Perfluorocarbon

Fluorocarbons, sometimes referred to as perfluorocarbons or PFCs, are, strictly speaking, organofluorine compounds with the formula CxFy, i.e. they contain only carbon and fluorine, though the terminology is not strictly followed.

Compounds with the prefix perfluoro- are hydrocarbons, including those with heteroatoms, wherein all C-H bonds have been replaced by C-F bonds.

Fluorocarbons can be perfluoroalkanes, fluoroalkenes and fluoroalkynes and perfluoroaromatic compounds. Fluorocarbons and their derivatives are used as fluoropolymers, refrigerants, solvents, and anesthetics.

Tumour hypoxia limits the effectiveness of radiation therapy. Delivering normobaric or hyperbaric oxygen therapy elevates pO2 in both tumour and normal brain tissue. However, pO2 levels return to baseline within 15 minutes of stopping therapy.

IV injections of perfluorocarbon (PFC) emulsions followed by 1h carbogen breathing, radiosensitises GL261 intracranial tumors [1)].

Spinal cord injury (SCI) often results in irreversible and permanent neurological deficits and long-term disability. Vasospasm, hemorrhage, and loss of microvessels create an ischemic environment at the site of contusive or compressive SCI and initiate the secondary injury cascades leading to progressive tissue damage and severely decreased functional outcome. Although the initial mechanical destructive events cannot be reversed, secondary injury damage occurs over several hours to weeks, a time frame during which therapeutic intervention could be achieved. One essential component of secondary injury cascade is the reduction in spinal cord blood flow with resultant decrease in oxygen delivery. Our group has recently shown that administration of fluorocarbon (Oxycyte) significantly increased parenchymal tissue oxygen levels during the usual postinjury hypoxic phase, and fluorocarbon has been shown to be effective in stroke and head injury. In the current study, we assessed the beneficial effects of Oxycyte after a moderate-to-severe contusion SCI was simulated in adult Long-Evans hooded rats. Histopathology and immunohistochemical analysis showed that the administration of 5 mL/kg of Oxycyte perfluorocarbon (60% emulsion) after SCI dramatically reduced destruction of spinal cord anatomy and resulted in a marked decrease of lesion area, less cell death, and greater white matter sparing at 7 and 42 days postinjury. Terminal deoxynucleotidyl transferase dUTP nick end labeling staining showed a significant reduced number of apoptotic cells in Oxycyte-treated animals, compared to the saline group. Collectively, these results demonstrate the potential neuroprotective effect of Oxycyte treatment after SCI, and its beneficial effects may be, in part, a result of reducing apoptotic cell death and tissue sparing. Further studies to determine the most efficacious Oxycyte dose and its mechanisms of protection are warranted [2)].

Perfluorocarbon emulsions have been shown to improve outcomes in stroke models. This study examined the effect of Oxycyte, a third-generation perfluorocarbon emulsion (04RD33; Synthetic Blood International, Inc., Costa Mesa, CA) treatment on cognitive recovery and mitochondrial oxygen consumption after a moderate lateral fluid percussion injury (LFPI). METHODS:

Adult male Sprague-Dawley rats (Harlan Bioproducts for Science, Indianapolis, IN) were allocated to 4

groups: 1) LFPI treated with a lower dose of Oxycyte (4.5 mL/kg); 2) LFPI with a higher dose of Oxycyte (9.0 mL/kg); 3) LFPI with saline infusion; and 4) sham animals treated with saline. Fifteen minutes after receiving moderate LFPI or sham surgery, animals were infused intravenously with Oxycyte or saline within 30 minutes while breathing 100% O2. Animals breathed 100% O2 continuously for a total of 4 hours after injury. At 11 to 15 days after LFPI, animals were assessed for cognitive deficits using the Morris water maze test. They were sacrificed at Day 15 after injury for histology to assess hippocampal neuronal cell loss. In a parallel study, mitochondrial oxygen consumption values were measured by the Cartesian diver microrespirometer method.

We found that injured animals treated with a lower or higher dose of Oxycyte had significant improvement in cognitive function when compared with injured saline-control animals ($P < 0.05$). Moreover, injured animals that received either dose of Oxycyte had significantly less neuronal cell loss in the hippocampal CA3 region compared with saline-treated animals ($P < 0.05$). Furthermore, a lower dose of Oxycyte significantly improved mitochondrial oxygen consumption levels ($P < 0.05$).

The current study demonstrates that Oxycyte can improve cognitive recovery and reduce CA3 neuronal cell loss after traumatic brain injury in rats [3)].

