DOI: 10.7600/jpfsm.4.279

**JPFSM: Review Article**

**Skeletal muscle dysfunction and oxidative stress in patients with chronic obstructive lung disease**

Shuji Oh-ishi*, Kenji Nemoto and Takefumi Saito

Department of Respiratory Medicine, National Hospital Organization, Ibaraki-higashi National Hospital, 825 Terunuma, Tokai-mura, Naka-gun, Ibaraki 319-1113, Japan

Received: June 25, 2015 / Accepted: July 9, 2015

**Abstract**慢性阻塞性肺疾病（COPD）是一种日益重要的全球性健康问题，包括日本。COPD与对气道和肺部的刺激物的增强炎性反应有关，特别是在吸烟。吸烟包含有气态和粒子氧化物，被认为是导致COPD发展的主要致病因素。气态氧化物在吸烟中诱导炎症，而炎症则引起肺部分组织的破坏。炎症和氧化应激是紧密联系的，且似乎在COPD的发展和/或进展中起着关键作用。COPD患者表现出全身性炎症的存在，导致肺外表现，包括肌力下降和其它伴发病。氧化应激也观察到存在于COPD患者的骨骼肌中。因此，全身性炎症和氧化应激可能与COPD患者的骨骼肌功能障碍有关，导致肢肌肉力下降和运动耐力下降，以及健康状况和生活质量的下降。肺部康复对于提高COPD患者的运动能力以及健康相关的生活质量非常重要。然而，主要的肺部康复组成部分是身体运动，而身体运动在COPD患者中会增加氧化应激。因此，建立既能改善运动能力又可减少运动诱导的氧化应激的康复项目在将来会是必要的。

**Keywords**: chronic obstructive pulmonary disease, skeletal muscle dysfunction, oxidative stress, inflammation, exercise

**Introduction**

慢性阻塞性肺疾病（COPD），作为四大死亡原因之一在2004年，是日益重要的全球性健康问题。COPD与对气道和肺部的刺激物的增强炎性反应有关，特别是吸烟。吸烟包含有气态和粒子氧化物（大约10^15自由基每“抽”3）和粒子氧化物（焦油；超过10^17稳定的长寿命自由基每克）5，且被认为是导致COPD发展的主要致病因素。气态氧化物在吸烟中诱导炎症，而炎症则引起肺部分组织的破坏。因此，肺部康复是COPD患者的重要组成部分。然而，身体运动是肺部康复的主要组成部分，身体运动是已知的通过增加自由基的产生（特别是超氧化物阴离子）来增加氧化应激。氧化应激在COPD患者中观察到骨骼肌。因此，建立既能改善运动能力又可减少运动诱导的氧化应激的康复项目在将来会是必要的。

*Correspondence: oshuji@ad.cyberhome.ne.jp
In patients with COPD, short periods of exercise can induce systemic oxidative stress, suggesting that even activities of daily living could cause oxidative stress. In the current review, we will attempt to briefly summarize the pathophysiology of skeletal muscle dysfunction in COPD patients, focusing on oxidative stress and inflammation.

Overview of reactive oxygen species and exercise-induced oxidative stress

The term ROS describes a wide variety of highly reactive metabolites originating from the oxygen molecule (Table 1). Among these metabolites, superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hydroxyl radical (OH$^-$), singlet oxygen (¹O$_2$), and peroxynitrite (ONOO$^-$) are thought to be the most important ROS in humans in vivo. These ROS are thought to be involved in various physiological and pathophysiological conditions such as aging, carcinogenesis, atherosclerosis, diabetes, and neurodegenerative disorders, and are induced by exercise.

Even under normal physiological conditions, ROS are generated continuously. However, mammalian tissue contains a wide variety of ROS scavengers that protect against or minimize the oxidative tissue damage caused by ROS.

