

Presenting Author Name

Ahmed Al-Khaffaf

Phonetic spelling of your (full) name

AH-med al-khah-FAHF

Presenting Author Category

Masters Student

Supervisor Name

Shyamala Dakshinamurti

GBD Audio File

Ahmed recording.m4a

Headshot

IMG_3997.jpeg

Short Bio (100 words)

Ahmed Al-Khaffaf is an M.Sc. student in Physiology and Pathophysiology at the University of Manitoba, researching pulmonary artery smooth muscle cell dysfunction in persistent pulmonary hypertension of the newborn within the Dakshinamurti Lab at CHRIM. A trained physician with over five years of clinical experience, including delivering primary health care to internally displaced populations in Iraqi Kurdistan, Ahmed brings a unique blend of medical practice and research to his work. He is a Fellow of the President's Student Leadership Program (PSLP) at the U of M, dedicated to advancing leadership, youth mentorship, and science communication among students in the life sciences.

Research Category

Basic Science

Abstract Title

DIVING INTO LIFE: WHEN DO NEONATAL PULMONARY ARTERY MYOCYTES LOSE THEIR ABILITY TO ACCOMMODATE LOW OXYGEN?

Authors

Name	Role	Profession
Ahmed Al-Khaffaf	Presenting Author	Graduate
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Background

The diving reflex includes protection of human fetuses from hypoxia, through upregulating their antioxidant system to protect protein function. But in hypoxic newborns, oxidative-stress increases and the pulmonary vasculature fails to relax, causing persistent pulmonary hypertension of the newborn (PPHN). Up to 30% do not respond to first-line therapy with inhaled nitric oxide, suggesting impaired relaxation of pulmonary artery smooth muscle cells (PASMCs). We have shown that NO increases protein S-nitrosylation in hypoxic PASMCs, impairing Adenylyl Cyclase 6, and decreasing cAMP – causing vasoconstriction. One key regulator of S-nitrosylation is glutathione (GSH), which, besides its antioxidant function, denitrosylates proteins, forming GSNO in the process. We hypothesized that hypoxia (10% oxygen) depletes GSH in PASMCs after 72-hours, contributing to further cellular stress and vasoconstriction.

Objective

To determine when, during hypoxia, neonatal PASMCs lose their glutathione-based antioxidant defense.

Methods

3rd-6th generation pulmonary arteries microdissected from <24hr old piglet lungs; PASMCs cultured to confluence, and serum-deprived to synchronize in contractile phenotype. Hypoxic myocytes were exposed to 10%O₂ for 72 hours; normoxic controls remained in 21%O₂. GSH pathway mRNA or protein measured by qPCR or Western-Blot. GSH level and GSH/GSSG ratio determined using GSH/GSSG assay; GSH levels at serial timepoints measured using Thioltracker™. Data presented as mean±SEM.

Results

Glutamyl-cysteine ligase catalytic and modifier units(GCLC, GCLM), Glutathione Reductase(GSR), and Glutathione Peroxidase1(GPx1) mRNA abundance increased modestly in hypoxia while Glutathione Synthetase(GSS) decreased. GSR protein level significantly increased while GSNOR decreased. GSH gradually increased in hypoxia up to 48h after exposure but then decreased alongside GSH/GSSG ratio by 72h.

Conclusion

PASMCs initially responded to hypoxia through upregulating GSH synthesis and recycling machinery, producing more GSH to counter cellular stress. But somewhere between 48 and 72h of hypoxia, myocyte GSH stores significantly dropped, depriving them of their evolutionary protection and allowing unchecked S-nitrosylation, contributing to failure of pulmonary artery relaxation in PPHN.