Personal Exposure to Submicrometer Particles and Heart Rate Variability in Human Subjects

Chang-Chuan Chan,1 Kai-Jen Chuang,1 Guang-Ming Shiao,2 and Lian-Yu Lin3

1Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan; 2Chest Department, Taipei Veterans General Hospital, Taipei, Taiwan; 3Internal Medicine Department, National Taiwan University Hospital, Taipei, Taiwan

We conducted a study on two panels of human subjects—9 young adults and 10 elderly patients with lung function impairments—to evaluate whether submicrometer particulate air pollution was associated with heart rate variability (HRV). We measured these subjects’ electrocardiography and personal exposure to number concentrations of submicrometer particles with a size range of 0.02–1 µm (NC0.02–1) continuously during daytime periods. We used linear mixed-effects models to estimate the relationship between NC0.02–1 and log-transformed HRV, including standard deviation of all normal-to-normal intervals (SDNN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.40 Hz), adjusted for age, sex, body mass index, tobacco exposure, and temperature. For the young panel, a 10,000-particle/cm³ increase in NC0.02–1 with 1–4 hr moving average exposure was associated with 0.68–1.35% decreases in SDNN, 1.85–2.58% decreases in r-MSSD, 1.32–1.61% decreases in LF, and 1.57–2.60% decreases in HF. For the elderly panel, a 10,000-particle/cm³ increase in NC0.02–1 with 1–3 hr moving average exposure was associated with 1.72–3.00% decreases in SDNN, 2.72–4.65% decreases in r-MSSD, 3.34–5.04% decreases in LF, and 3.61–5.61% decreases in HF. In conclusion, exposure to NC0.02–1 was associated with decreases in both time-domain and frequency-domain HRV indices in human subjects. Key words: air pollution, autonomic system, epidemiology, heart rate variability, submicrometer particle. Environ Health Perspect 112:1063–1067 (2004). doi:10.1289/ehp.6897 available via http://dx.doi.org/[Online 4 March 2004]

Many studies have documented significant cardiovascular effects by coarse particles with diameters < 10 µm (PM10) and fine particles with diameters < 2.5 µm (PM2.5) (Pope and Dockery 1999; Samet et al. 2000). By contrast, relatively few studies reported such effects from either submicrometer particles with particle sizes < 1.0 µm in diameter (PM1.0) or ultrafine particles with particle sizes < 0.1 µm in diameter. One recent epidemiologic study showed that exposure to ultrafine particles measured by number concentrations (NC0.02–1) are associated with HRV changes in both young adults and the elderly patients with lung function impairments.

Materials and Methods

Subjects. This panel study was designed to monitor changes in PM concentrations and HRV continuously and simultaneously in study subjects in general environments. There were two panels of our study subjects: 9 young adults and 10 elderly patients with lung function impairments. Young and healthy adults were recruited through on-campus advertisement at National Taiwan University. Fifteen students responded to our advertisement, but only nine were willing to participate in our study after we explained to them our monitoring protocols (response rate = 60%). The elderly patients were recruited from the Chest Department of Taipei Veterans General Hospital. Our selection criteria for lung function impairment was that the patient’s ratios of forced expiratory volume in 1 sec (FEV1) to forced vital capacity (FVC), FEV1/FVC, should be < 85%. To avoid the effects of coexisting diseases on HRV, we selected our elderly subjects based on the following exclusion criteria: those with hyperthyroidism, acute cardiopulmonary failure, paced cardiac rhythm, or using medications that may affect cardiac rhythm, such as anticholinergics, beta-blockers, anti-arrhythmic agents, and so forth. Nineteen patients met our selection criteria, but only 10 were willing to participate in our study after we explained to them our monitoring protocols (response rate = 53%). The FEV1/FVC values for these 10 elderly patients were all < 84%. No participant used cardiac-rhythm–related medication during the monitoring period. The Institutional Review Board of Taipei Veterans General Hospital approved the

Address correspondence to C.-C. Chan, Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Room 1447, 1st Section, No. 1 Jen-ai Rd., Taipei 100, Taiwan. Telephone/Fax: 886-2-2322-2362. E-mail: ccechan@ha.mc.ntu.edu.tw

