Heart Rate Variability Following Controlled Exposure to Particles and Ozone in Asthma

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Introduction

- Heart rate variability (HRV) describes normal beat-to-beat variations in heart rate that occur in response to changes in respiration and blood pressure.
- Decreased HRV has been shown to correlate well with increased risk of cardiovascular morbidity and mortality.
- Increased particulate and ozone air pollution is also associated with increased cardiovascular morbidity and mortality.
- In previous studies, ambient air particles, concentrated air particles (CAPS), and ambient ozone have been associated with decreased HRV.

Introduction

- HRV may serve both as an indicator for the increased risk of morbidity and as a potential mechanistic link between particle exposure and cardiovascular mortality.
- The physiological mechanism underlying the pollution effect on HRV is unknown, but may involve elevation of systemic inflammatory mediators or activation of pulmonary irritant receptors that mediate stimulation of neurogenic pathways.
- Therefore, it was hypothesized that inhalation of an air pollutant known to induce airway inflammation and activate neurogenic pathways, ozone, would decrease HRV to a greater extent than generated particles known to cause little airway inflammation.

HRV Definitions: Time Domain

- **SDNN:** Standard deviation of all NN intervals. Estimate of overall HRV.
- **SDANN**: Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording. Estimate of long-term components of HRV.
- **SDNN Index:** Mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording. Estimate of short-term components of HRV.
- **r-MSSD:** The square root of the mean of the sum of the squares of differences between adjacent NN intervals. Estimate of short-term components of HRV (reflects Vagal tone).

HRV Definitions: Frequency Domain

- **Total Power:** The variance of NN intervals over the entire 5-min segment as determined by power spectral density analysis.
- **VLF:** Power in the very low frequency range (<0.04Hz). The physiologic significance is unclear.
- **LF:** Power in the low frequency range (0.04-0.15Hz). Represents both sympathetic and parasympathetic modulation.
- **HF:** Power in the high frequency range (0.15-0.4Hz). Indicates parasympathetic (vagal) influence on heart rate.
- **LF/HF:** Ratio of LF to HF. Increases with standing or with increased sympathetic tone.

