# Associations Between Submicrometer Particles Exposures and Blood Pressure and Heart Rate in Patients With Lung Function Impairments

Kai-Jen Chuang, MSc
Chang-Chuan Chan, ScD
Guang-Ming Shiao, MD
Ta-Chen Su, MD

## Learning Objectives

- State whether the concentration of sub-micrometer particles ranging from 0.02 to 1 μm in diameter ($NC_{0.02-1}$) correlated with ambient levels of air pollutants.
- Identify any correlation found in this study of persons with impaired lung function between $NC_{0.02-1}$ or particles less than 1.0 μm in diameter ($PM_{1.0}$) and elevations in systolic and diastolic blood pressure and heart rate.
- Explain the implications of these findings with respect to the risk of cardiovascular disease.

## Abstract

**Objective:** *The objective of this study was to evaluate whether submicrometer particle is associated with elevated blood pressure (BP) and heart rate (HR).* **Methods:** *We measured ambulatory systolic BP (SBP), diastolic BP (DBP), and HR using a portable BP monitoring system and number concentrations of submicrometer particle with a size range of 0.02 to 1 μm ($NC_{0.02-1}$) by a P-TRAK Ultrafine Particle Counter for 10 patients with lung function impairments.* **Results:** *We found $NC_{0.02-1}$ exposures at 1- to 3-hour moving averages were associated with the elevation of SBP, DBP, and HR. There were 1.4 to 3.4-mm-Hg increases in SBP, 1.4 to 2.2-mm-Hg increases in DBP, and 0.3 to 3.5-beats/min increases in HR for 10,000 particles/cm³ increases in $NC_{0.02-1}$ at 1- to 3-hour moving averages.* **Conclusions:** *Exposures to submicrometer particles were associated with short-term increases in BP and HR in patients with lung function impairments.* (J Occup Environ Med. 2005;47:1093–1098)

Epidemiologic studies have shown associations between particulate air pollution and cardiovascular mortality[1] and morbidity.[2] Nevertheless, the underlying mechanisms or pathways of particulate matter-induced cardiovascular mortality and morbidity still remain largely unclear. The linkage between decreasing heart rate variability (HRV) and particulate matter less than 10 μm in diameter ($PM_{10}$) and less than 2.5 μm in diameter ($PM_{2.5}$) has been documented in many panel studies.[3–8] Several studies have also reported that increased mass concentrations of total suspended particulate matter (TSP), $PM_{10}$, and $PM_{2.5}$ were associated with elevating blood pressure (BP)[9–11] and heart rate (HR)[8,12,13] in the general population or patients with cardiopulmonary diseases. Comparatively few studies were conducted on the cardiovascular effects by smaller particles such as submicrometer particles with particle size less than 1.0 μm in diameter ($PM_{1.0}$) or ultrafine particles with particle size less than 0.1 μm in diameter. We recently reported that exposures to submicrometer particles with a size range of 0.02 to 1 μm measured by number concentrations ($NC_{0.02-1}$) were associated with lowering HRV in both susceptible and normal populations.[14] As a follow up of the previous study on patients with lung function impairments, we further investigate whether exposures to submicrometer particles are also associated with changes in their BP and HR in this panel study.

## Materials and Methods

### Study Subjects

As described in the previous study,[14] our study panel included 10 patients with lung function impairments who were recruited from the Chest Department of Taipei Veterans General Hospital. The ratios of their forced expiratory volume in 1 second ($FEV_{1.0}$) by forced vital capacity (FVC), $FEV_{1.0}$/FVC, were all less than 84%. None of them had hyperthyroidism, hypoxemia, hypercapnia, acute cardiopulmonary failure, or paced cardiac rhythm, or used medication of anticholinergics, beta blockers, or antiarrhythmic agents during the study period. The Institutional Review Board of Taipei Veterans General Hospital approved the research protocol, and written informed consent was obtained from each subject.

