International Journal of Scientific and Innovative Research 2015; 3(1) : 17-26,
P-ISSN 2347-2189, E- ISSN 2347-4971

BIOMEDICAL APPLICATIONS OF HELIUM : AN OVERVIEW

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ABSTRACT

Helium has varied applications in biomedicine. The research studies with hyperpolarized helium-3 (^{3}He) and xenon-129 (^{129}Xe) magnetic resonance imaging (MRI) have been found useful in developing non-radiation based and sensitive approaches for chronic obstructive pulmonary disease (COPD). The applications of atmospheric pressure plasmas (APPs) in biomedicine are becoming better treatment protocols for various chronic diseases as the research studies have shown their potential in bacterial sterilization, blood coagulation and wound healing, dermatology and cancer treatment. It is interesting to emphasize that the atmospheric pressure helium plasma jet driven by pulsed dc voltage has been utilized to treat human lung cancer cells in vitro. This plasma device may serve as a valuable tool for reactive oxygen species (ROS) – promoting cancer therapy, a boon for cancer patients. Helium based low temperature atmospheric pressure plasma has been found to break Amyloidfibrils into smaller units in vitro and can be used as plasma based therapy of neurodegenerative diseases such as Alzheimer and Parkinson's. Attempts have been made to present the biomedical applications of helium and its utility in health and diseases. However, multidisciplinary scientific studies on the interaction of helium based low temperature atmospheric pressure plasma on the sub cellular and molecular levels in disease conditions could be useful in strengthening its application in biomedicine to address the health challenges for ailing humanity.

Keywords *: Helium, Hyperpolarized helium-3 (^{3}He) and Xenon-129 (^{129}Xe) Magnetic Resonance Imaging (MRI), Atmospheric Pressure Plasmas (AAPs), Chronic Obstructive Pulmonary Disease (COPD), Cancer, Alzheimer, Parkinson's*

INTRODUCTION

The unexpected prolonged exposure of human beings to large number toxic chemicals and xenobiotics present in the environment and unhealthy life styles have become the major cause of the complex diseases crippling the human subjects in the world. This has also resulted in multi -drug resistance problems in the society .In the present situation, clinicians and biomedical scientists throughout the world are in search of developing suitable diagnostic tool for the diseases .Radio- diagnosis has emerged as more accurate diagnostic technique for disease diagnosis at early stage and measuring the clinical conditions of the diseased people during treatment. X-ray and CT scan commonly employed by clinicians in diagnosing the diseases have been found to produce harmful effects on the patients as they produce radiations harming the body thereby making the human system immunologically deficient. In this scenario, scientists are exploring the use of noble gases in developing non-radiation based sensitive approaches for the diagnosis and treatment of complex diseases.

Naturally occurring noble gases are Helium (He), Neon (Ne), Argon(Ar), Krypton(Kr), Xenon (Xe) and radioactive Randon (Rn) which are also known as rare gases. They were once also called as inert gases as they were said to be incapable in producing chemical reactions with other elements. They are a group of chemical elements with very similar properties. They are all colourless, odourless, monoatomic gases and have very low chemical reactivity. The very low boiling and melting points of these gases make them useful as cryogenic refrigerants. Among these noble gases, helium has been found varied applications in health care. Liquid helium, which boils at 4.2K (-

268.95°C;-452.11°F) has been found useful for superconducting magnets which are needed in Nuclear Resonance Imaging and Nuclear Magnetic Resonance. The use of liquid helium in Magnetic Resonance Imaging (MRI) is continuously increasing in medical field because of the utility of MRI in diagnosis of complex diseases by medical profession. Helium is used as the carrier medium in gas chromatography, as a filler gas for thermometers and in devices for measuring radiation, such as the Geiger counter and the bubble chamber. Helium is sometimes used to improve the ease of breathing of asthma sufferers. The recent studies with hyperpolarized helium-3 (^{3}He) and xenon-129 (^{129}Xe) magnetic resonance imaging (MRI) have been found useful in developing non-radiation based and sensitive approaches for chronic obstructive pulmonary disease (COPD).[1] Atmospheric pressure plasmas (APPs) based on helium have also been developed as new tools in the biomedicine and have proved their effectiveness in biomedical applications such as treatment of living cells, sterilization, blood coagulation, wound healing and air purification.[2] Attempts have been made to present the biomedical applications of helium and its utility in health and diseases.

