ABSTRACT SUBMISSION FORM

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Exploring the role of sex and gender on health research

CHILD HEALTH RESEARCH DAYS

CHRD 2020: Abstract Submission Form

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Title
Oxidized Phosphatidylcholines Mediate Airway Narrowing by Inducing Airway Smooth Muscle Cell Contraction: Novel Mechanisms and Implications for Asthma

Background
Asthma is associated with airway narrowing and airflow limitation, which affect nearly 1-in-10 Canadian child. Oxidative stress, a feature of asthma, causes lipid peroxidation in lung which leads to formation of pro-inflammatory oxidized phosphatidylcholines (OxPCs). We have reported that in parallel with emergence of airway hyperresponsiveness, OxPCs accumulate in the lungs of mice and humans after inhaled allergen challenge.

Objective
We test the hypothesis that OxPCs induce airway narrowing by increasing cytosolic concentration of Ca2+ ([Ca2+]i) in human airway smooth muscle (HASM) cells.

Methods
We used murine thin-cut-lung-slices (TCLS) and phase-contrast video microscopy to assess airway narrowing. Changes in [Ca2+]i in cultured HASM cells were measured by Fura-2 fluorescent microscopy. Changes in airway lumen area of TCLS or [Ca2+]i in HASM cells were assessed after OxPCs exposure (10-80 µg/mL). To decipher the source of [Ca2+]i in HASM cells, responses to OxPCs were measured in the presence and absence of extracellular Ca2+, and after pre-exposure to xestospongine (5 µM, IP-3 channel antagonist), or ryanodine channel inhibitors (ryanodine-100 µM, and caffeine-25 mM).

Results
In TCLS, OxPCs dose dependently induced airway narrowing (e.g. 15% at 80 µg/mL, Figure 1). In HASM cells, OxPCs dose dependently induced a rapid rise to peak [Ca2+]i (e.g. 200.8 ± 28.7 nM at 80 µg/mL, OxPCs), as well as later repeated [Ca2+]i flux in some cells (81% of cells at 80 µg/mL OxPCs). Removing extracellular Ca2+ did not affect OxPC-induced peak [Ca2+]i, but did eliminate OxPCs-induced repeated Ca2+ waves. Notably, ryanodine receptor inhibition significantly reduced OxPCs-induced [Ca2+]i peak and

waves, whereas IP3 receptor inhibition was without effect.

Conclusion
These are the first data showing that asthma-associated OxPCs directly induce airway narrowing, likely via a mechanism involving rapid ryanodine receptor mediated [Ca2+]i release, as well as later influx of extracellular Ca2+. This suggests that OxPCs could directly promote airway responsiveness associated with asthma.

Theme:
Basic Science

Do you have a table/figure to upload?
Yes

Untitled
Figure 1.0.pdf

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

Presenter Status:
PhD Student

What was your role in the project?
Design, Perform Experiments, Analyze Data, Write Abstract

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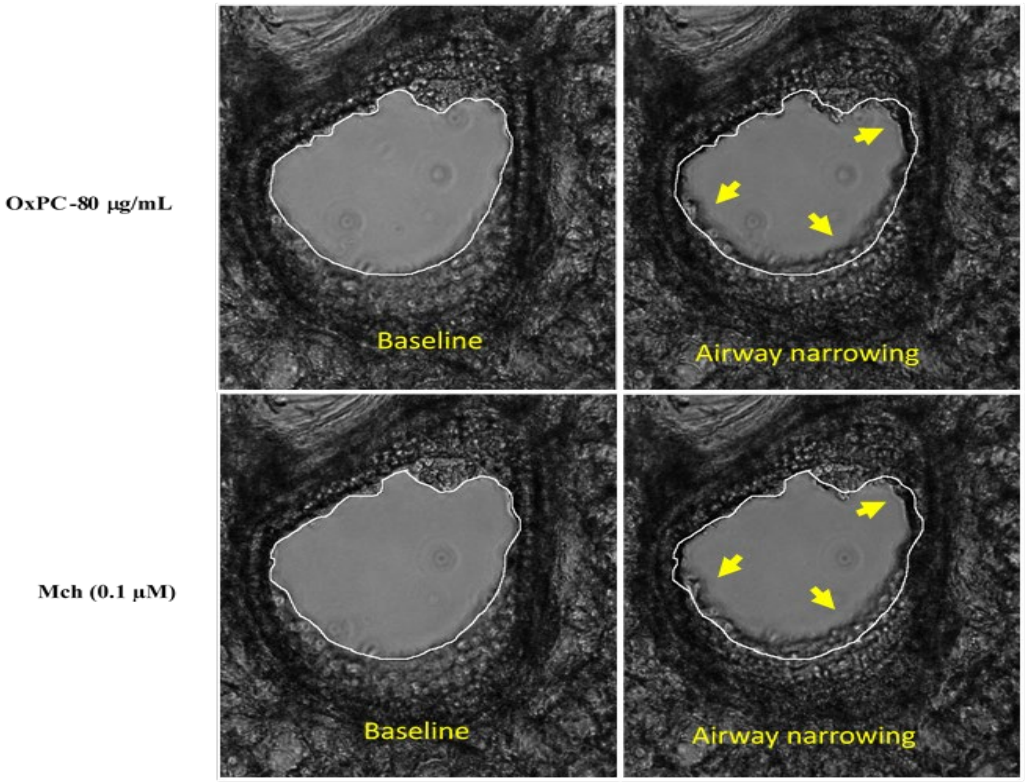
Figure 1


OxPC-80 µg/mL
Baseline
Airway narrowing
Mch (0.1 µM)
Baseline
Airway narrowing