Under normal physiological conditions, ROS are usually eliminated by ROS scavengers such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and other enzymatic and non-enzymatic antioxidants (Table 2, Fig. 1). Oxidative stress is defined as an imbalance between the generation of ROS and the antioxidant defense in favor of the former; and the increased generation of ROS is known to cause a wide spectrum of cellular damage via processes such as enzyme inactivation, lipid peroxidation, and nucleic acid damage.

Strenuous physical exercise markedly increases oxygen uptake by active organs and tissues (including locomotor muscles and diaphragm), leading to an increased generation of ROS. In 1978, Dillard et al. published the first study of exercise-induced oxidative stress in humans. The authors of that study reported that the level of expired pentane (a biomarker of lipid peroxidation) increased significantly after 60 min of endurance exercise at 60% of VO$_2$ max; and that both resting and exercise-induced pentane production were reduced in subjects administered the antioxidant vitamin E. The authors concluded that exercise can increase oxidant production, but the source of increased oxidant production was unknown. Since that first study, there has been much research into exercise-induced oxidative stress at various exercise intensities, exercise durations, and exercise modes in animals and humans.

Many of these studies have identified increases in biomarkers of oxidative damage (e.g., lipid peroxidation products, protein carbonyl levels, and oxidized DNA) in human skeletal muscle. However, the source of increased oxidant production remains unclear.

### Table 1. Reactive oxygen species in vivo

<table>
<thead>
<tr>
<th>1.</th>
<th>Superoxide: O$_2^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Hydroxyl radical: HO$^-$</td>
</tr>
<tr>
<td>3.</td>
<td>Hydroperoxy radical: HOO$^-$</td>
</tr>
<tr>
<td>4.</td>
<td>Peroxy radical: LOO$^-$</td>
</tr>
<tr>
<td>5.</td>
<td>Alkoxyl radical: LO$^-$</td>
</tr>
<tr>
<td>6.</td>
<td>Singlet oxygen (¹O$_2$)</td>
</tr>
<tr>
<td>7.</td>
<td>Hydrogen peroxide: H$_2$O$_2$</td>
</tr>
<tr>
<td>8.</td>
<td>Peroxynitrite: ONOO$^-$</td>
</tr>
<tr>
<td>9.</td>
<td>Hypochlorous acid: HOCl</td>
</tr>
</tbody>
</table>

### Table 2. Enzymatic and non-enzymatic antioxidant defense in vivo

<table>
<thead>
<tr>
<th>1.</th>
<th>SOD: superoxide dismutase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>u,Zn-SOD (SOD1):cytosol</td>
</tr>
<tr>
<td></td>
<td>Mn-SOD (SOD2):mitochondria</td>
</tr>
<tr>
<td></td>
<td>EC(extracellular)-SOD (SOD3):extracellular space</td>
</tr>
<tr>
<td>2.</td>
<td>GPX: glutathione peroxidase</td>
</tr>
<tr>
<td>3.</td>
<td>CAT: catalase: peroxisome, red blood cell, etc.</td>
</tr>
<tr>
<td>4.</td>
<td>Glutathione</td>
</tr>
<tr>
<td>5.</td>
<td>Glutathione reductase</td>
</tr>
<tr>
<td>6.</td>
<td>Thioredoxin</td>
</tr>
<tr>
<td>7.</td>
<td>Thioredoxin reductase</td>
</tr>
<tr>
<td>8.</td>
<td>Peroxyredoxin</td>
</tr>
<tr>
<td>9.</td>
<td>Ceruloplasmin</td>
</tr>
<tr>
<td>10.</td>
<td>Transferin</td>
</tr>
<tr>
<td>11.</td>
<td>Ferritin</td>
</tr>
<tr>
<td>12.</td>
<td>Metallothionein</td>
</tr>
<tr>
<td>13.</td>
<td>Ascorbic acid (vitamin C)</td>
</tr>
<tr>
<td>14.</td>
<td>α-Tocopherol (vitamin E)</td>
</tr>
</tbody>
</table>
the skeletal muscle and blood\textsuperscript{25-27}. In 1982, Davies et al.\textsuperscript{11} demonstrated that the levels of ROS in muscle double after exhaustive exercise, and the findings of subsequent studies suggest that ROS cause exercise-induced oxidative damage in active tissues\textsuperscript{18,19,28)}.

