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Chronic Hypoxia as a Potential Factor in Human Life-threatening Diseases

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ABSTRACT

The review article focuses on the importance of adequate oxygen levels in the body as cure and therapy for many ailments. It is known that hypoxia is the cause for cellular damage and if it can be applied to major patho-physiology's, it can be observed that slow and chronic hypoxic conditions are the cause for most of the diseases. On the contrary, providing each cell of the body with proper oxygen may be helpful in maintaining the immunity of the body and therefore treating many disease conditions. This theory, if tested may show positive results in heart related diseases, neuronal disorders, stresses, digestive disorders and the unresolved cancer too. Slow decrease in the levels of atmospheric oxygen could be a reason to induce chronic hypoxia. According to Dr. Otto Warburg, a Noble laurate, a normal cell when deprived of oxygen, may get converted to a cancerous cell, whereas a cancerous cell cannot survive in aerobic conditions. If this part of his research be concentrated on, there could be fruitful results in the treatment of cancer. To maintain adequate levels of oxygen in the body, simple yogic breathing practices are helpful. And to maintain the adequate atmospheric oxygen, trees and plants which cleanse the atmospheric air are useful. Clinical surveys on volunteers who have been practicing regular breathing exercises can prove the fact that proper and concentrated respiration could prevent many diseases. Thus, supplementing breathing exercises along with the regular treatment for cancer patients could be helpful in alleviating cancer and other diseases.

KEYWORDS: Chronic Hypoxia; Yoga-Breathing exercises; Hypoxia in Cancer; Oxygen deprivation; Oxygen therapy.

Introduction

It is universally known that the most basic and vital functions of the body cannot be performed in the absence of oxygen. But the fact, that providing the body with adequate amounts of oxygen could be used as the cure for major disorders, is being ignored. Hypoxia, deprivation of oxygen, is known to be the major cause of cellular damage, which in turn can cause damage to the corresponding organs and their functions.

Oxygen is the only component of the air that we can breathe and is capable of supporting life. Air is mainly composed of approximately 21% oxygen, 78% nitrogen and other trace components. However, the addition of any gas, except oxygen, to air reduces the oxygen concentration through displacement and dilution. Deprivation of oxygen at a higher percentage acutely, is supposed to have many disastrous effects on the body. A list of the effects corresponding to the percentage of oxygen concentration are given in the Table 1.

Hypoxia as Root Cause of Cancer

If the percentage of oxygen is decreased at a smaller rate and for a longer time, that is in cases of chronic hypoxia, there could be many physiological and pathological changes in the body. All the cells have multiple responses to low or zero oxygen concentrations. In the complete absence of oxygen, cells undergo cell death through apoptosis, and not necrosis (Brunelle and Chandel, 2002).

TABLE 1
Effects of oxygen-deficient exposure.

Oxygen concentration (% vol)	Health effects
19	Some adverse physiological effects occur, but they may not be noticeable.
15-19	Impaired thinking and attention. Increased pulse and breathing rate. Reduced coordination. Decreased ability to work strenuously. Reduced physical and intellectual performance without awareness.
12-15	Poor judgment. Faulty coordination. Abnormal fatigue upon exertion. Emotional upset.
10-12	Very poor judgment and coordination. Impaired respiration that may cause permanent heart damage. Possibility of fainting within a few minutes without warning. Nausea and vomiting.
<10	Inability to move. Fainting almost immediate. Loss of consciousness. Convulsions. Death.

TABLE 2

Various conditions caused due to chronic hypoxia that can be improved by Yoga Breathing Exercises.

