/week for 5 weeks) | BALF, EB, and lung tissue | PT: with no changes in leukocytes, [IL-6], [IL-10], nor [TNF-α] in BALF; with no changes in [NO] in EB; ↑ expression of IL-6 and Mn-SOD in the lung, but no changes of activity of GSH-Px and GR in the lung |
Toledo et al. 2012 [126] | Regular physical exercise in an experimental mouse model exposed to cigarette smoke* | C57BL/6 mice divided into control mice (C), trained (T), exposed to cigarette smoke (Sk), and Sk plus T (Sk+T) | Comparison of baseline samples in T at moderate intensity on treadmill (T: 50% MS for 60 min/d, 5 d/week for 24 weeks) | BALF and lung tissue | PT: <[ROS] in BALF of En compared to C; >GSH-Px activity, but not of Mn-SOD nor CuZn-SOD in lungs of T compared to C; with no changes in the expression of IL-1ra, TNF-α, and IL-10 between T and C |
Yang 2011 [127] | Chronic exercise and expression of cytokines related to inflammation in the lung tissue | Old male Sprague-Dawley rats, group with trained rats (T) and sedentary control rats (C) | Comparison of baseline samples between rats trained on treadmill (T: 25 m/min for 120 min/day for 1 week) and control rats | Lung tissue | >expression of mRNA for TNF-α and IL-4 and <expression of mRNA for IFN-γ of group T versus C |

BALF: bronchoalveolar lavage fluid; BW: body weight; DEP: diesel exhaust particles; DNA: deoxyribonucleic acid; EB: exhaled breath; 8-OH-dG: 8-hydroxydeoxyguanosine; GR: glutathione reductase; GSH: glutathione reduced; GSH-Px: glutathione peroxidase; IFN-γ: interferon gamma; IL-1ra, IL-4, IL-6, or IL-10: interleukin-1ra, interleukin-4, interleukin-6, or interleukin-10; ILP: lipid peroxidation; MDA: malondialdehyde; MS: maximal speed; mRNA: messenger RNA; M5: maximal speed; NF-kB/p65: factor nuclear kappa-B/p65; NO: nitric oxide; NO2−: nitrite; ROS: reactive oxygen species; SOD: superoxide dismutase; CuZn-SOD: copper-zinc-superoxide dismutase; Mn-SOD: manganese-superoxide dismutase; TBARs: thiobarbituric acid reactive substances; TNF-α: tumor necrosis factor-alpha. In “Oxidative or inflammatory main results,” PE: postexercise and PT: posttraining. In “Aim,” *the effect of exercise was not the primary object.
shown controversial results. In swimmers, Bonsignore et al. [57] reported a decreased eNO after 5 km (∼179 min) in slightly chlorinated pool; when performing the same test at the sea no changes were observed in this pair but the same distance was maintained at the sea. In other studies, also a decreased eNO after exercise has been observed in healthy subjects [64, 70, 88, 91]. However, in youngsters not trained in swimming, Carbonnelle et al. [58] found increases of eNO after swimming 2 sessions of ∼1300 m in 45 min in a pool sanitized with electrical process (nonchlorinated water). Also, De Gouw et al. [61] found an increased eNO in healthy subjects after cycling for 6 min using dry air, while ventilation was kept constant in 40–50% of his or her predicted maximal voluntary ventilation (35 × FEV₁). Other studies showed no changes in the eNO after exercise; Font-Ribera et al. [65] found no differences in eNO concentrations in pool swimmers; the same occurred with eNO in swimmers after an exercise of 45 min [81] and in healthy subjects after either cycloergometry [66, 94] or treadmill incremental exercise test [80].