**Sources of reactive oxygen species during exercise**

Exercise can increase the levels of oxidative stress markers in plasma and/or muscle, not only in healthy subjects but also in COPD patients\textsuperscript{12,29,30}. There are a number of potential sources for the generation of ROS \textit{in vivo} (Table 3), including the mitochondrial electron transport system, cytoplasmic xanthine oxidase (XO) enzyme system, sarcolemmal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, and NADPH oxidase in phagocytic cells such as neutrophils and macrophages.

Early studies reported that 2% - 5% of the total oxygen consumed by mitochondria may undergo one-electron reduction with the generation of superoxide\textsuperscript{31)}. Recent work has indicated that complexes I and III of the electron transport chain are the main sites of superoxide production in mitochondria after exhaustive exercise\textsuperscript{32}). During heavy exercise, the energy expenditure in skeletal muscle increases markedly (>100 fold) leading to a massive oxygen flow to mitochondria\textsuperscript{33}). Therefore, it is not surprising that mitochondrial generation of ROS is significantly enhanced during exercise\textsuperscript{34}). However, St-Pierre et al.\textsuperscript{34} estimated that less than 0.15% of the oxygen consumed by mitochondria is used to form superoxide, much lower than the earlier estimate of 2% - 5%. Therefore, the generation of ROS in mitochondria during exercise could be much less than previously thought, although further research is required to confirm this finding.

NADPH oxidase is an enzyme that catalyzes the production of superoxide by transferring electrons from NADPH to molecular oxygen\textsuperscript{35}). NADPH oxidase is located in sarcoplasmic reticulum, transverse tubules, and sarcolemma, and is considered to be one of the major sources of ROS production during exercise\textsuperscript{36,37}).

The role of XO in ischemic/reperfusion injury has been elucidated by McCord et al.\textsuperscript{37}). They proposed that, during ischemia, xanthine dehydrogenase is converted to XO via the activation of a calcium-dependent protease, and that XO utilizes molecular oxygen as an electron acceptor and

![Fig. 1](image_url) **Fig. 1** Brief metabolic map for the formation of reactive oxygen species (ROS) and their derivatives

\(O_2^-\): superoxide, \(H_2O_2\): hydrogen peroxide, \(OH^-\): hydroxyl radical, \(ONOO^-\): peroxynitrite, \(HOCl\): hypochlorous acid, SOD: superoxide dismutase, GPX: glutathione peroxidase, CAT: catalase, NO: nitric oxide, MPO: myeloperoxidase.

<table>
<thead>
<tr>
<th>Table 3. Main sources of ROS \textit{in vivo}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mitochondrial electron transport system</td>
</tr>
<tr>
<td>2. NADPH* oxidase in sarcolemma and sarcoplasmic reticulum</td>
</tr>
<tr>
<td>3. Xanthine dehydrogenase/oxidase system in cytoplasm of vascular endothelium</td>
</tr>
<tr>
<td>4. NADPH* oxidase in phagocytic cells (neutrophils, macrophages)</td>
</tr>
<tr>
<td>5. Cytochrome P450 system in endoplasmic reticulum (microsomal fraction)</td>
</tr>
<tr>
<td>6. Prostanoid metabolism (phospholipase A2 and lipoxygenase)</td>
</tr>
<tr>
<td>7. Peroxysome (catalase)</td>
</tr>
<tr>
<td>8. Auto-oxidation of catecholamines</td>
</tr>
</tbody>
</table>

* NADPH: Nicotinamide adenine dinucleotide phosphate
generates superoxide during the formation of uric acid from hypoxanthine and xanthine. Radak et al. found a significant linear relationship between the concentrations of lactic acid and XO in blood, indicating that XO could be involved in ROS generation during anaerobic exercise and that a similar mechanism could explain ischemia/reperfusion injury. In human skeletal muscles, strenuous exercise has been reported to increase the expression of XO.

