COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/icop20

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To cite this article: Camillo Di Giulio (2013) Is Intermittent Hypoxia A Cause of Aging?, COPD: Journal of Chronic Obstructive Pulmonary Disease, 10:4, 542-544, DOI: 10.3109/15412555.2012.761961

To link to this article: https://doi.org/10.3109/15412555.2012.761961

Published online: 28 Mar 2013.

COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 10:542–544, 2013
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2012.761961

PERSPECTIVE

Is Intermittent Hypoxia A Cause of Aging?

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Abstract

Insufficient tissue oxygenation occurs in a wide range of physiological and pathological conditions. Reactive oxygen species (ROS) are physiological products of aerobic life and their accumulation affects aging. Chronic intermittent hypoxia can lead to oxidative stress that could predispose the organism to cumulative acceleration of the aging process.

Introduction

Oxygen is essential for life, and it first appeared on Earth 2.5 billion years ago. In 1604, Sendivogius wrote: "*Man was created on Earth and lives by virtue of air; for in the air there is a secret food for life*" (1). Two centuries later, Priestly was the first to isolate and describe oxygen; meanwhile Lavoiser, on his own, made the same observations and named this invisible species "oxygen."

The biological effects of oxygen have a double nature; low or high oxygen levels imply adaptation that brings cells either to survive or death. Insufficient tissue oxygenation occurs in a wide range of physiological and pathological conditions, including embryonic development, high altitude, wound healing, sleep apnea, anemia, cancer, inflammation, stroke and infarction.

Chronic intermittent or episodic hypoxia occurs during a number of disease states with devastating effects, and prolonged exposure to hypoxia can result in either cell injury or death. Indeed, hypoxia activates a number of signaling pathways that are involved with oxygen sensing, oxidative stress, metabolism, catecholamine biosynthesis, and immune responsiveness. Over time, the cumulative effects of these processes could undermine cell integrity and lead to a decline in physiological functions. In adult animals, intermittent hypoxia leads to a series of cellular, molecular, and pathophysiological responses due to oxidative stress (2) and lipid peroxidation, so increasing production of stress responsive proteins and neuronal apoptosis (3). The long-term consequences of chronic intermittent hypoxia may have detrimental effects, including hypertension, cerebral and coronary vascular diseases, developmental and neurocognitive deficits, and neurodegeneration. Aging is correlated with a reduction in cell oxygen supply on the one hand, and a parallel decrease in oxygen demand by tissues on the other (4). During aging, reactive oxygen species (ROS) are generated, which have detrimental effects on structural and functional components of membranes. ROS are generated in hypoxic conditions, and free radical accumulation reduces tissue ability to remove them.

ROS are produced as a normal product of aerobic life; in physiological conditions 1–5% of the oxygen used by mitochondria is converted in

Keywords: Hypoxia, aging, ROS

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ROS. Antioxidant defense mechanisms maintain ROS at harmless levels, so preventing damage. Weather life span could be correlated with both oxygen supply and ROS damage remains to be elucidated. However, an increased metabolic rate, intense physical exercise and stress induce release of several substances that could affect aging speed. The greater the oxidative damage, the shorter the life span. ROS increase has been widely recognized as being related to diabetes, hypertension, arteriosclerosis, and oxidative stress. These interact with other factors such as smoking, low vegetable or fruit intake, cold, and ultraviolet light, so becoming one of the main causes of aging. Chronic intermittent hypoxia may lead to oxidative stress and inflammation, which could predispose the body to cumulative injury and acceleration of the aging processes.

Hypotheses on aging

Several hypotheses have been proposed to explain aging, like the mitochondrial theory, cell oxidative damage, and damage accumulation in mitochondrial DNA related to ROS. The crucial aging mechanisms reside in the mitochondrion, considering that more than 90% of the cell oxygen supply is used by mitochondria. ROS damage at altitude hypoxia seems to accelerate the aging processes via loss of mitochondrial function, which seems to be one of the prime aging factors. For each organ, the total mitochondrion volume is an index of cell life span, and maximal oxygen uptake is correlated with both the volume and function of mitochondria (5). The observation that during hypoxia the number and volume of mitochondria decrease with lipofuscin accumulation witnesses a general reaction to stress that is consistent with the accumulation of such a molecule observed during aging (6).

Considering that physical activity is necessarily accompanied by oxidative stress, hypoxic inducible factor-1α (HIF) cell accumulation may result as a consequence of excessive ROS production during intermittent hypoxia, and this may promote acceleration of the aging processes. Intermittent hypoxia could represent the pathophysiological basis of many diseases. Moreover, life span is correlated with metabolic rate; mitochondria are the site of oxygen consumption in response to acute or chronic hypoxia; HIF plays a crucial role in adaptation processes. The correlation among oxygen consumption, ATP production and HIF levels is still to be understood, but considering that HIF regulates gene expression, when accumulated at either altitude or during recurrent sleep apnea it would mimic chronic intermittent hypoxia that increases with aging. Obstructive sleep apnea, characterized by more than 60 obstructions per hour, seems to modulate neurotransmitter release and cell injury, so repeated exposure to hypoxia induces adverse consequences.

Discussion

Hypoxia may be one of the factors underlying muscle dysfunction during aging and in patients with heart failure or lung diseases. Because hypoxia per se modulates mitochondria activity and oxygen consumption, hypoxia and aging could share some link. The correlation between hypoxia and life span remains open until we solve the question of how cells sense oxygen. Additional research is required to fully elucidate the correlations between aging and hypoxia, but intermittent hypoxia represents an experimental model adequate for studying aging processes. From adulthood to old age, maximum aerobic capacity declines at altitude, and mitochondrial oxidative capacity contributes to this decline (7). Moreover, during aging the oxidative capacity decreases in parallel with the reduction in total mitochondrion volume. The same can be observed in people living at altitude who do not need so many mitochondria because of the low atmospheric oxygen (6). The correlation between oxygen supply and mitochondrion volume and function is interesting, but all these factors need to be associated with the physiological requirements during both rest and physical exercise. On the contrary, highlanders feel ill when they move to sea level as a consequence of the relative hyperoxia and their incapacity to buffer all the oxygen supply to cells. In these conditions a relative hyperoxia is not capable of increasing the metabolic machinery and membrane damage results. ROS are physiological products of aerobic life and their accumulation affects aging.

Indeed, free radical species are generated during both hypoxia and hyperoxia, which damage membrane structural and functional components. Therefore, oxygen tissue distribution seems to be age dependent, and our hypothesis is that also oxygen sensitivity mechanisms are age dependent. During chronic intermittent hypoxia, nitric oxide synthase activity increases along with ROS, which seem to accelerate the aging processes. Intermittent or acute hypoxia, sleep apnea, exposure to altitude hypoxia, and incorrect physical exercise all lead to biological damage so accelerating aging processes. A lack of oxygen can directly damage brain cells; for example, periodic breathing, typical of altitude and aging, is a homeostatic mechanism that tends to reduce respiratory work, even though increased ROS production results (8).

At altitude the question is how high is the level and how long is needed to reach that level. During motion from altitude to sea level, intermittent hypoxia and physical exercise, a modulation of ROS buffering exists. If oxygen distribution within tissues were age dependent and related to HIF response, then tissue pO_2 could be used as a marker of aging. Furthermore, the acute increases or decreases in oxygen cell supply could generate excess in ROS, determining intermittent hypoxia and an increase in the aging processes. The determination of the reversibility of adaptive

tissue responses to intermittent hypoxia might help in finding new markers that could be useful for capturing of the signs of aging.

Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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