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EDUCATION, BRAIN PLASTICITY AND MUSCULAR FATIGUE: DOES HYPOXIA CAUSE SARCOPENIA?

Sarcopenia is the physiological age-related reduction of muscle mass and strength. Considering that life span is correlated with metabolism rate and mitochondria are the site of oxygen consumption, muscle mitochondria volume densities were determined by morphometric analysis. We found a tight correlation between aging and hypoxia with decrease in muscle total mitochondria volume. Therefore, hypoxia and aging seem to share some common pathways, allowing hypoxic models to be used for the study of aging processes. Motivated rehabilitation approaches that would interact with the brain plasticity and new educational health programs are needed to counteract disabilities and to make the quality of life better. Additional research will be required to fully elucidate the correlations between aging, sarcopenia and hypoxia, but the present findings provide a starting point for such investigations.
Key words: *sarcopenia, hypoxia, age, rehabilitation, mitochondria*

In both humans and animals, aging is characterized by numerous modifications, including progressive losses of muscle mass, strength and oxidative capacity (Doherty, 2003). With increasing age, human skeletal muscles, progressively, reduce in volume, mainly due to a reduced number of motor units and muscle fibers, and reduced size of type 2 fibers (Thompson, 2002). Moreover, age induces important qualitative changes in the structure of key skeletal muscle proteins that are manifested in alterations of contractile properties (Gelfi et al., 2006). A consistent feature of age is limb muscle atrophy and the loss of peak force and power (Thompson, 2002, Vogt et al., 2001). Similarly sarcopenia is the physiological age-related reduction of muscle mass and strength. The multifactorial etiology underlying this process involves changes in muscle metabolism and endocrine system, alteration of nutritional, mitochondrial and genetic factors (Mishra and Misra, 2003) as well as a decrease in the number of motor neurons (Doherty, 2003).

In general, age-related changes of muscle mass and functional properties are a result of cellular adaptive responses. During aging, reactive oxygen species (ROS) are generated and these oxidants result in a detrimental effect on structural and functional components of membranes. ROS are generated under hypoxic conditions and the accumulation of free radicals during life reduces the ability of tissues to remove ROS. In fact, total antioxidant capacity is correlated to a fine balance between production and removal of ROS (Lu and Finkel, 2008). The loss of muscle mass that occurs with aging is associated with a decline in muscle protein content, mitochondrial protein synthesis and mitochondrial enzyme activity, and in a reduction of oxidative capacity

(D'Antona et al., 2003). Our data indicate that prevention of hypoxia and preservation of muscle mass through physical activity may help prevent sarcopenia and the associated decreases in metabolism. Tissue hypoxia, a physiological situation in aging, is related to the reduction of O_2 flow from the lungs to peripheral tissues and the resulting low cellular pO_2 leads to overproduction of reactive O_2 species capable of causing oxidative damage to proteins, nucleic acids, and lipids. The blood pO_2 decreases with age, and the reduction of blood flow to muscles causes atrophy, ROS formation and morphological muscle changes (Gunnarson et al., 1996, Muller et al., 2007, Porter et al., 1995)

The ventilatory response to hypoxia is characterized by an increase of volume and ventilatory frequency, related to the degree of hypoxia. This response is attenuated with aging (Fukuda, 1992) and the changes are correlated with age-dependent structural and functional modifications (Guenard, 1998). The basal reduction of oxygen requirements is manifested through geometrical adaptation in tissue, leading to increased diffusion distances and decreased oxygen supply to mitochondria (Gunnarsson et al., 1996, Sohal et al., 1986).

The literature shows that obstructive sleep apnea (OSA), the most common form of sleep-disordered breathing. It is characterized by recurrent episodes of intermittent hypoxia and intermittent hypoxia affects gene expression (Hoffmann et al., 2007). During aging there is an increase of recurrent OSA, which is similar to chronic intermittent hypoxia (Janssens et al., 2000), and patients with chronic intermittent hypoxia caused by recurrent apnea exhibit muscle atrophy (Agusti et al., 2002). Hypoxia combined with hypercapnia is the result of systemic consequences of lung disease such as COPD (chronic obstructive pulmonary diseases) or cardiovascular diseases, and arteriosclerosis itself causes hypoxia through reduction of blood flow and oxygen supply to tissues. Patients with chronic heart failure or COPD lose skeletal muscle mass during the course of their disease (Gosker et al., 2000), contributing to their observable weight loss, exercise limitations and decrease of the quality of life.

