CYCLING, AIR POLLUTION AND HEALTH: Oxidative Stress as a Mediator of Systemic Inflammation

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OBJECTIVES

1. **To determine the potential consequences of air pollution exposure in healthy cyclists**
2. **To investigate the role of systemic inflammation and oxidative stress as a mediator of these effects**

HYPOTHESIS

Short-term cycling along a route with higher traffic-related air pollution will result in observed systemic inflammatory effects compared to cycling along a route with lower levels of pollution. These observed effects will be mediated by oxidative stress.

INTRODUCTION

- Cycling is promoted as a healthy transportation choice, but by sharing roads with automobiles, cyclists may be exposed to elevated levels of air pollution.
- Traffic-related air pollution is linked to systemic inflammation, which can lead to cardiovascular morbidity and mortality.
- It has been hypothesized that this inflammation results from oxidative stress, characterized by a pulmonary imbalance of reactive oxygen species [ROS].
- Few air pollution studies have examined inflammation and oxidative stress simultaneously especially in healthy individuals.
- This information will help the development of healthy cycling infrastructure and will add to the understanding of the biological mechanisms by which air pollution may adversely impact human health.

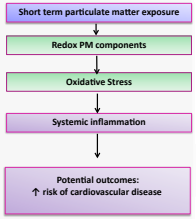


Figure 1: Hypothesized mechanism by which air pollution may induce systemic inflammation. Chemical species particle surfaces deposit on lung-lining and produce high levels of reactive oxygen species [ROS] that overwhelm antioxidant capacity. ROS activate signalling cascades in nearby cells to produce inflammatory molecules that enter the systemic circulation.

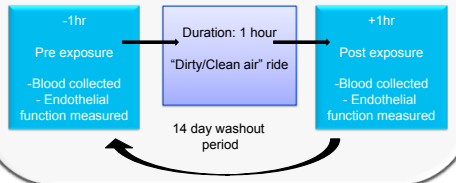
METHODS

Figure 2: Air pollution monitors on the study bicycle measured PM exposures along each route.

Study design:

- 38 healthy cyclists (ages 19-39)
- Randomized crossover study: 1 hr cycling on two routes (separated by 14 days) with differing levels of traffic-related air pollution (Figure 3).
- Each ride was separated by at least 14 days.
- Systemic inflammatory (CRP, IL-6 and endothelial dysfunction) and oxidative stress (8-OHdG) markers were measured before and after each ride.

Figure 3: Study design.



Measures

Table 1: Summary of systemic inflammation and oxidative stress markers.

Systemic Inflammation markers	
Interleukin-6 [IL-6] (Quantikine, R&D Systems)	Pro-inflammatory molecule (cytokine) involved in the onset of fever, white blood cell differentiation, and production of other cytokines.
Endothelial dysfunction (as measured by Reactive Hyperemia Index, EndoPat, Itamar Medical, ltd.).	The inability of the cell wall to vaso -dilate or -constrict, result from induction of systemic inflammation. Predictor of risk of cardiovascular disease.
C-Reactive Protein [CRP] (CardioPhase hsCRP, Siemens Healthcare Diagnostics Inc.)	Acute phase protein produced by liver in response to IL-6. Particularly toxic in that it aggressively targets damaged tissues for phagocytosis leading to damage of tissue and endothelial cells.
Oxidative Stress marker	
8-hydroxy-2'-deoxyguanosine [8-OHdG] (Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan)	Reactive oxygen species from oxidative stress are able to cause DNA damage. 8-OHdG is the product of the interactions between the hydroxyl radical (OH·) and nucleobase guanine. To prevent incorrect base pairing, DNA repair mechanisms including nucleotide excision is initiated, and 8-OHdG (with no further metabolism) is injected into serum and then excreted in urine. It can therefore be studied in vivo in human models.

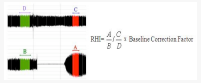


Figure 4: Assessment of endothelial dysfunction by Reactive Hyperemia Index [RHI]. EndoPat examines the ability of the endothelium to vasodilate the vascular smooth muscle cells in response to an increase in blood flow (known as hyperemia) after an occlusion of the blood vessel. Peripheral arterial tone is measured using arterial pulsatile volume changes. **Lower mean amplitude:** ¦ RHI (Below 1.68 → indication of endothelial dysfunction). **High mean amplitude**: ↑ RHI (Normal = 1.68-2).