Through the exhaled breath condensate (EBC) analysis, to observe the oxidative effects of the moderate acute exercise, Nowak et al. [79] subjected a group of healthy subjects to a submaximal exercise on cycloergometer during ∼6 min; they found no changes in H₂O₂ and thiobarbituric acid reactive substances (TBARs). Araneda et al. [46] found no changes of H₂O₂ in EBC after three maximal cycle ergometrics of 1 min in elite cyclists carried out at 670 and 2160 masl, but malondialdehyde (MDA) was higher at 2160 meters. Marek et al. [72], in two submaximal cycle ergometrics to 60 W (∼7 min) and 120 W (∼5 min), and later in maximal exercise (∼13 min), found no differences in H₂O₂ concentration in EBC [73]; however, in both studies, increases were found in the flow of formed H₂O₂ after exercise. On the same prooxidant, Mercken et al. [76] found an increase after maximal cycle ergometry in healthy subjects, with increments of 10 w/min, but they did not find any differences in subjects with chronic obstructive pulmonary disease after exercise. However, in another study they found no differences in H₂O₂ when healthy subjects performed a cycle ergometry with one leg (40% P_max) during 20 min [77]. Marek et al. [74] found that, after 50 min of high intensity running developed at ∼18°C and ∼−15°C of environmental temperature, the concentration and production rates of H₂O₂ in EBC were higher when the exercise was carried out in a cold environment. Recently an increase in H₂O₂ and nitrite concentrations and correlations between both metabolites in the EBC of 21 and 42.2 km race participants were found. Also in this study, while nitrite increased in EBC, plasmatic nitrite showed no modifications and no correlations between these variables, which suggests a probable localized origin of this process [53].

Until now, only two studies have determined one of the potential sources of prooxidants; thus, it has been described as an increment of xanthine oxidase activity in the pulmonary homogenate of rats that performed strenuous exercise (∼15 min) on a treadmill (20 m/min), besides MDA and NO [111]. Likewise, Huang et al. [110] observed an increase of the activity of xanthine oxidase and lung MDA in older rats after running on a treadmill until fatigue, during ∼63 min at 70% VO₂max. Prigol et al. [115] and Akil et al. [105] found increases in TBARs in rats that swim for 20 min and 30 min, respectively, while Reddy et al. [114] found increases in MDA in rats with a vitamin E deficient diet that swim until fatigued. Also in rats, increases of TBARs after swimming during ∼2.5 h until fatigue were found [106]. The same result was found in pulmonary homogenates of untrained rats which
swam until exhaustion [119]. A strenuous exercise protocol of ∼66 min (80–85% VO2_max) showed no changes in TBARs in rats [107].

In healthy horses, no differences were observed in isoprostane 8-epi-PGF2α of supernatant of bronchoalveolar lavage fluid (BALF) after 50 min of running [13]. An increment of carbonyls in the lungs of rats was observed by Radák et al. [113] after an exercise till exhaustion on the treadmill. However, after an hour of a moderate intensity run in young and old rats, no changes were observed in the lung carbonyls [109].

With regard to the pulmonary antioxidant enzymes, after an hour of acute moderate exercise protocols on treadmills, young rats' lungs showed an increase in the activity of enzymes superoxide dismutase (SOD) of the type CuZn-SOD, Mn-SOD, of the catalase (CAT), without changes in the glutathione peroxidase (GSH-Px). The mRNA expression for these enzymes did not show differences [109]. Lin et al. [111] found an increase in SOD and glutathione reductase (GR) activity with no changes in CAT and GSH-Px activity in rats that ran at 30 min/m and 10% slope until fatigued. Finally, acute and prolonged exercise (more than an hour) at 80–85% VO2_max showed no changes in the activity of GSH-Px and SOD [107]. In acute exercise protocols, using swimming, Reddy et al. [114] found an increase in SOD and glutathione transferase (GST), while mild decreases in GSH-Px activity were observed in rats that swam until fatigued. Prigol et al. [115] found increase in CAT activity in rats that swim for 20 min. In rats that exercise for an hour, Terblanche [116] found increased CAT activity without differences between males and females. In rats 18 months old, Huang et al. [110] described an increase of SOD activity and the maintenance of levels of CAT, GSH-Px, and GR after 51 min on treadmill at 70% of VO2_max. Strenuous exercise increased the activity of GSH-Px, with no changes in GR [119]. In a report of Al-Hashem et al. [106], rats that exercised until fatigue decreased the activity of SOD and CAT.

Acute exercise has also altered the levels of nonenzymatic antioxidants; an increase of uric acid has been described, with no changes in total glutathione, in GSH, and in GSSG in BALF, after 50 min of incremental exercise in healthy horses [13]. In a study of rats that ran during ∼81 min at 70–75% VO2_max until fatigued, no variations were found in the homogenized lung GSH [111]. In rats that swim until fatigued (∼2.5 h), no differences were found at 600 m of altitude, but there was a decrease of GSH levels at 2270 meters [106]; in this same report, it was found that supplementation with nonenzymatic antioxidants such as VitC (20 mg/kg) and VitE (20 mg/kg), a single dose one hour before starting the exercise, decreases pulmonary lipid peroxidation and SOD and CAT activities increases, in both altitudes. Additionally, supplementation shows higher levels of GSH compared to animals not treated in altitude [106].