Central nervous system	Mild amnesia, depression, neuronal dysfunction, altered synaptic signaling, neuroinflammation, angiogenesis due to HIF-1 and tumors.
Respiratory systems	Chronic obstructive pulmonary disease (COPD), asthma, pneumothorax, sleep apnea, emphysema, chronic bronchitis, colds, and lung cancer
Cardiovascular dysfunctions	Ischemia, myocardial necrosis, arrhythmias, myocardial infarction, anemia, cyanotic congenital heart disease, and chronic cor pulmonale.
Renal system	Tubulointerstitial injury leading to progressive renal diseases, decrease in glomerular filtration rate, glomerulonephritis, nephrotoxicity, renal calculus, and kidney failure.
Pregnancy	Alters DNA synthesis, critical injury to vital organs, intrauterine growth restriction (IUGR), asphyxia, multi-organ failure, premature delivery, and perinatal demise. Long-term disabilities such as cerebral palsy, hearing loss, retinopathies, and chronic lung disease.

Dr. Otto Warburg, a Noble Laurate, stated the following in his research on root cause of cancer, (Warburg, 1966): "Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fer mentation of sugar. All normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. All normal body cells are thus obligate aerobes, whereas all cancer cells are partial anaerobes. From the standpoint of the physics and chemistry of life this difference between normal and cancer cells is so great that one can scarcely picture a greater difference. Oxygen gas, the donor of energy in plants and animals is dethroned in the cancer cells and replaced by an energy yielding reaction of the lowest living forms, namely, a fermentation of glucose".

"All normal cells have an absolute requirement for oxygen, but cancer cells can live without oxygen – a rule without exception. Deprive a cell 35% of its oxygen for 48 hours and it may become cancerous."

Dr. Warburg also found that cancer cells are anaerobic (do not breathe oxygen) and cannot survive in the presence of high levels of oxygen. However, Warburg's belief that his basic discoveries would result in cure for cancer were not enhanced, but research continues today in this potentially fruitful area. (Richard and Brand, 2010)

Oxygen availability is known to play a key role in the growth-regulatory process underlying carcinogenesis. In a study, (Mercedes et al., 2000) the general involvement of HIF-1 (hypoxia-inducible factor-1) in the transcriptional response to hypoxia was demonstrated. Since then, several established growth modulation factors, including Epo, VEGF, Tf, ET-1, and insulin-like growth factor binding protein 1 (IGFBP-1), have been shown to be under HIF-1 transcriptional control. Based on some previous reports, showing that AM (adrenomedullin) functions as an autocrine growth factor for certain human tumor cell lines, a comprehensive study was done to determine whether hypoxia could influence the expression of AM via HIF-1 in human tumor cell lines as an *in vitro* approach for similar conditions occurring in solid human cancers.

In conclusion of this study, an evidence was shown in favour of hypoxia as an inducer of AM mRNA and protein expression in human tumor cell lines. The data obtained from HIF-1 knockout mouse cell lines, biochemical modulation of HIF-1 activity, and transfection experiments gave solid proof on the involvement of HIF-1 in the up-regulation of AM mRNA under hypoxic conditions.

Thus, from the above studies, it can be confirmed that, chronic hypoxia could be the primary reason for increasing cases of cancer in the population. If this long-term deprival of oxygen can cause cancer, it might also be the cause for many other chronic disease conditions in the body. Let us highlight some of them here.

Effect on Heart Function

In patients with chronic pulmonary diseases there may be obsevere hypoxia during exercise and sleep. Experiments in healthy individuals showed that breathing hypoxic gas mixtures considerably increased coronary blood flow: a reduction of the inspired concentration of oxygen to 10% led to a doubling of coronary flow as the coronary arterial oxygen content was reduced (Davies and Wedzicha, 1993).

In a study, exposure to chronic hypoxia resulted in a lower resting heart rate and a blunted cardiovascular responsiveness to beta-adrenergic receptor stimulation. The results suggest that changes in beta-adrenergic receptor density may partially explain the hemodynamic adaptation that occurs with chronic hypoxia. These may be due to a loss of functional beta-adrenergic receptors caused by chronical hypoxia.

