ABSTRACT SUBMISSION FORM

LET'S TALK ABOUT

SEX + GENDER

Exploring the role of sex and gender on health research

CHRD
CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

Submitter Name
Matthew Martens

Email
marten22@myumanitoba.ca

Title
Protecting the Neonatal Heart: Misoprostol Prevents Hypoxia-Induced Cardiac Dysfunction and Cardiomyocyte Bioenergetic Collapse Through Bnip3 Phosphorylation

Background
Systemic hypoxia resulting from preterm birth, altered lung development, and cyanotic congenital heart disease impairs cardiomyocyte metabolism and negatively effects cardiac function. Although the mechanisms remain unknown, it is clear that hypoxia-induced expression of Bnip3, a mitochondrial-targeted death gene, plays a role. Emerging evidence suggests cardioprotective roles for both prostaglandin (PG) E1 signalling, and for Bnip3 inhibition through phosphorylation.

Objective
We hypothesize that the PGE1 analogue, misoprostol, activates these protective pathways to inhibit Bnip3-induced cardiac dysfunction and bioenergetic collapse in the hypoxic neonatal heart.

Methods
Using our mouse model of neonatal hypoxia we assessed cardiac function by echocardiography, and mitochondrial metabolism by gene expression array and biochemical analysis (n=8). To explore the underlying mechanism, we used rat primary neonatal cardiomyocytes (PVNCs), and Bnip3 knockout MEFs in combination with hypoxia (1% oxygen) and misoprostol drug treatments, analyzing mitochondrial function by extracellular flux analysis and epifluorescent imaging (n=4).

Results
Hypoxia-exposed mice demonstrated significant contractile dysfunction, including reduced ejection fraction and fractional shortening, both of which were restored to control levels with the addition of misoprostol ($p<0.01$). This dysfunction is concurrent with Bnip3 dephosphorylation and a significant downregulation of genes associated with mitochondrial respiration, which were all rescued by misoprostol. This resulted in hypoxia reducing ATP production while driving lactate production in the PND10 heart, both of which were also prevented with misoprostol treatment ($p<0.05$). In PVNCs we observed that hypoxia elevates

mitochondrial-fragmentation and ROS, while reducing mitochondrial membrane potential, which were restored to control levels with misoprostol treatment ($p<0.01$). Using the same endpoints in Bnip3 KO MEFs, we confirmed that hypoxia-induced mitochondrial dysfunction and the misoprostol-driven rescue directly hinge on Bnip3 being present in the cell.

Conclusion
Our results demonstrate that misoprostol prevents hypoxia-induced cardiac dysfunction and bioenergetic collapse through Bnip3 phosphorylation and inhibition, which represents a significant advancement in protecting the hypoxia-exposed neonatal heart.

Theme:
Basic Science

Do you have a table/figure to upload?
No

Are you willing to participate in Goodbear's Den?
Yes

Presenter Status:
PhD Student

What was your role in the project?
Design, Experimentations, Data Analysis and Abstract Writing

Authors

Name	Email	Role	Profession
Matthew D. Martens	marten22@myumanitoba.ca	Presenting Author	Graduate
Nivedita Seshadri	seshadrn@myumanitoba.ca	Co Author	Graduate
Donald Chapman	DChapman@chrim.ca	Co Author	Technician
Bo Xiang	Bo.Xiang@umanitoba.ca	Co Author	Technician
Spencer B. Gibson	Spencer.Gibson@umanitoba.ca	Co Author	Full Professor
Christine A. Doucette	CDoucette@chrim.ca	Co Author	Assitant Professor
Jason M. Karch	Jason.Karch@bcm.edu	Co Author	Assitant Professor
Vernon W. Dolinsky	Vernon.Dolinsky@umanitoba.ca	Co Author	Associate Professor
Adrian R. West	Adrian.West@umanitoba.ca	Co Author	Associate Professor
Christof Rampitsch	chris.rampitsch@agr.gc.	Co Author	Scientist

	ca		
Joseph W. Gordon	joseph.gordon@umanitoba.ca	Co Author	Associate Professor