Thus, the increase in lung prooxidants and its consequences (lipid peroxidation) due to acute exercise appear to be related to the high intensity and duration of the effort, in terms of either minute ventilation or oxygen consumption, and are enhanced by a hostile environment (hypoxia, pollution, cold, etc.). However, a mainly enzymatic antioxidant adaptive response is still controversial. In contrast, the use of vitamin reducers (C and E) allows the antioxidant capacity to be increased and oxidative damage to be controlled (see Tables 1(a) and 1(b)).

5. Pulmonary Redox Balance and Chronic Exercise

In a first study of pulmonary prooxidants and chronic exercise, Carraro et al. [97] found no differences in eNO of child swimmers (trained 1 h/week during 6 months). Martin et al. [102] observed no differences in eNO of athletes based in pool and not based in pool exposed to pool environment during 5 and 0.5 h/week, respectively. For oxidative damage, Heinicke et al. [47] found a tendency towards increase of 8-isoprostanes in the EBC of biathletes who trained at 2800 meters during 6 weeks (4–6 h/d with 1 d/weeks of rest), which included extensive cross-country skiing, strength training, and shooting technique training.

In a model of physical training of rats, which jogged in 3 months a total of 24 sessions of 20 min/d at 60% VO2_max, no differences were found in pulmonary carbonyls, nitrite, or TBARs [121]. After 24 weeks of training at 50% VO2_max for 60 min/d for 5 d/week, ROS decreased in BALF and no changes of increase were found in pulmonary 8-isoprostanes in trained mice [126]. Using the same load and frequency as before, the levels of eNO and MDA were not altered in lung homogenates of rats trained during 5 weeks [15]. However, during the 8 weeks of training in rats that swim with a 2% of additional body weight during ∼50–80 min, an increment of pulmonary carbonyls and MDA was observed [119]. Gündüz et al. [122] found increases of TBARs in older rats (21 months) versus young rats (9 months), without any variations between old rats which were either trained or untrained in swimming during 12 months 1 h/d for 5 d/week. Altan et al. [117] found increases in MDA in rats trained at 3000 meters of altitude (120 min/d for 4 d/week during 9 weeks) compared to sedentary control rats and the ones not trained maintained at sea or height level. In Sprague-Dawley rat that was trained during 8 weeks on a treadmill, an increase in pulmonary TBARs and protein carbonyls was observed [123]. Regarding oxidative stress on nucleic acids, Asami et al. [118] found increases in 8-hydroxydeoxyguanosine in rats after a forced race on treadmill for five weeks in daily sessions with a gradual increase in the time of 30–90 min.

The chronic exercising has also had as a subject of study the potential changes of the expression/activity of the enzymes and nonenzymes pulmonary antioxidant. Likewise, Reis Gonçalves et al. [15] found an increase in the lung Mn-SOD expression of mice subjected to five weeks of training at moderate intensity (60 min/d in 3 d/wk); however, no changes were observed in the GSH-Px, GR, GST, and CAT activities. In another study, Olivo et al. [125] observed an increased expression in pulmonary CuZn-SOD and Mn-SOD postmaximal exercise test of trained mice during 4 weeks at 50% of the maximal speed on treadmill. Altan et al. [117]
found increases of SOD activity after nine weeks of progressive training in a normobaric environment (5 to 30 min/d for 4 d/week), with no differences with a trained group at 3000 meters of altitude. da Cunha et al. [121] observed a higher pulmonary CAT activity in the ones trained on a treadmill during 12 weeks at 60% VO\textsubscript{max} (20 min/d), compared to control rats. In another study, Menegali et al. [124] found an increase of the CAT and SOD activity in lung of trained rat in swimming during 8 weeks. In mice trained on a treadmill for 24 weeks at 50% \( V\text{\textsubscript{max}} \) (60 min/d and 5 d/week) increases of GSH-Px were observed without changes of expression of CuZn-SOD, Mn-SOD, and Ec-SOD, studied in sections of pulmonary tissue [126]. In another study, older animals of 21 months that were trained for a year (1 h/d and 5 d/week) had a greater amount of SOD in comparison to control rats of their same age and to young rats. No differences were found in CAT activities, while GSH-Px had a greater activity than a group of their same age [122]. Finally, Aydin et al. [119] observed a decrease in the concentrations of GSH and an increase of GSH-Px activity in pulmonary homogenates of rats, after eight weeks of swimming with overload and progressive weekly time increment (50–80 min).

