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A Review on the Nobility and Medical Importance of Helium

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ABSTRACT: The colourless, odourless and monoatomic gas, helium, is considered as the second most abundant element in the universe after hydrogen. Helium is classified as a noble gas and it is the lightest noble gas. Noble gases including helium, although extremely inert chemically, display a remarkable spectrum of clinically useful biological properties. Medically, helium's applications range from respiratory care, where it facilitates easier breathing through heliox mixtures, to cardiology and neurology, where it offers cardioprotection and neuroprotection during ischemia/reperfusion injuries.

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Helium is a colourless, odourless and monoatomic gas and it is regarded as the second most abundant element in the universe after hydrogen (Eric, 2023). Helium is classified as a noble gas and it is the lightest noble gas (Chhandak *et al*., 2017). The noble gases, formerly known as inert gases or areogens, are a group of elements located at the extreme right of the periodic table (Bauzá and Frontera, 2015). The noble gases are a group of elements with filled outermost shell and so remain chemically inert since their valence orbitals are already completely filled (Miao, 2020). Noble gases including helium, although extremely inert chemically, display a remarkable spectrum of clinically useful biological properties (Winkler *et al*., 2016).

Articles were searched online including PubMed, Scopus, Embase, ResearchGate up to 2024, of which 39 articles were adapted for this review. The keywords that directed our literature search included noble gases, helium, chemical elements, cardioprotection, **r**espiratory care, helium ion microscopy, radiology, and magnetic resonance imaging (MRI) machines.

The Nobility of Helium: Helium, symbolized as "He", is characterized by its exceptional chemical inertness and unique properties. Helium is regarded as a noble

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gas because it does not react with other elements to form a compound. Helium was first discovered in the solar system before it was discovered on earth (Chhandak *et al*., 2017). In 1868, Pierre J. C. Janssen travelled to India to measure the solar spectrum during a total eclipse and observed a new yellow line. It was Lockyer who proposed that the line was due to a new element, which he named after the Greek word for sun "helios" which is interpreted as "helium" (Carlos *et al*., 2013). In 1895, helium was then discovered on earth by some scientists who found helium emanating from the uranium ore cleveite. It was then first isolated by a British Chemist named William Ramsey who treated the mineral cleveite with mineral acids (Harris and Barnes, 2008).

Helium is known to be the lightest noble gas and the one with the least melting and boiling points among all elements. It has a molecular weight of 4 g/m and a density lesser than oxygen and nitrogen (0.179g/me) and an absolute viscosity of 201.8 mp (Ding *et al*., 2017).

Helium's chemical inertness is due to its closed-shell electronic structure, zero electron affinity, and unparalleled ionization potential (Dong *et al*., 2017). Helium does not form compounds under normal settings due to its extreme inertness. This chemical stability is because of the lack of available electrons for bonding, as the 1s orbital is fully occupied and any higher energy orbitals are empty in its neutral state. Helium contains two electrons that entirely fill its 1s orbital. The 1s orbital of helium is completely occupied by two electrons, giving rise to the configuration $1s^2$. The lowest energy level is fully occupied, which results in a very stable electron configuration. The Pauli Exclusion Principle, which stipulates that no two electrons in an atom may have the same set of quantum numbers, adds even more support to the stability. Helium is therefore both chemically non-reactive and highly beneficial as its two electrons must have opposing spins.

Although helium is predominantly inert, recent studies have shown that it can form compounds under extreme conditions. For instance, at very high pressures, helium can form stable compounds with sodium, such as Na_2He, indicating that its chemical behavior can be altered in unusual conditions (Dong *et al*., 2017).

The Use Of Helium In Respiratory Care: Heliox gas mixture, a combination of 79% helium and 21% oxygen when produced, has a density six times lower than atmospheric air. However, other combinations may exist such as 70/30 and 60/40. Heliox is a medical treatment that is used to treat people who have trouble breathing because it passes through the lungs' airways with less resistance than atmospheric air, requiring the patient to exert less effort to breathe in and out (Hashemian and Fallahian, 2014). Inhaling heliox causes a significant decrease in turbulence because of its reduced density, especially in the distal regions of the lung. This results in less overall airway resistance and a higher percentage of laminar flow. During heliox inhalation, the reduced turbulence impact causes flow rates to rise by as much as 50% (Hashemian and Fallahian, 2014).