Phagocytic cells such as neutrophils and macrophages are known to produce large amounts of superoxide in the phagocytic process, particularly when they phagocytose bacteria and fungi. When phagocytes encounter inhaled particles from irritants, such as cigarette smoke or other mediators such as inflammatory cytokines from inflammation, the membrane-bound NADPH oxidase of the phagocytes is activated, sometimes leading to excessive generation of superoxide and tissue damage. Exhaustive exercise has also been shown to activate circulating neutrophils in animals and humans. The neutrophilic enzyme, myeloperoxidase (MPO), provides an excellent quantitative index of neutrophils in tissues and its activity is elevated with prolonged running in most rat tissue, including skeletal muscle. In our previous study, we found increased activity of MPO in rat diaphragm after exhaustive exercise, suggesting the accumulation of neutrophils in active muscle. MPO catalyzes the oxidation of halides (e.g. Cl) by H2O2 to form hypohalous acids (e.g. hypochlorous acid, HOCl) (Fig. 1). Therefore, phagocytic cells, such as neutrophils and macrophages, could also play an important role in exercise-induced muscle damage.

**Skeletal muscle dysfunction and oxidative stress in COPD**

As mentioned earlier, skeletal muscle dysfunction is one of the main extra-pulmonary manifestations of COPD. Muscle dysfunction is usually reflected by loss of muscle strength and/or endurance. A number of studies have reported loss of muscle strength and fat-free mass (FFM) in the limbs of COPD patients. Skeletal muscle is a major component of FFM and its loss represents skeletal muscle depletion. Most studies have focused on the lower limb muscles, particularly the quadriceps, although there are some studies on the upper limb muscles. Muscle wasting, as reflected by loss of quadriceps strength and thigh muscle bulk, is a predictor of mortality in COPD, independent of airflow obstruction, smoking, and body mass index (BMI). Reduced skeletal muscle endurance reflected in reduced exercise endurance has also been reported in COPD patients. More than half of the COPD patients with very severe airflow obstruction show no evidence of limb muscle dysfunction, whereas limb muscle dysfunction exists in approximately 30% of COPD patients with mild to moderate airflow obstruction. Moreover, skeletal muscle weakness is associated with the loss of FFM in the extremities, but not with air-flow obstruction in COPD patients. Therefore, impaired lung function does not seem to be the main factor underlying muscle dysfunction in COPD patients.

The mechanisms of locomotor muscle dysfunction in COPD patients remain to be elucidated. However, muscle disuse appears to be an important factor. Muscles that remain active in daily life, such as the diaphragm and adductor pollicis, are not usually weak, whereas muscles that are typically inactive in COPD patients, such as the quadriceps and vastus lateralis, are weak. Muscle disuse may result from the sedentary lifestyle that many COPD patients lead to avoid exertional dyspnea. In addition, limb muscle dysfunction can also contribute to a further reduction in physical activity, creating a vicious circle. Kondo et al. demonstrated that immobilization causes oxidative stress in skeletal muscle. Their findings of increased Cu-Zn-SOD (mainly located in the cytosol) and decreased Mn-SOD (mainly localized in mitochondria) in atrophied muscle may reflect increased generation of superoxide anions in the cytoplasm rather than the mitochondria, and increased activity of superoxide-generating XO also supports this possibility. Indeed, oxidative stress has been found not only in the lungs but also in the blood and muscles of stable COPD patients.

For example, there is a negative correlation between the level of oxidative stress within the muscle tissue and muscle strength. Barreiro et al. reported that the levels of lipid peroxidation (4-hydroxy-2-nonenal [HNE] formation) and 3-nitrotyrosine (indicating the generation of peroxynitrite formed by the reaction of superoxide and nitric oxide) were elevated in muscles of COPD patients compared with that in control subjects. This finding suggests that both oxidative and nitrosative stress (O&NS) exists in the quadriceps of COPD patients resulting in muscle dysfunction. Increased expression of muscle Mn-SOD in COPD patients has also been reported, probably reflecting the increased ROS production in the mitochondria and suggesting that the mitochondria are also an important source of ROS generation in COPD patients, unlike pure immobilization. Interestingly, chronic cigarette smoke exposure also causes a significant increase in several oxidative stress markers in the limb muscles of healthy smokers.

