CARBON DIOXIDE SHOWS PROMISING PRECLINICAL ABILITY TO PREVENT TRAUMATIC BRAIN INJURY IN MICE

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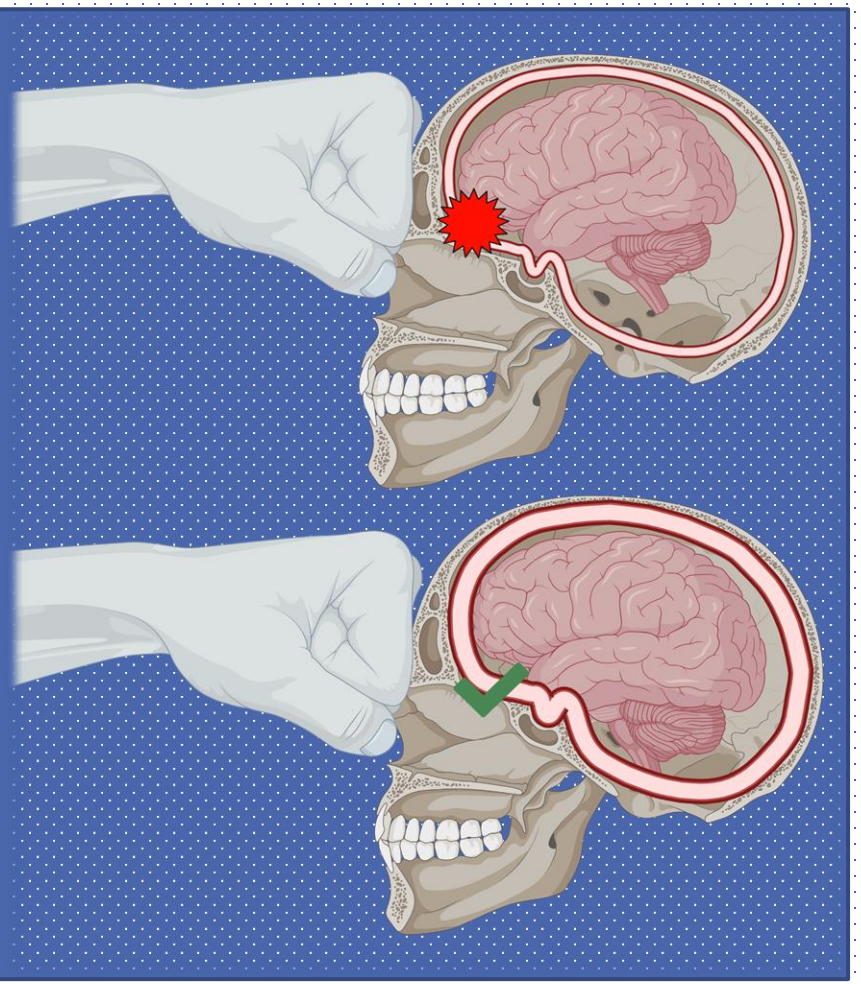
Traumatic Brain Injury Is a Big Issue

- Traumatic brain injury (TBI) is one of the leading causes of death and long-term disability worldwide [1]
- In 2014, there were nearly 3 million TBI-related hospitalizations and deaths in the United States alone [2]
- TBI often leads to secondary complications like Parkinson's disease, chronic traumatic encephalopathy (CTE), and Alzheimer's disease [3]
- $4 to $15 billion are spent on costs related to TBI each year [4]
- The "signature injury" of the military intervention in the Middle East [5]
- Common among contact sports players as well as laypeople due to accidents and falls [5]
- Advances in helmet technology have failed to improve incidence or outcomes for TBI due to design constraints [6]
- There is an urgent need to develop new preventative measures against TBI to address this public health crisis