SOURCES

Scientists have observed that helium is the most abundant element found in the universe and is extracted from natural gases. All natural gases have trace quantities of helium. Scientists have been able to detect the helium in abundance by spectroscopic method in hotter stars. Helium has been found to be an important component in proton-proton reaction and carbon cycle accounting for the energy of the sun and stars. It has been found that the helium content of the atmosphere is about 1 part in 200,000. Helium has been found to be present in radioactive minerals. The free world supply of this noble gas in bulk quantity is obtained from USA especially from wells in Texas, Oklahoma and Kansas while outside the United States, the only known helium extraction plants in 1984 were in Eastern Europe (Poland), the USSR, and a few in India .

CHEMISTRY OF HELIUM

It has been found that helium is the second lightest and second most abundant gas in the universe (hydrogen being one). Since no helium compounds are known, this family of gases was once thought to be inert. In the year 1962, scientists could be able to prepare first noble gas compound with xenon. Helium occurs in un-combined form. It is believed that it must be extracted from the atmosphere by liquefaction of air or separated from deposits of natural gas. Research studies have predicted that some of the terrestrial helium is the product of the alpha decay of radioactive isotopes beneath the crust. Helium is said to be the only element which cannot be converted to a solid by cooling.

Chemists have found that helium possess lowest melting point of any element. It is widely used in cryogenic research because its boiling point is close to absolute zero. Helium has been found to be a vital element in the study of super conductivity. Research studies have revealed that liquid helium can be used in obtaining temperatures of a few micro kelvins by the adiabatic demagnetization of copper nuclei.[3] Helium is known to be only liquid which could not be solidified by lowering the temperature and remains in liquid down to absolute zero at ordinary pressure. It has ability to solidify by increasing the pressure while solid ^{3}He and ^{4}He can be changed in volume in volume (more than 30 percent) by applying pressure. The specific heat of helium gas is high sand the density of helium vapor at normal boiling point is also very high with vapour expanding greatly when heated at room temperature. Although helium has weak chemical reactivity to combine with other elements, scientific studies have been carried towards preparation of helium difluoride. [4] Further, scientists have also investigated on molecular ions of helium like He^{+} and He^{++}. Seven isotopes of helium are known: Liquid helium (He-4) exists in two forms: He-4I and He-4II, with sharp transition point at 2.174K. He-4I (above this temperature) is a normal liquid, but He-4II (below it) is unlike any other known substance. It expands on cooling, its conductivity for heat is enormous, and neither its heat conduction nor viscosity obeys normal

rules.[5,6]

BIOMEDICAL APPLICATIONS

The very low boiling and melting points of noble gases make them useful as cryogenic refrigerants. Among these noble gases, helium has been found varied applications in health care. Liquid helium, which boils at 4.2K (-268.95°C; -452.11°F) has been found useful for supercond-ucting magnets which are needed in Nuclear Resonance Imaging and Nuclear Magnetic Resonance. The use of liquid helium in Magnetic Resonance Imaging (MRI) is continuously increasing in medical field because of the utility of MRI in diagnosis of complex diseases by medical profession. Magnetic resonance imaging (MRI), nuclear magnetic resonance imaging (NMRI) or magnetic resonance tomography (MRT), is a medical imaging technique used in radiology to investigate the anatomy and physiology of the body in both health and disease . MRI scanners use strong magnetic fields and radio waves to form images of the body. The technique is used in hospitals for medical diagnosis, staging of disease and for follow- up without exposure to ionizing radiation.