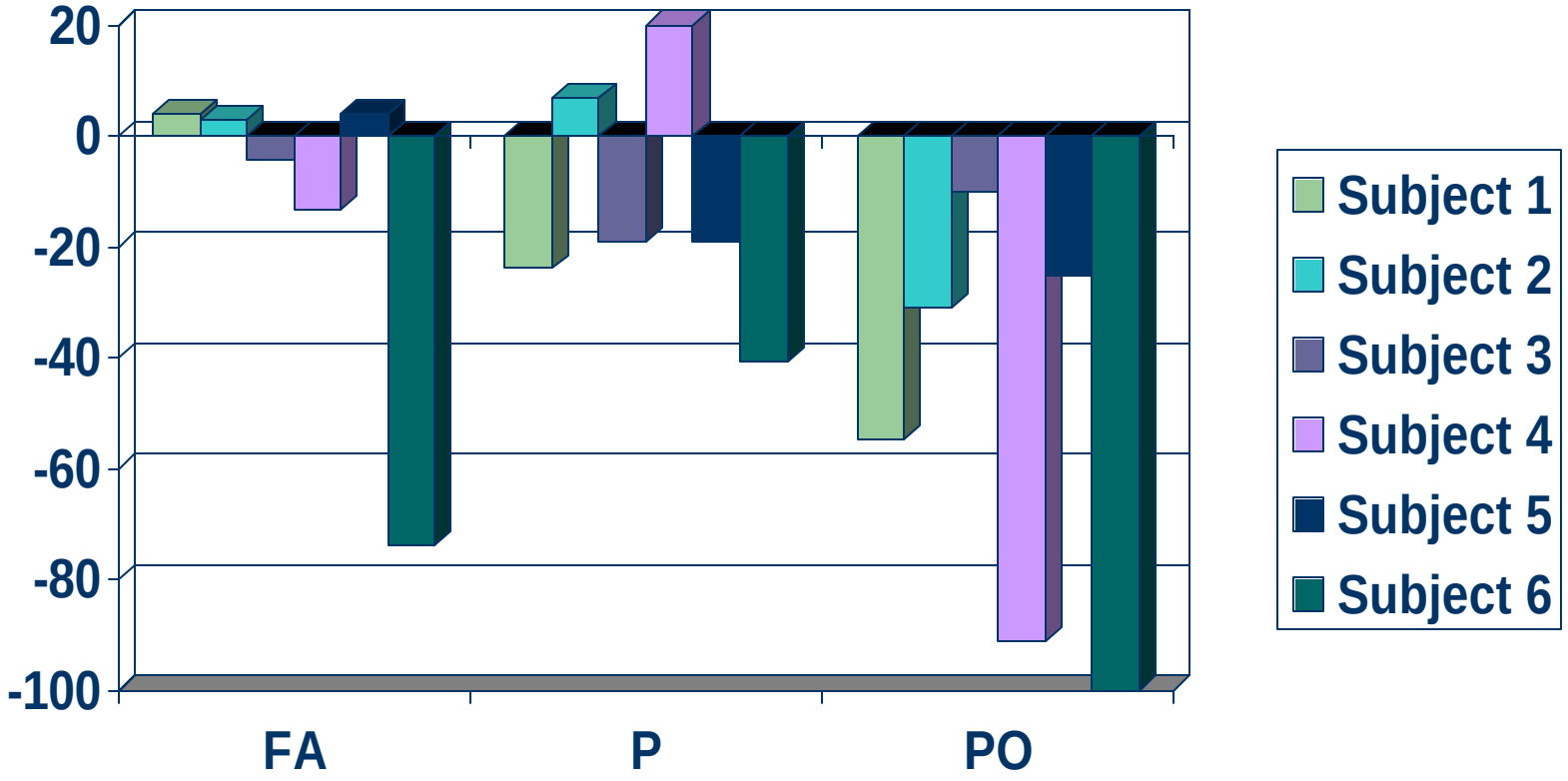
Methods

- Electrocardiogram (ECG) Holter monitoring was performed for 20 min before (pre), and during the final 20 min of (post), each exposure.
- For each 20-min ECG, the subject lay supine for 5 min, stood for 5 min, lay supine again for 5 min, then took 20 slow respirations (modified “Gold” protocol). Frequency domain variables were obtained from two 5-min segments of the ECG, the first supine, and the second standing.
- All ECGs were scanned and edited for mislabeled beats by a single investigator, Dr. Power.
- The HRV analysis was performed using the manufactures’ computer software (Forest Medical: Trillium 3000 Holter monitor).