Several studies have reported systemic inflammation in COPD patients, as evidenced by increases in blood levels of leucocytes and biomarkers, such as C-reactive protein, fibrinogen, and proinflammatory cytokines [e.g. tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8] in COPD patients. The cytokines are produced in many different cells, such as macrophages, neutrophils, monocytes, lymphocytes, endothelial cells, and fibroblasts, and play key roles in inflammatory and other responses to injury. Proinflammatory cytokines (e.g. IL-1, IL-6, and TNF) are often produced in response to oxidative stress, and also cause oxidative stress in their target cells. When nuclear factor-κB (NF-κB) is activated through ROS as a signal for the
expression of inflammatory mediators, those cytokines are produced and, in turn, this can increase NF-κB activation. Indeed, an increased level of NF-κB activation is observed in COPD patients, particularly muscle-wasted patients. Therefore, oxidative stress and inflammation are mutually interrelated in COPD patients, causing skeletal muscle dysfunction.

**Acute exercise and exercise training in COPD**

As stated earlier, strenuous or intense exercise is associated with oxidative exercise in humans as well as animals. Vina et al. reported the impact of acute exercise on oxidative stress in COPD patients. That study found increases in oxidized glutathione (GSSG) and reduced glutathione (GSH) ratio (GSSG/GSH) after COPD patients performed cycle ergometry at a similar intensity to normal activities of daily living [approximately three metabolic equivalents (METS)] until exhaustion. The post-exercise increase in GSSG and GSSG/GSH was partially prevented by the administration of oxygen. Heunks et al. also reported that incremental cycle ergometry in COPD patients caused an increase in GSSG and malondialdehyde (MDA, a lipid peroxidation product) as well as a decrease in GSH, which was prevented by administration of allopurinol (an inhibitor of xanthine oxidase [XO]) prior to exercise. Taken together, these findings suggest that XO may be an important source of ROS production during acute exercise in COPD patients because the impairment of pulmonary function in COPD patients could result in an imbalance between oxygen supply and demand during and after exercise. Moreover, because even light exercise increases oxidative stress in COPD patients, they are likely to develop oxidative stress while performing the regular activities of daily life. In addition to the above studies, many other studies have shown increased oxidative stress in both acute maximal and submaximal aerobic exercise. Although conflicting data exist about antioxidant levels in COPD patients, the levels of antioxidants, such as GSH and vitamin E, have been shown to be lower in COPD patients, particularly muscle-wasted patients, than that in control subjects. These findings suggest that an impaired antioxidant defense mechanism may be a contributing factor to increased exercise-induced oxidative stress in COPD patients. Several studies also have suggested that antioxidants, such as vitamin E, vitamin C, and N-acetylcysteine, can prevent or minimize the oxidative stress associated with acute exercise and improve exercise capacity in COPD patients. However, a recent study by Rossman et al. found that an antioxidant cocktail (vitamins C and E, and alpha-lipoic acid) prevented the production of free radicals, but did not improve quadriceps exercise performance in COPD patients. Although antioxidants could reduce the increased generation of ROS during and after acute exercise, excess ROS may still induce oxidative stress in active tissues.