### Ambulatory Blood Pressure and Heart Rate Monitoring and Recording

We recorded each subject's BP and HR every 15 minutes during wake time (7:00 AM through 11:00 PM) and every 30 minutes during sleep time (11:00 PM through 7:00 AM) continuously by using a portable BP monitoring system (DynaPulse model 5000A; Pulse Metric, San Diego, CA). The DynaPulse system can measure a subject's arterial pulsation signals, known as the arterial wave form, through a noninvasive cuff device. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR readings by Dyna-Pulse have been validated against the traditional mercury sphygmomanometer measurements.[15,16] Each subject carried a DynaPulse system for 24 hours to complete his continuous BP and HR monitoring. To avoid sleep effects on BP and heart rate, we used the monitor measurements when the subjects were awake between 7:00 AM and 11:00 PM in our data analysis. Each subject obtained approximately 60 successful BP and

HR measurements for further data analysis.

### Personal Exposures to Submicrometer Particles

A detailed description of the sampling procedures and data validation is given in our previous study.[14] In brief, $NC_{0.02-1}$ monitoring was conducted for each subject by a technician carrying a P-TRAK Ultrafine Particle Counter (model 8525; TSI Inc., Shoreview, MN). The raw data of 1-minute $NC_{0.02-1}$ measurements were first matched with the sampling time of BP and HR monitoring and then computed to moving averages if 75% of the data were present. We obtained approximately 700 measurements of $NC_{0.02-1}$ moving averages for each subject in our data analysis.

### Exposures to Ambient Air Pollution

In addition to personal $NC_{0.02-1}$ exposure monitoring, we also included ambient air pollution as our study subjects' exposure data in this study. The concentrations of particulate matters with aerodynamic diameter less than 10 μm ($PM_{10}$), nitrogen dioxide ($NO_2$), carbon monoxide (CO), sulfur dioxide ($SO_2$), and ozone ($O_3$) measured at fixed-site air-monitoring stations were used to represent subjects' exposures to ambient air pollution. There were 12 fixed-site air-monitoring stations in Taipei, which were operated by Taiwan Environmental Protection Agency (TEPA). Each of our study subjects can be assigned to one fixed-site monitoring that is within 1 km of his residence. The hourly data of $PM_{10}$, $NO_2$, CO, $SO_2$, and $O_3$ in each monitoring station were obtained and matched with the sampling time of BP and HR monitoring to represent our subjects' exposures to ambient air pollutants during the monitoring period. The moving averages were computed and approximately 48 measurements of each air

pollutant were obtained for each subject in our data analysis.

### Statistical Analysis

We applied linear mixed-effects regression models to examine the association between air pollutants and BP and HR by using S-PLUS 2000 (MathSoft, Inc.). Our mixed-effects models included BP and HR as outcomes, random effects for subjects, and fixed effects for age, body mass index, tobacco exposure, 1-hour moving averages of temperature, and 1- to 4-hour moving averages of air pollutants including $NC_{0.02-1}$, $PM_{10}$, $NO_2$, CO, $SO_2$, and $O_3$. The 1-hour moving average of temperature was adjusted in our models because it was the only time lag that was associated with HR and BP among 1- to 4-hour moving averages of temperature tested in this study. To assure that changes in BP and HR were not the result of diurnal variation of the cardiovascular system, our models also contained hour of day as an indicator variable of fixed effects. We initially conducted single-pollutant models for each of these six air pollutants. We then included the air pollutants, which were significantly associated with BP or HR in single-pollutant models, in our multipollutant models. Outcomes in their original scales were used for further analysis because their distributions were normal as determined by Shapiro-Wilk test.[17] Autocorrelation within each outcome variable was diagnosed by using autocorrelation residual plots, and no time-dependent autocorrelation was observed in all our models. Model selections were based on the criteria of minimizing Akaike's Information Criterion (AIC). Effects were estimated for changes of BP and HR per 10,000 paricles/$cm^3$ of $NC_{0.02-1}$ (β coefficient × 10,000) and per unit of $PM_{10}$, $NO_2$, CO, $SO_2$, and $O_3$ (β coefficient). Our mixed-effects models were further applied separately to analyze the association between BP and $NC_{0.02-1}$ for all 10 subjects as a

whole, two subgroups of HR $\leqq 72$ beats/min, and HR $>72$ beats/min.

