Argon: The Future Organ Protectant?

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One of the major concerns following a successful resuscitation after a cardiac arrest is the severity of brain damage. The success of every organ harvested for transplant is highly dependent on the effectiveness of organ protection. In spite of all advances made in medical research, success in terms of organ protection can be best described as modest. Human endeavor to identify the ideal organ protectant/protection technique still continues!

Argon belongs to the last column of the periodic table, along with other “noble gases” such as argon, xenon, neon, helium, krypton, and radon. The complete electron valence shell of these gases makes them unlikely to form covalent bonds with other elements, and hence, they are termed as “inert gases.” Although argon was first noted by Henry Cavendish in 1785 as an “impurity” in atmospheric air, it was Lord Rayleigh and William Ramsay who were subsequently able to identify this impurity as “argon.” Argon is considered as an “inert gas,” but recent evidence has shown that argon is capable of physical and biological activity. The biological effect is probably related to its atomic structure interaction with enzymes and receptors through charge-induced dipole and van der Waals interactions.

The structural similarity between argon and xenon has triggered a number of studies that looked at beneficial properties in argon similar to that seen with xenon. The major advantage of argon is that it is much more abundant than xenon (9340 ppm vs. 0.09 ppm), making it the third most abundant gas in the atmosphere.

The narcotic effects of argon are well described in divers at high atmospheric pressures (>10 atm). This is in contrast to xenon, which manifests its narcotic effects at atmospheric pressure. These anesthetic effects of argon are believed to be secondary to its physical rather than its chemical effects. The exact mechanism by which these narcotic effects are manifested is still debated although stimulation of the γ-aminobutyric acid type A receptor or antagonism of the N-methyl-D-aspartate receptors is the proposed mechanisms.[1,2] Both these mechanisms are associated with reduced dopamine released from the brain. In addition, through a complex mechanism, the extracellular signal-regulated kinases 1/2 have also been suggested to be the mechanism of protection offered by argon.[3]

However, the area in which argon has received maximum attention is in its role as a neuroprotectant. The *in vitro* studies looked at models of middle cerebral artery occlusion (MCAO), traumatic brain injury (TBI), and oxygen-glucose-deprived (OGD) environment. These *in vitro* studies have shown that the gas has not only a concentration-dependent effect in brain protection but also that these protective effects were efficient when given up to 72 h after brain injury.[4]

The *in vivo* studies not only confirmed that helium, argon, and xenon improved cell survival, brain structural integrity, and neurological recovery but also showed that these gases could reduce infarct size. In addition, it was also confirmed that among the noble gases, argon had the most protective effects.[5] However, not all studies are supportive of the neuroprotective effects of argon. David *et al*. showed that although argon was useful in TBI and OGD models of brain injury, in MCAO-induced brain injury, argon increased subcortical brain damage with no improvement on behavioral or motor functions.[2]

At present, the only approved current therapy for ischemic stroke is the use of tissue plasminogen activator (tPA). Ventilation with argon in combination with tPA has shown a dose-dependent beneficial effect. At concentrations, below 50% argon inhibits, and at higher concentrations, the gas augments the thrombolytic effect of tPA. This has important clinical implications in the future for the management of ischemic stroke.[6]

The major concern following a cardiac arrest is the extent of neurological damage. At present, the major focus on reducing brain damage is directed at achieving moderate hypothermia. Argon by virtue of its neuroprotectant effect has been the focus of animal studies to reduce the extent of brain damage following experimental cardiac arrest. These studies have used argon to ventilate the patients for varying periods after the cardiac arrest. Argon in various concentrations has shown a faster and more complete recovery, and this has been confirmed through histopathological and serum neuron-specific enolase levels.[7] The beneficial effects were seen when argon ventilation was started as late as 3 h after the cardiac arrest. Unfortunately, the assumption that a combination of hypothermia with argon ventilation would be more beneficial has turned out to be debatable.[8,9] It has also been shown that ventilation with argon is associated with a reduction in the myocardial infarct size and improved ventricular function.

The use of argon has not been associated with any systemic hemodynamic changes. There are no studies that has shown any detrimental effects when argon was used as a ventilating gas. However, being less soluble than carbon dioxide, there is a potential for gas embolism when used for insufflation for creating pneumoperitoneum. Even prolonged ventilation with argon has not shown any adverse effects after cardiac arrest.[9]

The beneficial effects of argon are not restricted to neuroprotection as more studies are now emerging where its use as an organ protective agent is becoming more apparent. Kidneys preserved in argon-containing solution have shown benefits in terms of urine output, creatinine clearance, and limitation of acute tubular necrosis. Similar studies are ongoing for lung transplant too. Ventilation with argon following myocardial infarction has been shown to reduce the myocardial infarct size. The ever-expanding role of argon as an organ protectant is one area where a lot of research is awaited. As argon has not been shown to have any detrimental hemodynamic or systemic effects, human studies can soon be initiated. If the beneficial effects of the gas seen in animals can be translated into humans, then a new chapter in organ protection will be initiated.

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The Future

The potential of argon as a clinical utility tool is enormous – although most of the potential benefits are in the experimental stages. It also fulfills the dreams of an ideal neuroprotective agent – being simple, easily available, easy to use, and effective. There is no doubt that the greatest clinical use of argon will be as a neuroprotectant. However, there are concerns related to this, as not all studies have unequivocally shown a beneficial effect on brain protection. There is also a major concern whether high concentrations of argon can be given to patients who have impaired pulmonary function when sustaining or after sustaining a cardiac arrest. Similarly, more studies are required before argon can be used after an ischemic cerebral infarct.

In this issue of Annals of Cardiac Anaesthesia, Nespoli *et al*. have given an exhaustive account of the utility of argon.[10] Although most of the studies have been in animal models, the fact that its use in deep-sea divers has not been associated with any detrimental effects brings the gas closer to clinical practice and human studies. The reported beneficial effects in postcardiac arrest patients and organ protection during transplant are exciting! The authors' must be congratulated for the effort that they have taken to generate this work.

At a time when millions of dollars are being poured into research, specifically in the field of neuroprotection, if argon can fulfill the promise that has been projected, our next neuroprotective agents should come "out of thin air."

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References

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