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research consent was obtained from each participant. Continuous Holter monitoring and tape processing. We performed continuous ambulatory electrocardiographic (ECG) monitoring on each study subject by using a three-channel ambulatory ECG recorder (PacerCorder model 461A; Del Mar Medical Systems LLC., Irvine, CA, USA) with a sampling rate of 250 Hz (4 msec). We sent ECG tapes to National Taiwan University Hospital and analyzed them by using a Delmar 563 Holter analysis system (version 2.47; Del Mar). The electrocardiographic wave complexes (QRS) were automatically classified and manually verified as normal sinus rhythm, arterial or ventricular premature beats, or noise by comparison of the adjacent QRS morphologic features. The NN intervals were deduced from the adjacent normal sinus beats. The NN interval time series were then transferred to a personal computer and postprocessed by a program written in Matlab language (version 5.2; MathWorks Inc., Natick, MA, USA). The missing intervals of the raw NN data were linearly interpolated and resampled at 4 Hz by the Ron-Berger method. Each 5-min segment of NN intervals was taken for HRV analysis. The time-domain measurements of HRV were SDNN and r-MSSD. The frequency-domain measurements of HRV were LF and HF, which were calculated by Welch’s averaged periodogram of the NN intervals (Task Force 1996; Welch 1967). To avoid sleep effects on HRV, we used the Holter measurements when the subjects were awake between daytime normal activities. We used a general-purpose condensation particle counter (CPC; model 3022A; TSI Inc.), which measured NC_{0.005–1} to validate the measurements of NC_{0.02–1} by the P-TRAK before performing the study. Concurrent measurements of submicrometer particles by the CPC and the P-TRAK in our aerosol laboratory showed high association between two monitors in total counts of submicrometer particles (\( r^2 = 0.99 \)) during the experimental period. The CPC with a wider size range also consistently reported approximately 30% more counts of submicrometer particles than the P-TRAK in our validation test. We also performed a zero check on P-TRAK by measuring HEPA-filtered air before each field application.

Other personal variables. Each participant’s age, sex, body mass index (BMI), and medical history were recorded by a standardized questionnaire. Young adults themselves and the technician for the elderly recorded the participant’s time–activity patterns and environmental tobacco smoke exposures during the monitoring period.

Statistical analysis. We first plotted NC_{0.02–1} by HRV indices for individual subjects to determine whether there were observed associations between these two variables and whether such associations were heavily influenced by any outliers or were homogeneous across subjects. We then applied linear mixed-effects regression models to estimate the association between NC_{0.02–1} and log_{10} transformed HRV measurements by using general additive procedures in the S-PLUS 2000 program (MathSoft Inc., Cambridge, MA, USA). We treated subjects’ sex, age, BMI, and tobacco exposure as time-invariant variables, and NC_{0.02–1}, temperature, and HRV as time-varying variables, in our data analysis. The exposure variables were 1–4 hr moving averages of NC_{0.02–1} in our models. The outcome variables were log_{10} transformed HRV, which were SDNN, r-MSSD, LF, and HF. Such mixed-effects models had the advantage of adjusting for invariant variables by fixed-effects models and accounting for individual differences by random-effects models. In our mixed-effects models, we treated subjects’ sex, age, BMI, tobacco exposure, ambient temperature, and NC_{0.02–1} as fixed effects and each subject as a random effect. To control all key variables in a relatively small sample size, we stratified the age variable at 65 years of age for the elderly panel and the BMI variable at 22 kg/m^2 for both panels in our models. A total of eight sets of mixed-effects models were constructed separately to estimate NC_{0.02–1} effects on HRV at 1–4 hr moving averages for the young panel and the elderly panel.

Results Study participants’ personal characteristics and environmental exposures of two study panels are summarized in Table 1. The 9 young adults (7 males, 2 females) were 19–29 years of age (mean ± SD, 23.2 ± 2.9 years), and their BMI ranged from 20.1 to 34.4 kg/m^2 (mean ± SD, 24.8 ± 4.3 kg/m^2). The 10 elderly patients were all male and were from 42 to 79 years of age (mean ± SD, 58.3 ± 13.4 years), and their BMI values were from 20.6 to 33.8 kg/m^2 (26.9 ± 3.9 kg/m^2). Subjects in the elderly panel averaged about 35 years older than those in the young panel.

The values of HRV indices in Table 1 were the means of the averages for each participant during the 16-hr monitoring period. Average heart rates were 87.5 ± 9.2 beats per minute (bpm) in the young adults and 75.9 ± 8.6 bpm in the 10 elderly patients. The log_{10} SDNN, log_{10} r-MSSD, log_{10} LF, and log_{10} HF in the two panels were, respectively, 1.66 ± 0.15 msec, 0.99 ± 0.15 msec, 3.02 ± 0.50 msec^2, and 2.45 ± 0.51 msec^2 in the young panel, and 1.61 ± 0.25 msec, 1.01 ± 0.28 msec, 2.42 ± 0.59 msec^2, and 2.11 ± 0.67 msec^2 in the elderly panel. The heart rate and most HRV indices in the young panel were significantly higher than those in the elderly panel, except for r-MSSD.