Regular physical activity lowers the rates of hospital admission and all-cause and respiratory mortality in COPD patients, and pulmonary rehabilitation reduces the symptoms of dyspnea and improves exercise capacity and health-related quality of life. Consequently, pulmonary rehabilitation is recommended as an integral part of the management of COPD patients. In general, physical exercise training can increase the antioxidant and oxidative capacity in skeletal muscle of healthy subjects. Exercise training has also been reported to improve skeletal muscle oxidative capacity in patients with moderate to severe COPD. In addition, pulmonary rehabilitation has been shown to not only increase exercise capacity but also to decrease exercise-induced oxidative stress in COPD patients, based on exhaled H2O2 and urinary MDA as markers for pulmonary and systemic oxidative stress, respectively. Therefore, exercise training in COPD patients would be expected to upregulate antioxidant capacity and oxidative capacity in active tissues. However, to date, investigators have found that COPD patients exhibit only a minor increase or even a decrease in muscle antioxidant potential following exercise training, although there is a lack of data about the relationship between exercise training and muscular antioxidant capacity in COPD patients. Even though endurance exercise training is performed as part of pulmonary rehabilitation, it could cause oxidative stress in patients with severe COPD. For example, Barreiro et al. found increased nitrotyrosine (a marker for nitrosative stress) in quadriceps muscle of COPD patients after a 3-week endurance exercise program. Nemoto et al. reported an increase in urinary 8-hydroxydeoxyguanosine (a marker for oxidized DNA) in COPD patients with very severe airflow obstruction, but not in moderate-to-severe COPD patients following an 8-week pulmonary rehabilitation program. It should be noted that even standard exercise programs could cause oxidative stress in COPD patients, particularly muscle-wasted or severely affected COPD patients. Moreover, increasing evidence suggests that ROS are generated during exercise and modulate signaling pathways and the level of muscle contraction, implying a dose-response phenomenon in the relationship between the level of ROS and muscle contraction that can be explained by a hormetic curve; low levels of ROS stimulate the cellular function in muscles, whereas high levels cause muscular damage. It is important to consider this concept to improve or amend pulmonary rehabilitation programs. This form of rehabilitation is already established as the main non-pharmacologic treatment for COPD, but there is still scope for improvement.

**Conclusion**

The Nippon COPD Epidemiology (NICE) Study reported that COPD is an increasingly important health problem in Japan with a prevalence of 8.6% in the Japa-
The authors declare that there is no conflict of interests.

Essential to establish more effective pulmonary rehabilitation programs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

References


1124.

59) Barreiro E, Gea J, Corominas JM and Hussain SN. 2003. Ni-
tric oxide synthases and protein oxidation in the quadriceps
femoris of patients with chronic obstructive pulmonary dis-

60) Rodriguez DA, Kalko S, Puig-Vilanova E, Perez-Orlabarria
M, Falciani F, Gea J, Cascante M, Barreiro E and Roca J.
2012. Muscle and blood redox status after exercise training

61) Barreiro E, Peinado VI, Galdiz JB, Ferrer E, Marin-Corral J,
Sánchez F, Gea J and Barberá JA; ENIGMA in COPD Proj-
et. 2010. Cigarette smoke-induced oxidative stress: a role in
chronic obstructive pulmonary disease skeletal muscle dys-

62) Halliwell B and Gutteridge JMC. 2007. Free Radicals in Bi-
ology and Medicine, 4th Ed, 1-851, Oxford University Press,
Oxford, NY, USA.

63) Fermoselle C, Rabinovich R, Ausín P, Puig-Vilanova E,
Does oxidative stress modulate limb muscle atrophy in se-

64) Van Helvoort HA, Heijdra YF, Thijs HM, Vina J, Wanten GJ
and Dekhuijzen PN. 2006. Exercise induced systemic effects
in muscle-wasted patients with COPD. Med Sci Sports Exerc
18: 3543-1552.

65) Agaciken I, Basiyigit I, Ozden M, Yildiz F, Ural D, Maral
of antioxidants on exercise-induced lipid peroxidation in pa-
ients with COPD. Respirology 9: 38-42.

66) Mercken EM, Hageman GJ, Schols AM, Akkermans MA,
Bast A and Wouters EF. 2005. Rehabilitation decreases ex-
ercise-induced oxidative stress in chronic obstructive pulmo-

67) van Helvoort HA, Heijdra YF, de Boer RC, Swinkels A, Thijs
HM and Dekhuijzen PN. 2007. Six-minute walking-induced
systemic inflammation and oxidative stress in muscle-wasted

68) Koechlin C, Couillard A, Simar D, Cristol JP, Bellot H, Hayot
endurance in chronic obstructive pulmonary disease? Am J
Respir Crit Care Med 169: 1022-1027.

