

ARIC Manuscript Proposal # 860

PC Reviewed: 02/13/02

Status: A

Priority: 1

SC Reviewed: 02/14/02

Status: A

Priority: 1

1.a. Full Title:

Association between air pollution and cardiac autonomic control

b. Abbreviated Title (Length 26 characters):

Pollutants and cardiac control.

2. Writing Group (list individual with lead responsibility first):

Lead: **Duanping Liao, MD, Ph.D**

Associate Professor

Department of Health Evaluation Sciences, A210

Penn State University Hershey Medical Center

600 Centerview Drive, Suite 2200

P.O. BOX 855

Hershey, PA 17033-0855

Phone: 717-531-4149

Fax: 717-531-5779

E-mail: DLiao@psu.edu

Writing group members:

Gerardo Heiss, Pentti M. Rautaharju, Ronald Prineas, Eric Whitsel, Gregory Evans, Yinkang Duan,
Vern Chinchilli, Sharon Xie

3. Timeline:

Data preparation and analysis (3 month), Manuscript preparation (6 months)

4. Rationale:

Our ancillary studies to relate air pollution and cardiovascular responses have been funded by US EPA and NIEHS. This proposal address research questions for these ancillary studies.

A considerable number of published epidemiological studies show an association between exposure to airborne pollutants below the current national air quality standard and excess mortality and morbidity. These studies have been extensively reviewed in the US EPA final report - Air Quality Criteria for Particulate Matter⁽¹⁾. In over 20 time-series studies, a consistent relationship was found between daily variations of ambient particles and all-cause mortality, with a stronger effect among the elderly, and from CVD and pulmonary disease. These effects were robust across different statistical models, persisted after adjusting for season and weather, and were not confounded by other pollutants. Consistent with the mortality findings, epidemiologic studies⁽²⁻¹³⁾ also have demonstrated significant associations between ambient particles and hospital admissions for respiratory and CVD. The effects of gaseous criteria pollutants (including O₃, CO, NO₂, and SO₂) and CVD risk also have been reported in few studies⁽¹⁴⁻¹⁷⁾. For example, Schwartz reported that an inter-quartile (1.75 ppm) increase in CO was associated with a 2.79% increase in hospital admissions of heart disease in the elderly, independent of day-of-the week and season⁽¹⁵⁾. In a systematic analysis performed by Samet⁽¹⁶⁾, ambient PM and mortality association was not meaningfully altered after controlling for weather effects using various methods. Samet⁽¹⁶⁾ also confirmed previous reports that individual air pollutants (PM, SO₂, and O₃) were associated with increased daily mortality, and concluded that the observed association of pollution with daily mortality cannot be reliably attributed to any single pollutant. Samet⁽¹⁶⁾ did not find a significant association between NO₂ and daily mortality, in contrast to that reported by Moolgavkar⁽¹⁷⁾, who identified a significant NO₂ effect on daily mortality. This discrepancy may be due to different methods used to adjust for other copollutants. Recently, Samet⁽¹⁸⁾ reported the association between daily PM levels and daily mortality rates in 20 US cities for the period 1987-1994, independent of season and other copollutants. In this report, daily O₃ was weakly but significantly associated with mortality in the summer, but not in the winter when the O₃ levels were very low.

Most of the previous epidemiological studies on pollution and CVD did not have measurements at the individual level, and thus could not address the injury mechanisms, nor appropriately adjust for confounders, particularly the individual level covariables, such as age, race, sex, social economic status, other CVD risk profiles, and history of CVD. Moreover, most of the previous epidemiological studies were not powered to identify potential health conditions or population sub-groups that would enhance susceptibility to adverse PM health effects and how host susceptibility factors influence the dose response relationship. Studies are also needed to investigate the biological mechanisms associated with enhanced susceptibility to adverse PM health effects.

