



***Perfluorocarbon Oxygen Therapeutic Emulsions
Improve Outcome Following Traumatic Brain
Injury From Repetitive Air Blast Insults***

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Technical Objectives

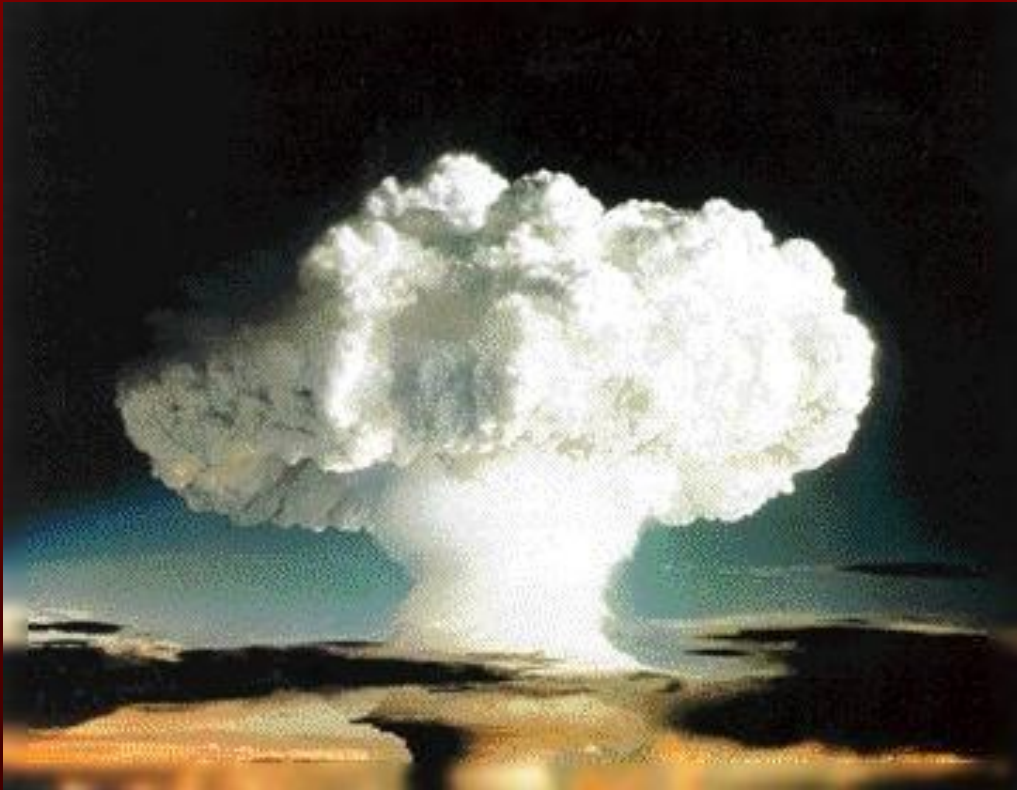


ULTIMATE GOAL is to provide a treatment (PFC) that could be readily administered by medical or other personnel in the field to victims of blast exposure that would decrease or prevent brain damage and improve neurological outcomes.

- Develop a reproducible model of mild to moderate traumatic brain injury (TBI) caused by exposure to repetitive blast.
- Determine whether administration of PFC after exposure to first blast can decrease neurological deficits (ie be protective) from exposure to a second blast.
- Garner data for off label use of PFC for treatment of TBI from repetitive blast exposure once FDA approval is in place for use of PFC in either DCS (Mahon) or impact TBI (Clinical Trials)
- scientific basis: decreased oxygen supply to brain regions secondary to blast is a potential mechanism of neuronal damage. PFC is an oxygen therapeutic that can carry more oxygen to watershed tissue than red blood cells in low flow situations and can deliver oxygen to tissue that red blood cells cannot reach.