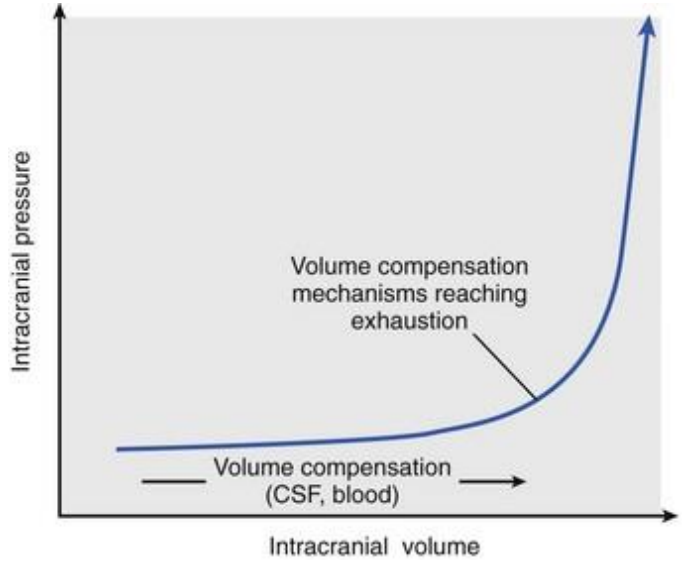
What Happens in a Concussion

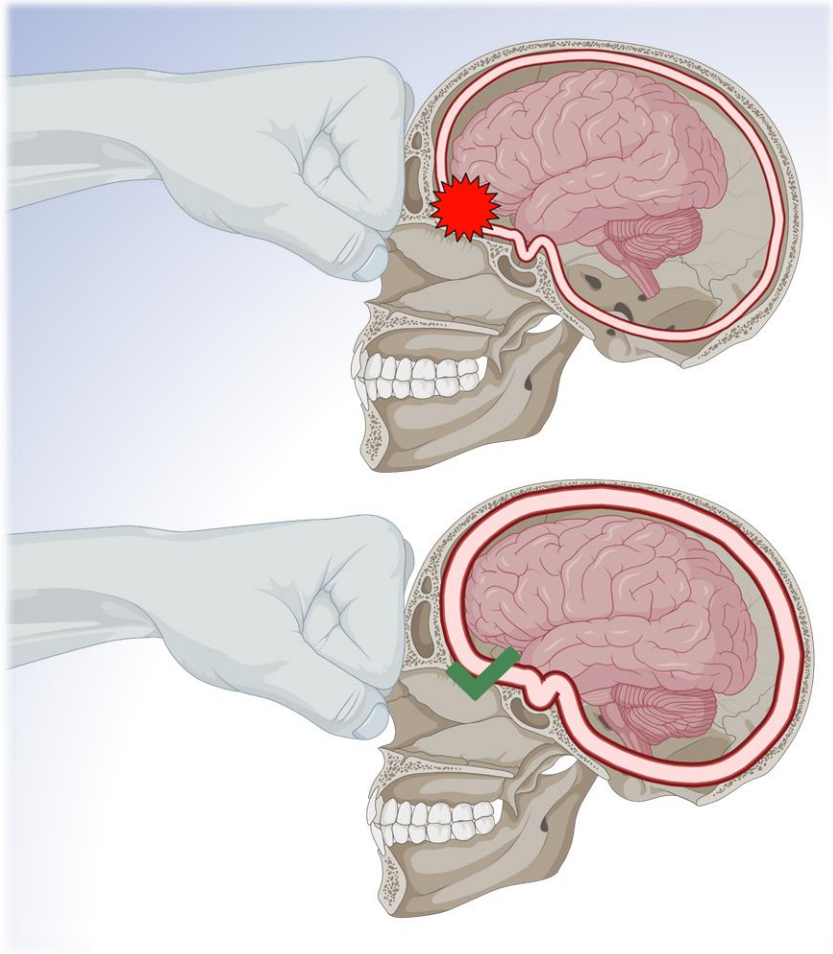
- Mild TBI, or mTBI is also known as concussion, and it is the most common type of TBI [7]
- Injury occurs when the brain rapidly accelerates and decelerates
- Brain impacts the walls of the skull or twists with respect to the spinal cord [4, 8]
- The reason the brain is able to impact the walls of the skull or rotate is that it is free to move relative to the skull [9]
- The reason the brain is can move relative to the skull is a small amount of "free" space known as the compensatory reserve volume or cranial reserve volume (CRV) [10]