Atmospheric pressure plasmas (APPs) based on helium have been developed as new tools in the biomedicine and have proved their effectiveness in biomedical applications such as treatment of living cells, sterilization, blood coagulation, wound healing and air purification[2]. Low temperature plasmas have potential to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) having diverse biological implications such as ROS effects on cell membrane : per oxidation of lipids, oxidation of proteins, DNA strands and RNS effects on biological cells : cell signalling. The applications of helium based MRI and low temperature atmospheric pressure plasmas in chronic complex diseases such as chronic obstructive disease (COPD), cancer, neurodegenerative diseases etc. are discussed in this review article.

Pulmonary Diseases

Complex respiratory disorders like chronic obstructive pulmonary disease (COPD) characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases present in the environment.[7] COPD has emerged as the 4th leading cause of death worldwide.[8,9] Several research studies have shown the efficacy of nuclear medicine , computed tomography (CT) and magnetic resonance imaging (MRI) in evaluating chronic obstructive pulmonary disease and developing imaging biomarkers for assessment of disease progression and treatment response.

Magnetic resonance imaging (MRI) inhaled hyperpolarized noble gases helium-3 (^{3}He)[10-23] and xenon-129 (^{129}Xe)[24, 25] have been shown to provide structural and functional measurements in healthy volunteers as well as subjects with a range of respiratory conditions. These strategies are based on the research studies conducted by Albert and colleagues[24] showing the effectiveness of inhaled hyperpolarized or magnetized noble gas for pulmonary magnetic resonance imaging (MRI). It is interesting to emphasize that hyperpolarized gas MR imaging helps the clinicians in quantifying important structural and functional components of the lung such as Ventilation Defect Measurements and Apparent Diffusion Coefficient as biomarkers[26-30]which play vital role in diagnosis and treatment of complex respiratory disorders like chronic obstructive pulmonary disease (COPD).

The need for sensitive regional and surrogate measurements of lung structure and function in COPD continues to motivate the development of non-radiation based and sensitive imaging approaches, such as hyperpolarized helium-3 (^{3}He) and xenon-129 (^{129}Xe) magnetic resonance imaging (MRI). ^{3}He ventilation defect measurements in COPD have been found to correlate with spirometric measurements of airflow limitation. [27, 31] Studies on ^{3}He MRI in COPD cases revealed heterogeneous signal intensity and ventilation abnormalities or “defects’’, representing local hypoventilation of the lung. [10] Hyperpolarized ^{3}He MRI with xenon-133 scintigraphy has been found to produce encouraging response in evaluating ventilation abnormalities in COPD cases.[32] Studies have shown that ^{3}He ADC can serve as a good imaging biomarker to measure lung

tissue destruction in early disease.[31,33-38] Further, hyperpolarized gas MR diffusion-weighted imaging has been found useful in COPD.[39-44]

Extensive studies have been conducted to evaluate the potential of hyperpolarized ^{3}He MRI in diagnosis and treatment of COPD using various imaging biomarkers and significant results have been achieved thereby suggesting that hyperpolarized gas MRI can be used in assessing the lung structural and functional changes in chronic obstructive pulmonary disease (COPD).[45-53] In addition to above mentioned studies, the experimental and clinical applications of functional MR imaging of pulmonary ventilation using hyperpolarized noble gases have been studied and it has been found that 3- helium (^{3}He) and 129- xenon (^{129}Xe) can be hyperpolarized by optical techniques such as spin exchange or metastability exchange in sufficient amounts and can be used for assessment of ventilation- distribution , structural changes of lung parenchyma, such as emphysema and fibrosis.[54]