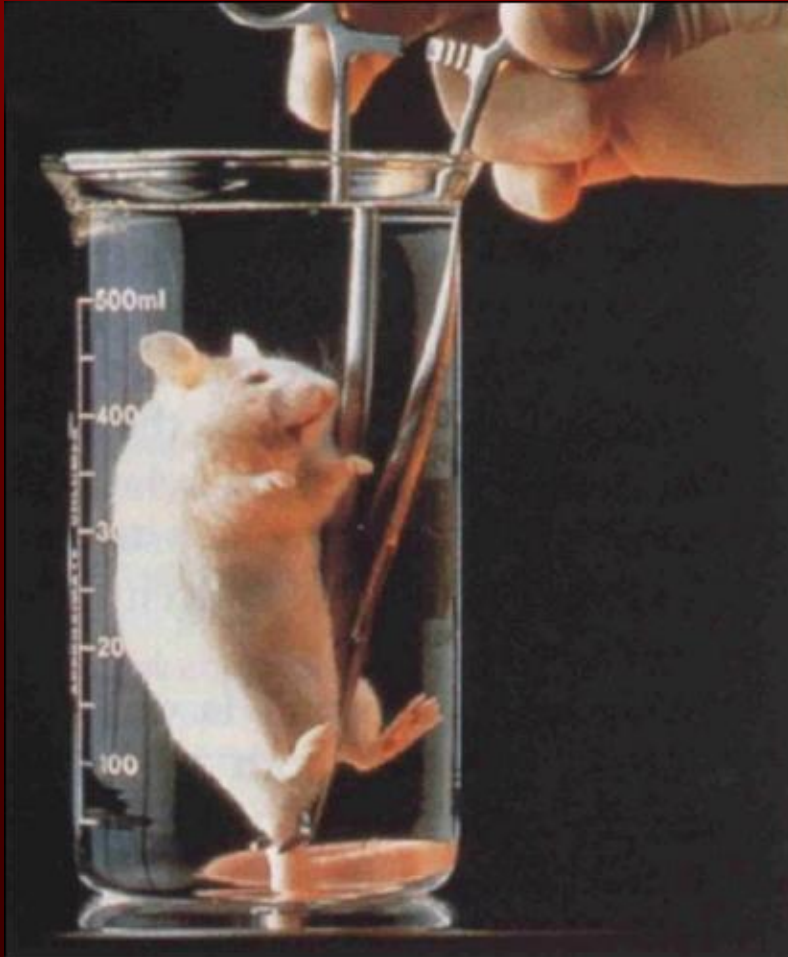
PFC



- 1930's Manhattan Project
- 1966 mouse breathing liquid PFC
- 1980s and early 1990's blood substitute
- used in eye surgery and imaging
- presently Oxygen Biotherapeutic



PFC



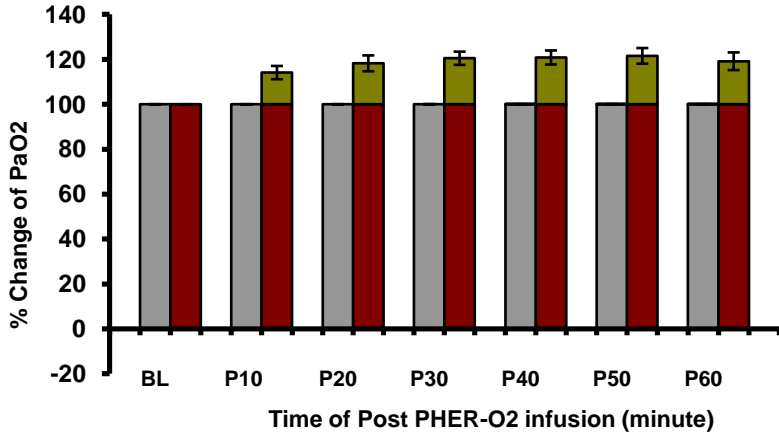
- Hydrocarbons with all H atoms replaced with F thus extremely non-polar.
- PFC carries inert gases (O₂ and N₂) by enhanced solubility.
- Inert gases are relatively insoluble in aqueous media (i.e. plasma)
- Pure PFC can dissolve up to 60 volume % O₂
- Whole blood can dissolve up to 21 volume % O₂ (due to hemoglobin binding)
- Plasma can only dissolve 0.35 volume % O₂
- PFC must be emulsified to be used as an intravenous therapeutic agent
- Current 2nd and 3rd generation PFC emulsions can dissolve up to 7 volume % O₂