## Results

Subjects' personal characteristics and environmental attributes are summarized in Table 1. The 10 patients were all male and aged from 42 to 79, and their body mass indices were from 20.6 to 33.8 kg/m$^2$. The outcome measurements along with relevant pollution data over the 16-hour monitoring period are also shown in Table 1. Our subjects' averages of SBP, DBP, and HR were $133.9 \pm 15.7$ mm Hg, $78.0 \pm 11.3$ mm Hg, and $76.5 \pm 13.4$ beats/min, respectively. The 1-hour averaging $NC_{0.02-1}$ measurements ranged from 2169 to 93,666 particles/cm$^3$. The means of 1- to 4-hour averaging $NC_{0.02-1}$ measurements were $23,785.0 \pm 13,417.0$ particles/cm$^3$, $24,110.6 \pm 10,947.5$ particles/cm$^3$, $23,891.4 \pm 11,583.1$ particles/cm$^3$, and $23,674.9 \pm 11,621.0$ particles/cm$^3$. Air pollution levels averaged at $54.1 \pm 29.5$ $\mu$g/m$^3$, $27.6 \pm 18.2$ ppb, $1.0 \pm 0.7$ ppm, $22.4 \pm 20.0$ ppb, and $3.5 \pm 4.7$ ppb for $PM_{10}$, $NO_2$, CO, $O_3$, and $SO_2$, respectively. Pearson correlation was low among these air pollutants except moderate correlation for $NC_{0.02-1}$ with $NO_2$ ($r = 0.53$) and CO ($r = 0.46$), and for $NO_2$ with CO ($r = 0.61$) and $PM_{10}$ ($r = 0.57$).

Table 2 list changes in BP and HR for 10,000 paricles/cm$^3$ $NC_{0.02-1}$ exposures at 1- to 4-hour moving averages estimated by the single-pollutant models for all 10 subjects and two subgroups. We only examined the time course of $NC_{0.02-1}$ exposures up to 4–hour moving averages because available data became substantially decreased for moving averages greater than 5

## TABLE 1
Study Participants' Characteristics, Air Pollution Levels, and Meteorologic Variables

| | No. | Mean | Standard Deviation | Range |
|---|---|---|---|---|
| Age, year | 10 | 58.3 | 13.4 | 42–79 |
| Body mass index, kg/m$^2$ | 10 | 26.9 | 3.9 | 20.6–33.8 |
| Systolic blood pressure, mm Hg | 444 | 133.9 | 15.7 | 94.0–180.0 |
| Diastolic blood pressure, mm Hg | 444 | 78.0 | 11.3 | 60.0–115.0 |
| Heart rate, beats/min | 316 | 76.5 | 13.4 | 44–112 |
| Personal exposure | | | | |
|   1-hr moving average $NC_{0.02-1}$, particles/cm$^3$ | 6578 | 23,785.0 | 13,417.0 | 2169.0–93,666.0 |
| Ambient exposure | | | | |
|   1-hr average $PM_{10}$, $\mu$g/m$^3$ | 470 | 54.1 | 29.5 | 10.3–139.8 |
|   1-hr average $NO_2$, ppb | 452 | 27.6 | 18.2 | 1.9–123.5 |
|   1-hr average CO, ppm | 472 | 1.0 | 0.7 | 0.1–4.5 |
|   1-hr average $O_3$, ppb | 460 | 22.4 | 20.0 | 0.2–134.1 |
|   1-hr average $SO_2$, ppb | 454 | 3.5 | 4.7 | 0.1–71.0 |
| Meteorologic variable | | | | |
|   1-hr average temperature, °C | 451 | 23.4 | 1.9 | 20.0–27.1 |