Cancer

Atmospheric pressure plasmas (APPs) have been found to be of great potential in diverse biomedical applications. Their applications in bacterial sterilization, blood coagulation, and wound healing, dermatology and cancer treatment have been explored.[55-61] Atmospheric pressure plasmas have also been found to produce effects on living cells.[62-66] The interactions of plasma with cancer cells have been demonstrated to induce cell death in different cancer cell types which might be due to production of reactive oxygen species (ROS) such as super oxide (O_2^{-2}), hydrogen peroxide (H_2O_2), oxygen atom (O), and hydroxyl radical (OH) .[61, 67-75] Plasma-induced ROS in the gas phase could result in intracellular ROS generation and apoptotic cell death. Atmospheric pressure plasmas based on helium with only small fractions of oxygen (less than 5%) have been studied in order to increase concentrations of ROS and prevent plasma instability simultaneously [76] thereby indicating the potential of He/O_2 plasmas as a good source of reactive oxygen species. Admixture of helium and oxygen has been used to produce more radicals in atmospheric pressure plasma jets.[77-79] Recently the atmospheric pressure helium plasma jet driven by pulsed dc voltage has been utilized to treat human lung cancer cells *in* vitro. The studies have shown effects of additive oxygen on the plasma state including helium and oxygen – related radicals and considerable correlation between the concentration of intracellular and extracellular reactive oxygen species (ROS) and also increase in expression levels of p 53 and the phospho-53 in the presence of additive oxygen flow compared with those from pure helium plasma treatment thereby representing this plasma device a valuable tool for ROS-promoting cancer therapy. [80]

In another study, air, argon (Ar) and helium (He) plasma sources driven by AC or micro wave power has been found useful in the treatment of cancer cells, sterilization, tooth whitening and blood coagulation. Various types of non-thermal APPs operated in low frequency (20kHz) and microwave frequency (900MHz and 2.45GHz) power feeding argon, helium, and even in the ambient air have been shown to possess biomedicine applications such as treatment of cancer cells, sterilization, tooth whitening, and blood coagulation. It has been demonstrated that the antibody – conjugated GNPs have ability to enhance to kill cancer cells exposed to plasmas.[81]

Non-thermal atmospheric plasma jets using helium have been extensively studied in various kinds of cancer and antitumor effect has been observed *in vitro* on carcinogenic cell lines related to cancer of skin (melanoma), brain (glioblastoma), colon, liver, lungs, breast, cervix, bladder and in oral and ovarian carcinoma or in leukemia.[82, 83, 84, 85] It is important to mention that PG helium NTP used in this research study [87] has capability to produce reactive species and to generate transient electric field. The results of the study provide a novel NTP- based adjuvant therapy for cancer treatment. [86] Besides these studies, several studies on the role of low temperature atmospheric air plasma on various types cancer on animal models and human subjects have also been conducted and encouraging response have been achieved.[88-92] The study has been carried out to find out the

effect of low-level helium-neon (He-Ne) laser in the prevention and treatment of radiation induced mucositis in head and neck cancer patients and beneficial results have been obtained. [93]

Neurodegenerative Diseases

Studies have been conducted to evaluate the potential of helium based low temperature atmospheric pressure plasma in treatment of neurodegenerative diseases such as Alzheimer and Parkinson's which are associated with Amyloidfibrils. It has been found that low temperature atmospheric pressure plasma can break Amyloidfibrils into smaller units *in vitro.* The study has been able to provide the plasma based therapy of these progressive and debilitating diseases. [94]

Application of Helium- Oxygen Mixtures in Cough, Asthma, Chronic Obstructive Pulmonary Diseases (COPD), Anaesthesia

Helium-oxygen mixtures have been found very effective in various disease conditions. It is very interesting to mention that Heliox (a mixture of 21% O_2 and 79% He) has been used medically since the early 1930s and it was used in the treatment in acute asthma before the advent of bronchodialators. [95-99] Heliox has been found effective in conditions of large airway narrowing such as upper airway obstruction from tumors or foreign bodies and vocal cord dysfunction. Heliox is also used in conditions of the medium airways like croup, asthma and chronic obstructive pulmonary disease. Patients with these conditions suffer a range of symptoms like dyspnea, hypoxemia and weakening of respiratory muscles due to exhaustion leading to respiratory failure. Heliox has been found very effective in reducing these effects thereby making the patients capable to breathe easily. [100] It is also useful in weaning of patients off mechanical ventilation and in the mobilization of inhalable drugs, particularly for elderly. [101] Helium- oxygen mixtures have also been found useful in delivery of anaesthesia. [102]