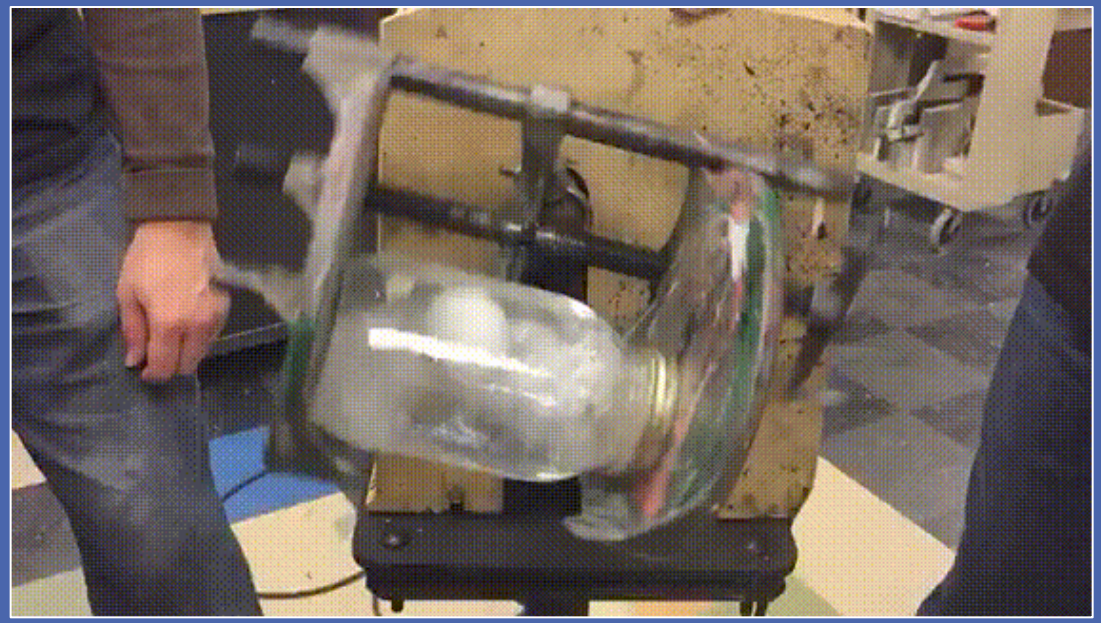


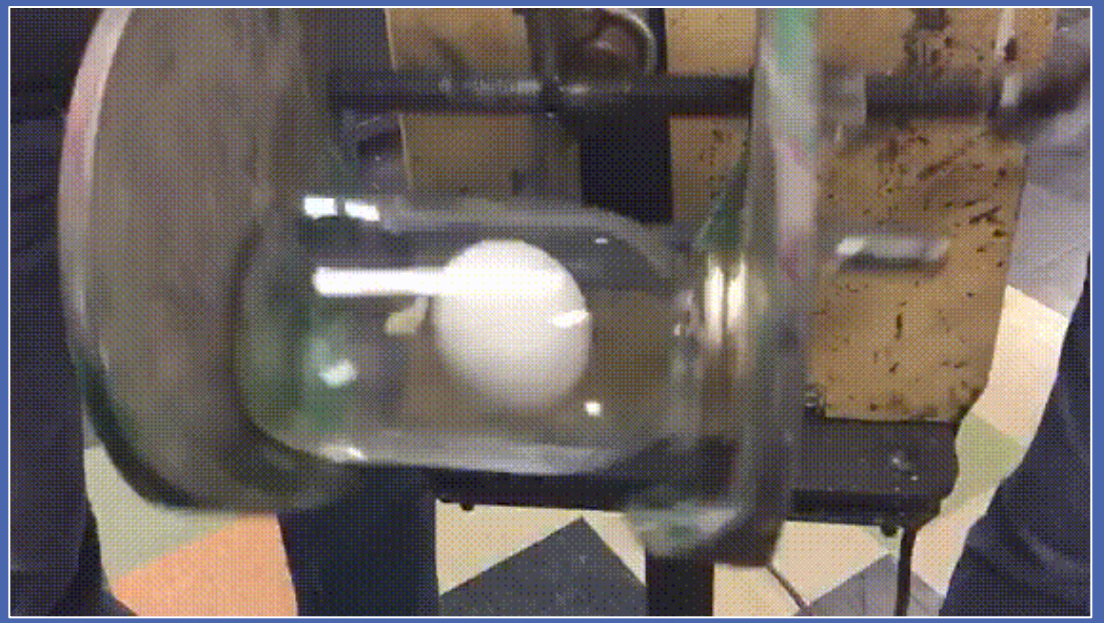
The Compensatory Reserve Volume

- While the skull is full of brain, blood, and cerebrospinal fluid, there's a little bit of pliancy [11]
- A certain volume of fluid can be added to the skull without increasing intracranial pressure [11]
- Once this volume is filled (exhausted), intracranial pressure starts to rise [11]
- This holds the brain in place more firmly
- If we could fill the compensatory reserve volume, we could prevent the brain from impacting the skull