## TABLE 2
Changes* in Blood Pressure and Heart Rate for $NC_{0.02-1}$ Exposures of 10,000 Particles/cm$^3$

| | 1-Hr Moving Average | | 2-Hr Moving Average | | 3-Hr Moving Average | | 4-Hr Moving Average | |
|---|---|---|---|---|---|---|---|---|
| | Changes | 95% CI | Changes | 95% CI | Changes | 95% CI | Changes | 95% CI |
| Systolic blood pressure, mm Hg | | | | | | | | |
|   All subjects | 1.40 | 0.05–2.76 | 3.40 | 1.16–5.67 | 2.60 | −0.10–5.34 | −1.10 | −3.07–0.95 |
|   Subjects with heart rate >72 beats/min | 1.00 | −0.96–2.96 | 4.00 | 0.67–7.33 | 1.89 | −2.33–6.12 | 1.00 | −3.72–3.72 |
|   Subjects with heart rate $\leqq$72 beats/min | 0.60 | −1.16–2.36 | 1.00 | −2.00–4.03 | 1.59 | −2.03–5.21 | −1.73 | −3.76–0.30 |
| Diastolic blood pressure, mm Hg | | | | | | | | |
|   All subjects | 1.40 | 0.46–2.25 | 2.20 | 0.81–3.68 | 1.90 | 0.10–3.62 | −0.70 | −2.03–0.67 |
|   Subjects with heart rate >72 beats/min | 1.76 | 0.42–3.10 | 3.22 | 1.13–5.32 | 2.35 | −0.42–5.13 | 1.80 | −0.71–4.30 |
|   Subjects with heart rate $\leqq$72 beats/min | 0.62 | −0.67–1.91 | 0.57 | −1.58–2.72 | 0.96 | −1.38–3.29 | −2.52 | −5.01–0.03 |
| Heart rate, beats/min | 0.28 | 0.34–2.22 | 1.22 | 0.43–4.02 | 3.50 | 1,51–5.57 | 0.50 | −1.03–1.98 |

*Model was adjusted for age, body mass index, tobacco exposure, hour of day, and 1-hr moving average of temperature.
CI indicates confidence interval.

hours. Our single-pollutant models showed that $NC_{0.02-1}$ was significantly associated with SBP and DBP and HR. $NC_{0.02-1}$ exposures at 1- to 3-hour moving averages significantly increased all subjects' SBP, DBP, and HR. For 10,000 particles/$cm^3$ $NC_{0.02-1}$ exposures, the single-pollutant models showed 1.4 to 3.4-mm-Hg increase in SBP, 1.4 to 2.2-mm-Hg increase in DBP, and a 0.3 to 3.5-beats/min increase in HR, respectively. For the patients with HR >72 beats/min, we found their SBP change was significantly associated with $NC_{0.02-1}$ exposures at 2-hour moving average and DBP change was associated with $NC_{0.02-1}$ exposures at 1- to 2-hour moving averages. By contrast, no association was found between BP and $NC_{0.02-1}$ in subjects with HR ≦72 beats/min.

The modeling results of the other five ambient air pollutants by our single-pollutant models are list in Table 3. We found a significantly positive association between CO exposure and HR among our study subjects. For 1 ppm CO exposures at 1-hour and 2-hour moving averages, we found 3.7 beats/min and 3.9 beats/min increases in HR, respectively. The observed trends between $PM_{10}$ and $NO_2$ and HR, although positive, were not statistically significant. Our single-pollutant models showed no association between BP with $PM_{10}$, $NO_2$, CO, $SO_2$, or $O_3$.

Multipollutant models with $NC_{0.02-1}$ and CO were performed to estimate the partial effects of $NC_{0.02-1}$ on HR with CO exposures and other key personal and environmental attributes being adjusted. We found

only $NC_{0.02-1}$ remained positively associated with HR in the multipollutant models. As shown in Figure 1, our subjects' heart rates were increased by approximately 0.6 beats/min and 3.9 beats/min for every
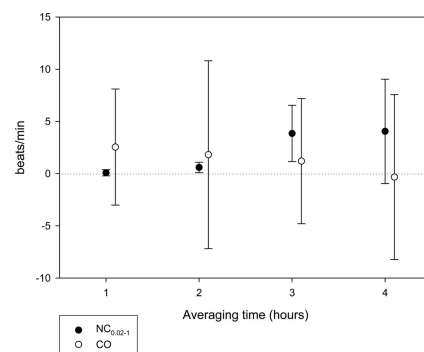


**Fig. 1.** Changes in heart rate per 10,000 particles/$cm^3$ $NC_{0.02-1}$ and 1 ppm CO estimated by multipollutant mixed-effects models.