This reflects the fact that oxidative stress induced by chronic pulmonary exercise in animals is closely associated with high-intensity protocols, but not with those of moderate intensity (see Table 1(b)). However, when moderate chronic exercise was executed while at high altitude, both human and animals presented pulmonary oxidative damage (see Tables 1(b) and 2(b)). In contrast, antioxidant adaptation seems to be more closely related to the animal training time, with an increase in the activity of SOD and CAT in the medium term and the expression of SOD in the short term (see Table 2(b)).

6. Acute Exercise-Induced Lung Inflammation

In horses, Kirschvink et al. [13] found no cellular count variation in BALF after 50 minutes of exercise. In runners’ sputum of 10 km (∼35.4 min), 12 km (∼46.4 min), and 21 km (∼89.1 min) a trend of increasing polymorphonuclear neutrophils (PMNs) in samples of induced sputum was found [40]. In the same direction, Bonsignore et al. [56] reported a higher percentage of PMNs in induced sputum, compared to values previous to exercise and an increase in these cells after the marathon (∼179 min). Also in induced sputum of runners, Denguezli-Bouzgarrou et al. observed in 2006 [62] and 2007 [63] an increase of PMNs after 60 minutes of moderate racing. In the latter study, higher concentrations of histamine, interleukin-8 (IL-8), LTB\textsubscript{4}, and LTE4 were also detected, subsequent to acute exercise during the precompetitive phase versus the competitive phase [63]. Chimenti et al. [5], in a 20-kilometer race (∼90 min), reported an increase in IL-8 in the supernatant. Races in smaller time frames (∼18 min) showed no changes in the amount of PMNs in induced sputum [93]. In rowers, after a short test of high intensity (1000 m in ∼3 min), there was a trend towards an increase of epithelial cells and a positive association between the pulmonary ventilation/body weight (L/kg) and macrophages in induced sputum [78]. In swimmers, increases in lymphocytes and eosinophils and a decrease in macrophages were observed in induced sputum, after a 5 km race in the ocean (hypertonic environment) in relation to the same test performed in an open pool with low concentration of chlorine. However, there is no evidence of the increase in inflammatory cell activation [57]. In a chlorinated pool, in high performance swimmers, no changes were observed in the cellular composition of the induced sputum and the pH in EBC after 45 min at moderate intensity [81]. Larsson et al. [32] found an increase of granulocytes and macrophages in subjects that performed one hour of exercise, on a treadmill, at ∼23 C, without IL-8 changes in BALF samples. Derivatives of arachidonic acid have been studied in three works; thus, in a maximum acute exercise of approximately 12 min, increases in E\textsubscript{2} prostaglandin and B\textsubscript{2} thromboxane in EBC after exercise were found in men [83]. The leukotrienes in EBC were studied by Bikov et al. [54]; thus, after an eight-minute test on a treadmill no differences in the concentration of cysteinyl leukotrienes were found in normal people. In a test of 4 km of cycling with a 12% hill sloping during ∼7 min, an increase of leukotriene B\textsubscript{4} in BALF of athletes was found in comparison to the control subjects [67]. Also in EBC, Zietkowski et al. [95] found no changes in high sensitive C-reactive protein after 9 minutes of cycle-ergometry at 85% of HR\textsubscript{max} in healthy subjects.

The pH in EBC (EBC\textsubscript{pH}) is a potential marker of pulmonary inflammation that has been used in pathologies that have this condition. In acute exercise, the results have been variable; thus, Marek et al. [73] did not find differences after an exercise until fatigue (∼13 min) in EBC\textsubscript{pH} of amateur athletes. Bikov et al. [55] did not observe changes in the EBC\textsubscript{pH} of healthy subjects after exercise, while there are other reports that show increases in pH after outdoor exercise [128] and after low-intensity (60% HR\textsubscript{max}) exercise (∼30 min) in nonathlete healthy subjects [84]. In races up to 10 km, no changes have been reported up to 80 min after the race, in both amateur runners [52] and physically active runners [53]. However, there are inverse correlations between changes in prooxidants and changes of EBC\textsubscript{pH} [53]. In distances that exceed 21 and 42 km, ∼101 min and ∼246 min, respectively, an acute decreasing trend of EBC\textsubscript{pH} was observed [52]. However, in an animal study conducted in horses, the group of Cathcart et al. [108] found an increase in EBC\textsubscript{pH} after running 1.6 km.

