



Identification and surfactant intervention of mechanotransductional events triggering endothelial cell response to air embolism

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Introduction

- Decompression carries risk of gas embolism, but treatment options are limited
 - 30 years of research, no drug translated to the clinic
 - Gas microemboli can cause changes in blood flow and organ function in the absence of vessel obstruction
 - Air bubble contact with endothelial cells causes a transient increase in intracellular calcium which is associated with cell injury/death
- Hypothesis: Interfacial interactions with plasma and endothelial surface macromolecules initiate intercellular pathways that lead to cell dysfunction, injury or death
 - Surfactants provide a means of mitigating the interactions between the air interface and the endothelial surface layer

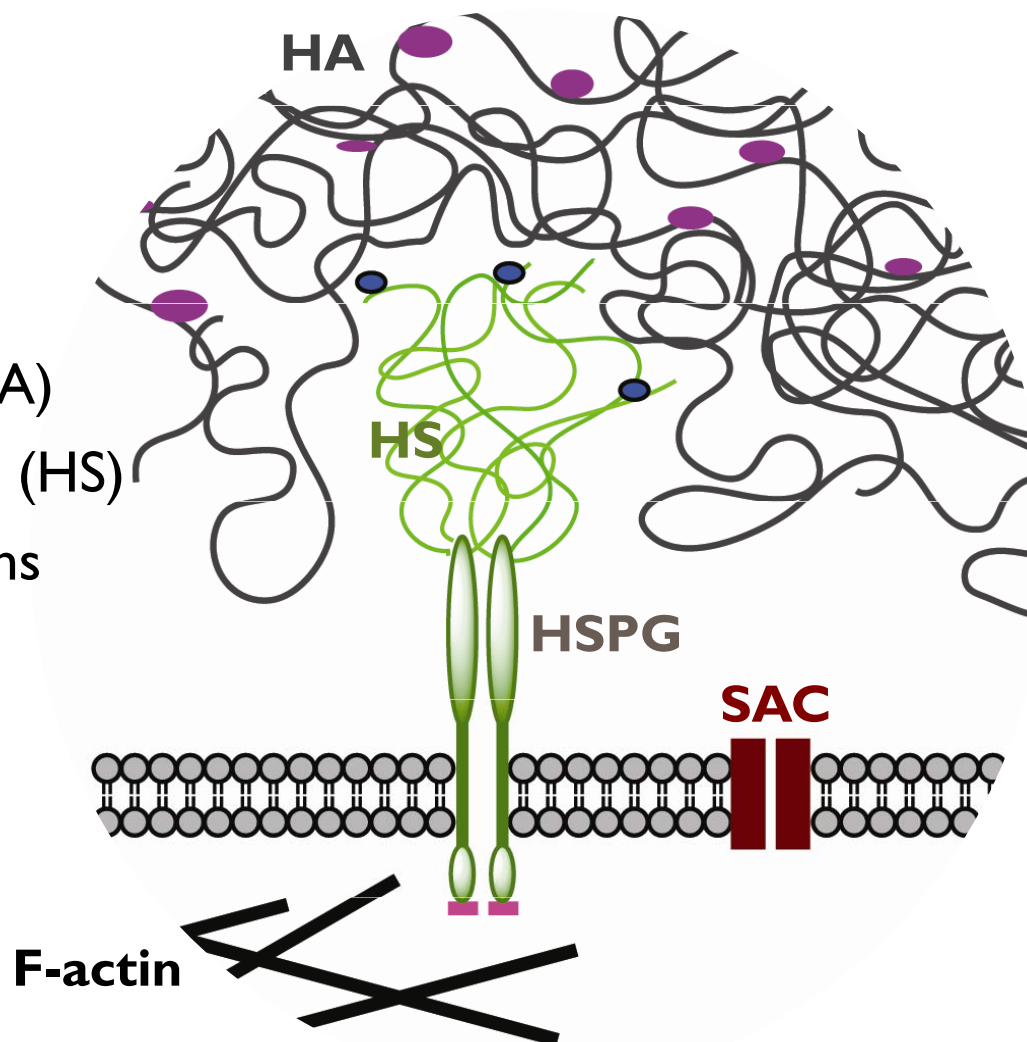
Endothelial surface layer

- ESL proteins



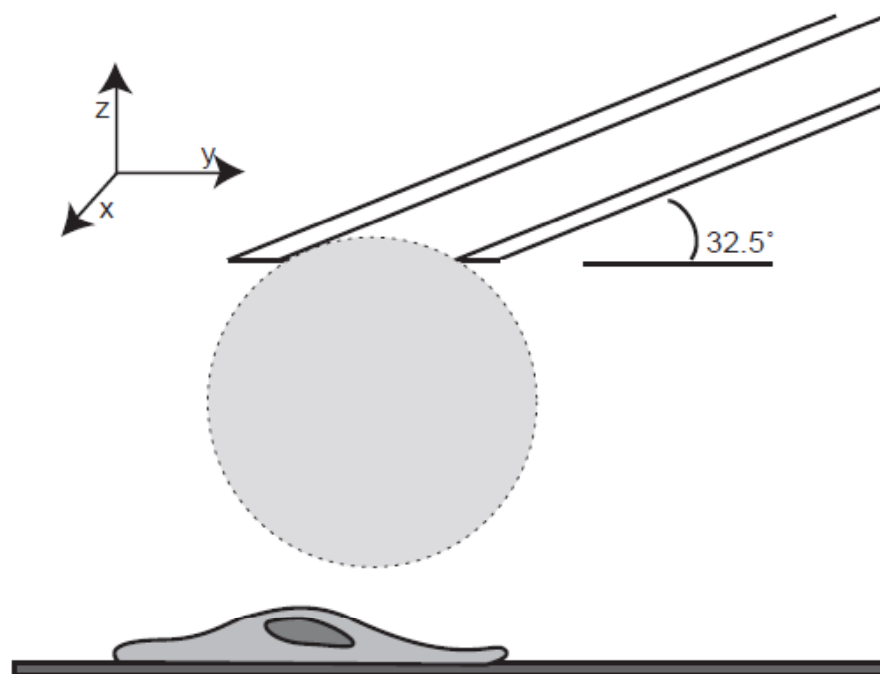
- Glycocalyx

- Hyaluronate (HA)
- Heparan Sulfate (HS)
- HS proteoglycans (HSPG)