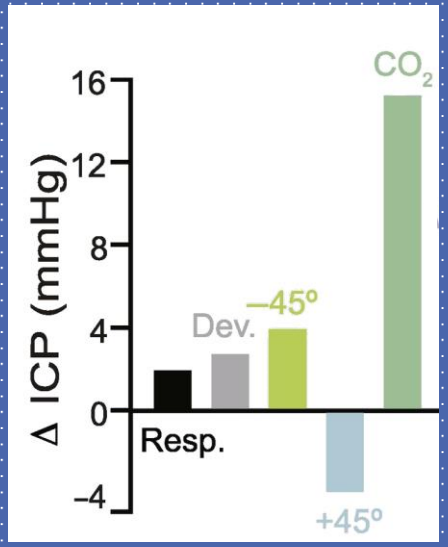


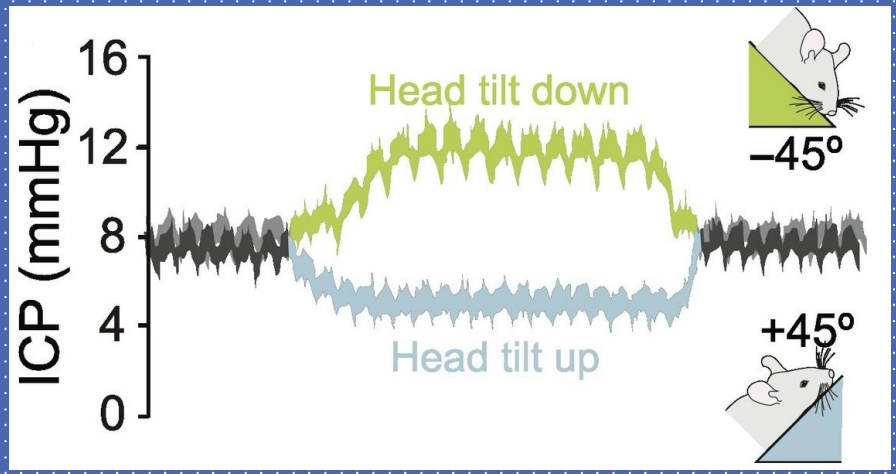


Images courtesy of our collaborator David Smith MD, tbi-innovations.com

Filling the Compensatory Reserve Volume

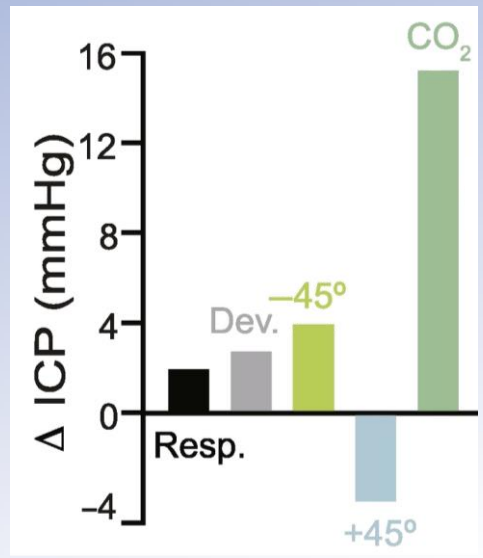
- There are numerous factors affecting intracranial pressure, and thus the amount to which the compensatory reserve volume is filled [12]
- Something as simple as changing the angle of the head relative to the body can elicit significant changes in intracranial pressure [12]

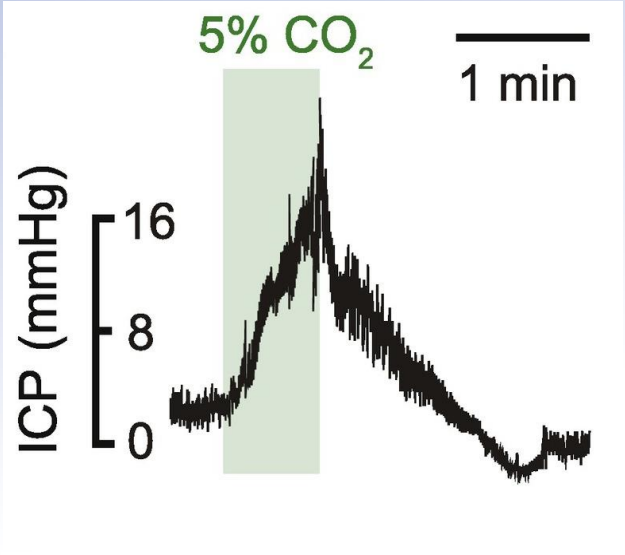


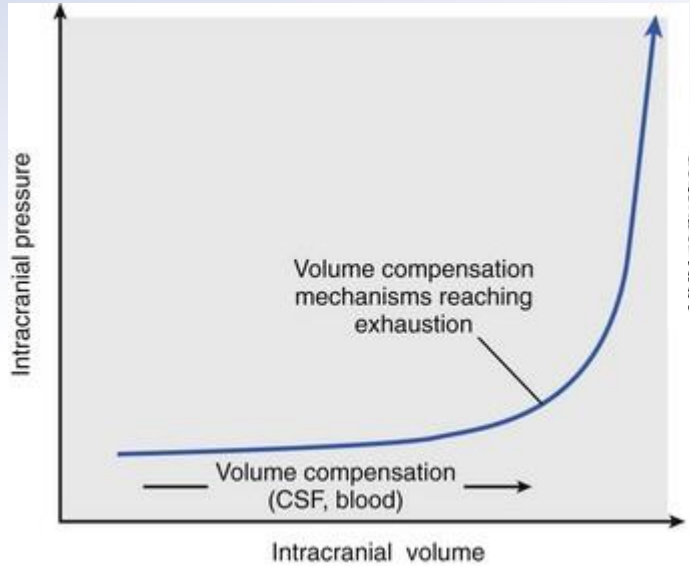


Carbon Dioxide

- A faster, and more powerful way increase intracranial pressure is to increase the amount of inhaled CO2 [12]
- Inhaling a higher than normal amount of carbon dioxide results in dilation of cerebral arteries, causing more blood flow to the brain, filling the compensatory reserve volume and increasing intracranial pressure [12]