DISCUSSION

At early stage scientists thought that noble gases helium, neon, argon, krypton, xenon and radon also called as inert gases or rare gases could not have any application in daily life as these gases are incapable to produce chemical reactions with other elements because of their stable electronic configurations with no unpaired electrons to share. Later chemists found that krypton, xenon and radon with outer electrons held less firmly, can form compounds mainly with fluorine. Rare though they are, these gases are now a part of everyday life, as evidenced by the helium in balloons, the neon in signs and the harmful radon in some American homes. Noble gases have very low boiling and melting points which make them useful as cryogenic refrigerants. Among these noble gases, helium has been found varied applications in health care. Liquid helium, which boils at 4.2K (-268.95°C; -452.11°F) has been found useful for superconducting magnets which are needed in Nuclear Resonance Imaging and Nuclear Magnetic Resonance. The use of liquid helium in Magnetic Resonance Imaging (MRI) is continuously increasing in medical field because of the utility of MRI in diagnosis of complex diseases by medical profession. Medical professionals are using medical imaging technique such as magnetic resonance imaging (MRI), nuclear magnetic resonance imaging (NMRI) or magnetic resonance tomography (MRT) to investigate the anatomy and physiology of the body in both health and disease. MRI scanners use strong magnetic fields and radio waves to form images of the body. This technique is widely used in hospitals and clinics for medical diagnosis, staging of disease and for follow- up without exposure to ionizing radiation and has become very successful in diagnosis and treatment of chronic complex diseases like chronic obstructive pulmonary disease (COPD) which has emerged as the 4th leading cause of death worldwide and is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases present in the environment . The recent studies with hyperpolarized helium-3 (^{3}He) and xenon-129 (^{129}Xe) magnetic resonance imaging (MRI) have been found successful in developing non-radiation based and sensitive approaches for chronic obstructive pulmonary disease (COPD).

The applications of atmospheric pressure

plasmas (APPs) in biomedicine are becoming better treatment protocols for various chronic diseases as the research studies have shown their potential in bacterial sterilization, blood coagulation, and wound healing, dermatology and cancer treatment. It is interesting to emphasize that the atmospheric pressure helium plasma jet driven by pulsed dc voltage has been utilized to treat human lung cancer cells *in vitro*. This plasma device may serve as a valuable tool for reactive oxygen species (ROS) – promoting cancer therapy, a boon for cancer patients. Various types of non-thermal APPs operated in low frequency (20kHz) and microwave frequency (900MHz and 2.45GHz) power feeding argon, helium, and even in the ambient air have shown potential in treatment of cancer cells, sterilization, tooth whitening, and blood coagulation. The antibody – conjugated GNPs have ability to enhance to kill cancer cells exposed to plasmas. Furthermore , helium based non-thermal atmospheric plasma jets have been found useful in different kinds of cancer such as skin cancer (melanoma), brain cancer (glioblastoma) ,colon, liver, lungs, breast , cervix, bladder and in oral and ovarian carcinoma or in leukemia and may be an effective NTP- based adjuvant therapy for cancer treatment. Low-level helium-neon (He-Ne) laser has been found useful in the prevention and treatment of radiation induced mucositis in head and neck cancer patients. Helium based low temperature atmospheric pressure plasma has been found to break Amyloidfibrils into smaller units in vitro and can be used as plasma based therapy of neurodegenerative diseases such as Alzheimer and Parkinson which are progressive and debilitating diseases . Additionally, the applications of simple helium – oxygen mixtures in various chronic conditions like cough, asthma and chronic obstructive pulmonary disease etc. have enhanced the potential of helium in biomedicine.

Although helium in various modes has been found useful in disease conditions ranging from simple cough to dreadful diseases like cancer, chronic obstructive pulmonary disease, Alzheimer and Parkinson's , multidisciplinary scientific studies on the interaction of helium based low temperature atmospheric pressure plasma on the sub cellular and molecular levels in disease conditions may enhance its application in biomedicine to address the health challenges for ailing humanity.

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