Environmental Carbon Monoxide Level Is Associated With the Level of High-Sensitivity C-Reactive Protein in Peritoneal Dialysis Patients

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Abstract: Inflammation is highly prevalent among peritoneal dialysis (PD) patients. High-sensitivity C-reactive protein (hs-CRP) is the most widely used inflammatory marker in clinical medicine and is correlated with mortality in PD patients. Air pollution is associated with systemic inflammation. The aim of this cross-sectional study was to assess the role of air pollutants and other clinical variables on hs-CRP values in PD patients.

We recruited a total of 175 patients who had been undergoing continuous ambulatory PD or automated PD for at least 4 months and regularly followed up. Air pollution levels were recorded by a network of 27 monitoring stations near or in the patients’ living areas throughout Taiwan. The 12-month average concentrations of particulate matter (PM) with an aerodynamic diameter of <10 and <2.5 μm (PM10 and PM2.5), sulfur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), and ozone (O3) were included.

In stepwise linear regression, after adjustment for related factors, white blood cell count (β: 0.27, 95% confidence interval [CI] [0.71, 2.11]) and CO level (β: 0.17, 95% CI [2.5, 21.32]) were positively associated with hs-CRP and serum albumin levels (β: −0.25, 95% CI [−13.69, −3.96]) and normalized protein nitrogen appearance (NPNA) was negatively associated with hs-CRP. However, serum indoxyl sulfate and p-cresyl sulfate levels were not significantly associated with hs-CRP (P > 0.05).

In PD patients, the environmental CO level was positively correlated with hs-CRP level.

INTRODUCTION

The prevalence of inflammation among peritoneal dialysis (PD) patients is high. Inflammation is a powerful predictor of mortality and cardiovascular death in patients with end-stage renal disease (ESRD). The causes of inflammation in PD patients are complex and multifactorial, including factors related or unrelated to dialysis.1 The dialysis-related factors causing chronic inflammation in PD patients include peritoneal catheter use, glucose in the dialysate, peritonitis, exit-site infection, and endotoxins/cytokines from the dialysate; those factors unrelated to dialysis include loss of residual renal function,2–5 accumulation of uremic toxins, other comorbidities, malnutrition, or other infections.1 Chronic kidney disease (CKD) may act as a potent stimulus of inflammation.6,7 Protein-bound uremic toxins such as p-cresyl sulfate (PCS) and indoxyl sulfate (IS) are associated with atherosclerosis and endothelial dysfunction, and activation of atherosclerotic proinflammatory markers.8–11 C-reactive protein (CRP) is the most widely used inflammatory marker in clinical medicine. A change in residual kidney function has also been associated with an increase in CRP in PD patients.12 Several other studies reported a similar association between increased CRP level and increased mortality in both hemodialysis13,14 and PD patients.15–17 Interestingly, several studies have revealed that air pollution is associated with systemic inflammation.18–20 The 6 most common air pollutants are particulate matter (PM), lead (Pb), sulfur dioxide (SO2), nitrogen oxides (NOx), ozone (O3), and carbon monoxide (CO).21 Poor air quality has a profound and lasting effect on human health, particularly on the respiratory, cardiovascular,22,23 and central nervous systems.24–26 In a recent study, chronic CO exposure was associated with arterial wall thickness and an elevated level of high-sensitivity CRP (hs-CRP).27 To our knowledge, few studies have investigated air pollution as a dialysis-unrelated factor causing chronic inflammation in PD patients. The aim of this prospective cross-sectional study was to assess the role of air pollutants and other clinical variables on hs-CRP values in PD patients.

MATERIALS AND METHODS

This study was approved by the ethical committee of the Chang Gung Memorial Hospital, Linkou, Taiwan, and performed in accordance with the principles of the Declaration of Helsinki. All the data were analyzed anonymously, and all patients’ records and information were anonymized and de-identified before analysis. Furthermore, all information was

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Key Words: Inflammation, peritoneal dialysis, high-sensitivity C-reactive protein, carbon monoxide, particulate matter.