## TABLE 3
Changes* in Blood Pressure and Heart Rate for Ambient Air Pollutant Exposures

| | $PM_{10}$ (1 μg/$m^3$) | | Nitrogen Dioxide (1 ppb) | | Carbon Monoxide (1 ppm) | | Sulfur Dioxide (1 ppb) | | Ozone (1 ppb) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Changes | 95% CI | Changes | 95% CI | Changes | 95% CI | Changes | 95% CI | Changes | 95% CI |
| Systolic blood pressure | | | | | | | | | | |
| 1-hr moving average | −0.12 | −0.24−0.00 | −0.10 | −0.31−0.11 | 0.04 | −4.54−4.62 | −0.29 | −1.25−0.66 | −0.07 | −0.24−0.11 |
| 2-hr moving average | −0.17 | −0.34−0.00 | −0.11 | −0.33−0.10 | −0.49 | −5.33−4.36 | −0.38 | −1.03−0.26 | −0.07 | −0.25−0.11 |
| 3-hr moving average | −0.20 | −0.40−0.01 | −0.09 | −0.32−0.13 | −0.31 | −5.65−5.02 | −0.34 | −1.07−0.39 | −0.10 | −0.28−0.08 |
| 4-hr moving average | −0.18 | −0.37−0.01 | −0.10 | −0.34−0.15 | −0.58 | −6.48−5.32 | −0.47 | −1.31−0.37 | −0.13 | −0.31−0.06 |
| Diastolic blood pressure | | | | | | | | | | |
| 1-hr moving average | −0.07 | −0.16−0.01 | −0.07 | −0.21−0.08 | 0.61 | −2.53−3.76 | −0.51 | −1.15−0.14 | −0.08 | −0.19−0.04 |
| 2-hr moving average | −0.10 | −0.20−0.00 | −0.06 | −0.20−0.09 | 0.67 | −2.66−3.99 | −0.11 | −0.56−0.33 | −0.07 | −0.19−0.06 |
| 3-hr moving average | −0.13 | −0.27−0.01 | −0.07 | −0.23−0.09 | 0.72 | −2.95−4.38 | −0.26 | −0.76−0.24 | −0.09 | −0.21−0.03 |
| 4-hr moving average | −0.14 | −0.28−0.00 | −0.08 | −0.25−0.09 | 0.20 | −3.91−4.30 | −0.38 | −1.00−0.20 | −0.09 | −0.22−0.03 |
| Heart rate | | | | | | | | | | |
| 1-hr moving average | 0.02 | −0.08−0.12 | 0.04 | −0.12−0.20 | 3.71 | 0.10−7.32 | −0.19 | −0.93−0.55 | −0.01 | −0.13−0.10 |
| 2-hr moving average | 0.01 | −0.10−0.13 | 0.02 | −0.14−0.19 | 3.93 | 0.65−7.21 | −0.31 | −1.14−0.52 | −0.02 | −0.13−0.10 |
| 3-hr moving average | 0.03 | −0.09−0.16 | −0.00 | −0.17−0.17 | 3.40 | −1.02−7.82 | 0.00 | −0.61−0.61 | −0.03 | −0.14−0.09 |
| 4-hr moving average | 0.03 | −0.11−0.17 | 0.00 | −0.19−0.19 | 3.63 | −1.64−8.91 | 0.25 | −0.44−0.93 | −0.05 | −0.17−0.07 |

*Model was adjusted for age, body mass index, tobacco exposure, hour of day, and 1-hr moving average of temperature.
CI indicates confidence interval.

10,000 particles/cm$^3$ increase in 2-hour and 3-hour NC$_{0.02-1}$ moving averages, respectively. We also intentionally forced performed PM$_{10}$ to our multipollutant models with NC$_{0.02-1}$ to see whether it could modify NC$_{0.02-1}$ effects on BP and HR. We found the partial effects of NC$_{0.02-1}$ on BP and HR remained the same as those in the models without PM$_{10}$. By contrast, we found PM$_{10}$ was not associated with BP and HR changes in the models (data not shown).