Also presented in Table 1 are the personal monitoring results of 5-min NC_{0.02–1}. The 5-min NC_{0.02–1} ranged from 6,127 to 351,003 particles/cm^3 for the young panel and from 1,712 to 210,973 particles/cm^3 for the elderly panel. Means of 5-min NC_{0.02–1} exposures were comparable between the young panel (23,407 ± 19,836 particles/cm^3) and the elderly panel (25,529 ± 20,783 particles/cm^3) during the study. However, wide fluctuation

| Characteristics | Young panel | Elderly panel | Difference between panels |
|-----------------|-------------|---------------|--------------------------|
| No. of subjects | 9           | 10            |                          |
| Sex (no.)       |             |               |                          |
| Female          | 2           | 0             |                          |
| Male            | 7           | 10            |                          |
| Age (years)     | 23.2 ± 2.9 (19–29) | 58.3 ± 13.4 (42–79) | * |
| BMI (kg/m^2)    | 24.8 ± 4.3 (20.1–34.4) | 26.9 ± 3.9 (20.6–33.8) | * |
| Heart rate (bpm)| 87.5 ± 9.2 (70–130)  | 75.9 ± 8.6 (61–89)   | * |
| Time-domain HRV (msec) |                |                |                          |
| Log_{10} SDNN                                           | 1.66 ± 0.15 (1.10–2.02) | 1.61 ± 0.25 (0.88–2.05) | * |
| Log_{10} r-MSSD                                          | 0.99 ± 0.15 (0.54–1.48) | 1.01 ± 0.28 (0.42–1.64) | * |
| Frequency-domain HRV (msec^2)                           |                |                |                          |
| Log_{10} LF                                              | 3.02 ± 0.50 (0.96–3.90) | 2.42 ± 0.59 (1.00–3.88) | * |
| Log_{10} HF                                              | 2.45 ± 0.51 (1.44–3.33) | 2.11 ± 0.67 (0.48–3.85) | * |
| NC_{0.02–1}, 5-min mean (particles/cm^3)                 | 23,407 ± 19,836 (6,127–351,003) | 25,529 ± 20,783 (1,712–210,973) | * |
| Temperature (°C)                                         | 25.6 ± 2.4 (18.9–30.8) | 24.4 ± 5.7 (12.6–34.4) | * |

* Significant difference between young and elderly panels, t-test, p < 0.05.
in NC0.02–1 as expressed in large standard deviations in particle statistics indicated wide within-subject and between-subject variations in NC0.02–1 exposure during the study period. The hourly ambient temperature during each participant’s monitoring period ranged from 18.9 to 30.8°C for the 9 young adults and from 12.6 to 34.4°C for the 10 elderly patients.

The plots of NC0.02–1 by HRV indices revealed consistently negative associations between these two variables across all study subjects (data not shown). The observed associations seemed not to be influenced by any outlier observations. In our modeling results, regression of time-domain HRV indices on previous moving averages adjusted for potential confounders showed significantly negative associations between NC0.02–1 moving averages and 5-min SDNN and r-MSSD values. Personal characteristics such as age, BMI, sex, and tobacco exposure did not affect the observed associations between NC0.02–1 and time-domain HRV indices. However, temperature was negatively associated with time-domain HRV indices. Table 2 lists percent changes in time-domain HRV indices for 10,000 particle/cm3 NC0.02–1 exposures, averaged for the young and the elderly, respectively. NC0.02–1 exposures significantly decreased LF and HF at 1-hr to 4-hr moving averages for the young panel, but significantly decreased LF and HF at 1-hr to 3-hr moving averages for the elderly panel. For 10,000-particle/cm3 NC0.02–1 exposures, LF was decreased by 1.41–1.61% for the young panel and 3.34–5.04% for the elderly panel. For 10,000-particle/cm3 NC0.02–1 exposures, HF was decreased by 1.57–2.60% for the young panel and 3.61–5.61% for the elderly panel. The elderly panel had greater decreases in frequency-domain HRV indices in response to NC0.02–1 exposure than did the young panel. Only the elderly panel exhibited a time course effect of NC0.02–1 on frequency-domain HRV indices. The magnitude of decreasing LF and HF was the greatest at 2-hr moving averages for the elderly panel.

