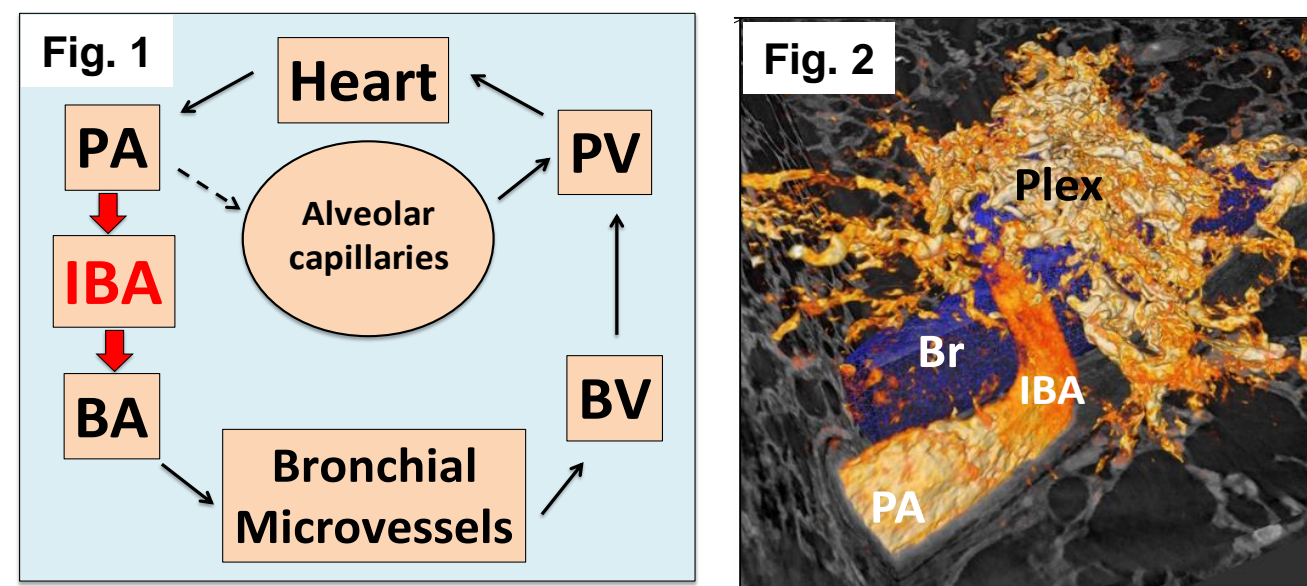


Intrapulmonary Right to Left Shunt via Bronchial Circulation and Bronchial Endothelial Dysfunction in Experimental Pulmonary Hypertension Animal Models

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Background

- The bronchial circulation (BC) is vital in lung health as it provides oxygen and nutrition, but its role in pulmonary vascular disease has been largely overlooked.
- Intrapulmonary bronchopulmonary anastomoses (IBA) form parallel microcirculatory network to connect bronchial and pulmonary circulation (PC) with a diameter ranges from 20-400µm.
- IBAs are open in fetal life and closed after birth but recruited in diseases with pulmonary hypertension (PH).
- Recruited IBA's allow deoxygenated blood to bypass alveolar capillaries, leading to intrapulmonary right to left shunt (IRLS) and hypoxemia in PH (Fig. 1).
- IBA and BC have been shown to contribute to plexiform lesions in human PH (Fig. 2).
- Whether IRLS utilizing BC plays a role in PH has not been investigated in experimental PH animal models.



Hypothesis

In PH, there is increased PC to BC blood flow that contributes to IRLS, which is partly mediated by altered vasoactive factor expressions of bronchial endothelial cells in neonatal and adult PH rat models.