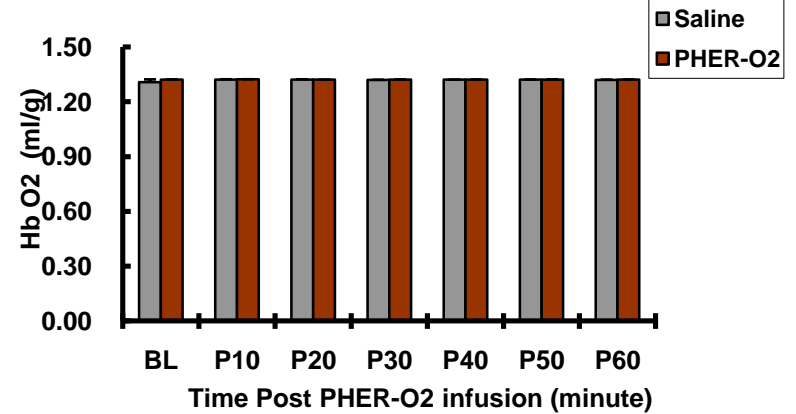
PFC



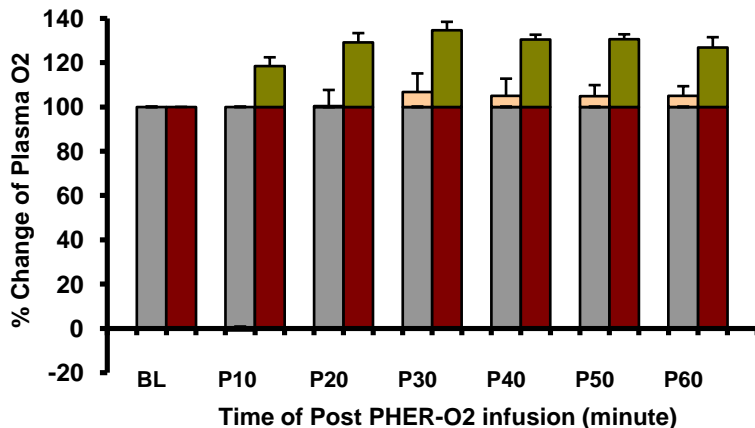
PaO₂, % change PHER-O₂ vs Saline



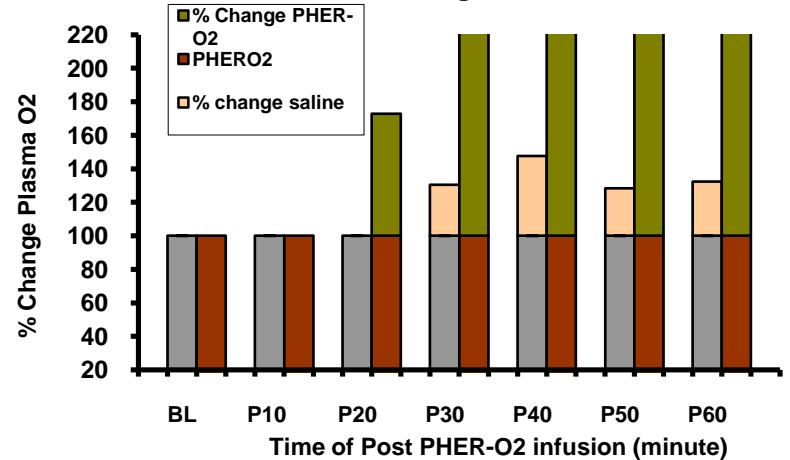
Arterial Hb O₂ Content: Saline vs PHER-O₂



Arterial Plasma O₂, % change PHER-O₂ vs Saline



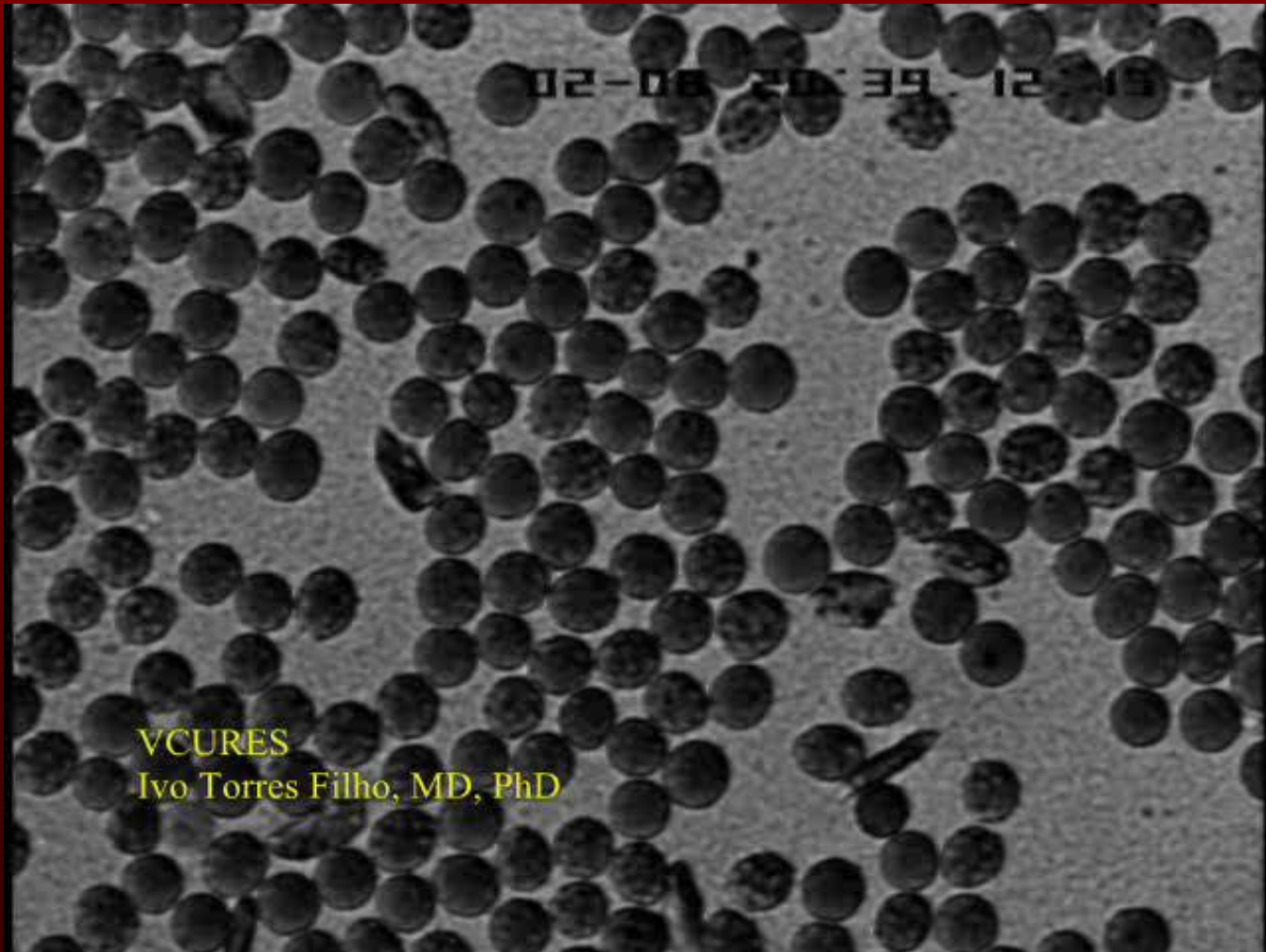
A-V Plasma O₂, % change PHER-O₂ vs Saline