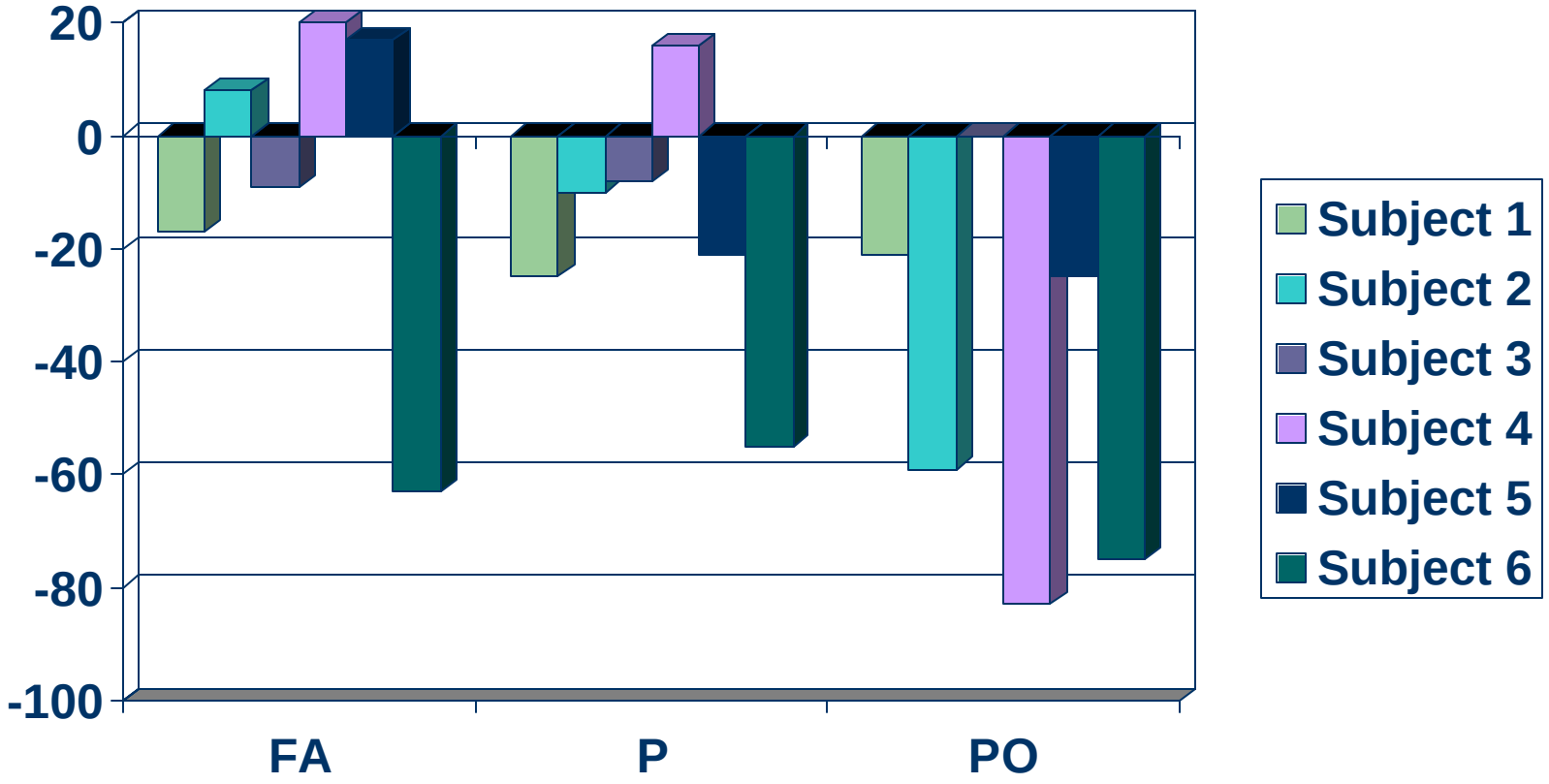
Methods

- In the HRV analysis, only normal beats were used. Artifacts, ectopy (both supraventricular and ventricular), and uninterpretable complexes were not considered for analysis.
- Beat-to-beat intervals whose duration was <80% or >120% of that of the running R-R average were excluded to eliminate intervals related to premature supraventricular complexes.
- Four time-domain variables (SDNN, SDANN, SDNN Index, RMSSD) and five frequency-domain variables (Total Power, VLF, LF, HF, LF/HF) were compared before and after each exposure to determine change in HRV across the exposure (Delta HRV).
- Statistical comparisons used the Wilcoxon Signed-Rank test on group Medians.

