Preliminary Assessment of Human Biological Responses to Low-level Ozone

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***Abstract*—Multi-modal wearable sensors monitoring physiology and environment simultaneously would offer a great promise to manage respiratory health, especially for asthmatic patients. In this study, we present a preliminary investigation of the correlation between ozone exposure, heart rate, heart rate variability, and lung function. As the first step, we tested the effect of low-level ozone exposure in a sample size of four healthy individuals. Test subjects underwent controlled exposure from 0.06 to 0.08 ppm of ozone and filtered air on two separate exposure days. Our results indicate an increment in mean heart rate in three out of four test subjects when exposed to ozone. We have also observed that changes in mean heart rate has a positive correlation with changes in lung function and a negative correlation with changes in neutrophil count. These results provide a baseline understanding of healthy subjects as a control group.**

***Index Terms*—asthma, ECG, ozone exposure, SQI, wearables**

I. Introduction

Ozone (O_3) is a common trigger for asthma attacks and promotes lung inflammation. Studies suggest that O_3 exposure at levels even below the US National Ambient Air Quality Standards (NAAQS) of 0.07 parts per million (ppm) can decrease lung function and increase respiratory symptoms in susceptible populations such as individuals with asthma [1], [2]. An estimated 19 million adults and 6 million children are currently living with asthma in the US, resulting in millions of physician's office or emergency room visits to resolve asthma exacerbations [3]. Annual health care spending on uncontrolled asthma in the US alone was over 82 billion dollars in 2013 [4], making it one of the most expensive chronic health conditions. Therefore, there is an urgent need for an improved and cost-effective approach to improve asthma control.

The National Science Foundation Engineering Research Center for Advanced Self-Powered Systems of Integrated Sensors and Technologies (ASSIST) at NC State University is working towards developing multi-modal, wearable systems for vigilant monitoring of physiological and environmental conditions of an individual with the goal of improving health outcomes [5], [6]. Wearable low-power systems can assess environmental conditions locally with higher spatial and temporal resolutions in contrast to more global and averaged weather station readings available online. These real-time environmental measurements correlated with physiological parameters could be used to identify changes in a user's physiologic conditions and can be used to predict asthma exacerbations through advanced data analytics. The benefits of such wearable monitoring devices can be extended beyond the quality of life of asthmatic patients and would positively impact the economy and healthcare practices in general.

This paper presents the preliminary testing results of a group of four healthy test subjects. We collected heart rate variability (HRV) data and biological samples to understand the correlation of these with exposure to O_3 and its impact on lung function.

II. Study Protocol

We conducted a randomized, double blinded, crossover pilot study to investigate if low level O_3 exposure (compared to a clean air exposure) under sedentary conditions will cause measurable changes in lung function and in airway inflammation. We recruited healthy non-smoking volunteers 18-50 years of age without asthma. Written consent was obtained from all participants, and the study was approved by the University of North Carolina at Chapel Hill IRB. An IRB Authorization Agreement was set up with NC State University.

Subjects were exposed to either filtered clean air or O_3 for 6.6 hours at 24°C ± 1.1°C and 40% RH ± 5% RH in an environmental chamber. For the O_3 exposure sessions, the concentration started at 0.06 ppm, increased to 0.08 ppm in 30 minutes, and then decreased back to 0.06 ppm in the next 30 minutes. This pattern was repeated throughout the entire exposure session for an average overall O_3 concentration of 0.07 ppm, corresponding to NAAQS for ground level O_3 on a summer day. The subjects rested on a chair during the exposure sessions. They were only permitted to walk intermittently on a treadmill at a pace mild enough to not cause any abrupt changes to the HRV or respiratory rate. Electrocardiography (ECG) was recorded using an off-the-shelf wearable ECG sensor – Shimmer3 (from Shimmer) – and calculated HRV was used to assess the response during the O3 and air exposures. Participants underwent spirometry based lung function testing before and after exposure sessions. Neutrophil recruitment to sputum was assessed at baseline and 24 hours after each exposure session as a marker of airway inflammation. Subjects were scheduled for a second exposure after a washout period of a minimum of 2 weeks or maximum of 6 months from the first exposure session.

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III. Data Analysis Methodology for ECG

Signal Quality Index. It is essential to determine what data is reliable enough to extract relevant features for analysis. In particular, for ECG signals, a number of artifacts could be present ranging from electrical noise to motion artifacts and muscle activation. For this purpose, we made use of a *Signal Quality Index* (SQI) providing a normalized value between 0 and 1 to capture the detection consistency of heart beats from multiple detectors. SQI is scored lower when the beat detectors disagree and vice versa. Fig. 1 illustrates an example of ECG signals and the SQI values. The beat detector tools used are *jqrs*, a modified version of the Pan Tompkins algorithm [7], and *wqrs*, a QRS detector based on the length transform [8]. The Cardiovascular System toolbox in MATLAB was used to compute RR intervals and signal quality [9].