No significant change in MAP, MCVP, pH or other physiological parameters



PFC



VCURES
Ivo Torres Filho, MD, PhD



TBI and PFC



Animal studies demonstrated improved outcomes following TBI when Perfluorocarbon emulsions were administered

-Conducted by VCURES clinicians at Virginia Commonwealth University Medical Center led by M. Ross Bullock and Bruce D. Spiess

1. Perfluorocarbon emulsions improve cognitive recovery after lateral fluid percussion brain injury in rats.

Zhou Z, Sun D, Levasseur JE, Merenda A, Hamm RJ, Zhu J, Spiess BD, Bullock MR. *Neurosurgery*. 2008 Oct;63(4):799-806; discussion 806-7.

2. Perfluorocarbon emulsion improves cerebral oxygenation and mitochondrial function after fluid percussion brain injury in rats.

Daugherty WP, Levasseur JE, Sun D, Spiess BD, Bullock MR. *Neurosurgery*. 2004 May;54(5):1223-30; discussion 1230.



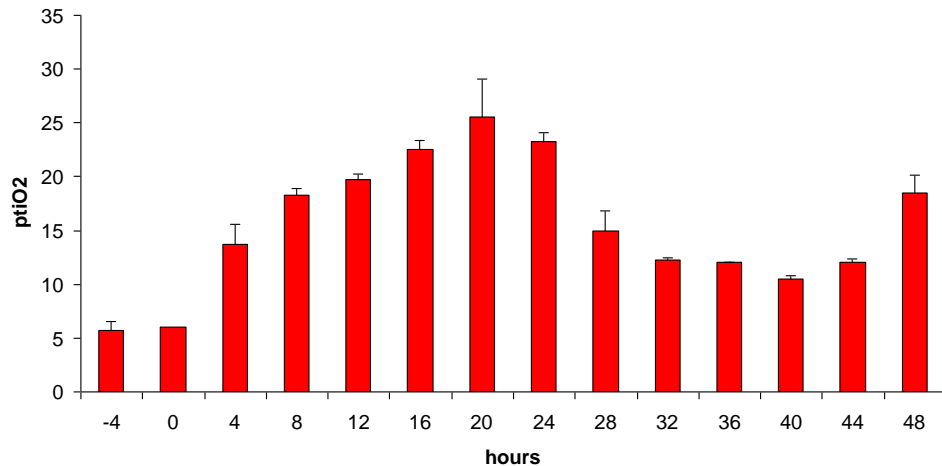
TBI and PFC



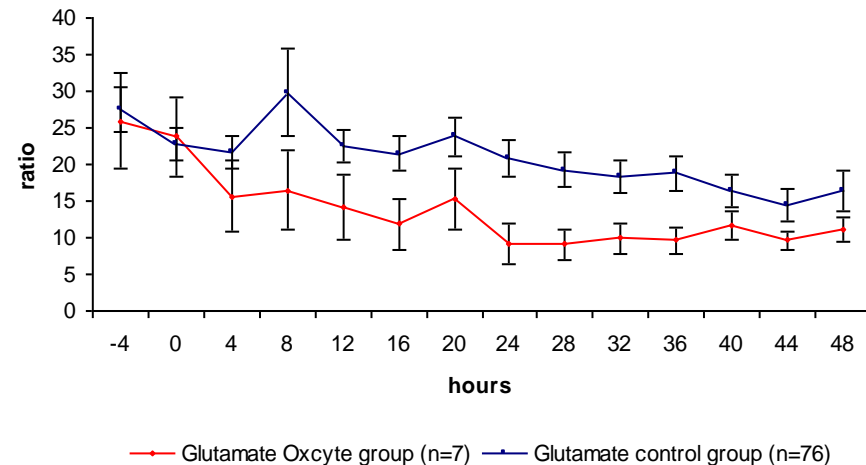
Human studies demonstrated improved outcomes following TBI when Perfluorocarbon emulsions were administered

- 9 patient pilot clinical trial for PFC treatment of closed head impact TBI
- Conducted by VCURES clinicians at Virginia Commonwealth University Medical Center led by M. Ross Bullock and Bruce D. Spiess
- Patients enrolled had GCS scores that would typically result in 60+% mortality rate
- 7 out of 9 patients receiving PFC had a complete recovery

ptiO2 patient 6, FiO2 1.0



Biochemistry Oxycyte group vs control group





Preliminary Data



A 1 year pilot study funded by ONR FHP FNC (N000140810366) generated the following:

- small animal blast chamber
- a unique model of blast induced TBI
- preliminary data showing beneficial effects of PFC with respect to MRI and behavioral outcomes

modification of that originally described by JH Jaffin et al. J Trauma 1987; 27:349-56.