It is stated in a study that (Davies and Wedzicha, 1993) "It is perhaps surprising how little is known about the effects on the heart of hypoxia as opposed to ischemia. The cardiovascular responses of healthy individuals to hypoxia have been studied in the laboratory and during ascent to high altitudes, but the effects of hypoxia on diseased hearts are not well understood. Chronic hypoxic lung disease and sleep apnea have many effects on the heart and circulation and it is not known whether hypoxia itself or other mechanisms are more important. Potentially serious arrhythmias during sleep apneas and in heart failure may be triggered by hypoxemia. It is important to be aware of these effects because episodes of hypoxia occur in various conditions, and are probably under diagnosed. It is possible that oxygen therapy will be beneficial in some circumstances but much work remains to be done."

Oxygen therapy was mentioned as a possible treatment for major heart disorders as per the above study. This proves that deprivation of oxygen in long

term may affect the functions of heart and lungs, and would also lead to major heart diseases.

Brain Functions during Hypoxia

As we know, the fuel of the body is ATP, for all the normal functions of the body. ATP is made by breaking down glucose. Oxygen is used to remove the electrons used in the process to create ATP (Electron Transport Chain). The electrons split up O_2 into two oxygen atoms that attach to hydrogen releasing H_2O. Because of its highly reactive nature, oxygen is readily available for these reactions.

Viceversa, without oxygen, no ATP is produced so no energy is available. This effects all the functions of the entire body, but if we focus on the brain, the brain utilizes approximately 25 percent of the body's total oxygen consumption and the gray matter consumes as much as 94 percent of cerebral oxygen. ATP is used in neurons to restore them to their initial stage after firing (neuronal transmissions). By using ATP, the Sodium-Potassium channels can reset the neuron so it can do its function of transmitting information continuously. Hence, in hypoxic conditions: Ataxia (loss of voluntary muscle coordination), confusion, disorientation, hallucinations, lower level of consciousness and eventually death may occur.

In a study, (Haddad and Donnelly, 1990) the neuronal response to hypoxia with maturation, hypoglossal neurons from adult and neonatal rat (3-7, 14-16, 21 and 28 days) brain stem slices were subjected to O_2 deprivation. All neurons were depolarized and showed no evidence of hyperpolarization at any time during the hypoxic period. The magnitude of depolarization was about three-fold larger in adult hypoglossal neurons (mean = 32.0 mV) than in young neonatal neurons (mean = 10.4-11.2 mV) during hypoxic exposure (15-20 Torr) of 5 min. During longer periods of hypoxia of 15-30 min, neonatal cells showed an increase in the magnitude of depolarization reaching a level close to 80% of that in the adult. These results suggest that neonatal neuronal tissue is more tolerant to hypoxia than the adult, with the inherent cellular properties being maintained in newborn but not in adult neurons.

It is also observed that at higher altitudes, due to deprivation in oxygen, people find it very difficult to solve a simple puzzle. This is in the case of acute hypoxia. Therefore, in conditions of chronic hypoxia, there could be serious nervous system disorders.

Fetal Health

In the womb, a fetus receives oxygen from its mother through the placenta and umbilical cord. And if this is varied the overall growth of the fetus is affected, thus disturbing all the normal functions of the body in the later stages of life. The mother's oxygenated blood flows in and out of the fetus through veins in the umbilical cord. In cases where this flow is impeded, the fetus will not receive enough oxygen to develop properly. The most common reason a fetus doesn't receive enough oxygen in the womb is a condition called placental abruption. This condition occurs when the placenta detaches, either partially or fully, from the wall of the uterus, which decreases the blood flow reaching the fetus. Exposure to cigarette smoke directly or breathing in hypoxic gases can also impede blood flow to the fetus, as can cocaine use. This lack of blood flow and therefore oxygen can cause permanent damage to the fetus. Cerebral palsy, stillbirths and heart diseases are some of the most common results of a fetus lacking oxygen in the womb.