69) Rossman MJ, Groot HJ, Reese V, Zhao J, Amann M and
Richardson RS. 2013. Oxidative stress and COPD: the ef-
flect of oral antioxidants on skeletal muscle fatigue. Med Sci
Sports Exerc 45: 1235-1243.

70) Garcia-Aymerich J, Lange P, Benet M, Schnohr P and Anto
JM. 2006. Regular physical activity reduces hospital admi-
mission and mortality in chronic obstructive pulmonary disease:

71) Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Mar-
rades RM and Anto JM. 2003. Risk factors of readmission to
hospital for a COPD exacerbation: a prospective study. Theo-
rax 58: 100-105.

72) Nicl L, Donner C, Wouters E, Zuwallack R, Ambrosino N,
Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey
C, Goldstein R, Gosselin R, Lareau S, Maclntyre N, Maltais
F, Morgan M, O’Donnell D, Prefaut C, Reardon J, Rochester
C, Schols A, Singh S and Troosters T; ATS/ERS Pulmonary
Rehabilitation Writing Committee. 2006. American Thoracic
Society/European Respiratory Society statement on pulmo-
nary rehabilitation. Am J Respir Crit Care Med 173: 1390-
1413.

73) Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mul-
lins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG,
Ionescu AA, Thomas J and Tunbridge J. 2000. Results at 1
year of outpatient multidisciplinary pulmonary rehabilitation:

74) Ries AL, Bauldoff GS, Carlin BW, Casaburi R, Emery CF,
Mahler DA, Make B, Rochester CL, Zuwallack R and Her-
AACVPR Evidence-Based Clinical Practice Guidelines.
Chest 131 (5 Suppl): 48-42S.

75) Jenkins RR, Friedland R and Howald H. 1984. The relation-
ship of oxygen uptake to superoxide dismutase and catalase

76) Oh-ishii S, Kizaki T, Nagasawa J, Izawa T, Komabayashi T,
of endurance training on SOD activity, content, and mRNA
expression in rat muscle. Clin Exp Pharmacol Physiol 24:
326-332.

J, Carrier L and Belleau R. 1996. Skeletal muscle adaptation
to endurance training in patients with chronic obstructive pul-

78) Mercken EM, Hageman GJ, Schols AM, Akkermans MA,
Bast A and Wouters EF. 2005. Rehabilitation decreases ex-
ercise-induced oxidative stress in chronic obstructive pulmo-

79) Rabinovich RA, Ardite E, Troosters T, Caboň N, Alonso J,
Gonzalez de Suso JM, Vilaró J, Barberá JA, Polo MF, Ar-
gilés JM, Fernandez-Checa JC and Roca J. 2001. Reduced
muscle redox capacity after endurance training in patients
with chronic obstructive pulmonary disease. Am J Respir
Crit Care Med 164: 1114-1118.

80) Rabinovich RA, Ardite E, Mayer AM, Polo MF, Vilaró J, Ar-
gilés JM and Roca J. 2006. Training depletes muscle glutath-
one in patients with chronic obstructive pulmonary disease
and low body mass index. Respiration 73: 757-761.

81) Barreiro E, Rabinovich R, Marin-Corral J, Barberá JA, Gea J
and Roca J. 2009. Chronic endurance exercise induces quad-
riceps nitrosative stress in patients with severe COPD. Tho-
rax 64: 13-19.

Urinary 8-hydroxydeoxyguanosine is a potential indicator for
estimating pulmonary rehabilitation-induced oxidative stress

Exercise, oxidative stress and hormesis. Ageing Res Rev 7:
34-42.

84) Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A,
Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa
H and Zacher C. 2004. COPD in Japan: the Nippon COPD

85) Gea J, Agustí A and Roca J. 2013. Pathophysiology of muscle