In summary, the majority of published papers demonstrate the infiltration of inflammatory cells (macrophages or granulocytes) after acute exercise in humans. A factor that probably influences this is the duration of the exercise, as the increase in PMNs was found only in protocols involving longer periods (see Table 1(a)). Cellular infiltration was found to be due to cold or chlorine. The role of exercise training is difficult to assess, given that the studies were conducted almost exclusively in trained subjects. We must add to this the reported changes in soluble inflammatory mediators. As a whole, these could be an expression of an asymptomatic acute inflammatory process similar to that observed in other tissues (muscle tissue). This would happen in a self-limiting way whenever the necessary conditions of time, environmental factors, and intensity are encountered.
7. Chronic Exercise-Induced Lung Inflammation

Studies in animals have shown that training during 120 min/d for a week on treadmill at 25 m/min increases the expression of mRNA to tumor necrosis factor-alpha (TNF-α) together with promoting a decrease of interferon gamma in pulmonary tissue samples [127]. Chimenti et al. [120] trained mice at moderate intensity for 6 weeks (5 d/week), showing leukocyte infiltration in the airway. At this level of epithelia, an increase of apoptosis and a decrease of the ciliated cells were also observed. In mice that trained 60 min/d to 50% $V_{\text{max}}$ for 24 weeks (5 d/week), no variation was observed in the number of macrophages in BALF, but it was possible to see a decrease of the capacity of these cells to form free radicals [126]. However, it is possible that the elaboration of training programs at moderate intensity (66% VO$_2$max) generates a reduction of the inflammatory response after the completion of ischemia and pulmonary reperfusion, which was considered as a decrease of the release of interleukin 1β and tumor necrosis factor-α (TNF-α) at plasmatic level in a model performed in rats [129]. An analogous result was described by Toledo et al. [126], who did not find differences in TNF-α, interleukin 10, monocyte chemotactic protein, and interleukin 1 receptor antagonist, quantified in lung sections of mice, after training to 50% $V_{\text{max}}$ for 1 h/day, 5 days per week, for 24 weeks.

In studies conducted in humans, it has been reported that the participation in a long distance race training program over the course of a year generates a persistent inflammatory process with no apparent clinical repercussion and an increase in PMNs and in IL-8 concentrations, leukotriene $E_4$, and histamine in the supernatant of induced sputum samples [130]. Subjects who participated in high performance athletic training in sessions of 1 h/day for 10 days, interspersed with rest 5 days, had lower pH values in EBC compared to healthy control subjects [98]. The same result in this parameter was reported in runners by Greenwald et al. [128]. In the same direction, in amateur runners (~50 km/week) low levels of pH were reported compared to values of healthy control subjects [52]. High performance pool swimming showed no differences in basal inflammatory parameters when compared with non-pool-based athletes; however, the analysis of the subgroup of athletes that had a positive result in the voluntary hyperventilation test (exercise-induced bronchial hyperreactivity indicator) presented a higher concentration of eNO and a higher count of eosinophils and of epithelial cells when compared to the group that had negative results on this test [102]; among other factors, this could be related to the number of years of practice of pool swimming, since no differences in eNO, in EBC pH, and in cellularity of induced sputum in adolescents were found when compared to normal subjects [131]. Elite swimmers, who trained between 800 and 3380 km/year, had more eosinophils and PMNs in induced sputum compared to nonathlete control subjects [99]. The cessation of the training for 3 months of swimmers decreases eosinophils and lymphocytes in induced sputum compared to active swimmers (~1870 km/year) [100]. The comparison between healthy athletes who are swimmers and others who are engaged in land exercise has shown an increased number of PMNs in induced sputum samples [96]; the same comparison showed no differences in PMNs and eosinophils in induced sputum [102]. Chronic inflammation can be associated with pulmonary epithelial damage; thus, increases of clear cell protein (CC16) in plasma of swimmers who trained during 20 weeks in a chlorinated pool have been reported [132].