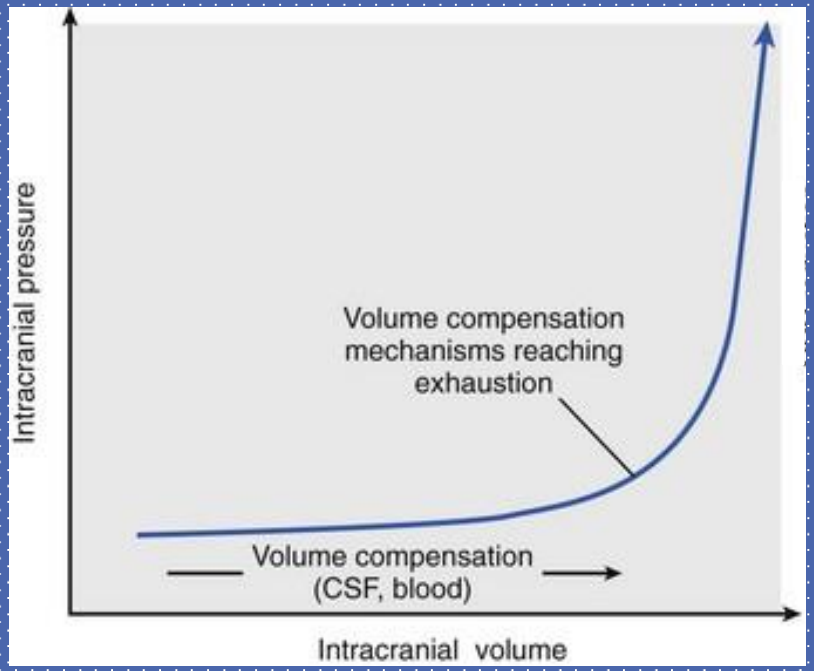


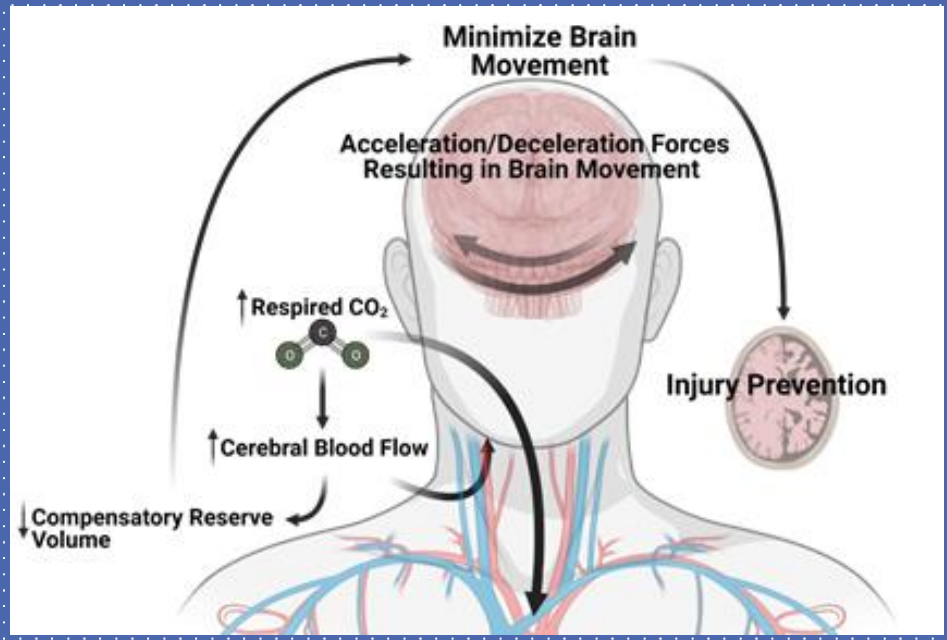




Our Hypothesis

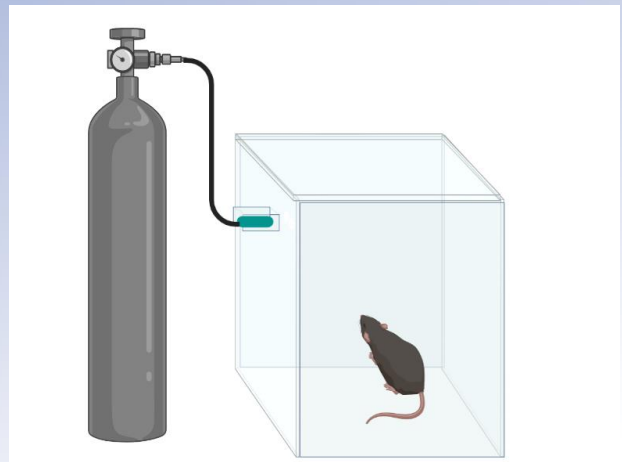
- Carbon dioxide, due to its ability to dilate cerebral arteries, increasing the blood flow to the brain and filling the compensatory reserve volume, preventing the brain from moving during injury, will reduce the incidence and severity of TBI in mice

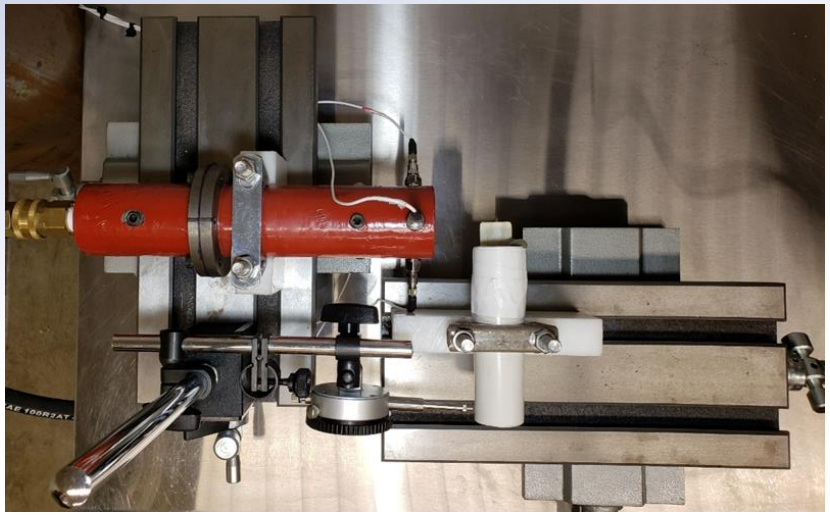




Testing Our Hypothesis

- We subject mice to blast TBI using a scaled blast model
- Immediately before injury, mice are anesthetized with a mixture including either medical-grade air or 5% CO_2
- Mice are either exposed to a blast or no blast (sham) for the control group