According to Anna *et al*. (2016), the use of heliox has been beneficial in the treatment of patients with upper airway obstruction, although most case reports described short-term beneficial effects, such as improved breathing and oxygenation. The use of heliox has been advocated for in the treatment of several respiratory conditions, such as upper airway obstruction, extrinsic upper airway compression, postextubation stridor, croup, laryngotracheomalacia, bronchiolitis, ARDS, and obstructive lung diseases, due to its extremely low density and reduced adverse effects (Kleiman and Huffmyer, 2018). Heliox may enhance ventilation and the perfusion ratio by facilitating more penetration into the lungs' peripheral regions. Additionally, Heliox can promote CO_2 removal and gas mixing in the alveoli (Szczapa *et al*., 2022).

The Use Of Helium In Microscopy: Helium ion microscopy (HIM) is a sophisticated imaging method with sub-nanometer resolution that uses a concentrated stream of helium ions to provide high-resolution images (Schmidt *et al*., 2021). Sub-nanometer resolution is achievable with HIM, which is essential for studying biological specimens and materials at the nanoscale. Numerous publications have been published on the study of biological samples, which proved extremely difficult to analyze using scanning electron microscopy (SEM) or transmission electron miscroscopy (TEM) but were simple to view with HIM in a short amount of time (Minuti *et al*., 2022; Ogawa, 2022). Compared with traditional electron microscopy, helium ion microscopy has a number of benefits, such as improved surface sensitivity, higher resolution, and the capacity to image non-conductive materials without the requirement for coating.

The resolution acquired with HIM imaging is significantly higher than that obtained with a traditional field-emission scanning electron microscopy (FE-SEM) technique, according to Joens *et al*. (2013). The ability to photograph opaque, non-conductive specimens with a rather strong topography is one benefit of HIM. This is made feasible by the combination of the ability to compensate for charges and a broad field of focus (Schmidt *et al*., 2021). When compared to other methods, HIM's broad depth of field and ability to prevent sample charging with the electron flood gun are two advantages for application in biological tissue and cells (Wirtz *et al*., 2019). In addition to its capacity for surface-sensitive imaging, it can capture charge-compensated images on insulating samples like biological specimen or polymers without requiring a conductive coating layer (Emmrich *et al*., 2021).

Helium Useful In Cardiology: Helium induces cardio-protection by pre- and post-conditioning (Aehling *et al*., 2017). Zang *et al*., reported that helium preconditioning (HePC) can significantly reduce infarct size in myocardial ischemia/reperfusion injury model of rabbits, young rats but not aged rats (Zang *et al*., 2022). Helium decreases infarction size when used as an agent for both cardiac pre- and post-conditioning (Keliman and Huffymer 2018).
Helium-induced cardioprotection mechanisms include blocking mitochondrial permeability transition pore (mPTP) opening and NO production by eNOS, activating phosphoinositide 3-kinase (PI3K), p44/42 mitogen-activated protein kinase (MAPK) (ERK1/2), p70S6 kinase (p70s6K), cyclic AMP (cAMP)-dependent protein kinase (PKA), cyclooxygenase-2 (COX-2), opioid receptors, and mitochondrial ATP-regulated potassium (KATP) channels (which may produce minute amounts of ROS) (Zhang *et al*., 2022). In an open-label single arm intervention study conducted by Brevoord *et al*., it was found that helium ventilation is feasible and can be used safely in patients treated with hypothermia after cardiac arrest (Brevoord *et al*., 2016). Inhaling helium protects the heart against ischemia/reperfusion damage. In a study done to investigate how helium conditioning (HeC) affects cardiac fibroblasts, it was discovered that HeC accelerated the migration of cardiac fibroblasts in neonatal rats (Jelemenský *et al*., 2021). In another study carried out by Zhang *et al*., it was observed that helium protects against lipopolysaccharide-induced cardiac dysfunction in mice partially via inhibiting myocardial TLR4-NF-[kappa]B-TNF-a/IL-18 signaling (Zhang *et al*., 2020).

Helium Use In Neurology: According to Pan and his associates, inhaling heliox—a 70% helium and 30% oxygen mixture—24 hours following middle cerebral artery blockage can significantly lessen the extent of the infarction and enhance neurological function (Pan et al., 2007). Helium preconditioning was found to have a neuro-protective effect in a study of hypoxic ischemic disease in neonatal rats. This effect was demonstrated by reduced infarction area, reduced apoptotic cells, significant expression of antioxidant enzymes, reduced brain atrophy, and enhanced neurological function (Li et al., 2016). In addition to stimulating growth/neurotrophic factors (brain-derived neurotrophic factor and nerve growth factor), helium preconditioning can enhance nerve behavior following brain injury (Deng *et al.,* 2021).