Delta SDNN across Exposures



Delta SDANN across Exposures



Delta Means for Exposures

Time Domain Variables

	FA	P	PO
SDNN	-13.3*	-12.7	-52*
SDANN	-7.3	-17.2	-43.8
SDNNI	-9.8*	-3.5	-29.7*
RMSSD	-9	-4.2	-21.5

Delta Means for Exposures

Supine Frequency Domain Variable

	FA	P	PO
Total	-559	346.5	-2835.3
VLF	-313	533.3	-1962
LF	-82.7	-192.5	-480.5
HF	-163.3	12.5*	-392.8*
LF/HF	0.26	-0.75	4.52

Delta Means for Exposures
Standing Frequency Domain Variable

	FA	P	PO
Total	-1453.5	785*	-2960*
VLF	-1277.7	1400.5*	-2033.2*
LF	-39.2	-560.7	-769
HF	-136.8	-55.3	-157.7
LF/HF	1.47	-1.41	0.84

Results

- SDNN post-PO was significantly lower than SDNN post-FA and pre-PO.
- SDNNi post-PO was significantly lower than post-FA.
- There was a significantly larger decrease in Delta SDNN and SDNNi across PO than across FA.
- r-MSSD post-PO was significantly lower than post-FA.
- When supine, LF post-P and post-PO was significantly lower than post-FA, and LF post-PO was significantly lower than pre-PO.
- When supine, LF/HF post-PO was significantly higher than post-P.

Results

- When supine, HF post-PO was significantly lower than post-FA, post-P and pre-PO, and there was a significantly larger decrease in Delta HF across PO than across P.
- When standing, Total Power post-PO was significantly lower than post-FA, and there was a significantly larger decrease in Delta Total Power across PO than across P.
- When standing, there was a significantly larger decrease in Delta VLF across PO than across P.
- When standing, HF post-PO was significantly lower than post-FA and pre-PO.

Discussion

- As hypothesized, exposure to PO combined had a greater effect on HRV than exposure to P alone. The magnitude of effect was similar to that found in previous studies.
- One study demonstrated a 25-msec decline in both SDNN and r-MSSD with a 100$\mu g/m^3$ increase in ambient particle concentration, and 5.5-msec and 11-msec reductions in r-MSSD with 25% increases in ambient ozone, and ozone and particles combined, respectively. (Gold *et al*, 2000).
- Another study showed an 18-msec decrease in SDNN with a 100 $\mu g/m^3$ increase in PM10 (Pope *et al,* 1999).
- A study of 13 hypertensive patients showed a 2.0% reduction in HRV for every 10 ppb increase in 1-hour ozone; this effect was not seen in non-hypertensives (Holguin *et al*, 2003).

Discussion

- The magnitude of effect found with PO exposure (Delta HRV = -52) in this study may be clinically relevant.
- In a study of CHF patients, a RR = 1.62 (95% CI, 1.16 to 2.44) with a decrease in SDNN of 41.2ms and annual mortality rates of 5.5% for SDNN>100ms, 12.7% for SDNN 50-100ms, and 51.4% for SDNN<50ms, was reported (Nolan *et al,* 1998).
- In a study of recent MI patients who had an SDNN<50ms, the RR for cardiac mortality was 2.94 (p=0.03) (Lanza *et al,* 1999).
- The risk for sudden death, mortality from CAD, and all-cause mortality in men with SDNN <20ms, compared with men with SDNN of 20-39ms was 2.1 (95% CI, 1.4 to 3.0) (Dekker *et al,* 1997).

Discussion

- Our inability to show a significant decrease in HRV with P exposure could be attributed to poor power or to the bland nature of the generated carbon and ammonium nitrate particles.
- The primary limitation of this study was the lack of respiratory monitoring during ECG monitoring. However, in previous studies designed to investigate the impact of respiratory pattern on PM effects on HRV, the association between PM and r-MSSD did not diminish after controlling for respiratory rate.

Discussion: Future Directions

- Future studies are needed to investigate the physiologic link between ozone inhalation and HRV changes through measurement of respiratory pattern, inflammatory mediators, endothelins, and renin-angiotensin system proteins.
- Future studies are needed to investigate the effect of other important pollutants; such as NO_2, SO_2, on HRV. A recent study demonstrated decreased HRV with ambient NO_2, SO_2, as well as P and O exposure (Liao, *et al*., 2003).
- Potentially susceptible populations; the elderly, hypertensives, or persons with pre-existing cardiac disease, should also be studied.