In an *in vivo* study using sheep, the blood flow to fetal organs was studied 3 to 10 days after surgery by means of the microsphere technique over a range of fetal arterial O_2 content from 6 to 1 mM. Blood flows to neural tissues (cerebrum, cerebellum, brain stem), heart, and the adrenals increased in inverse relation to arterial O_2 content. Thus, the arterial supply of O_2 to these organs tended to remain constant over the O_2 range studied. Blood flow to the fetal lungs decreased progressively with hypoxia (Louis et al., 1979). The relationship between changes in fetal heart rate and fetal asphyxia has remained largely speculative. However, recent studies have defined a more precise relationship between the severity of fetal oxygen deprivation and changes in fetal vital signs, apart from the central role played by oxygen deficiency in producing fetal brain damage and death. (Myers, 1973).

Discussion

All the above studies conclude that oxygen deprivation can be a major cause of a range of diseases from impaired daily functions to carcinogenesis. Then, the question of treating these disorders by providing adequate amount of oxygen arises. Can we detect oxygen level available for body organs to cells? Can we artificially induce required amounts of oxygen? Is there enough atmospheric oxygen to perform our daily functions? Or is it reduced due to pollution and other conditions? Could this be the primary reason for increase in number of cases of cancer, heart diseases, brain dysfunctions? Could providing adequate oxygen cure or prevent cancer? These are some questions which are very little answered.

To answer these questions, some straight forward techniques, without any medical interventions and heavy treatments, were investigated and related to our anticipated condition. Surprisingly, the answer is simple -- ancient techniques of breathing through Yogic practices. Yoga can improve a number of health conditions (Table 2). However, breathing in the hypoxic atmosphere may not be that accommodating. Hence, methods to cleanse the atmosphere surrounding were also considered.

Yoga- Breathing Exercises

In Yoga practices, breathing techniques and patterns are regularly advocated for relaxation, stress management, control of psycho physiological states and to improve organ function (Ritz and Roth, 2003) by concentration on respiration. This would be helpful in gaseous exchange in lungs, thus providing every cell with adequate level of oxygen. Whereas, in regular heavy

running or cycling exercises, one is inducing the condition of hypoxia. This may be temporary, but it is shown in a clinical study on eight healthy volunteers, that baseline heart rate was elevated in proportion to the severity of the hypoxia. (Marielle et al., 1996).

Pranayama breathing is often performed in yoga and meditation. It means the practice of voluntary breath control referring to inhalation, retention and exhalation that can be performed quickly or slowly (Jerath et al., 2006). In many yoga stories and literature, the word 'prana' refers to the 'life force' or energy. There is clear evidence that pranayama breathing techniques can affect oxygen consumption and metabolism (Jerath et al., 2006).

If proper oxygen is provided to each cell through concentrated respiration, on regular basis, the cell would start functioning normally even in chronic hypoxia conditions. It may also affect cancerous cells, since cancer cells cannot grow in aerobic conditions (Warburg, 1966). Many other disorders like ischemia, sleep apnea, chronic pulmonary and heart disorders, blood, brain, spinal and neuronal dysfunctions could be controlled by regular breathing exercises (Davies and Wedzicha, 1993). Breathing exercises in pregnant women starting from early stages of pregnancy could help both mother and the fetus in maintaining body equilibrium.

Oxygen Rich Surroundings

Again, another question arises. Are we living in oxygen rich conditions? Is this the cause for chronic hypoxia? We are not sure about the answer. But there are some age old Indian traditions which revolve around providing with proper and adequate amounts of oxygen. It is known that Peepal tree (*Ficus religiosa*), uses CAM photosynthetic pathway to produce O_2 both during day and night. Peepal tree being a hemi-epiphyte and one of the largest trees is responsible for maximum air purification (Sunitha, 2012). Tulsi, the holy basil (*Ocimum tenuiflorum*), which every household is supposed to have, is said to give out oxygen for 20 hours and ozone for four hours a day along with the formation of nascent oxygen which absorbs harmful gases like carbon monoxide, carbon dioxide and sulphur dioxide from the environment (Marc, 2014).

Few more practices like, using leafy garlands for celebrations at the door step purifies the air entering the house, as the green part absorbs the harmful gases from the air. Since there would be big gatherings during celebrations, more amount of carbon dioxide would be released. Agnihotra (sacred fireplace) is helpful in detoxifying the surrounding air. It is said that families with agnihothra were not affected during the Bhopal gas tragedy of 1984, though not proven. Singing rhythmically also allows proper respiration and increases lung capacity, which in turn acts as a breathing exercise.