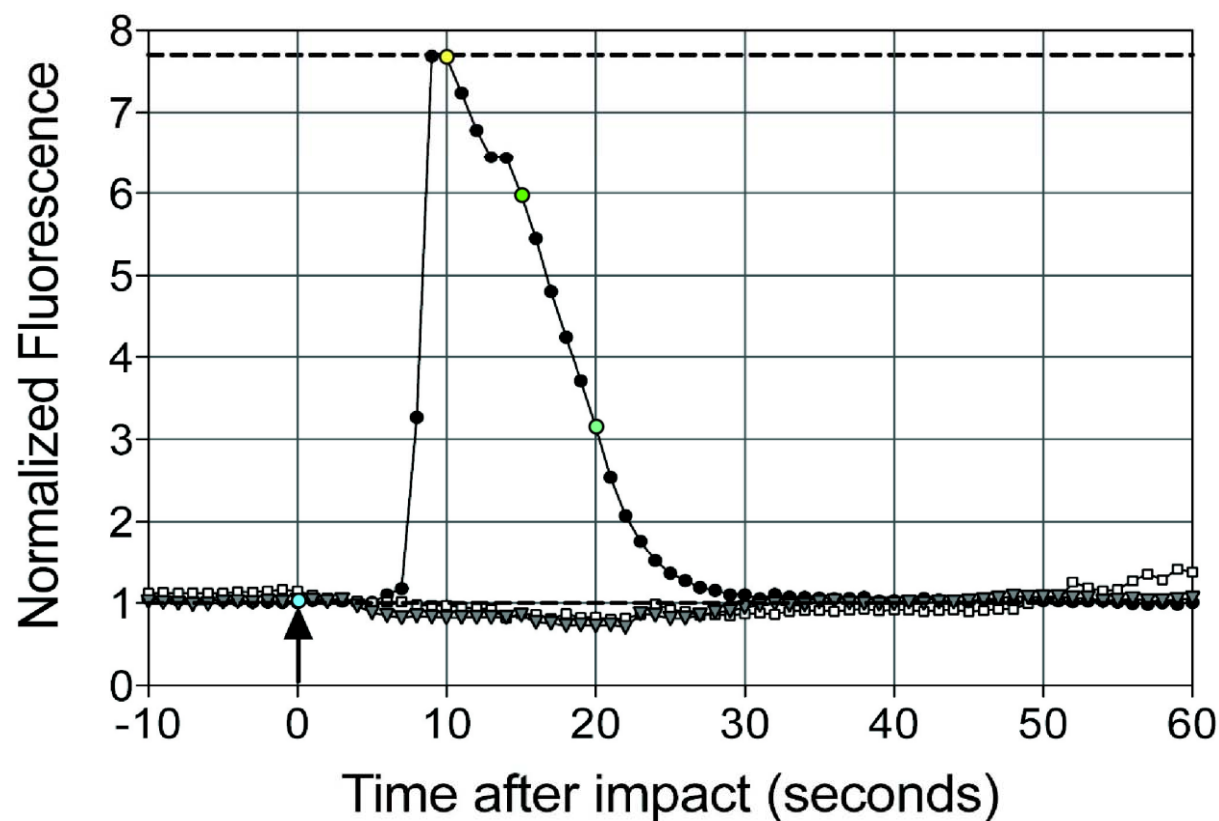
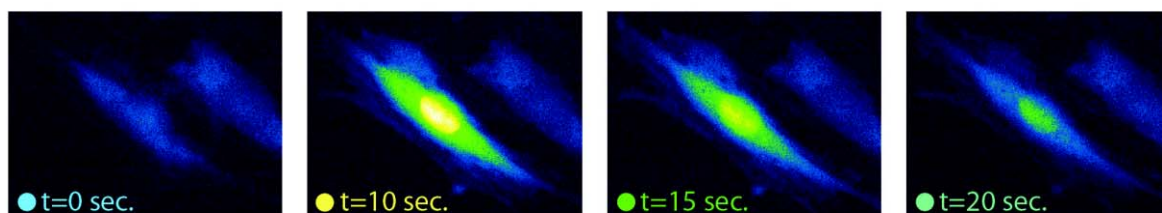