We computed SQI using a 20 s window with a 5 s overlap and a 0.1 s buffer. We computed RR with a high threshold of 1.5 s and a lower threshold of 0.375 s. Consecutive beats that differed more than the recommended 15% were removed.

Wavelet-Based Signal Processing. To determine the initial ECG QRS locations, we removed the noise components from the signal via the Pan Tompkins algorithm. We removed any RR intervals consisting of a heart rate (HR) greater than 180 bpm, maximum HR at which session would be halted. The minimum RR interval corresponded to an HR of 40 bpm, commonly used as a lower threshold for healthy participants [10].

This initial pre-processing created our baseline signal which we further processed using SQI and wavelet based cleaning. SQI was then recalculated subsequently. We would like to highlight the use of SQI in two different ways here. The first is by removing any data under a signal quality threshold τ. We refer to this process as *SQI Removal* and applied to both the raw and wavelet-based cleaned signals. The second way is to determine when to use the wavelet packet decomposition of the signal to clean the segments of the waveform with an SQI threshold less than τ. A second hand picked minimum SQI threshold ρ was used to specify when a signal's SQI was too low for processing. We observed that cleaning signals with too low of an SQI did not give any improvements. The MATLAB functions *wdenoise* and *modwpt* were used with a total of 10 levels to ensure proper frequency resolution of the ECG signal when decomposed. The wavelet *fk18*, was used with the Universal Threshold method. The noise estimate was set to be level dependent. The described method aggressively removed any components of the signal that were not QRS peaks. The SQI was computed again on the new signal. Any segments in the signal that did not show improvement in SQI were reverted to its pre-processed state. ρ was set to 0.3 empirically. To determine τ, two hour segments of the data were manually annotated as 'good' or 'bad' and the ROC was graphed against a range of possible τ. The value $\tau = 0.95$ returned the lowest false positive rate of approximately 0.08 and and a true positive rate 0.88.

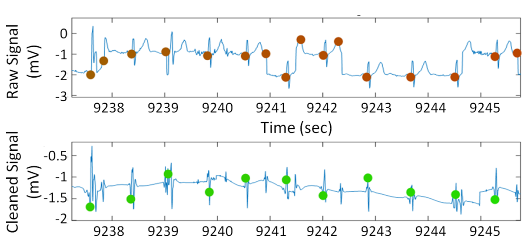

Fig. 1. Illustration of SQI. Raw ECG signal [Top] and Cleaned ECG signal [Bottom]. Each dot illustrates the locations where a QRS complex is detected, and its color ranging from green (high SQI) to red (low SQI) indicate the signal quality. The raw signal has false detection and low SQI.

Computing HRV. HRV indexes summarize statistics from the detected adjacent RR intervals. As described earlier, we removed certain QRS detection (and their adjacent RR-intervals) based on our SQI removal procedure. The HRV statistics were computed over a 5 minute window, as it is often done in the literature [11].

When computing the HR and HRV over a window, we only reported the value if the RR intervals removed cover less than 50% of the window. Fig. 2 illustrates a HRV feature extracted for the raw and cleaned ECG signals and their corresponding τ-SQI filtered results including the percentages of RR-intervals removed.

IV. Results and Discussion

A. Lung Function

Data are shown from four healthy individuals (two men and two women) (Fig. 3). Low level O_3 exposure under sedentary conditions provoked a decrease in lung function, namely Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 s (FEV1), that was more pronounced in the women than the men. We also found an elevated airway inflammatory response, with greater %neutrophils (%PMNs) in the sputum after O_3 exposure compared to filtered air exposure. Collectively, these data indicate that exposure to O_3 at 0.07 ppm can lead to reductions in lung function and relative increases in lower airway inflammation. Hence, O_3 exposure at accepted standard levels may lead to adverse respiratory effects in individuals with underlying lung conditions such as asthma.

B. Continuous Monitoring of ECG

Fraction of Data Removed. The Wavelet-based processing of the signals reduced the fraction of data removed from each session (Fig. 4). On average, the fraction removed for the raw signal after SQI filtering was 44%, and for the cleaned signal was 33%. This indicates an overall reduction of 26% on the amount of data removed through this filtering.