The dosage and timing of helium's application determine how effective its neuroprotective effects are (Scheid *et al*., 2023). Temperature regulation is another factor that could contribute to the action of helium. Helium treatment at 25°C was reported by David *et al*. to minimize brain infarction and motor impairments, whereas delivery at 33°C did not exert any neuroprotection (David *et al*., 2009). They also found that the degree of body temperature reduction was largely dependent on the gas temperature at which helium was applied, and that helium provided neuroprotection by causing hypothermia (David et al., 2009).

The Use Of Helium In Surgery: In order to treat a range of abdominal disorders, laparoscopic surgery is utilized to view the structures of the abdomen and make room for the manipulation of medical equipment. This procedure entails inflating the abdomen with carbon dioxide (CO_2) gas, which is absorbed by the peritoneum and modifies physiological characteristics. This can make surgery more difficult and result in major changes to the cardiovascular and pulmonary systems. Cheng et al. (2013) conducted a meta-analysis of all the research that used helium, nitrous oxide, and two additional medicinal gases to establish the pneumoperitoneum required for abdominal laparoscopic surgery. According to their findings, helium caused less cardiopulmonary alterations than carbon dioxide (Cheng *et al*., 2013). Helium is a safe substitute for insufflant in high-risk individuals having laparoscopic kidney surgery (Makarov *et al*., 2007; Berganza and Zhang, 2013, Yu *et al*., 2017). Patients with congestive heart failure, COPD (chronic obstructive pulmonary disease), malignant hyperthermia, chronic hypoxia from multiple pulmonary infarcts, and chronic hypoxia from an intrapulmonary shunt are among those who have been shown to benefit most from this treatment (Makarov et al., 2007).

Since helium has not caused respiratory acidosis that is typically associated with insufflation using CO_2 in laboratory and clinical trials, it is proposed as a potential alternative to CO_2 for abdominal insufflation in general surgery (Wong *et al*., 2005; Umano *et al*., 2021).

The Use of Helium in Radiology: Helium plays a crucial role in the field of radiology, particularly in the functioning of Magnetic Resonance Imaging (MRI) machines (Nazir *et al*., 2023). MRI is a non-invasive imaging method that uses electromagnetic and magnetic fields to produce high-resolution images of the body's internal structures. It is widely employed in medical diagnosis. The electromagnetic emissions are processed to create an image of the interior structure. It can be used to track the specifics of different bodily tissues that are invisible to x-rays and computed tomography scans, such as tendons, muscles, bones, and ligaments (Nazir et al., 2023).

MRI machines rely on superconducting magnets to generate the strong magnetic fields necessary for imaging (Parizh *et al*., 2017). These magnets must be maintained at extremely low temperatures to retain their superconducting properties, typically around 4.2 Kelvin (-269°C). Liquid helium, with a boiling point of 4.2 Kelvin, is used to cool these magnets, ensuring their optimal performance and stability (Lakrimi *et al*., 2011; Parizh *et al*., 2017; Wang *et al*., 2022).

Also, the superconducting magnets used in MRI machines require near-zero electrical resistance to generate stable and powerful magnetic fields. Liquid helium provides the necessary environment to minimize electrical resistance, enabling the magnets to function efficiently without significant energy loss. This is critical for producing clear and precise images required for accurate medical diagnosis. However, the global supply of helium is limited and subject to fluctuations, leading to concerns about the sustainability and cost of using helium for MRI cooling (Siddhantakar *et al.*, 2023).

Conclusion: Helium, with its exceptional inertness and unique physical properties, stands out as the lightest noble gas, providing numerous benefits across various scientific and medical fields. Medically, helium's applications range from respiratory care, where it facilitates easier breathing through heliox mixtures, to cardiology and neurology, where it offers cardioprotection and neuroprotection during ischemia/reperfusion injuries. Helium ion microscopy advances imaging techniques, allowing for superior resolution and surface sensitivity, which is crucial for studying biological specimens. In surgical procedures, helium proves to be a safer alternative for insufflation, especially for high-risk patients; in radiology, its critical role in cooling MRI machines cannot be overlooked despite concerns over global supply limitations.

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Data Availability Statement: Data are available upon request from the first author or corresponding author or any of the other authors.

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