Study Questions

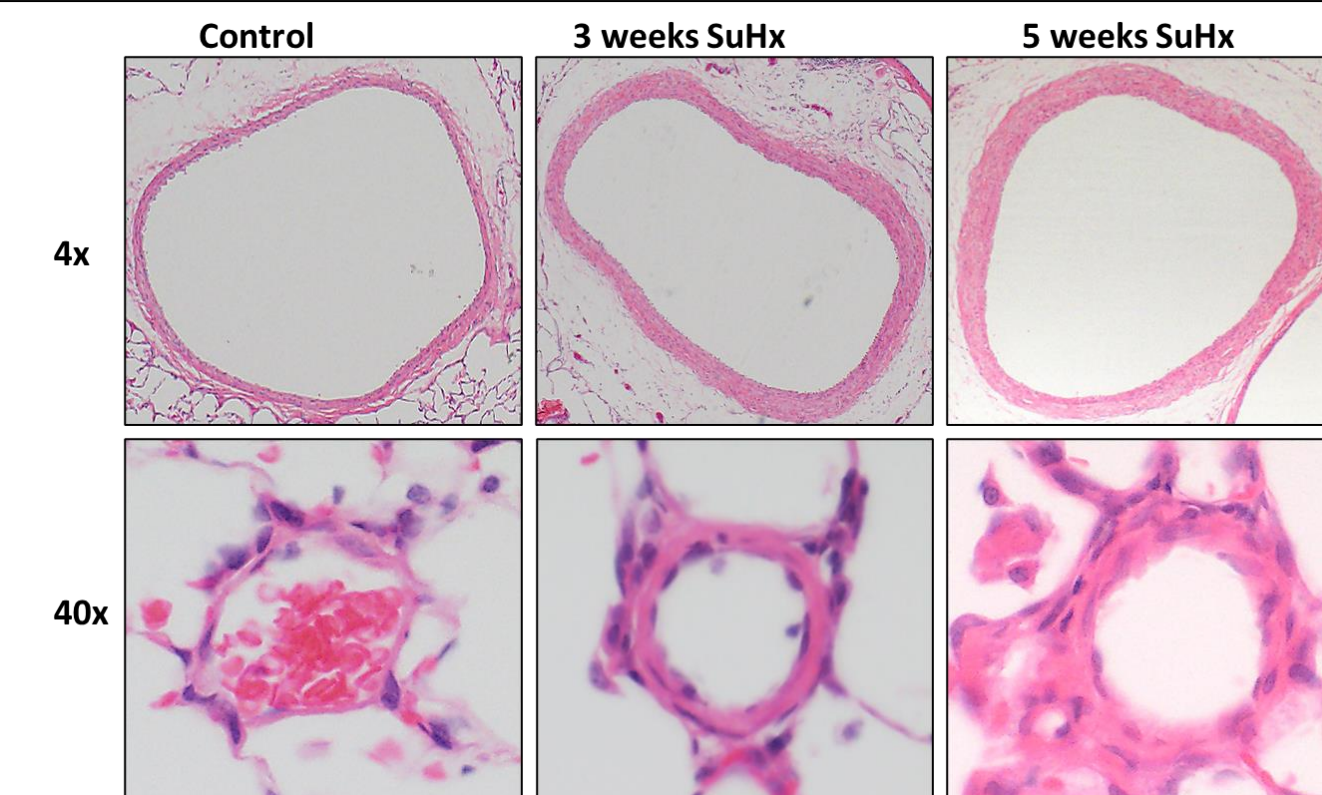
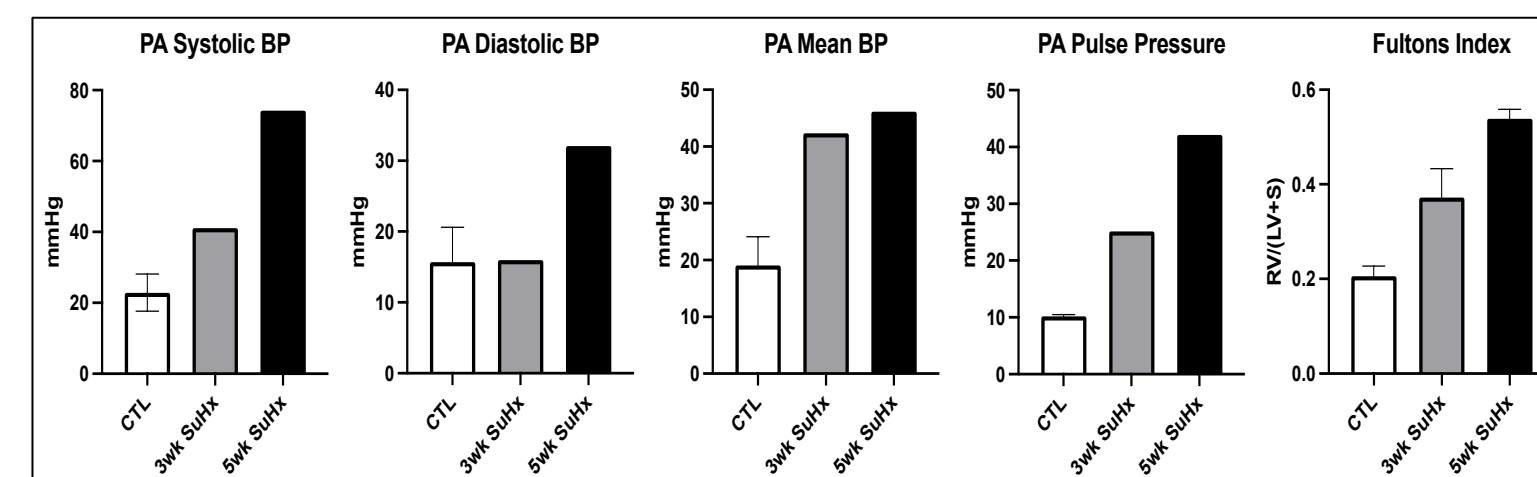
- Will PH rat models demonstrate bronchial vessel filling from right to left shunting?
- Will experimental PH alter the expression of bronchial endothelial cell-mediated (BEC) vasomotor signals?