Conclusion

Thus, checking the levels of oxygen intake clinically in a group of healthy volunteers, can prove that hypoxia and hypoxia related disorders can be reduced with regular practice of yogic breathing exercises. Or on the contrary a survey on the disease conditions of volunteers who practice regular Yoga, can be related to the effects of hypoxia and related disorders. Breathing exercises can be moderately employed in cancer patients to check the effectiveness in disease reduction.

References

Collins C. (1998). Yoga: Intuition, preventive medicine, and treatment. *Journal of Obstetric, Gynecologic, and Neonatal Nursing.* **27(5):** 563-568.

G G Haddad and D F Donnelly, (1990). O2 deprivation induces a major depolarization in brain stem neurons in the adult but not in the neonatal rat, *J Physiol.* **429:** 411-428.

J. K. Brunelle, N. S. Chandel, (2002). Oxygen deprivation induced cell death: An update. **7(6):** pp 475-482.

Jerath, R., Edry J.W, Barnes, V.A., and Jerath, V. (2006). Physiology of long pranayamic breathing: Neural respiratory elements may provide a mechanism that explains how slow deep breathing shifts the autonomic nervous system. *Medical Hypothesis.* **67(3):** 566-571.

Louis L.H. Peeters, Roger E. Sheldon, M. Douglas Jones Jr., Edgar L. Makowski and Giacomo Meschia, (1979). Blood flow to fetal organs as a function of arterial oxygen content, *American Journal of Obstetrics and Gynecology.* **135(5):** 637-646

Marc Maurice Cohen, (2014). Tulsi - Ocimum sanctum: A herb for all reasons, *J Ayurveda Integr Med.* **5(4):** 251-259.

Marielle Engelen, Janos Porszasz, Marshall Riley, Karlman Wasserman, Kazuhira Maehara and Thomas J. Barstow, (1996). Effects of hypoxic hypoxia on O2 uptake and heart rate kinetics during heavy exercise, *Journal of Applied Physiology Published.* **81(6):** 2500-2508

Mercedes Garayoa, Alfredo Martínez, Sunmin Lee, Rubén Pío, Won G. An, Len Neckers, Jane Trepel, Luis M. Montuenga, Heather Ryan, Randall Johnson, Max Gassmann, and Frank Cuttitta, (2000). Hypoxia-Inducible Factor-1 (HIF-1) Up-Regulates Adrenomedullin Expression in Human Tumor Cell Lines during Oxygen Deprivation: A Possible Promotion Mechanism of Carcinogenesis, *Molecular Endocrinology.* **14(6):** 848-862

Pal, G.K. Velkumary, S. and Madanmohan. (2004). Effect of short-term practice of breathing exercises on autonomic functions in normal human volunteers. *Indian Journal of Medical Research.* **120(2):** 115-121.

Richard A and Brand MD, (2010). Biographical Sketch Otto Heinrich Warburg, PhD, MD, *Clin Orthop Relat Res.* **468(11):** 2831-2832, DOI 10.1007/s11999-010-1533-z

Ritz, T. and Roth, W.T. (2003). Behavioral intervention in asthma. *Behavior Modification.* **27(5):** 710-730.

Ronald E. Myers, (1973). Threshold Values of Oxygen Deficiency Leading to Cardiovascular and Brain Pathological Changes in Term Monkey Fetuses, *Adv Exp Med Biol.* **37:** 1047-53.

S W Davies and J A Wedzicha, (1993). Hypoxia and the heart, *Br Heart J.* **69(1):** 3-5.

Sunita Panchawat, (2012). Ficus religiosa Linn. (Peepal): A Phyto-Pharmacological Review. **1(1)**

Warburg O, (1966). The prime cause and prevention of cancer - Part 1 with two prefaces on prevention. Available at: http://healingtools.tripod.com/primecause1.html/.

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