Perfluorocarbons (PFCs) offer great promise to carry and deliver O2 more efficiently than conventional measures. The authors investigated the use of Clark-type microelectrodes to monitor spinal cord oxygenation directly (intraparenchymal [IP] recording) and indirectly (cerebrospinal fluid [CSF] recording) in the context of SCI, O2 therapy, and PFC treatment. METHODS:

After placement of a subdural/CSF Licox probe in rats, incremental increases in the fraction of inspired O2 (FiO2) up to 100% were administered to establish a dose-response curve. The probe was then placed in the parenchyma of the same animals for a second dose-response curve. In a second study, rats with CSF or IP probes underwent SCI with the NYU Impactor and treatment with O2, followed by administration of PFC, or saline in the control group.

All animals in the first experiment responded to the FiO2 dose increase, with changes in PO2 evident in both CSF and IP levels. The SCI in the second experiment caused a marked drop in PO2 from a mean of 21.4 to 10.4 mm Hg, with most animals dropping to less than half their preinjury value. All animals responded to 100% O2 treatment. Every animal that received PFCs showed significant improvement, with a mean increase in PO2 of 23.3 mm Hg. Only 1 saline-treated animal showed any benefit. Oxygen values in the PFC treatment group reached up to 6 times the normal level.

Oxygen levels in SCI show a profound drop almost immediately postinjury. Administration of PFCs combined with 100% O2 therapy can reverse tissue hypoxia and holds promise for reducing ischemic injury [4)].

The current study demonstrates that a PFC emulsion can significantly increase cerebral oxygenation after TBI and enhance mitochondrial function at 4 hours after injury as compared with saline. This study demonstrates a new therapeutic potential for PFC to enhance cerebral oxygenation and aerobic metabolism after TBI. However, the increased free radical formation with high-dose PFCs suggests the need for further studies combining PFCs with free radical scavengers [5)].

For the usage as blood substitutes perfluorocarbons (PFC) have been developed as artificial oxygen carriers. In addition they may have potency for protective use in ischemic tissue. Formulation improvement achieved higher oxygen carrying capacity and better compatibility than the first generation of PFC. Preclinical studies have been performed in animal heart and brain. Former and progressed emulsification for intravascular use have been investigated for infarction and reperfusion injury. This investigations are reviewed and the potencies for the use of PFC in neurology, neurosurgery, diagnostics today and in the future are emphasized [6)].

Over the last 30 years, perfluorocarbons (PFCs) have been extensively investigated as oxygen carriers. Early studies indicated that these compounds could be used as blood substitutes or protective agents against ischemia. Adverse characteristics such as instability, short intravascular half-life, and uncertainties concerning possible toxicity precluded wide clinical application. However, advances in PFC technology have led to the development of improved second-generation oxygen carriers that incorporate well-tolerated emulsifiers (egg-yolk phospholipids). The authors review recent developments in this field and consider the potential role of PFCs in future neurosurgical practice. Diagnostic applications could include their use to assess cerebral blood flow, local oxygen tension, and brain metabolism or to achieve enhanced imaging and precise staging of inflammatory, neoplastic, or vascular disease processes by means of computerized tomography, ultrasonography, and magnetic resonance studies. Therapeutic applications could include cerebral protection, an adjunctive role in radiotherapy of malignant brain tumors, protection against air embolism, the preservation of organs for transplantation, and ventilatory support in head-injured patients with compromised lung function. In addition, PFCs have been used successfully as a tool in ophthalmic microsurgery and potentially they could fulfill a similar role in microneurosurgery [7)].

Perfluorocarbon, which can transport rich O2, was used to increase intratumoral PO2. Intratumoral PO2 increased to about 36 mmHg by using Perfluorocarbon with inhalation of O2. I conducted new Protocol, namely, irradiation method should be selected altered dose fractionation when hypoxic cell of the tumor change to normoxic cell. Perfluorocarbon was administered on the day when irradiation dose is high. Clinical result showed much better than previous our result, especially in the group of glioblastoma, the mean survival duration prolonged 8 months to 2 years [8)].

The left middle cerebral artery and both carotid arteries of 17 cats were occluded to evaluate the effects of oxygenated fluorocarbon emulsion on brain ischemia. Carotid and middle cerebral arteries were occluded concurrently for 2 hours, followed by occlusion of the middle cerebral artery only for another 24 hours. Six animals were treated with oxygenated fluorocarbon emulsion delivered by ventriculocisternal perfusion, 5 received ventriculocisternal perfusion with mock cerebrospinal fluid, and 6 were untreated. Perfusions were started 3 hours after the initial ischemic insult. Infarct size judged by tetrazolium staining and standard neuropathological stains was significantly smaller in the treated animals. The mechanism of protection is as yet unknown, but most likely reflects oxygen/nutrient diffusion into the ischemic middle cerebral artery zone from the ventricular fluorocarbon, or removal of harmful metabolites. The results imply that ventriculocisternal perfusion with fluorocarbon emulsion can preserve neuronal function during a major cerebral vessel occlusion. In the cat, therapy is effective if begun within 3 hours after ischemia starts [9)].