Several potentially important subclinical diseases and physiological responses in relation to air pollution are being investigated. One of which is the direct adverse effect of PM on cardiac autonomic control. We are among the first to hypothesize and report that increased PM₁₀ and PM_{2.5} levels stimulate the autonomic nervous system, leading to an imbalance of cardiac autonomic control, i.e. sympathetic activation relatively unopposed by parasympathetic influence. Such an imbalance of cardiac autonomic control may predispose persons, especially those who are more susceptible to PM, to higher risks of life-threatening arrhythmias and sudden cardiac death⁽⁴⁶⁾. Others have reported similar findings^(47, 55). In addition, arrhythmias and higher mortality in rats were observed after inhalation of combustion particles⁽⁵⁶⁾. ECG changes, including T-wave alternans and arrhythmias in dogs exposed to concentrated ambient air particles, have also been reported⁽⁵⁷⁾. It is likely that PM induces inflammatory responses in the lungs with a subsequent release of chemical mediators that alter the autonomic nervous control of cardiac rhythm⁽⁵⁸⁾.

We hypothesize that bronchial inflammation due to environmental pollution forms a chronic and repeated stimulation resulting in elevated systemic inflammation, increased blood coagulability, impaired cardiac autonomic balance, and increased heterogeneity of cardiac repolarization. The alteration of these factors may lead to increased risk of atherosclerosis and other forms of clinical manifestation of cardiovascular disease.

5. Main Hypothesis/Study Questions:

Our primary focus is particulate matter (PM₁₀ and TP), followed by O₃, SO₂, CO, and NO₂.

- (a) Are exposures to each individual ambient air pollutant prior to the clinical examination associated with (a) lower cardiac autonomic control as measured by 5-minute heart rate variability and heart rate corrected QT intervals? (b) higher frequency of arrhythmia as measured from 2-minute ECG rhythm strips.
- (b) Do other gaseous copollutants synergistically modify the PM-response variable associations?
- (c) Does previous history of cardiovascular disease, diabetes, or smoking modify the above relationships?
- (d) Do the above associations differ by age, sex, social economic status, and ethnicity?

6. Data (variables, time window, source, inclusions/exclusions):

This will be a cross-sectional study using the baseline and visit 4 data. The ARIC V1 and V4 data include variables in the derived data set, heart rate variability data, 2-minute ECG rhythm strip data, and standard 12-lead ECG data. Specifically, we will use 5-minute heart rate variability indices (HF, LF, SDNN, HR) as measures of cardiac autonomic function; 12-lead ECG-derived QT interval as a measure of ventricular repolarization; and 2-minute ECG derived premature ventricular complexes (PVC) as a measure of arrhythmia. We have derived from the USEPA Aerometric Information Retrieval System (AIRS) the air pollution exposures during the visit 1 and visit 4 periods for all the ARIC study participants. These exposures are measured as the average daily exposures to the ambient criteria pollutants for each of the 15,792 individuals prior to their cohort clinical examinations.

Major covariables of interests include age, sex, ethnicity/center, education, smoking, BMI, physical activity, prevalent chronic pulmonary disease, CHD, stroke, hypertension, and diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _____ Yes _____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