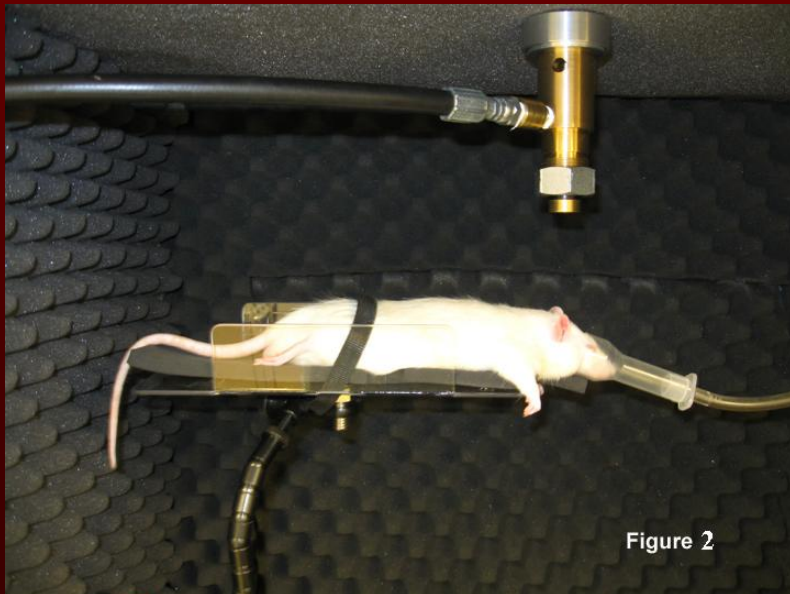


Figure 2

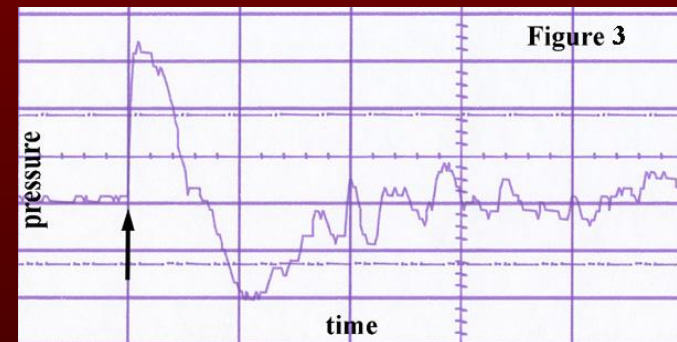


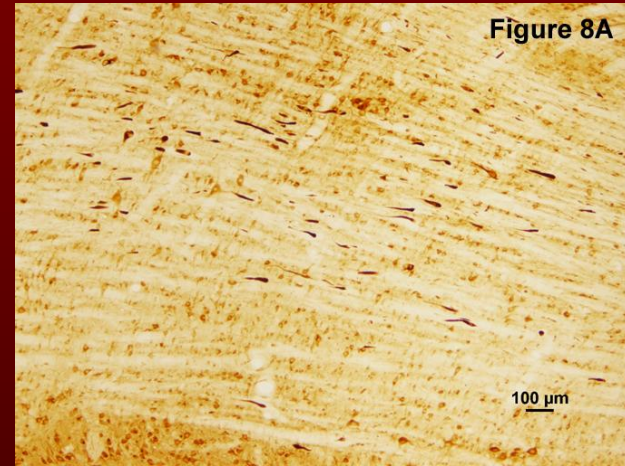
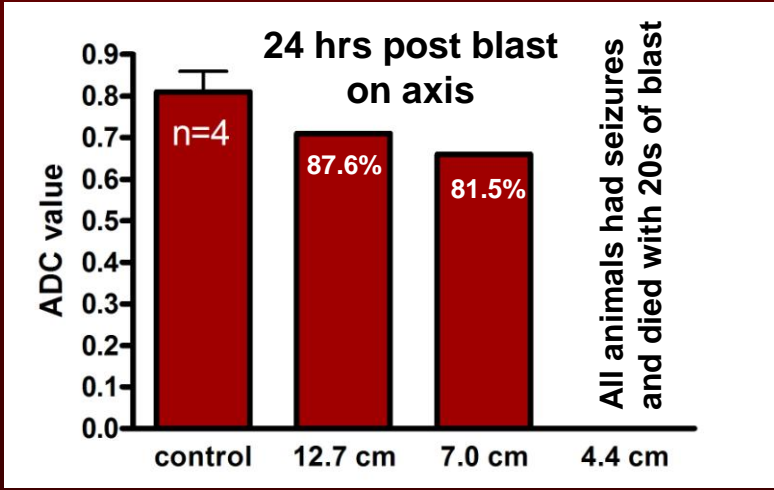
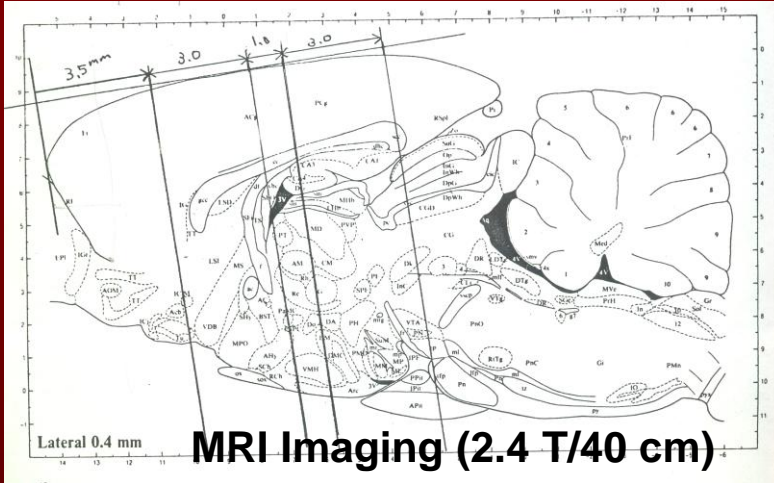
Figure 3