We employed an extravascular perfusion system through the subarachnoid space of the traumatized spinal cord of the cat for the delivery of oxygen utilizing a fluorocarbon emulsion containing essential nutrients, termed the oxygenated fluorocarbon nutrient solution (OFNS). Animals perfused for 2 hours with saline after impact injury of the spinal cord had significantly less edema at 1 cm below this site of injury than injured, untreated animals. However, in injured animals perfused with OFNS there was significant protection from spinal cord edema at both 1 and 2 cm below the site of injury. OFNS perfusion reduced the magnitude of hemorrhagic necrosis in both the gray and the white matter and protected the anterior horn cells against lysis at the site of injury. Adenosine triphosphate (ATP) is decreased within 1 minute and remains suppressed for 1 hour in gray and white matter of unperfused, injured animals. The level of ATP in both gray and white matter was significantly higher in injured OFNS-perfused animals than in saline-treated animals at the site below the spinal cord injury. Our data show that OFNS perfusion of the injured spinal cord reduced necrosis and edema and tended to normalize the levels of high energy ATP and intact anterior horn cells. These results demonstrate the feasibility of treating ischemic hypoxia of the spinal cord after trauma through an extravascular perfusion route that utilizes a fluorocarbon emulsion as a vehicle for the delivery of oxygen and other cellular nutrients [10)].

1)
Feldman LA, Fabre MS, Grasso C, Reid D, Broaddus WC, Lanza GM, Spiess BD, Garbow JR, McConnell MJ, Herst PM. Perfluorocarbon emulsions radiosensitise brain tumors in carbogen breathing mice with orthotopic GL261 gliomas. PLoS One. 2017 Sep 5;12(9):e0184250. doi: 10.1371/journal.pone.0184250. eCollection 2017. PubMed PMID: 28873460.
2)
Yacoub A, Hajec MC, Stanger R, Wan W, Young H, Mathern BE. Neuroprotective effects of perflurocarbon (oxycyte) after contusive spinal cord injury. J Neurotrauma. 2014 Feb 1;31(3):256-67. doi: 10.1089/neu.2013.3037. Epub 2013 Nov 21. PubMed PMID: 24025081; PubMed Central PMCID: PMC3904515.
3)
Zhou Z, Sun D, Levasseur JE, Merenda A, Hamm RJ, Zhu J, Spiess BD, Bullock MR. Perfluorocarbon emulsions improve cognitive recovery after lateral fluid percussion brain injury in rats. Neurosurgery. 2008 Oct;63(4):799-806; discussion 806-7. doi: 10.1227/01.NEU.0000325493.51900.53. PubMed PMID: 18981892.
4)
Schroeder JL, Highsmith JM, Young HF, Mathern BE. Reduction of hypoxia by perfluorocarbon emulsion in a traumatic spinal cord injury model. J Neurosurg Spine. 2008 Aug;9(2):213-20. doi: 10.3171/SPI/2008/9/8/213. PubMed PMID: 18764757.
5)
Daugherty WP, Levasseur JE, Sun D, Spiess BD, Bullock MR. Perfluorocarbon emulsion improves cerebral oxygenation and mitochondrial function after fluid percussion brain injury in rats. Neurosurgery. 2004 May;54(5):1223-30; discussion 1230. PubMed PMID: 15113478.
6)
Rebel A, Frietsch T, Quintel M, Lenz C, Waschke KF. [Cerebral effects of perfluorocarbons]. Nervenarzt. 1999 Aug;70(8):679-87. Review. German. PubMed PMID: 10483568.
7)
Sakas DE, Whittaker KW, Crowell RM, Zervas NT. Perfluorocarbons: recent developments and implications for neurosurgery. J Neurosurg. 1996 Aug;85(2):248-54. Review. PubMed PMID: 8755753.
8)
Kayama T, Sakurai Y, Yoshimoto T. [Analysis of PO2 in brain tumor and effectiveness of PFC (perfluorochemicals) to increase intratumoral PO2, blood flow and its clinical use]. Gan No Rinsho. 1989 Oct;35(13):1548-53. Review. Japanese. PubMed PMID: 2685395.
9)

Bose B, Osterholm JL, Payne JB, Chambers K. Preservation of neuronal function during prolonged focal cerebral ischemia by ventriculocisternal perfusion with oxygenated fluorocarbon emulsion. Neurosurgery. 1986 Mar;18(3):270-6. PubMed PMID: 3010170.
10)
Osterholm JL, Alderman JB, Triolo AJ, D'Amore BR, Williams HD. Oxygenated fluorocarbon nutrient solution in the treatment of experimental spinal cord injury. Neurosurgery. 1984 Sep;15(3):373-80. PubMed PMID: 6237276.