Methodology

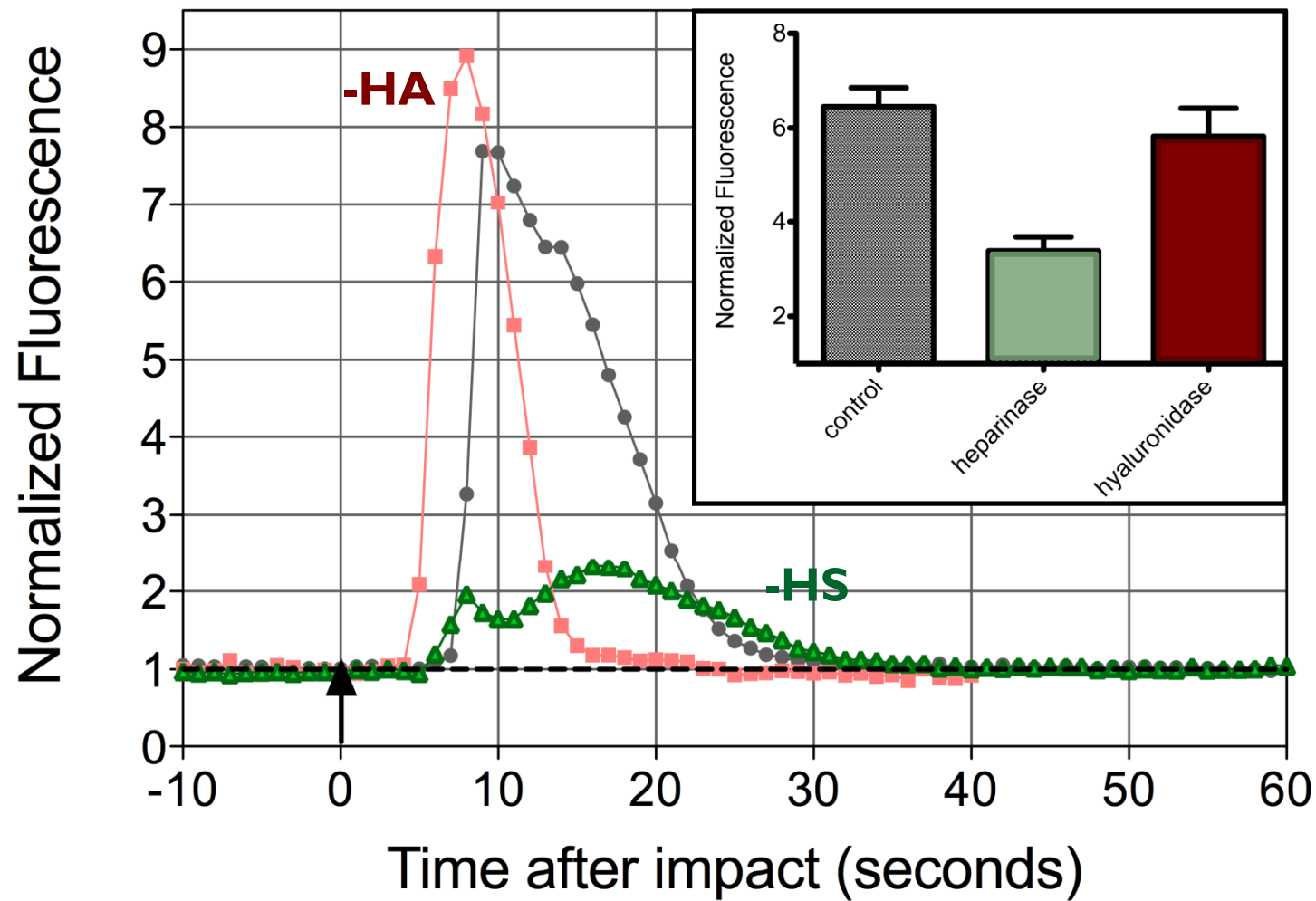
- *In vitro* cell culture
 - human umbilical vein endothelial cells (HUVEC)
- Load with Fluo-4
 - Calcium sensitive, fluorescent dye
- Blow and manipulate 50-150 μm air bubbles
- Examine using epifluorescence microscopy
- Focus on non-lethal air bubble contact



