

## ABSTRACT

Traumatic injury is the leading cause of death of Americans under the age of 45, with more than 200,000 such deaths occurring every year (Centers for Disease Control and Prevention, 2017). But there are also millions of people who are injured and survive. Trauma outcomes for older populations tend to have higher morbidity, mortality and disability rates than younger populations, with prognoses becoming incrementally worse for those beyond 40 years of age, regardless of injury severity and comorbidities. Surgery and concomitant exposure to general anesthetics (GAs) is common for survivors of life-threatening injury of all ages, but it is largely unknown to what degree GAs influence trauma outcomes, and the impact of age on such interactions has yet to be explored. Previously we found that in a blunt trauma model with traumatic brain injury (bTBI), GAs differentially affected the mortality of young adult (0-7 day old) fruit flies (*Drosophila melanogaster*) of the *w<sup>1118</sup>* standard laboratory strain (Fischer *et al.*, *Anesth Analg* 2018). Here we tested the effect of GAs on bTBI outcomes in aged (42-49 day old) *w<sup>1118</sup>* fruit flies.

To substantiate the results, young flies were tested alongside their aged counterparts for comparison. Pre exposure to both ISO and SEVO was protective for young flies, but this protective outcome was lost for aged flies and even bordered on aggravating, more so for ISO than for SEVO. Post exposure to ISO aggravated the  $MI_{24}$  of young flies but did not affect the  $MI_{24}$  of aged flies. And, finally, while post exposure to SEVO did not affect the  $MI_{24}$  of young flies, it did aggravate the  $MI_{24}$  of aged flies. These data indicate that age profoundly and differentially affects mortality outcomes from exposure to GAs, both before and after trauma.

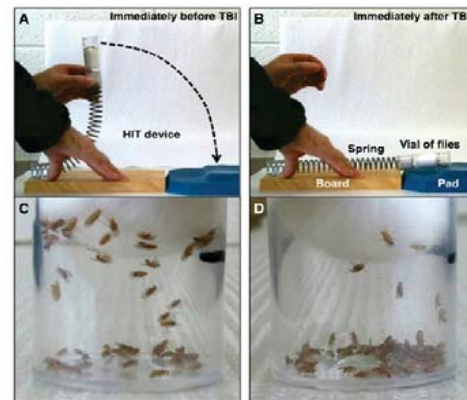
We conclude that GAs do modulate outcomes of life-threatening injury and that age exerts an independent effect on such interactions. These findings have important implications for vertebrate models of severe injury as results may be influenced by the universal mandate that trauma be inflicted under the influence of anesthetics. This makes it challenging to isolate the intrinsic effects of GAs on trauma pathophysiology and outcomes. Hence, the fruit fly is an invaluable model for investigating topics or hypotheses that are difficult to address in vertebrate models. Furthermore, fruit flies offer access to unparalleled genotypic diversity, which we plan to take advantage of in the future to explore the influence of genetic background on trauma-anesthetic interactions.

### Key Abbreviations:

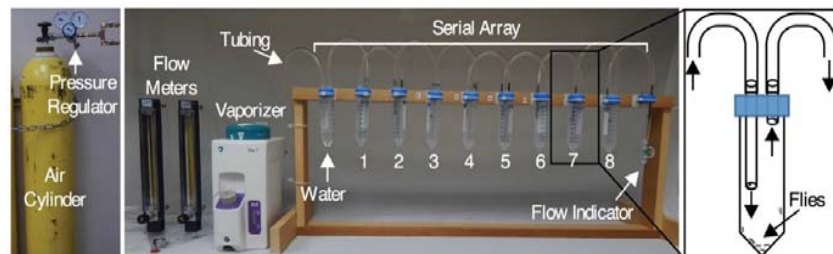
**$MI_{24}$ :** the Mortality Index at 24 hours, percentage of flies dead 24 hours after trauma, with no treatment (control) deaths subtracted  
**bTBI:** blunt trauma with Traumatic Brain Injury  
**VGA:** Volatile General Anesthetics  
**PRE:** 2hr exposure to VGAs prior to bTBI  
**POST:** bTBI prior to 2hr VGA exposure  
**ISO:** isoflurane (depicted in PURPLE)  
**SEVO:** Sevoflurane (depicted in YELLOW)  
**O<sub>2</sub>:** Oxygen (depicted in GREEN)  
**d.o.:** days old

## METHODS

We followed a blunt trauma model that uses a high-impact trauma (HIT) device to inflict calibrated acceleration-deceleration injury. (Katzenberger *et al.*, *PNAS* 2013)  
 Standard, equivalent doses of isoflurane (2%) or sevoflurane (3.5%) were administered for 2 hours either before (pre) or after (post) trauma.