Methods

- Adult Sprague Dawley rats were exposed to weekly injections of SU5416 (100mg/kg) with continuous exposure of hypoxia (14% oxygen) for 5 weeks.
- At 3 and 5 weeks, green ink was injected into either the main pulmonary artery (MPA) or into the aorta (AO).
- Neonatal Sprague Dawley rats were exposed to a single dose of Su5416 at day of life (DOL) 1.
- At DOL14 green ink was injected into the MPA or AO.
- BEC were isolated from large airways by positive selection with CD31-coated magnetic beads and were studied at passage 1-2.
- Western blots were performed on BEC lysates to measure vasomotor factor concentrations including those of endothelin-1 (ET-1), Alpha 2 adrenergic receptor (A2AR) and endothelial ectonucleotidase (CD39).

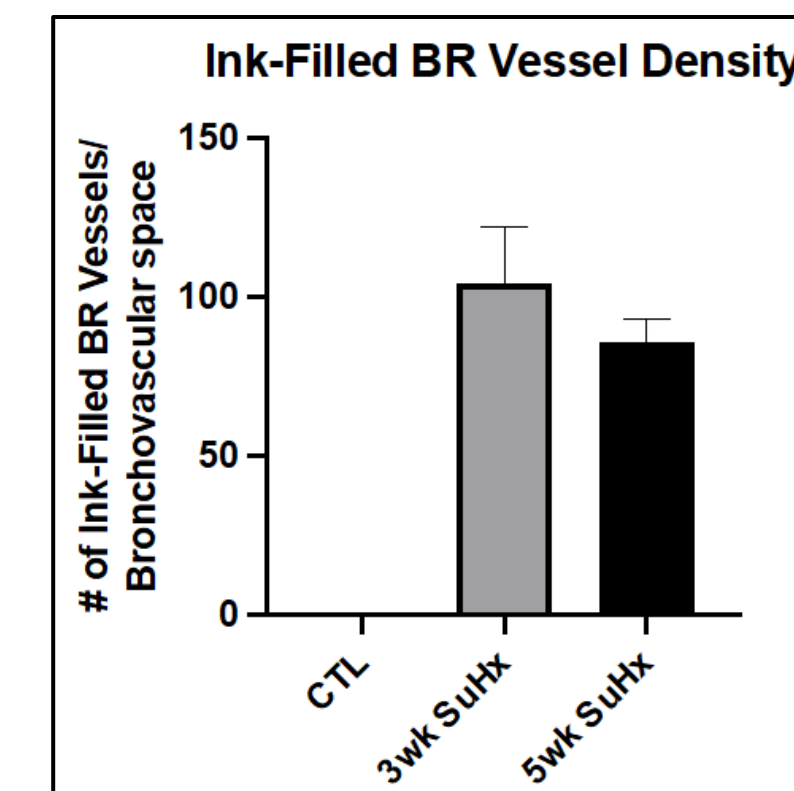
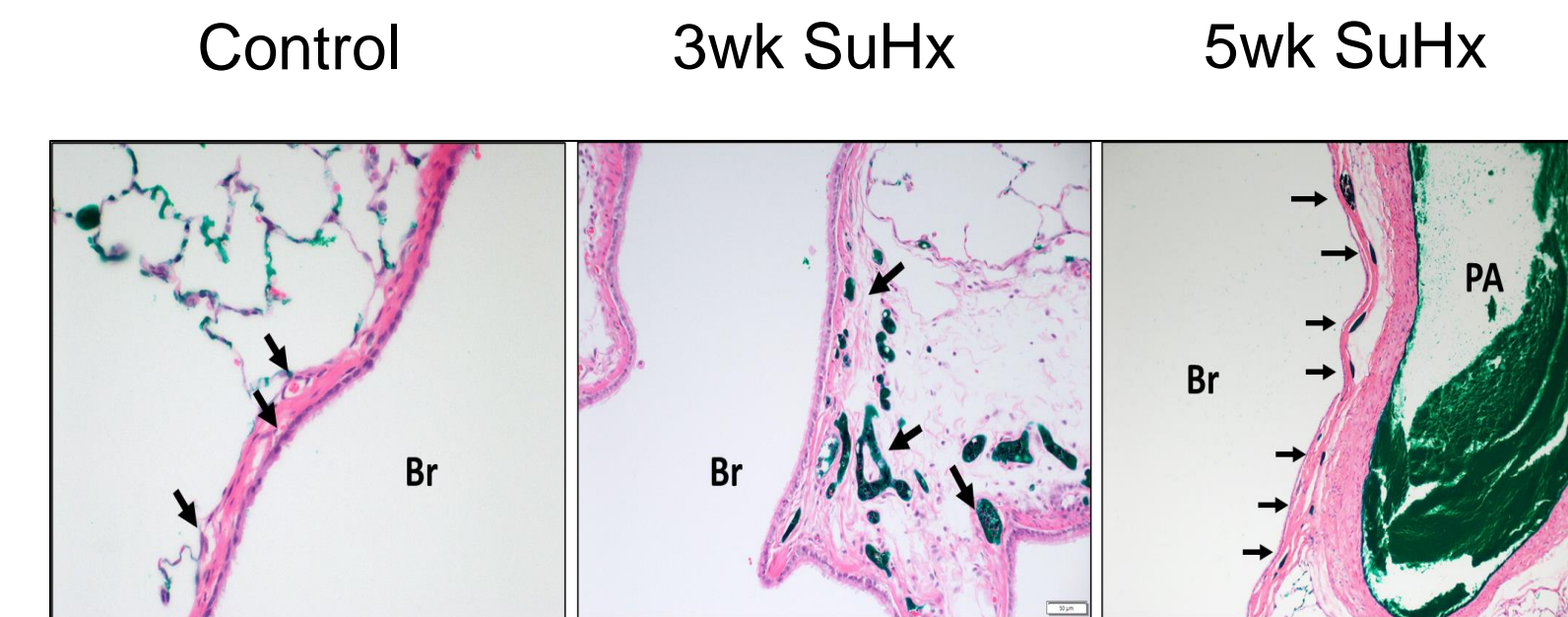
Results