Patterns on HRV. We computed several HRV indexes from the raw data with and without SQI removal, and the cleaned data with SQI removal. All features except for *pNNa50* were calculated for 5 minute windows. The features extracted were the mean of the heart rate (*meanHR*), the standard deviation of the differences between adjacent NN intervals (*mean-sdsd*), the standard deviation of NN intervals for each window (*mean-nnstd*), the mean of the root mean squared adjacent NN

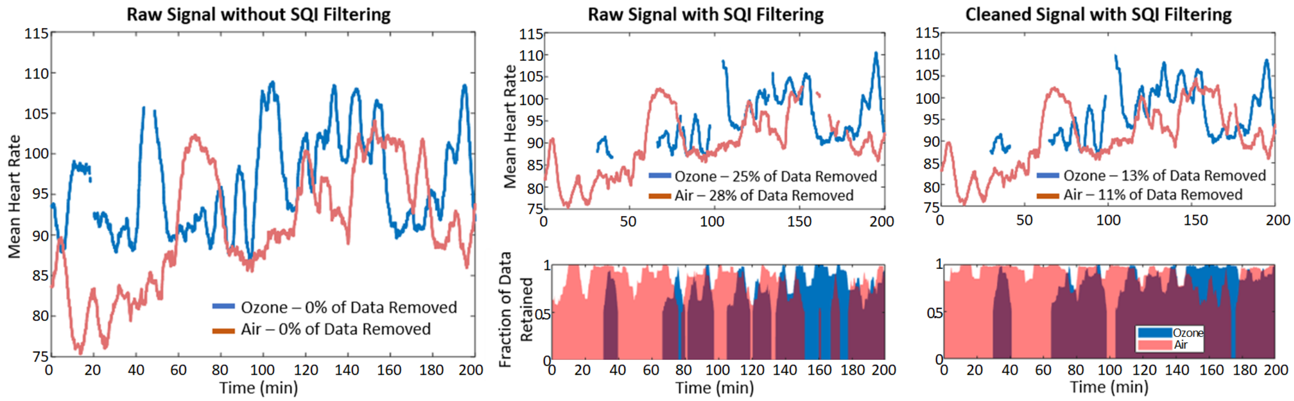

Fig. 2. Processing of SQI removal for raw and cleaned signal (representative data). The raw signal without any SQI removal (left), the raw signal with SQI removal (middle), and the cleaned signal with SQI removal (right). On the bottom, we observe the fraction of data retained on each window.

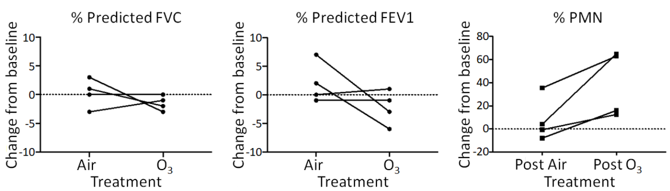

Fig. 3. Lung function and airway inflammation results. Healthy volunteers (n=4) experienced drops in Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second (FEV1), and increased airway inflamation (%PMNs) with low level O_3 exposure under sedentary conditions.

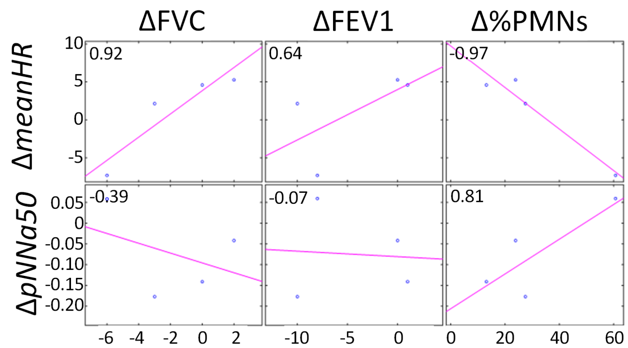

Fig. 5. Correlation between changes in HRV and lung function.

intervals (*mean-rmssd*), the standard deviation of the mean NN intervals (*mean-sdann*), the mean of the standard deviation of the standard deviations (*mean-sdnni*), and the percent of total NN intervals greater than 50 ms (*pNNa50*) [11]. Table I shows the results for *meanHR* and *pNNa50* from the raw and cleaned signals after SQI removal for which we had three subjects with similar trends on their response. We did not include the results from the raw signal without SQI removal since those results included errors in the R-peak detection.

Comparing HRV to Lung Function. We computed the correlation between the changes in HRV and lung function. We focused on the HRV features extracted using the cleaned signal after SQI removal. The changes in *meanHR* (Fig. 5) seems to have a positive correlation with changes in *FVC* and negative correlation with changes in *%PMN*. In contrast, *pNNa50* seems to have a positive correlation with *%PMNs*. A larger study is needed to properly justify these relationships due to the smaller sample size.