____XX____ Yes _____ No

References

1. U.S. Environmental Protection Agency. Air Quality Criteria for Particulate Matter. Vol III, EPA-600/P-95/001aF. Environmental Criteria and Assessment Office, Research Triangle Park, NC, 1995.
2. Thurston GD. Lippmann M. Scott MB. Fine JM. Summertime haze air pollution and children with asthma. *American Journal of Respiratory & Critical Care Medicine*. 155: 654-60 (1997)
3. Gordian ME. Ozkaynak H. Xue J. Morris SS. Spengler JD. Particulate air pollution and respiratory disease in Anchorage, Alaska. *Environmental Health Perspectives*. 104: 290-297 (1996)
4. Raizenne M. Neas LM. Damokosh AI. Dockery DW. Spengler JD. Koutrakis P. Ware JH. Speizer FE. Health effects of acid aerosols on North American children: pulmonary function. *Environmental Health Perspectives*. 104: 506-14 (1996).
5. Dockery DW. Cunningham J. Damokosh AI. Neas LM. Spengler JD. Koutrakis P. Ware JH. Raizenne M. Speizer FE. Health effects of acid aerosols on North American children: respiratory symptoms. *Environmental Health Perspectives*. 104: 500-5 (1996).
6. Pope CA 3rd. Particulate pollution and health: a review of the Utah valley experience. *Journal of Exposure Analysis & Environmental Epidemiology*. 6: 23-34 (1996).
7. Schwartz J. Air pollution and hospital admissions for the elderly in Detroit, Michigan. *American Journal of Respiratory & Critical Care Medicine*. 150: 648-55 (1994).
8. Pope CA 3rd. Kanner RE. Acute effects of PM10 pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. *American Review of Respiratory Disease*. 147: 1336-40 (1993).
9. Burnett RT. Dales RE. Brook JR. Raizenne ME. Krewski D. Association between ambient carbon monoxide levels and hospitalizations for congestive heart failure in the elderly in 10 Canadian cities. *Epidemiology*. 8: 162-7 (1997).
10. Delfino RJ. Murphy-Moulton AM. Burnett RT. Brook JR. Becklake MR. Effects of air pollution on emergency room visits for respiratory illnesses in Montreal, Quebec. *Am Journal of Respiratory & Critical Care Medicine*. 155: 568-76 (1997).
11. Poloniecki JD. Atkinson RW. de Leon AP. Anderson HR. Daily time series for cardiovascular hospital admissions and previous day's air pollution in London, UK. *Occupational & Environmental Medicine*. 54: 535-40 (1997).
12. Ackermann-Lieblich U. Leuenberger P. Schwartz J. Schindler C. Monn C. Bolognini G. Bongard JP. Brandli O. Domenighetti G. Elsasser S. Grize L. Karrer W. Keller R. Keller-Wossidlo H. Kunzli N. Martin BW. Medici TC. Perruchoud AP. Schoni MH. Tschopp JM. Villiger B. Wuthrich B. Zellweger JP. Zemp E. Lung function and long-term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. *American Journal of Respiratory & Critical Care Medicine*. 155: 122-9 (1997).
13. Ponka A. Virtanen M. Low-level air pollution and hospital admissions for cardiac and cerebrovascular diseases in Helsinki. *American Journal of Public Health*. 86: 1273-80 (1996).
14. Schwartz J, Morris R. Air pollution and hospital admissions for CVD in Detroit, Michigan. *Am J Epidemiol* 1995; 142:22-35.
15. Schwartz J. Air pollution and hospital admissions for heart disease in eight U.S. counties. *Epidemiology* 1999
16. Health Effects Institute: Particulate Air Pollution and Daily Mortality: Analyses of the effects of weather and multiple pollutants. The phase I.B report of the particle epidemiology evaluation project. HEI, Cambridge, MA.
17. Moolgavkar SH, Luebeck EG: A critical review of the evidence on particulate air pollution and mortality. *Epidemiology*. 1996; 7: 420-428.
18. Samet JM, Dominici F, Currier FC, Coursac I, Zeger SL: Fine Particulate Air Pollution and Mortality in 20 U.S. Cities, 1987-1994. *N Engl J Med*. 2000;343:1742-9
19. Liao D, Creason J, Shy C, Williams R, Watts R, Zweidinger R. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect* 107:521-525, 1999
20. Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC: Association of heart rate variability with occupational and environmental exposure to particulate air pollution. *Circulation*. 2001; 104:986-91.

21. Watkinson WP, Campen MJ, Costa DL. Cardiac arrhythmia induction after exposure to residual oil fly ash particles in a rodent model of pulmonary hypertension. *Toxicological Sciences*. 1998; 41:209-16
22. Godleski JJ, Nearing BD, Killingsworth CR, Krishna Murthy GG, Skornik WA, Verrier RL. Increased cardiac vulnerability during exposure to inhaled environmental particles. (Abstract) Health Effects Institute Annual Meeting, Boston, 1998.
23. Godleski JJ, Sioutas C, Katler M, Koutrakis P. Death from inhalation of concentrated air particles in animal models of pulmonary disease. *Am J Crit Care Med* 1996; 163; A15.