Blast nozzle - 6.3 x 2.4 cm diameter pressure chamber, affixed to the top of a blast chamber (6.5 ft tall x 3 ft wide x 2.5 ft deep) lined with acoustic cancellation foam giving approximately 5 ft of open space below the animal platform

minimize generation of complex waves and allow for the study of single / repetitive free field waves to the head



Preliminary Data

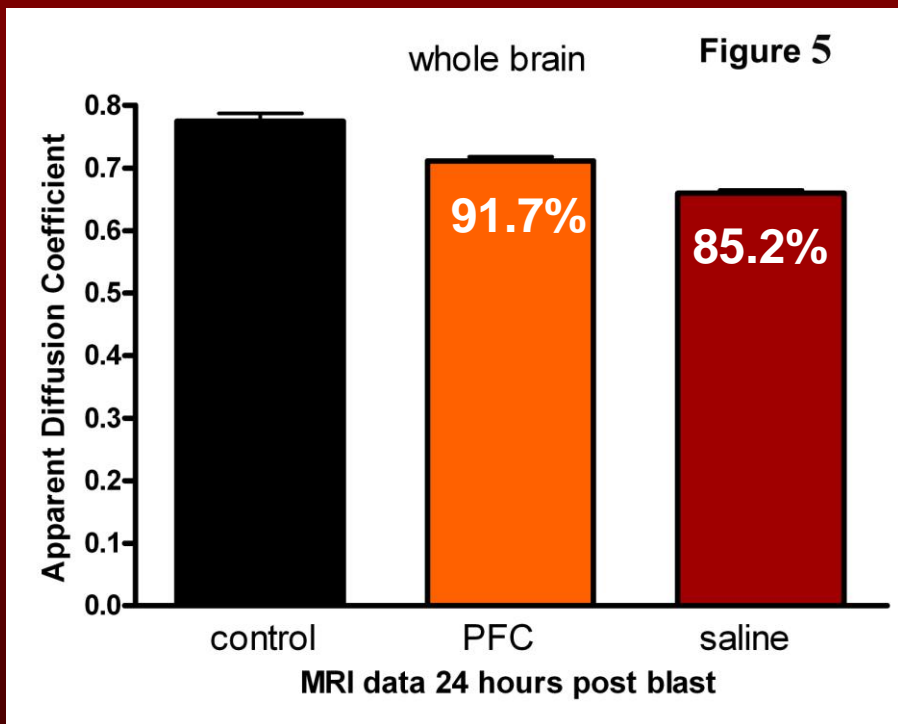


APP staining showing diffuse axonal injury in brainstem 24 hrs post blast 7 cm on axis

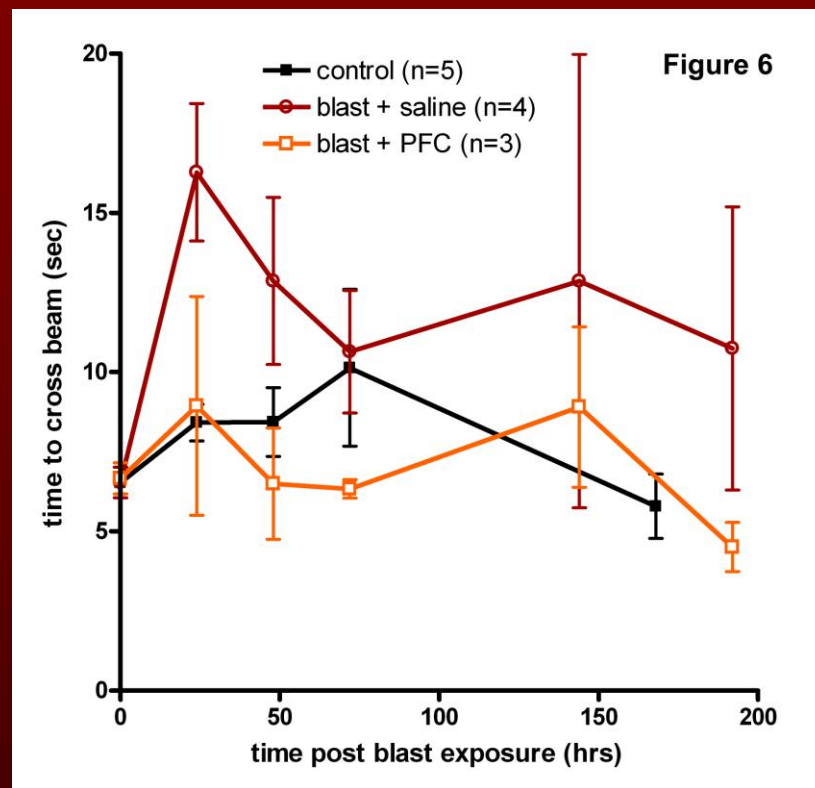
- Similar pattern was seen for FA values
- Similar pattern was seen 5 cm off axis
- Some rats at 12.7 and 7 cm had sz but did not die