Route design

The lower traffic ("clean") route was along the residential roads in Metro Vancouver, while the higher traffic ("dirty") route went through the Downtown core of Vancouver. Air pollution monitors on the subject's bicycle measured particulate matter <10, 2.5, and 1 microns, and ultrafine particle counts.

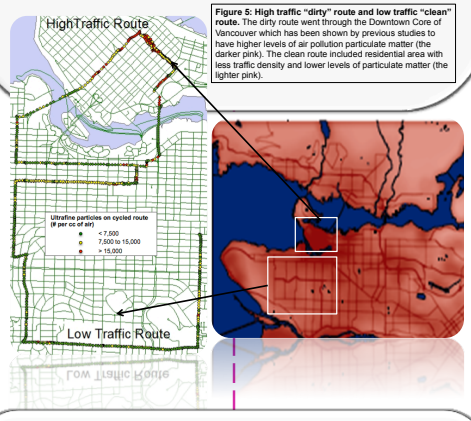


Figure 5: High traffic "dirty" route and low traffic "clean" route. The dirty route went through the Downtown Core of Vancouver which has been shown by previous studies to have higher levels of air pollution particulate matter (the darker pink). The clean route included residential area with less traffic density and lower levels of particulate matter (the lighter pink).

RESULTS

Measure	Mean Post-Pre "clean" route change (SD)	Mean Post-Pre "dirty" route change (SD)	Mean difference ("dirty" route change-"clean" route change) [95% CI]
RHI	0.25 [0.63] *	-0.18 [0.86]*	**-0.38 [-0.74,-0.02]***
IL-6 (pg/ml)	-0.45 [3.54] *	0.54 [3.30]*	0.95[-0.98,2.89]*
CRP (mg/dL)	0.01 [0.11]	0.01 [0.06]*	0.00 [-0.04, 0.05]
8-OHdG (ng/ml)	-0.02 [0.11] *	0.00 [0.11]	0.02 [-0.03,0.07]*

Table 2: Results of analysis of measurements summarized below. Post-pre differences refer to the magnitude of change from one hour before the ride to one hour after. Differences were compared by route type and by ultrafine particle levels (the route with the highest levels labelled as "high" and the route with the lowest levels were labelled as "low"). (*) indicates those measures that are in the hypothesized direction, and bolded measures indicate the markers that are statistically significant. (n=38).

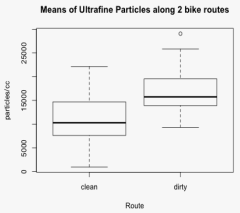
RESULTS

DIRTY ROUTE Correlation	CRP	IL-6	8-OHdG	RHI
CRP	x			
IL6	0.47*	x		
8OHdG	0.18	0.13	x	
RHI	0.13	0.19	-0.13	x
CLEAN ROUTE Correlation	**CRP**	**IL6**	**8OHdG**	RHI
CRP	x			
IL6	-0.01	x		
8OHdG	0.15	0.07	x	
RHI	-0.24	-0.19	-0.26	x

Table 3: Pearson Product-Moment Correlation coefficients for the post-pre changes between all markers (CRP, IL-6, 8-OHdG and RHI) for the higher "dirty" traffic route and the lower "clean" traffic route. (*) indicates values that are statistically significant (p<0.05).

RESULTS

- Mean ultrafine particle levels 56% higher on high vs low traffic route
- Endothelial function decreased in cyclists riding along the high vs low traffic route
- Small increase in IL-6 levels after riding along the high traffic route
- No change in CRP levels observed between routes.
- Slight increase in change of 8-OHdG levels for high vs low traffic route.
- Little correlation was seen between 8-OHdG and markers of systemic inflammation (p>0.05).



Overall, route type affected RHI, to a lesser degree IL-6 and 8-OHdG in the hypothesized directions, but did not affect change in CRP.

Figure 7: Ultrafine particle [UFP] (particulate matter size <0.1 µm) levels present on the clean and dirty routes. Mean particles/cubic centimeter (cc) on the dirty route [sd] = 14007.26 particles/cc [4319.27]. Mean clean UFP [sd] = 8976.23 particles/cc [5562.66]. Mean Difference for dirty-clean [95% Confidence interval] = 5031.03 particles/cc [2523.83, 7538.24]. (n=38)

CONCLUSIONS

These measurements suggest that cycling in regions of relatively increased traffic density may have an acute adverse effect on endothelial function but whether or not this is mediated through classical pathways of inflammation and oxidative stress remains unclear.

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ACKNOWLEDGMENTS

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Website: http://cyclinginicities.spph.ubc.ca/air-pollution/