SuHx Rat PH Model Demonstrates Progressive PH with PA Wall Thickening

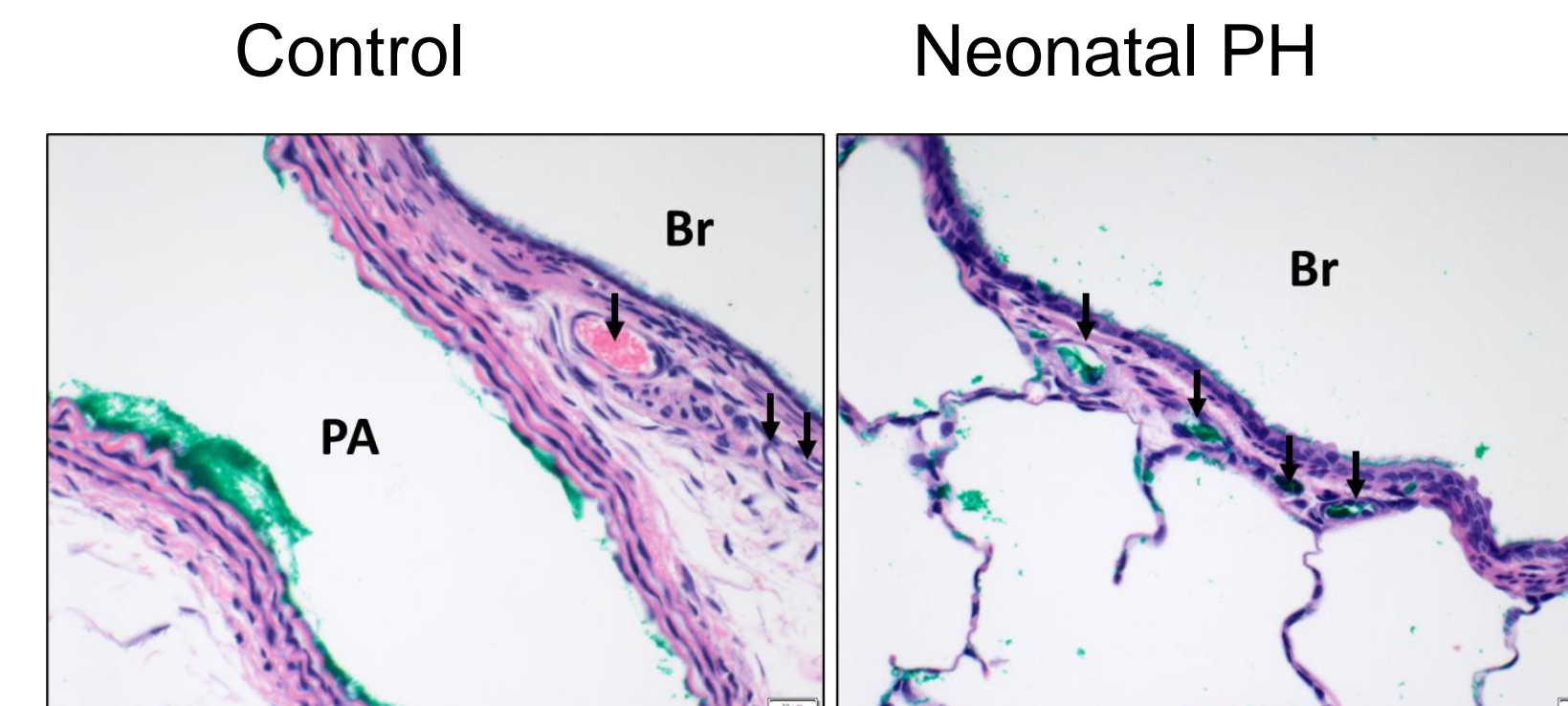


Results

Experimental Adult PH Induces Intrapulmonary Right to Left Shunt Demonstrated by Ink Filled Bronchial Vessels