In skiers, who trained 435 h/year, increase of lymphocytes and mast cells has been found, with no differences in the concentration of TNF-α and myeloperoxidase in BALF compared to nonathlete control subjects [103]. Karjalainen et al. [101] reported, through the study of bronchial biopsies, an increase in neutrophils, eosinophils, macrophages, and T lymphocytes in elite skiers (435 h/year) compared to healthy control subjects, along with air tract remodeling indicators as an increase in collagen I and collagen III deposits in the submucosa, a hyperplasia of raker cells, and a higher expression of type 5 mucin. The use of anti-inflammatory agents (800 micrograms/day of budesonide) by cross-country elite skiers (~427 h/year) during 20 weeks did not generate differences regarding the placebo (~468 h/year) in the cellularity (PMNs, macrophages, lymphocytes, eosinophils, and mast cells), studied in BALF and in endobronchial biopsy [104].

In summary, animal models of physical training show increases of soluble inflammatory mediators, which include TNF-α. Human studies have focused on subjects who have greater contact with irritants in the airway due to the specificity of their sport, whether runners (large ventilation volumes), skiers (cold), or swimmers (chlorine gas in the pool room). In these subjects, permanent tissue infiltration of granulocytes, macrophages, and lymphocytes has been observed. Evidence of these changes has been found in both noninvasive samples, such as induced sputum, and in biopsies in the bronchial region. At the same time, an increased presence of soluble proinflammatory substances has been reported. Overall, this suggests that these athletes in particular may suffer from persistent changes in tissue (chronic inflammation and airway remodeling) that have been associated with pulmonary symptoms and functional changes (see the bottom of Figure 1).

8. Oxidative Damage and Inflammation, Relations, and Potential Effects

The generation of prooxidant substances and the establishment of tissue oxidative damage are closely associated with inflammatory processes; thus, inflammatory cells are a known source of prooxidants derived from both oxygen and nitrogen [133]. At the same time, the increase of prooxidants has been involved in the intracellular signaling which leads to inflammatory cell activation, increased secretion of soluble mediators of inflammation [134], endothelial activation, and also increased expression of adhesion molecules and endothelial permeability [135]. This relation implies that, in many situations, the increase of prooxidants participates in the activation of inflammation and vice versa, demonstrating the close relationship between both phenomena [134].
The establishment of both oxidative damage and inflammation in the lungs has been involved in the origin/evolution of various pathological states; for example, both phenomena are a fundamental part of adult respiratory distress [136], asthma [137], chronic obstructive pulmonary disease [138], pulmonary hypertension [139], and viral infectious processes [140]. In the lungs, the relationship between oxidative changes and inflammation has rarely been studied as a main goal, but it is presumed that, in view of the studies conducted in other organs, it must be closely related. This is particularly important in subjects practicing sport, as both inflammation and oxidative damage have been implicated in the pathogenesis of phenomena of high prevalence in athletes such as rhinitis, bronchial hyperreactivity, asthma, and airway remodeling [27, 141]; so, most respiratory symptoms (coughing, wheezing, breathlessness, and chest tightness) in endurance athletes such as cross-country skiers are known [142]. In addition, cross-country skiers show a presence of PMNs and lymphocytes infiltration in the airways [101]. This phenomenon can also be extrapolated to other endurance athletes [143] such as marathon runners, cyclists, and swimmers, the latter of which are also exposed to the chlorine in swimming pools, which could be one of the main factors inducing increased eosinophils and leukocytes in the sputum.