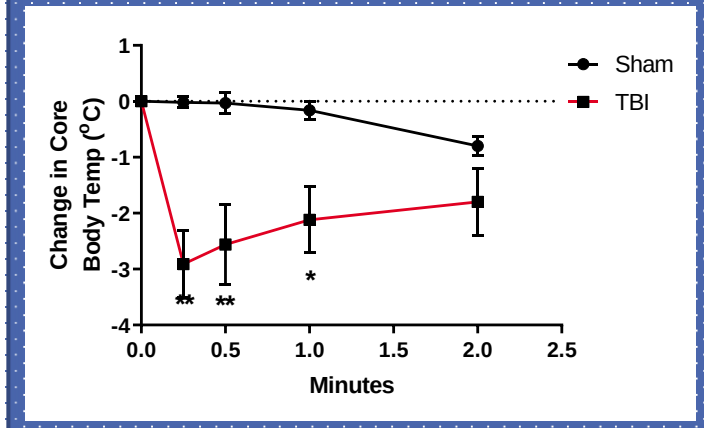


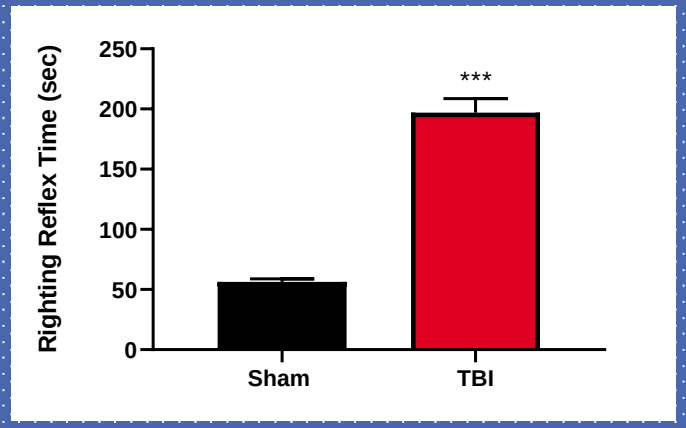


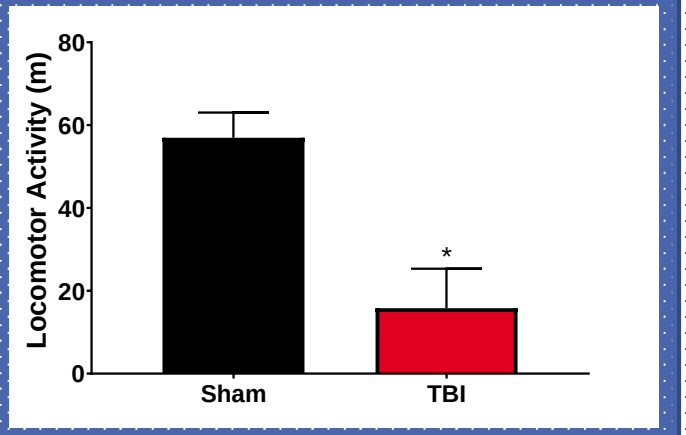
Testing Our Hypothesis

- We measure body temperature at several timepoints relative to injury
  - Mice exposed to blast TBI display significant reductions in body temperature
- We measure righting reflex time immediately after injury
  - A measure of consciousness similar to coma scales in humans
  - Mice exposed to blast TBI display significant increases in righting reflex time
- We measure locomotor activity three hours after injury
  - Mice exposed to blast TBI display significant decreases in locomotor activity

* - less than 5% probability results arose by chance, ** - less than 1% probability results arose by chance, *** - less than 0.1% probability results arose by chance