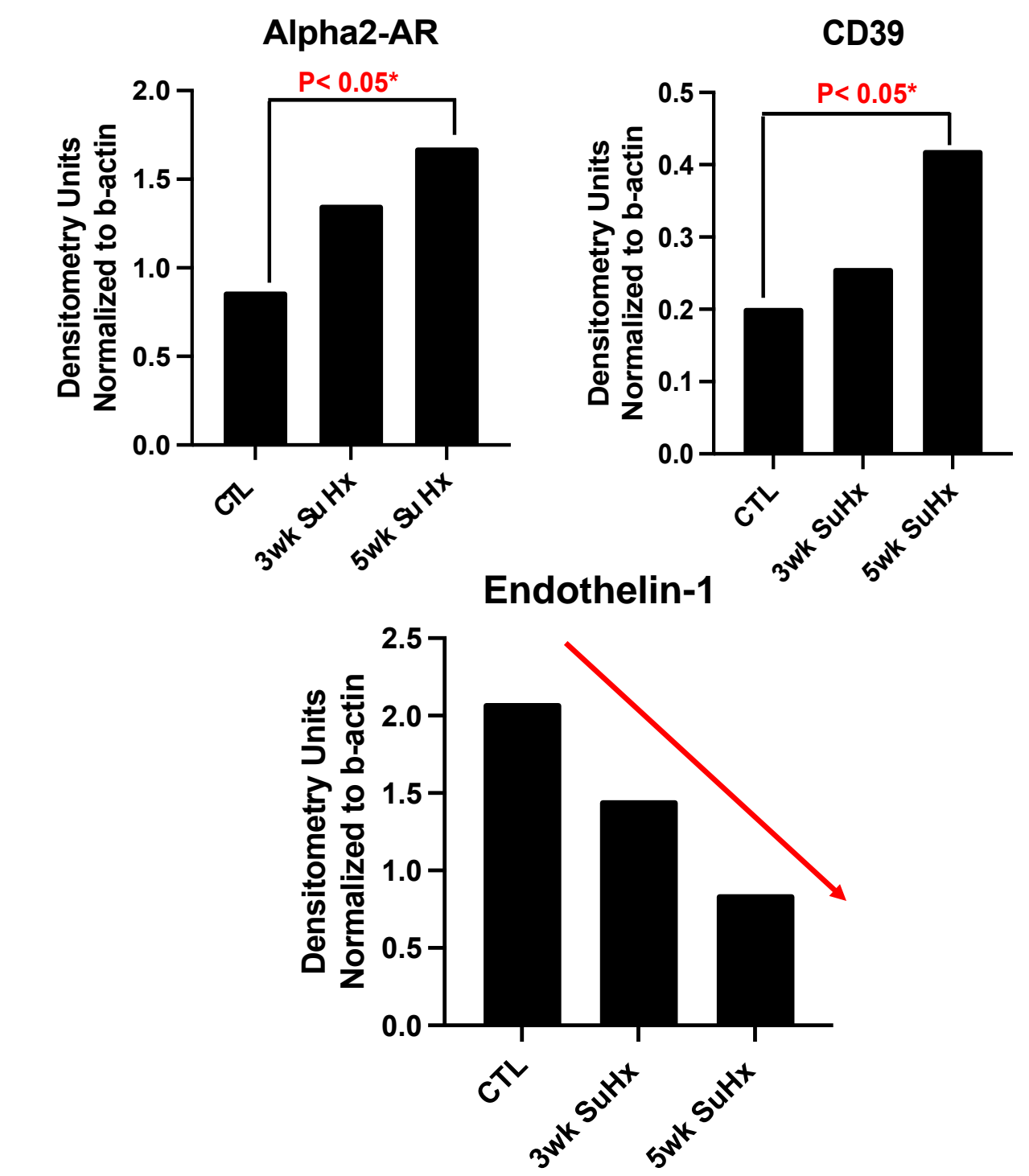


Experimental Neonatal PH Induces Intrapulmonary Right to Left Shunt Demonstrated by Ink Filled Bronchial Vessels



Results

Experimental Adult PH Induces BEC Signals that Mediate an Overall Vasorelaxation



Conclusion

- Neonatal and adult PH rats develop IRLS via pulmonary to bronchial circulation.
- BEC isolated from adult SuHx rats demonstrate signal inductions that promote vasorelaxation.

Speculation

Our findings support past human data of IBA recruitment in neonatal and adult PH patients and suggest that IRLS and BEC dysfunction may contribute to the pathobiology of PH.