Preliminary Data



- 7.0 cm on axis, 6.0 cc/kg PFC or saline, 3hrs O₂
- One way ANOVA revealed significant difference among animal groups ($p < 0.002$)
- PFC animals had approximately 40% less cytotoxic edema compared to saline
- Similar pattern observed for hippocampus scans



- 7.0 cm on axis, 6.0 cc/kg PFC or saline, 3hrs O₂
- at 24 and 48 hrs post blast, saline were 50% and 33% slower than control, respectively. PFC showed no deficits.
- One way ANOVA revealed data points at 24 hrs were significantly different ($p = 0.03$)



Methods



- subject animals to 1st Blast (7.0 x 0.9)
- administer saline or PFC (4-6 mL/kg) at 15 min post blast followed by 3 hours of treatment with 100% oxygen
- subject animals to 2nd Blast (7.0 x 0.9) 24 hours following 1st Blast with no subsequent treatment
- test for cognitive deficits using the morris water maze at days 13-17 following the second blast

Morris Water Maze

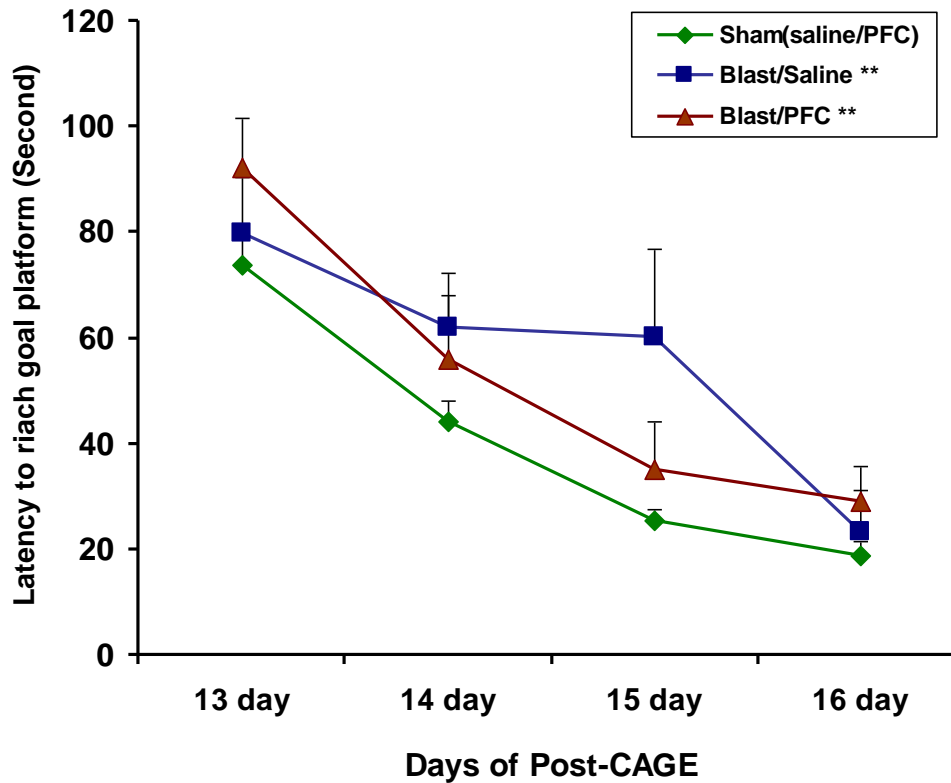
- animals are put into the water with no previous training and are given 120s to locate platform
- animals were given 3 trials a day for four days, the platform remains in the same quadrant.
- animals start from a different quadrant each of the four days
- on the fifth day, the animals are given a probe trial in which the platform is removed
- latency to find the platform, swim speed, goal proximity and latency to first enter the platform area were tested