There seems to be a tight correlation between the structural and functional changes observed during hypoxia and aging. For example, in sea level-dwelling animals or humans exposed to high altitudes for several weeks, hypoxia leads to weight loss through decrease in protein content, similar to the effects seen in patients suffering from chronic hypoxia that accompanies cardio-pulmonary diseases. At high altitude, protein depletion is caused by an inadequate intake of calories and protein, similar to the effects seen during aging and in patients with COPD. However, the physiological response to hypoxia differs with respect to the level and length of hypoxic exposure. Moreover, maximum oxygen consumption (VO_2 max) decreases progressively with increasing altitude, showing a profile similar to the decrease in VO_2 max during aging.

Anemic patients with a decreased oxygen supply show a reduction in muscle strength (Penninx et al., 2004). If the antioxidant capacity is decreased during hypoxia, free radical production is likely to affect the mitochondria, as seen in sarcopenia. Thus, blood gas analysis and tissue pO_2 measures become important for diagnosis and treatment of several pathologies. VO_2 max is reduced by 3.2% for each 1000 ft increase in altitude. The reduction of mitochondrial oxidative capacity contributes

to the reduction of VO2 max with aging (Babcock, et al., 1992, Hepple et al., 2002, Wallace, 1995).

Here, mitochondrial volume densities were determined by histochemical and morphometric analyses of muscle biopsies from the tibialis anterior muscles of rats exposed to chronic intermittent hypoxia for 12 hour per day. We found that during both aging and hypoxia, the oxidative capacity decreased along with a decrease in total muscle mitochondrial volume.

The low mitochondrial density observed during aging and hypoxia could mean that muscles experiencing hypoxic conditions do not need as many mitochondria due to decreased levels of oxygen supply. During aging and hypoxia, the oxidative capacity decreases in parallel with the decrease of mitochondrial density. The total loss of muscle mitochondrial volume was close to 30% in rats exposed to intermittent hypoxia for two weeks. We also found a reduction of VO2 max in rats during exercise and aging, as previously shown for humans under hypoxic conditions (Ferretti, 1990). In addition, we observed an increase in Hypoxic Inducible Factor (HIF-1a) in skeletal muscles from aged rats, similar to the increased HIF-1a levels found in young rats exposed to hypoxia. ROS formation can interfere with HIF-1 and with oxygen sensors in mitochondria, leading to age-related declines in mitochondrial function (Zhang et al., 2008). This cellular mechanism underlying the morphological changes that occur with aging is consistent with those observed in rats exposed to chronic hypoxia. The volume density of total mitochondria (Vv) in young control sedentary rats was 6.73±0.2, while that for trained rats was 10.37±1.2, and the post-hypoxia values were 3.99±0.17 and 5.51±0.19, respectively. In contrast, the Vv for aged rats were 4.91±0.25 for sedentary rats and 6.20±0.11 for trained rats, and the post-hypoxia values were 3.91±0.30 and 4.96±0.17, respectively.

If the crucial mechanism of aging is the cumulative result of oxidative damage, long-term hypoxia models could help us understand the correlation between aging and ROS accumulation. Tissue growth, differentiation and regeneration are oxygen-dependent processes mediated by the release of factors such as VEGF, NOS and HIF. Here, the observed decrease of the total mitochondrial numerical density supports the hypothesis that oxidative damage is a major contributor to the aging processes, and provides evidence that the mitochondria act as oxygen sensors via modulation of ROS formation.

The loss of muscle mass and mitochondrial content would explain the decline in aerobic work capacity seen under conditions of both altitude and aging. This possibility is supported by observations that residents of the Himalayas show accumulation of lipofuscin (a result of mitochondrial degradation in the presence of increased ROS) and structural signs of aging, as well as decreases in mitochondrial content of muscle fibers (Amicarelli et al., 1999, Hoppeler et al., 2003, Martinelli et al., 1990).

Aging could be correlated with decreased oxygen supply to cells, increased oxygen diffusion distance to tissues, and decreased tissue oxygen demand. Therefore, hypoxia and aging seem to share some common pathways, allowing hypoxic models to

be used for the study of some aging processes. Prevention of oxygen desaturation and reducing the causes of hypoxemia are important factors in reducing the incidence of sarcopenia in the elderly population. Aerobic exercise training may attenuate the age-related decline in protein synthesis; exercise appears to help stabilize HIF-1a levels, further preventing some aging effects (Vogt et al., 2001).

In conclusion, it appears as though hypoxia can cause sarcopenia, meaning that prevention of hypoxia could decrease the incidence of sarcopenia in the elderly. Additional research will be required to fully elucidate the correlations among aging, sarcopenia and hypoxia, but these findings provide a starting point for such investigations.

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