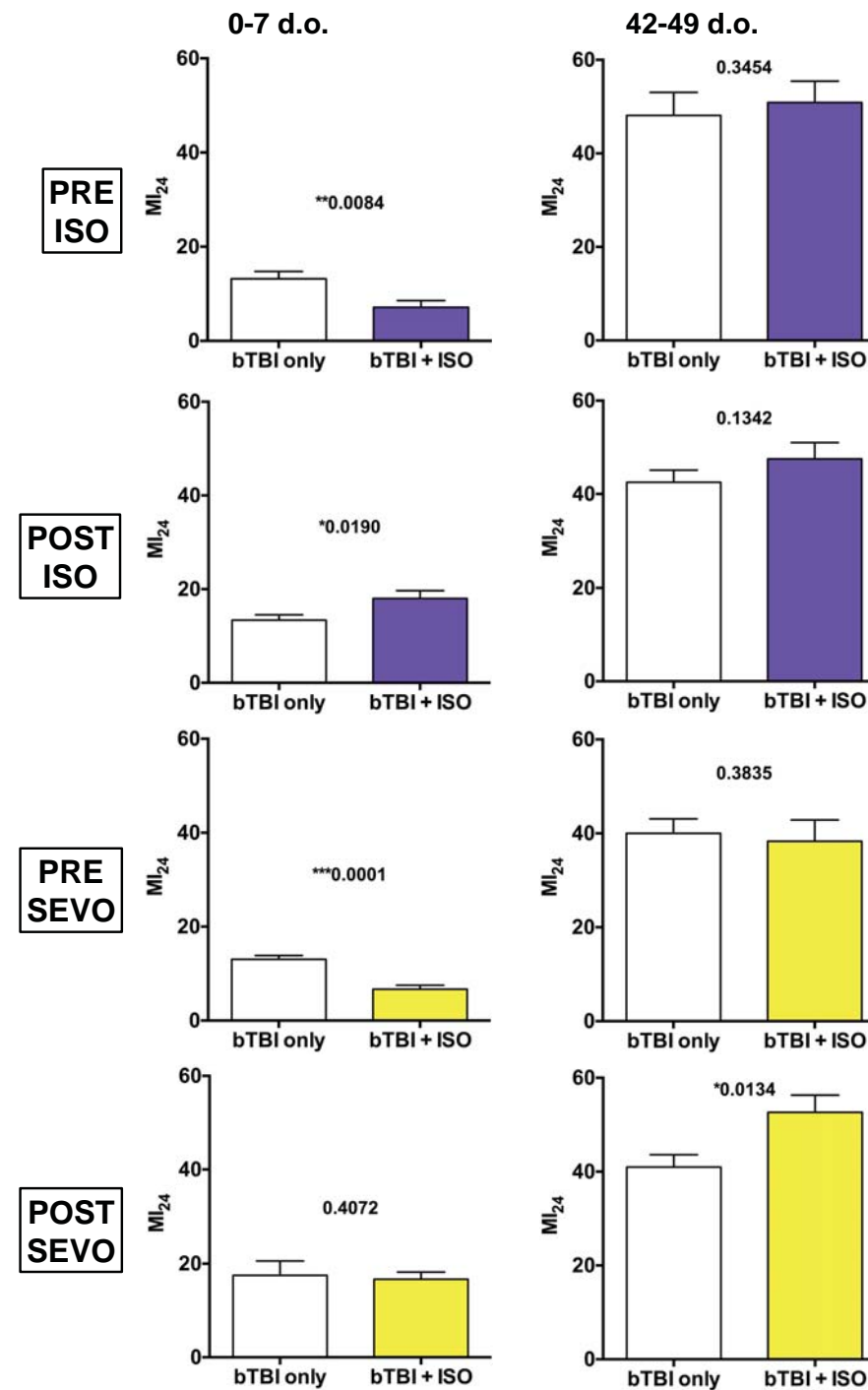
The High-Impact Trauma (HIT) device (Katzenberger *et al.*, *PNAS* 2013)



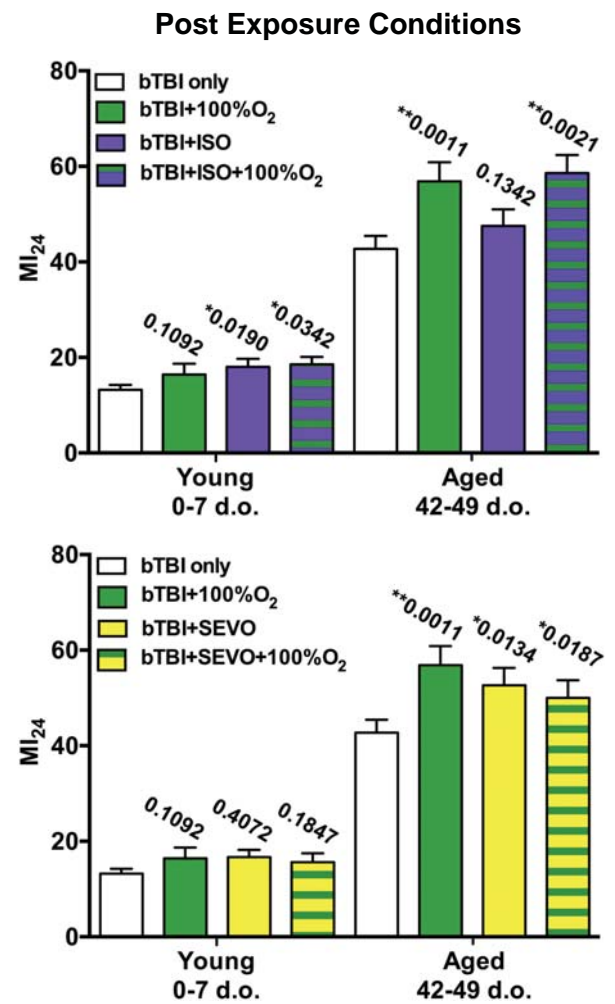
Serial Anesthesia Array (SAA)

## RESULTS

### 1. VGA Modulation of bTBI Outcome is Age Dependent



### 2. Hyperoxia Affects Aged Fly Mortality



### Key Points:

- Mortality ( $MI_{24}$ ) after TBI increases with age.
- VGAs differentially influence the  $MI_{24}$  after TBI.
- Age changes VGA mediated modulation of the  $MI_{24}$  after TBI.

## ONGOING INVESTIGATIONS

### Genetic Background Differentially Influences Outcomes from Trauma in 143 RAL Lines