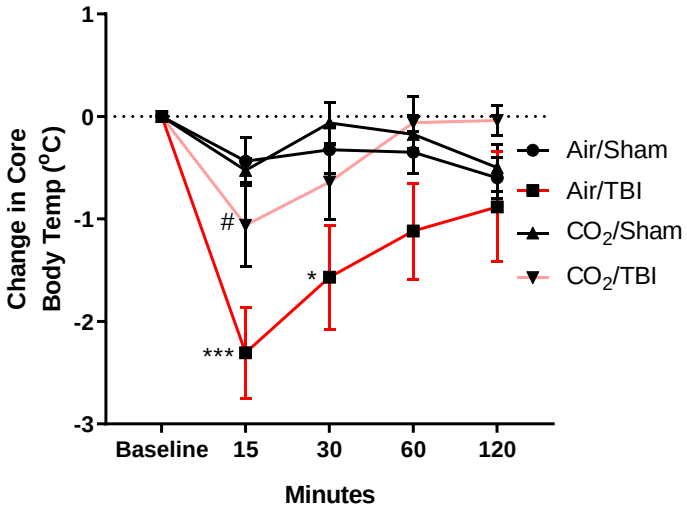


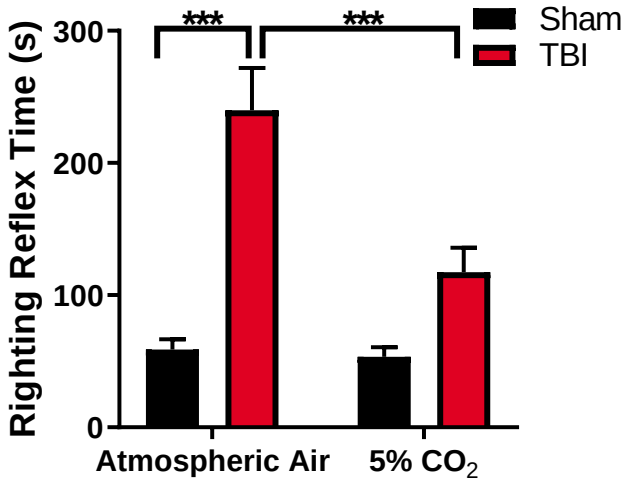


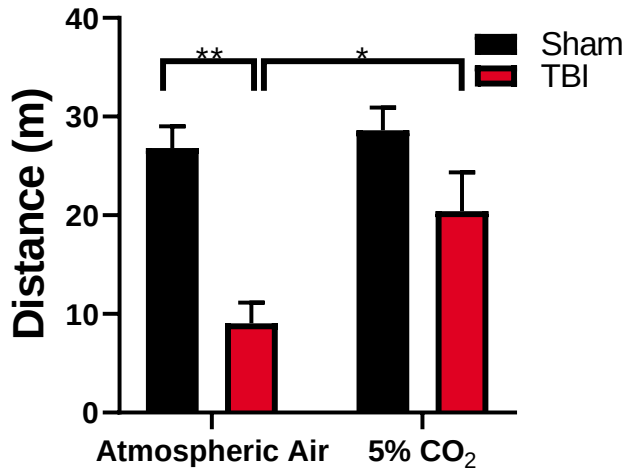


Carbon Dioxide Prevents TBI Deficits

- Mice exposed to a 5% carbon dioxide atmosphere for 10 minutes before blast TBI exposure had no alterations in body temperature
- Mice exposed to carbon dioxide before blast TBI also showed no difference in righting reflex time
- Carbon dioxide also prevented deficits in locomotor activity