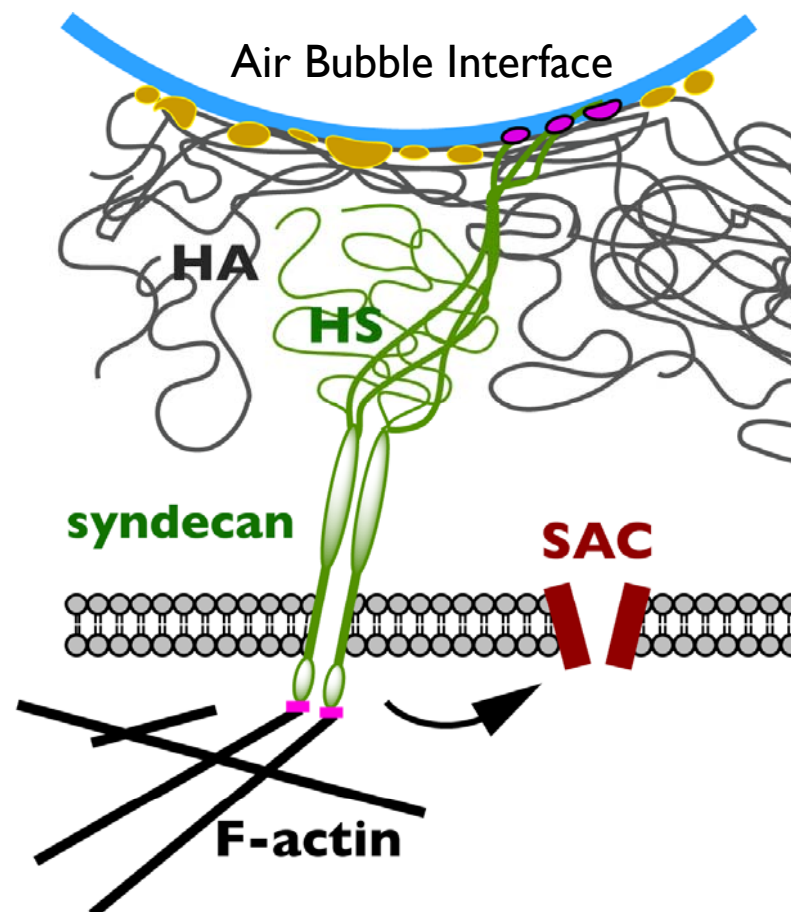
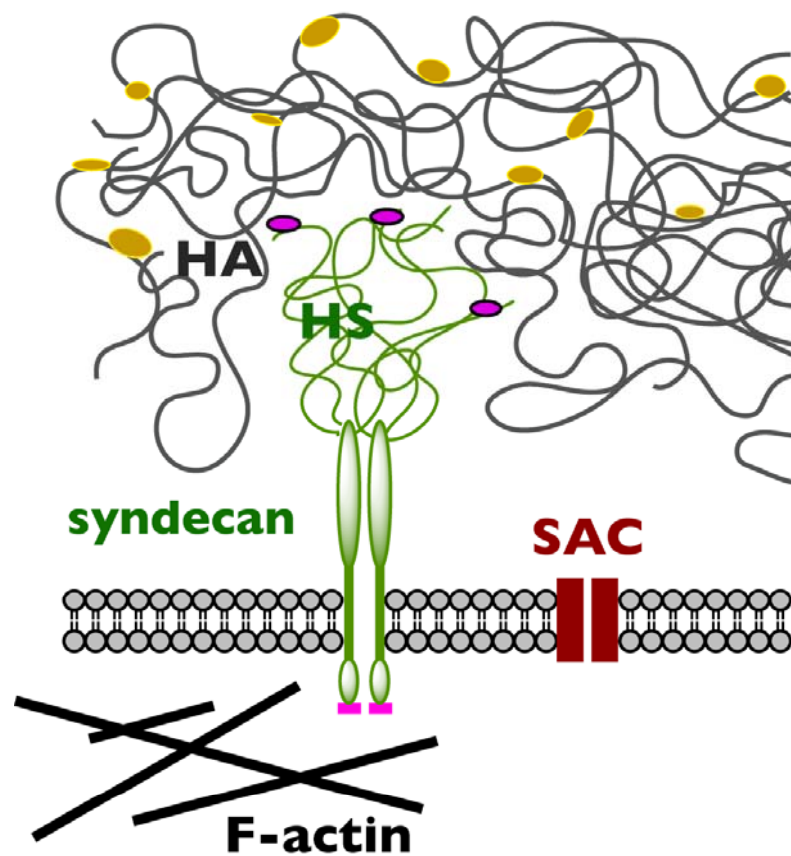
Typical intracellular Ca^{2+} response