MWM



MWM Performance of Blast Brain Injury

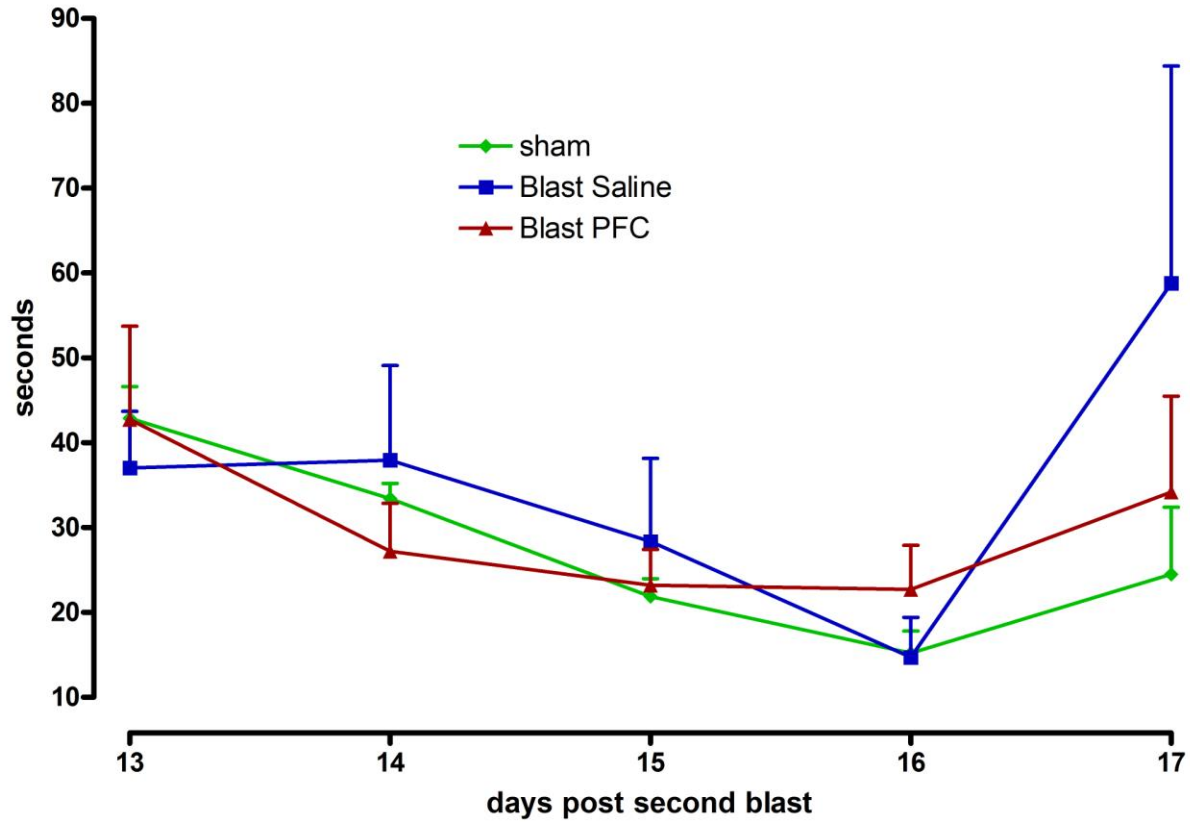




MWM



MWM Latency to first enter platform zone

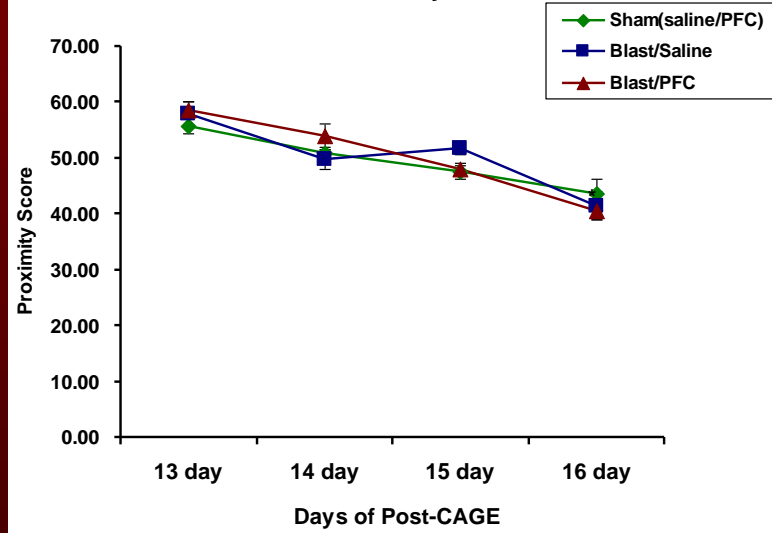




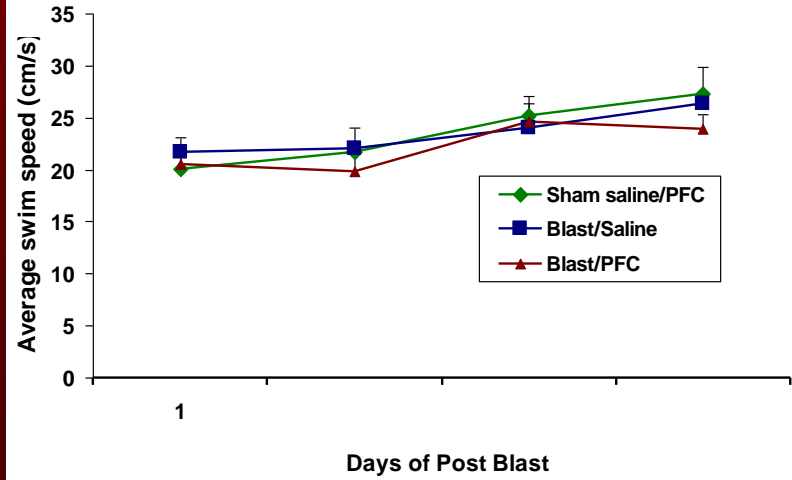
MWM



Goal Proximity of MWM



Swim Speed during MWM post-Blast





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Perfluorocarbons