**Discussion**

This is the first study to demonstrate that personal measurements of environmental exposure to NC0.02–1 can affect HRV in human subjects. The main effects of NC0.02–1 are to decrease both time-domain indices (SDNN, r-MSSD) and frequency-domain indices (HF, LF), which are consistent with the effects by PM2.5 in one previous study (Liao et al. 1999). Another interesting finding of our study is that NC0.02–1 seems to exert similar effects on HRV for both young adults and elderly patients. Our results further confirm that environmental PM can affect HRV both in the elderly with preexisting diseases (Gold et al. 2000; Pope et al. 1999) and in adults between 19 and 59 years of age (Magari et al. 2001). Our findings also support that the magnitudes of PM effects on HRV differ between elderly/less healthy and younger/healthy groups. For 1-mg/m3 PM2.5 exposures in 4-hr moving average, Gold et al. (2000) reported a 17.4-msec decrease in SDNN among the elderly, whereas Magari et al. (2001) reported a 4.5-msec decrease in SDNN among the young adults. The comparisons of these studies showed PM2.5-induced autonomic function imbalance in the elderly was approximately four times stronger than that in young, healthy adults. Our study showed that percent decreases in log10 SDNN were two times greater among the elderly than among the young adults for 10,000-particle/cm3 NC0.02–1 exposures at 1-hr to 3-hr moving averages. Apparently, these findings consistently show that the association between PM and HRV seems to be more pronounced among the elderly/less healthy population than among the younger/healthy population.

![Table 2](image)

**Table 2.** Percent changes (95% CI)* in time-domain HRV indices for NC0.02–1 exposures of 10,000 particles/cm3 estimated by mixed-effects models.

| Exposure matrix | Young panel | Elderly panel |
|-----------------|-------------|---------------|
| SDNN            |             |               |
| 1-hr moving     | -0.68* (-1.04 to -0.32) | -1.72* (-2.53 to -0.90) |
| 2-hr moving     | -1.20* (-1.71 to -0.69) | -3.00* (-4.22 to -1.78) |
| 3-hr moving     | -1.30* (-1.90 to -0.71) | -2.87* (-4.35 to -1.40) |
| 4-hr moving     | -1.35* (-1.98 to -0.72) | -0.70 (-2.00 to 0.60) |
| r-MSSD          |             |               |
| 1-hr moving     | -1.85* (-2.36 to -1.33) | -2.72* (-4.24 to -1.20) |
| 2-hr moving     | -2.58* (-3.29 to -1.88) | -4.65* (-6.65 to -2.45) |
| 3-hr moving     | -2.45* (-3.28 to -1.63) | -4.13* (-6.64 to -1.42) |
| 4-hr moving     | -2.11* (-2.97 to -1.25) | -1.53 (-4.02 to 0.96) |

CI, confidence interval.
*The model of the young panel was adjusted for sex, BMI, tobacco exposure, and temperature, whereas the model of the elderly panel was adjusted for age, BMI, tobacco exposure, and temperature. *p < 0.05.

![Table 3](image)

**Table 3.** Percent changes (95% CI)* in frequency-domain HRV indices for NC0.02–1 exposures of 10,000 particles/cm3 estimated by mixed-effects models.

| Exposure matrix | Young panel | Elderly panel |
|-----------------|-------------|---------------|
| LF              |             |               |
| 1-hr moving     | -1.41* (-2.11 to -0.71) | -3.34* (-4.64 to -2.07) |
| 2-hr moving     | -1.32* (-2.29 to -0.36) | -5.04* (-6.98 to -3.12) |
| 3-hr moving     | -1.03 (-2.09 to 0.02) | -4.35* (-6.77 to -1.94) |
| 4-hr moving     | -1.61* (-2.69 to -0.54) | -0.57 (-2.66 to 1.52) |
| HF              |             |               |
| 1-hr moving     | -2.60* (-3.45 to -1.75) | -3.61* (-5.23 to -2.00) |
| 2-hr moving     | -2.22* (-3.43 to -1.00) | -5.61* (-8.03 to -3.19) |
| 3-hr moving     | -1.57* (-2.99 to -0.15) | -4.97* (-7.93 to -2.00) |
| 4-hr moving     | -2.01* (-3.46 to -0.56) | -1.51 (-4.13 to 1.11) |

CI, confidence interval.
*The model of the young panel was adjusted for sex, BMI, tobacco exposure, and temperature, whereas the model of the elderly panel was adjusted for age, BMI, tobacco exposure, and temperature. *p < 0.05.
exposures are basically the same for both dysautonomic and nondysautonomic subjects. This suggests that there may be a common toxicologic mechanism of causing autonomic imbalance by submicrometer particles among various populations. However, the same physiologic perturbation of NC0.02–1 exposures may cause different detrimental effects to each population depending on their preexisting cardiac conditions. The decrease of r-MSSD and HF components represents the withdrawal of vagal activity, which is an indicator of increasing cardiovascular events (Bigger et al. 1992; Kleiger et al. 1987). Even though the LF decrease is previously thought to represent decreased sympathetic activity, its real physiologic meaning remains unclear and is still debatable (Task Force 1996). One possible reason for LF decrease in our study is the decrease in total HRV (SDNN) by NC0.02–1.