Glycocalyx digestion

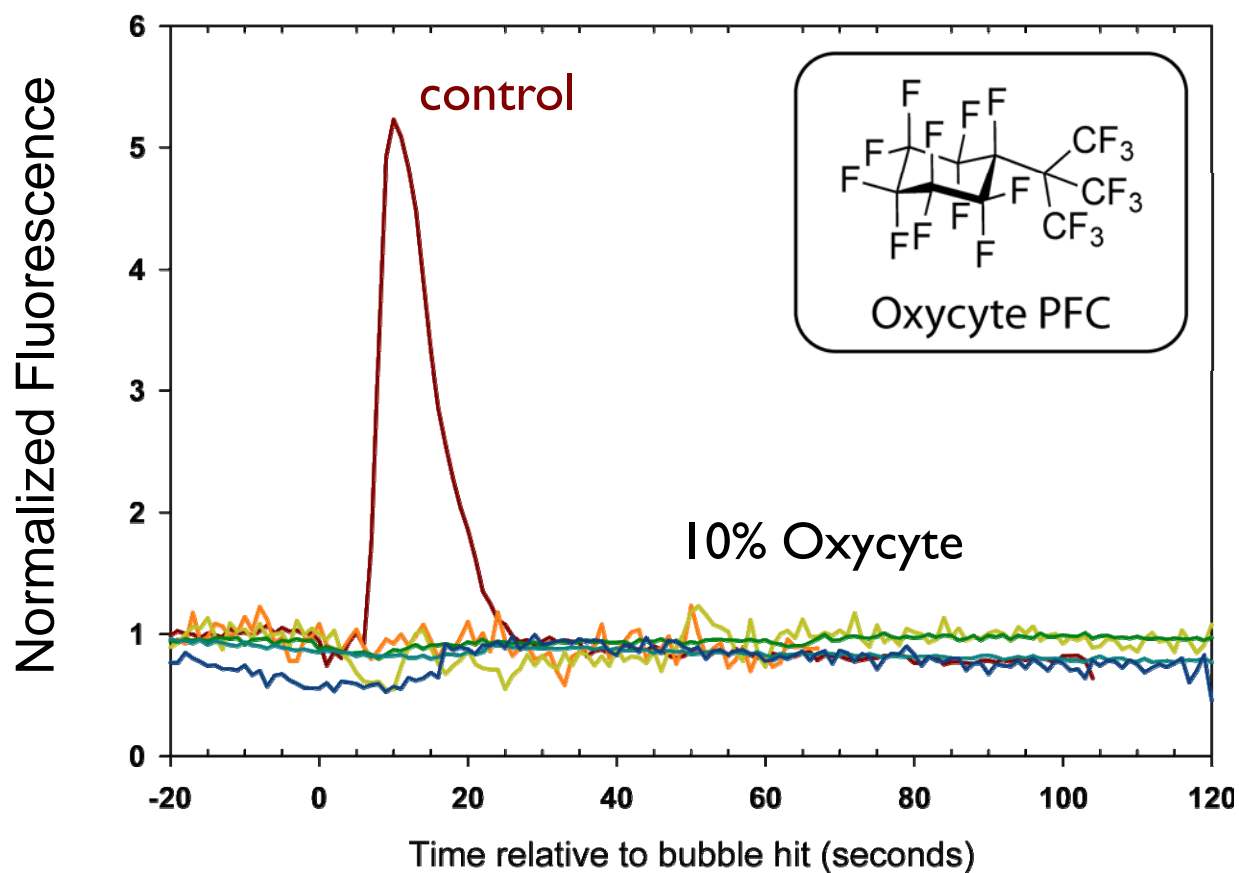


Channel Activation Model



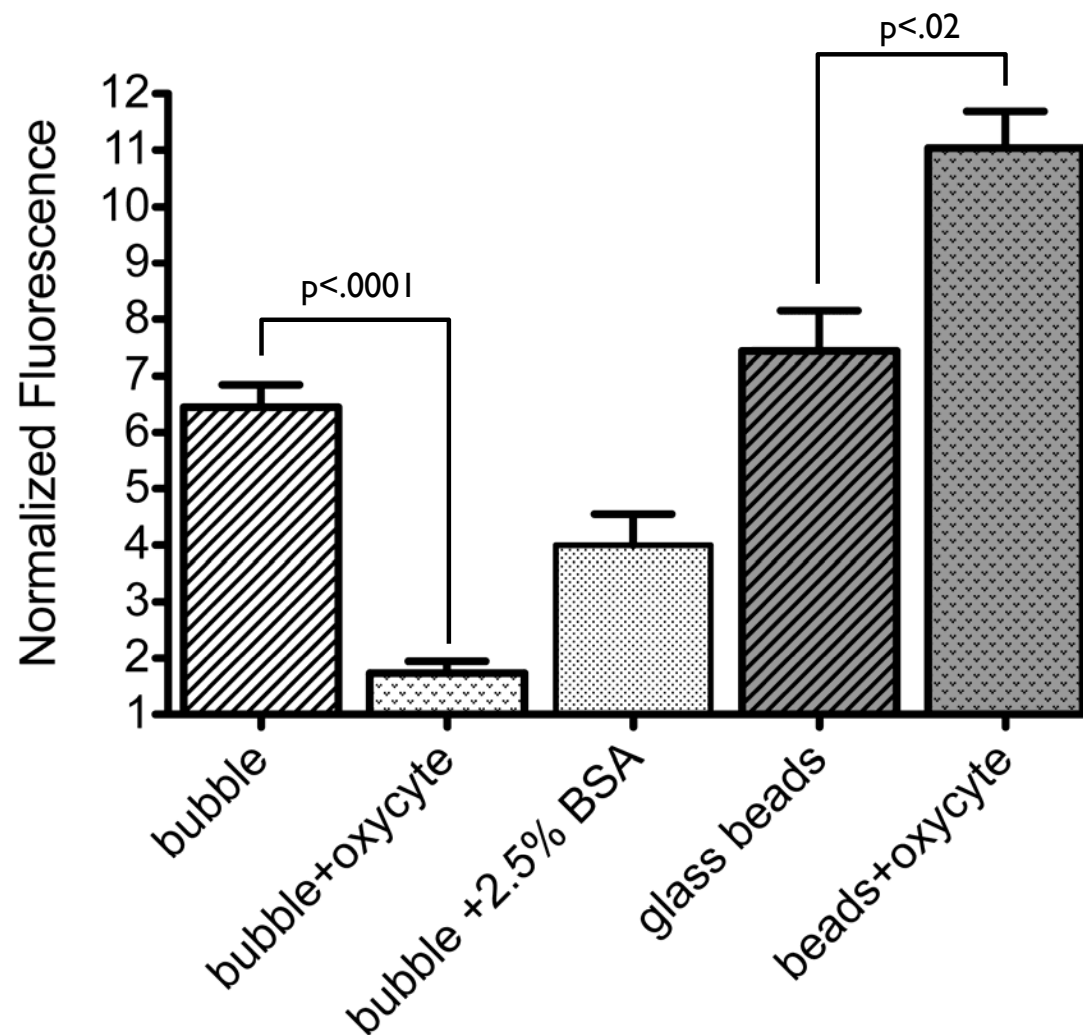
Surfactant Intervention

- Oxycyte: F-tert-butylcyclohexane supplied by Oxygen Biotherapeutics
 - 200 nm phosphatidylcholine micelle suspension