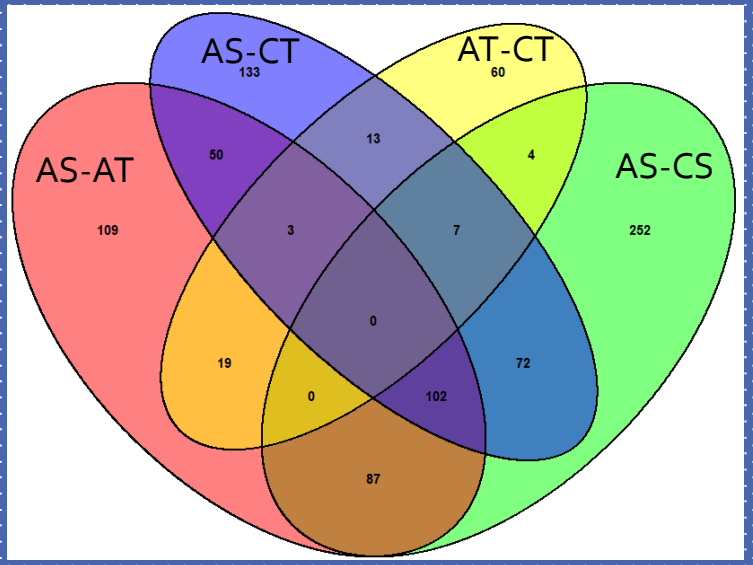


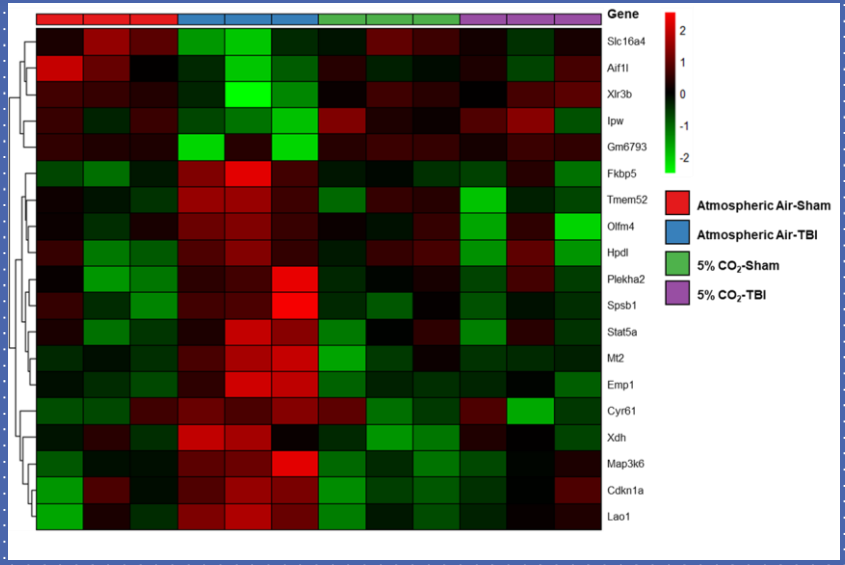




Carbon Dioxide Normalizes Gene Expression

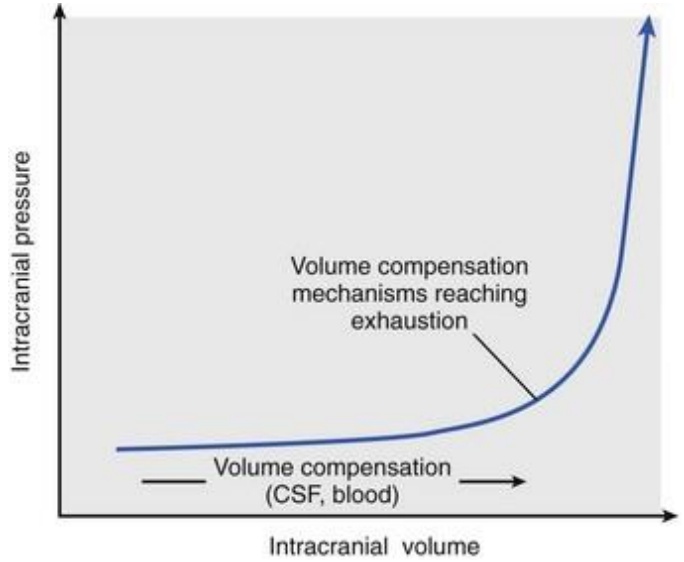
- TBI changes a miasma of genes expressed in the brain (370 in our data)
- We wanted to see whether and how carbon dioxide could ameliorate these changes
- We identified 19 genes altered by TBI but normalized by carbon dioxide, the therapeutic targets of preventing the brain from impacting the walls of the skull



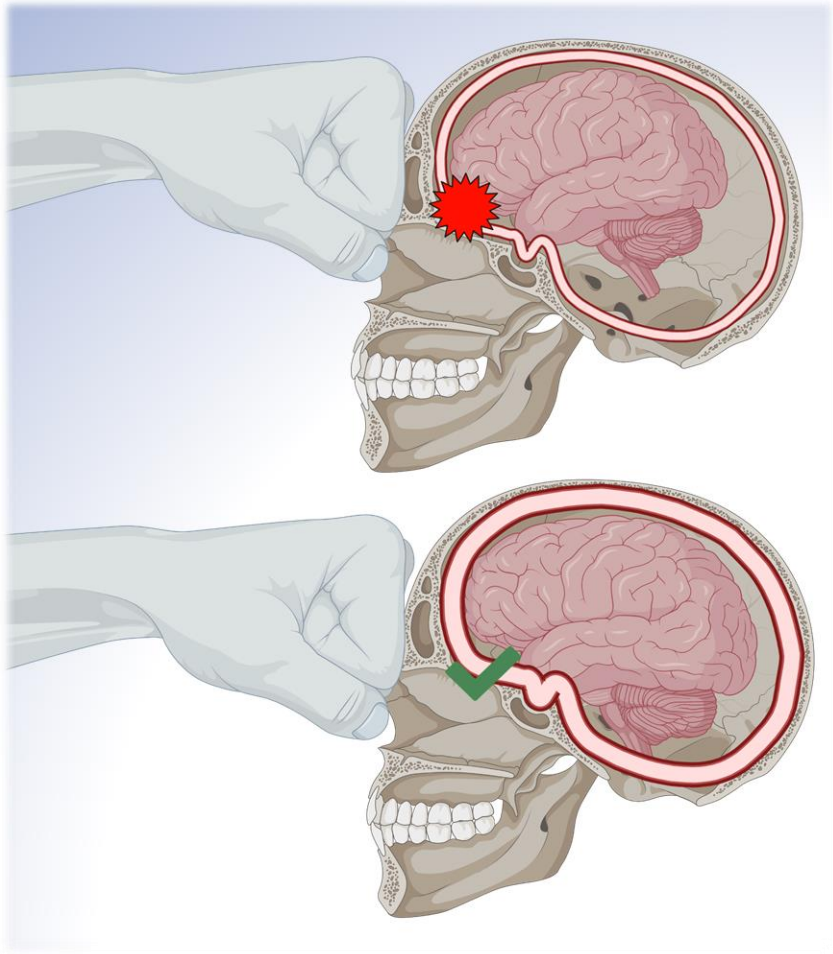


Conclusions

- We have demonstrated that carbon dioxide, by its ability to increase cerebral blood flow, fill the compensatory reserve volume, and prevent the brain from impacting the walls of the skull has a powerful ability to prevent TBI
- Mice exposed to carbon dioxide before injury appear behaviorally and physiologically normal, and many of the genes changed by TBI are normalized by carbon dioxide



- We posit that this principle can and should be developed into a preventative therapeutic for humans at high risk of TBI



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