## Discussion

The effects of NC$_{0.02-1}$ on elevating SBP and DBP among our subjects, who were patients with lung function impairments, were similar to the effects of PM$_{2.5}$ on cardiac rehabilitation patients reported by Zanobetti et al.[11] By contrast, the association among PM$_{10}$, SBP, and DBP increase was either relatively small among subjects with severe chronic obstructive pulmonary disease (COPD) in a Los Angeles[10] or not significant among healthy adults in a São Paulo, Brazil, study.[18] There was also a slight association between TSP and SBP increase among a general population aged 25 to 64 years in an Augsburg study, Germany.[9] These studies demonstrated that smaller PM, ie, PM$_{1.0}$ and PM$_{2.5}$, could have greater effects on BP than larger PM, ie, PM$_{10}$ and TSP. Another interesting finding of our study is that greater NC$_{0.02-1}$ effects on BP were observed for subjects with higher heart rates (HR >72 beats/min) compared with those with lower heart rates (HR ≦72 beats/min). One previous study also reported similar results, which showed PM$_{2.5}$ had greater effects on DBP for cardiac rehabilitation patients with higher heart rates (HR ≧70 beats/min) compared with those with lower heart rates (HR <70 beats/min).[11] Such findings imply that HR seems to work as a modifier in the particulate effects on blood pressure.

The effects of NC$_{0.02-1}$ on HR increase in our subjects were consistent with previous findings of PM$_{10}$ on HR increase in cardiopulmonary patients in Utah Valley and Rome, Italy.[12,13] Although CO was associated with elevated HR in single-pollutant models, we found no such association in the multipollutant models with both CO and NC$_{0.02-1}$. We think that CO may serve as a surrogate pollutant of submicrometer particles, which have not yet been routinely monitored in most air-monitoring stations. We believe our data generally support that changes in submicrometer particles rather than CO can lead to increases in HR among patients with lung function impairments.

Evidence has shown that activation of the sympathetic nervous system plays an important role in hypertension and alteration of BP and HR.[19,20] The findings of NC$_{0.02-1}$ exposures on BP and HR in this study and on HRV in our previous study[14] suggest that NC$_{0.02-1}$ can have both immediate and cumulative effects on cardiac autonomic function in patients with lung function impairments. In vivo studies have shown that particles can affect both sympathetic and parasympathetic nervous systems directly in the immediate phase after exposures.[21,22] Studies also showed that inhaled particles less than 100 nm could rapidly pass into the blood circulation of human subjects and experimental hamsters in a few minutes and peak around 20 to 30 minutes after exposure.[23,24] Such a direct effect of PM represents a plausible explanation for the occurrence of rapid cardiovascular responses to 1-hour moving average of NC$_{0.02-1}$ exposures. Studies also showed that vascular endothelial perturbation[25] and systemic inflammation[26–28] and then altered sympathetic nerve activity and blood pressure[29] would occur hours and days after PM exposures in either human subjects or experimental animals. Accordingly, we believe particles-induced systemic inflammation can also indirectly result in BP and HR changes in the delayed phase after NC$_{0.02-1}$ exposures. This may explain why BP and HR increase reaches its peak at 2 to 3 hours after NC$_{0.02-1}$ exposure in this study.

Our findings of the association between NC$_{0.02-1}$ and increase in BP and HR can be confounded by unavailable personal exposure data of other air pollutants in this study. The lack of personal exposure to NO$_2$, O$_3$, and SO$_2$ may still confound the observed associations between NC$_{0.02-1}$ and increase in BP and HR even though no such association has been found by using fixed-site monitoring data. Because these unmeasured air pollutants are usually correlated with PM, we may bias study outcomes toward either positive or null results.[30,31] Comorbidity and medication in our patients with lung function impairments can still confound our findings, although we have used very strict criteria to exclude cases with severe chronic diseases and specific medication from our study subjects. Larger sample size is still needed to extrapolate our findings because the effects of time-invariant variables such as age and body mass index on between-subjects BP and HR may not be completely evaluated by our relatively small sample size ($n$ = 10). However, we had sufficient sample size ($n$ = 444 of BP and 316 of HR) to evaluate the effects of time-varying environmental factors on within-subject changes in BP and HR.

Regardless of these limitations, we believe our data generally support that changes in NC$_{0.02-1}$ can lead to increases in BP and HR among patients with lung function impairments. Both elevated BP and HR can serve as markers for altered autonomic activity.[19,32] Cardiovascular mortality and morbidity are also reported to be increased by elevated BP[33,34] or higher HR.[35,36] However, it is still unknown whether short-term and small fluctuations of autonomic activity are associated with higher risks of cardiovascular diseases clinically. Therefore, further studies on environmental cardiology

are needed to determine whether the $NC_{0.02-1}$-associated autonomic activity fluctuations observed in this panel study will have meaningful implications on cardiovascular mortality clinically.

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