V. Conclusion

This work presents a preliminary assessment towards understanding the effect of low dose ozone on healthy individuals. Following this initial study on the control group, additional data analysis with a larger sample size and a follow up study with mild asthmatics are currently in progress with wearable devices developed by the ASSIST Center. The outcome of this work and the study in progress would enable appropriate asthma care and management through vigilant health monitoring and relevant data analytics.

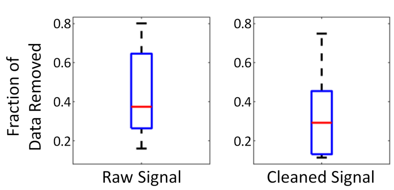

Fig. 4. Fraction of data removed per session after SQI filtering. We compared the results of the raw signal and the cleaned signal after Wavelet processing.

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TABLE I
ECG Results for Subjects after SQI Removal and Cleaned Wavelet Processed Signal

Subject	Signal	meanHR			pnna50		
		Ozone	Air	Change	Ozone	Air	Change
1	Raw	63.1	58.5	8%	0.035	0.045	-22%
	Cleaned	64.6	59.4	9%	0.043	0.085	-49%
2	Raw	93.0	88.1	6%	0.014	0.117	-88%
	Cleaned	93.8	89.2	5%	0.020	0.161	-88%
3	Raw	63.7	72.2	-12%	0.120	0.074	63%
	Cleaned	64.8	72.2	-10%	0.141	0.082	73%
4	Raw	64.3	63.2	2%	0.077	0.263	-71%
	Cleaned	65.1	63.0	3%	0.103	0.280	-63%

REFERENCES

[1] A. J. Burbank, A. K. Sood, M. J. Kesic, D. B. Peden, and M. L. Hernandez, “Environmental determinants of allergy and asthma in early life,” *Journal of Allergy and Clinical Immunology*, vol. 140, no. 1, pp. 1–12, 2017.

[2] M. L. Hernandez, R. Dhingra, A. J. Burbank, K. Todorich, C. E. Loughlin, M. Frye, K. Duncan, C. Robinette, K. Mills, R. B. Devlin *et al.*, “Low-level ozone has both respiratory and systemic effects in african american adolescents with asthma despite asthma controller therapy,” *Journal of Allergy and Clinical Immunology*, vol. 142, no. 6, pp. 1974–1977, 2018.

[3] Centers for Disease Control and Prevention. (accessed: 01.20.2020) Most recent national asthma data. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm.

[4] T. Nurmagambetov, R. Kuwahara, and P. Garbe, “The economic burden of asthma in the united states, 2008–2013,” *Annals of the American Thoracic Society*, vol. 15, no. 3, pp. 348–356, 2018.

[5] J. Dieffenderfer, H. Goodell, S. Mills, M. McKnight, S. Yao, F. Lin, E. Beppler, B. Bent, B. Lee, V. Misra *et al.*, “Low-power wearable systems for continuous monitoring of environment and health for chronic respiratory disease,” *IEEE journal of biomedical and health informatics*, vol. 20, no. 5, pp. 1251–1264, 2016.

[6] V. Misra, A. Bozkurt, B. Calhoun, T. Jackson, J. S. Jur, J. Lach, B. Lee, J. Muth, Ö. Oralkan, M. Öztürk *et al.*, “Flexible technologies for self-powered wearable health and environmental sensing,” *Proceedings of the IEEE*, vol. 103, no. 4, pp. 665–681, 2015.

[7] J. Behar, A. Johnson, G. D. Clifford, and J. Oster, “A comparison of single channel fetal ECG extraction methods,” *Annals of biomedical engineering*, vol. 42, no. 6, pp. 1340–1353, 2014.

[8] W. Zong, G. Moody, and D. Jiang, “A robust open-source algorithm to detect onset and duration of QRS complexes,” in *Computers in Cardiology, 2003*. IEEE, 2003, pp. 737–740.

[9] A. N. Vest, G. Da Poian, Q. Li, C. Liu, S. Nemati, A. J. Shah, and G. D. Clifford, “An open source benchmarked toolbox for cardiovascular waveform and interval analysis,” *Physiological measurement*, vol. 39, no. 10, p. 105004, 2018.

[10] R. M. Kliegman, B. M. Stanton, and J. S. Geme, “Nelson textbook of pediatrics, 2-volume set, 20e,” *Nelson Textbook of Pediatrics, 16th edn. Saunders, Philadelphia*, vol. 2, pp. 2163–2182, 2016.

[11] F. Shaffer and J. Ginsberg, “An overview of heart rate variability metrics and norms,” *Frontiers in public health*, vol. 5, p. 258, 2017.