The effects of different time course on HRV indicate that the magnitudes of decreasing SDNN, r-MSSD, LF, and HF increase as the averaging intervals of NC0.02–1 reach 2–3 hr. Our findings suggest that NC0.02–1 can have both immediate and cumulative effects on cardiac autonomic function. It has been reported that particles can affect both sympathetic and parasympathetic nervous systems directly in the immediate phase after exposure (Kodavanti et al. 2000; Lai and Kou 1998). One possible pathway of such a mechanism is the rapid passage of inhaled particles with diameters < 100 nm into the blood circulation reported in one recent study (Nemmar et al. 2002). In that study, ultrafine particles were found to diffuse into healthy volunteers’ systemic circulation 1 min after exposure and reached peak penetrations between 10 and 20 min after exposure. Because translocation of ultrafine particulates from airways into systemic circulation is reported to be very rapid, we speculate that direct myocardial effects rather than upper airway influences from air pollutants account for NC0.02–1 effects on HRV in the immediate phase. The other possible pathway is that ultrafine particles deposited in the alveoli may increase blood coagulation via mechanisms of pulmonary inflammation or direct action on red blood cells (Donaldson et al. 2001; Peters et al. 1997; Seaton et al. 1999). Accordingly, we believe particle-induced pulmonary inflammation can also indirectly result in HRV changes or autonomic imbalance in the delayed phase after NC0.02–1 exposures. This may explain why HRV decreases peaked at 2–3 hr after NC0.02–1 exposure in our study.

Short-term and small fluctuations of HRV indices have not been associated with higher risks of cardiovascular disease clinically. Cardiac death is a consequence of a complex interaction between the autonomic nervous system, a myocardial substrate altered in the course of disease processes, and myocardial vulnerability leading to arrhythmogenic or ischemic response. The presence of a single condition is usually not sufficient to trigger death by cardiovascular disease (Zareba et al. 2001). Our findings, however, show that submicrometer particles are an environmental stressor, which may trigger a cascade of events by increasing sympathetic activation and may potentially lead to ischemia or fatal arrhythmia in high-risk patients with underlying cardiac abnormalities.

We believe that some key physiologic and environmental information, which was not available in our study, could possibly confound our findings of HRV imbalance by NC0.02–1. First, we could not adjust the effect of breathing patterns on HRV because they were not measured during the monitoring period. It has been reported that the quantity, periodicity, and timing of cardiac output were associated with variations of respiratory depth and interval in conscious young adults (Eckberg 1983). Second, we could not adjust respiration-modulated autonomic activity, especially HF and LF, in our study because we were unable to measure key respiration parameters, such as nasal and mouth airflow, chest wall movement, and abdominal movement, by polysomnography during the daytime monitoring period. Third, comorbidity and medication among elderly patients could still confound our findings for NC0.02–1 effects on HRV even though we used very strict criteria to exclude cases with severe chronic diseases and specific medication from our study subjects. Fourth, the “personal cloud” effects of PM measurements could also confound our findings of the NC0.02–1 effects relevant to environmental NC0.02–1 (Harrison et al. 2002; Wallace 1996). Because exposure measurements for two panels were different, the measurement bias attributable to “personal cloud” effects could also be different between these two panels. The young subjects, who carried P-TRAK personally to measure their NC0.02–1 exposures, were expected to experience more diverse “personal cloud” effects than the elderly subjects, whose personal NC0.02–1 was measured by a single assistant. Fifth, other unmeasured personal effects on cardiorespiratory symptoms in elderly subjects.第六，other unmeasured personal effects on cardiorespiratory symptoms in elderly subjects. Sixth, other unmeasured personal effects on cardiorespiratory symptoms in elderly subjects. Sixth, other unmeasured personal effects on cardiorespiratory symptoms in elderly subjects.

Regardless of these limitations, we believe our data generally indicate that submicrometer particles can disturb autonomic function in human subjects. However, we do not know whether such effects are caused by particle physical size alone or by the combined effects of the chemical/biologic components of particles. We therefore recommend further studies to elucidate the clinical significance, biologic mechanisms, and dose–response relationships of the NC0.02–1 effects on HRV.

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