9. Methods for the Study of Lung Inflammation/Oxidative Damage by Exercise

The study of the oxidative/inflammatory damage in the lungs is challenging due to both anatomic functional limitations and the limitations of currently applied techniques. Current evidence on this topic focuses primarily on the study of lung diseases, while studies on the effect of exercise as a trigger effect of this phenomenon in healthy people are scarce. Summarizing what is known to date for the species analyzed, the determinations made and the samples obtained are shown in Tables 1 and 2. Lung tissue microenvironment has challenged developers of study methodologies, so, although systemic markers have been proposed (CC16, surfactant proteins A and B, and Krebs von den Lungen-6), they do not yet have sufficient capacity to indicate minor damage, which implies that the processes of the lung itself cannot always be ascertained. For this reason, it is preferable to test samples originated from the lung: those currently under study are exhaled breath (whether direct or condensate), fluids (BALF, induced sputum, and nasal lavage), and cells and portions of whole tissue (biopsies, tissue homogenates, and cut pieces of tissue). Unfortunately, today there is still much controversy regarding the interpretation of the results obtained with these methods. In relation to oxidative/inflammatory exercise phenomenon, in animals, exhaled breath [112], lung tissue homogenates [113, 114, 117, 118, 120, 121, 127], bronchoalveolar lavage [121, 126], and lung tissue sections [126] have been used. In humans, most methods are focused on noninvasive methods and, among these, the induced sputum is the most widely used [40, 56, 57, 62, 63, 78, 81, 93, 96, 99, 100, 102, 144]. Another sample studied corresponds to exhaled breath, which was analyzed whether directly [56, 57, 59, 65, 71, 75, 81, 89, 97, 102] or after being condensed at low temperature [46, 53, 65, 72–74, 77, 79, 81, 83, 84, 128, 139]. Very few studies have used bronchoalveolar lavage [32, 103, 104] and lung tissue obtained by endobronchial biopsy [101, 104].

10. Discussion

In summary, we found that in acute exercise (see Tables 1(a) and 2(a)) there is more evidence of changes in cellularity (predominantly granulocytes) when it was a prolonged high-intensity exercise. This change was not so evident in animals; however, this should be resolved in further studies because it is a parameter measured recently in this population. Long-term of acute moderate exercise (>60 min) in humans stimulated an increase of pulmonary inflammatory mediators (IL-8, LTD₄, and LTE₄). Now, regarding prooxidants, a systematic increase in humans is observed after more than thirty minutes of exercise. It is noteworthy that, in acute exercise in animals, reports of an increase in lung lipid peroxidation are the majority, while it has not been observed in humans, except for intense exercise at high altitudes. This may be partially explained by the techniques used: while tissue samples were analyzed in animals, EBC samples were analyzed in humans; in another aspect, the change with greater support in relation to the enzymatic activity corresponds to the maintenance or decreased levels of GSH-Px and to the increase in SOD.

With regard to chronic exercise (training) and its effects (see Tables 1(b) and 2(b)), the number of studies is still very small, but there is a tendency observed, seen in humans, towards changes in cellularity compatible with chronic inflammation of the airways, particularly in subjects exposed to cold and chlorine. In animals, changes in pulmonary cellularity (leukocyte infiltration) were observed in only one study [120]. For soluble inflammatory mediators, in animals the scientific evidence has shown an increase in the concentration of these substances (IL4, IL6, and mRNA TNF-α) subsequent to chronic exercise. The oxidative damage was observed in animals following moderate chronic exercise (>4 sem), specifically in older rats, and cold or altitude environment. In humans, only one study showed oxidative damage by altitude training [45, 47]. With regard to enzymatic antioxidants, a tendency towards higher levels in SOD and GSH-Px is observed in humans. As for nonenzymatic antioxidants, only one study showed a decrease in the concentration of pulmonary GSH in trained rats [119].

The problem requires further study to clarify numerous questions in order to have a more definitive overview; thus, several challenges for researchers in the field have arisen. Likewise, the activity of the sources of production of free radicals in the lung (mitochondria, xanthine oxidase, NADH oxidase, and NOS) should be studied and the knowledge of the status of antioxidant systems, particularly in humans, where there are no records available, should be improved. Regarding inflammatory parameters, the study of soluble mediators of inflammation should be extended; in addition, the effect of both substances with antioxidant and
anti-inflammatory effect should be explored. Furthermore, it is necessary to generate research projects which explore the parameters of oxidative/inflammatory mechanisms simultaneously in order to establish the interrelation mechanisms between both processes. It is also necessary to characterize the effect of time and intensity of performed exercise, the role of environmental conditions, and the level of training of the subjects on oxidative damage/lung inflammation by exercise. Finally, to advance the resolution of this problem, it is urgent to improve the technical conditions to allow obtaining representative samples of lung environment in its different compartments, and it is also necessary for these methods to be noninvasive and contribute to monitoring the athletes.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors are grateful to Cristian Evans for language assistance. This study is funded by Fondo de Ayuda a la Investigación (FAI), Universidad de los Andes, Project INOGTO2013, and the National Fund for Scientific & Technological Development (FONDECYT), Project no. 1130082 granted to O. F. Araneda.

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