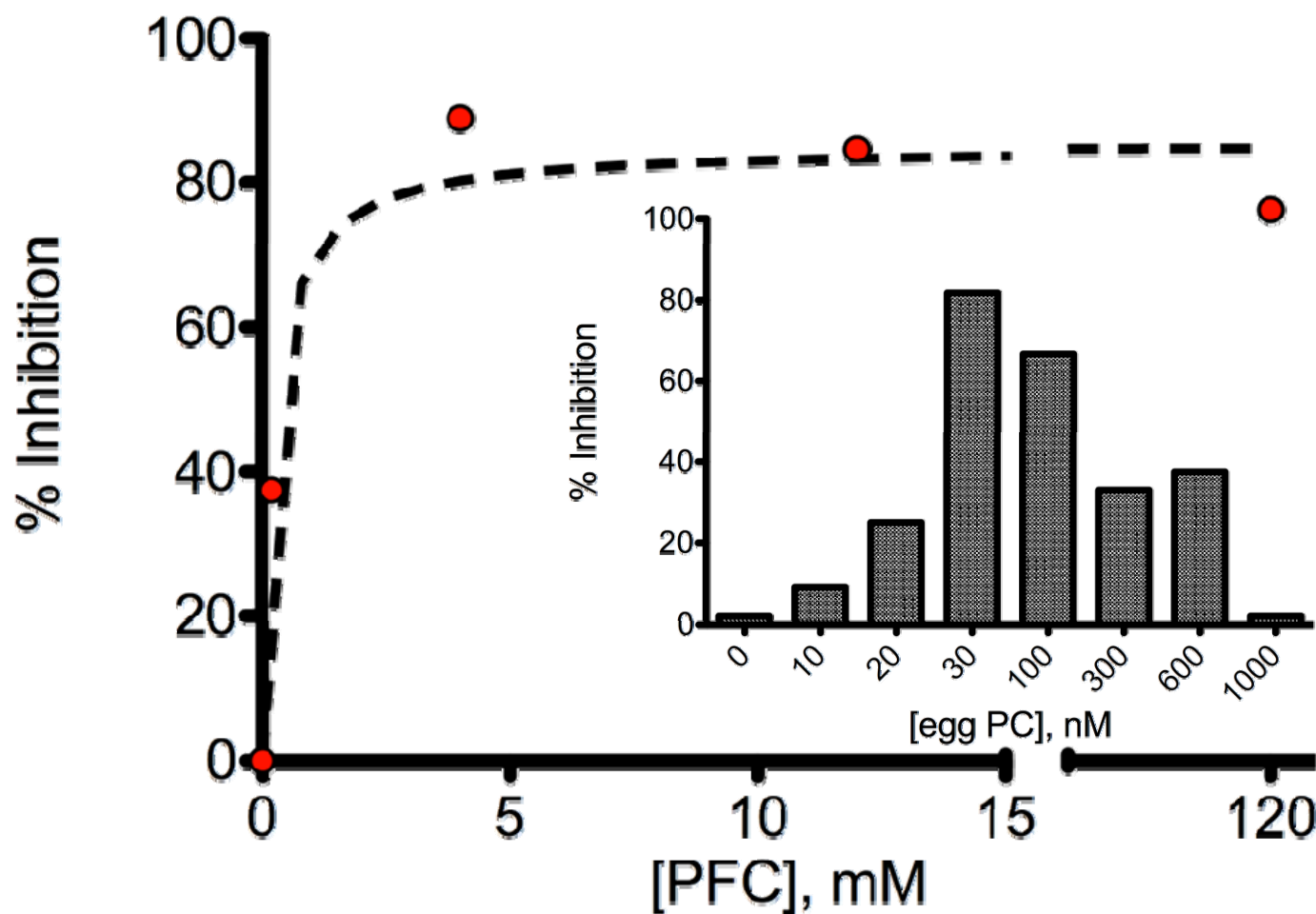
Surfactant Intervention

- Oxocyte ameliorates air bubble induced calcium transients, but not those induced by glass beads



Surfactant Intervention

- Oxocyte inhibits the intracellular calcium response to air bubbles in a dose dependent fashion



Conclusions

- Air-liquid interface interaction with ESL is the unique aspect of gas embolism injury
- Heparan Sulfate is necessary for the generation of air bubble-induced calcium transients, suggesting that activation of HS proteoglycan (such as syndecan-4) is a key mechanotransductional event
- Interfacial interactions offer an attractive target for preventative and therapeutic pharmacological intervention with surfactants
- Oxycyte inhibits air bubble induced calcium transients in a dose dependent fashion



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