Abbreviations: AI = blood aluminum, APD = automated PD, CAD = coronary artery disease, CAPD = continuous ambulatory PD, CKD = chronic kidney disease, CO = carbon monoxide, Cr = creatinine, CVD = cardiovascular disease, DM = diabetes mellitus, ESRD = end-stage renal disease, hs-CRP = high-sensitivity C-reactive protein, iPTH = intact parathyroid hormone, IS = indoxyl sulfate, NO2 = nitrogen dioxide, NPNA = normalized protein nitrogen appearance, O3 = ozone, PCS = p-cresyl sulfate, PD = peritoneal dialysis, PM = particulate matter, PM10 = particulate matter with an aerodynamic diameter ≤10 μm, PM2.5 = particulate matter with an aerodynamic diameter ≤2.5 μm, SO2 = sulfur dioxide, WBC = white blood cell count.
securely protected (by delinking identifying information from the main data set) and available to investigators only. Finally, all primary data were collected according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

**Study Population**

Initially, we randomly recruited a total of 175 patients who had been undergoing continuous ambulatory PD (CAPD) or automated PD (APD) for at least 4 months and regularly followed up at a PD center in Chang Gung Memorial Hospital. All patients were randomly recruited between October 1 and November 30, 2009. Patients with a history of dialysis-related infection or other types of active infections within 3 months before study inclusion were excluded. PD supplies (CAPD and APD solutions) were obtained from Baxter Healthcare SA, Singapore. All patients gave their informed written consent. Age, gender, and clinical data were obtained from the patients’ medical records. All medical records during the study period, including medical history, laboratory data, and inclusion and exclusion factors, were reviewed by 2 nephrology specialists (W-HH and T-HY) and 1 general physician (M-JC).

**Sample Collection**

Fasting blood, urine, and dialysate samples were collected on the same day between October 1 and November 30, 2009 during each patient’s yearly routine examination, which included a peritoneal membrane function test. The plasma, dialysate, and urine concentrations of creatinine (Cr), serum albumin, and urea nitrogen were measured using routine laboratory methods. On the basis of the studies on the contributions of PCS and IS in the pathogenesis of vascular injury through endothelial dysfunction, proliferation of vascular smooth muscle cells, activation of atherosclerotic proinflammatory markers, and suppression of endothelial repair, we measured the serum concentrations of total formed IS and PCS for their correlation with the hs-CRP level. Protein nitrogen appearance was normalized to body weight (nPNA). Anuria was defined as 24-hour urine volume <50 cm³. Residual renal function was calculated as follows: (renal normalized urea nitrogen clearance + renal normalized Cr clearance)/2. Owing to the lack of any definite hs-CRP cutoff level indicating an inflammatory state in PD patients, inflammation was defined as an hs-CRP level of ≥10 mg/L, a level that has been correlated with increased mortality risk in PD patients. Levels of the air pollutants were also categorized into high and low according to the median value of each of the 6 air pollutants. The method for testing of IS and PCS was referenced from a previous study.

**Air Quality Status and Analysis**

To verify our inference that levels of air pollutants are correlated with hs-CRP values in PD patients, we analyzed the database and cited the report on the air quality status in Taiwan, using the data from the Taiwan Air Quality Monitoring Network operated by the Environmental Protection Administration. We recorded and analyzed the difference in air quality from the previous 12-month average exposure concentration of air pollutants according to the patients’ living areas. To the best of our knowledge, the appropriate averaging time for the air pollution effect on inflammation is unclear. Previous studies showed that the effect is spread overall for several days,29,30 months,31 or even years.32 From the above-cited studies, we considered the previous 12-month average exposure concentration of air pollutants for each subject’s examination. The referenced items included previous 12-month average concentrations of PM with an aerodynamic diameter of <10 and <2.5 μm (PM_{10} and PM_{2.5}), SO₂, NOₓ, CO, and O₃. Air pollution levels were recorded by a network of 27 monitoring stations near or in the patients’ living areas throughout Taiwan. The most northern living area is Hsichih District and the most southern area is Changhua City.

**Statistical Analysis**

The Kolmogorov–Smirnov test was used to test if variables were to be normally distributed. A P value >0.05 was required to assume a normal distribution. Data are expressed in terms of median and interquartile range in nonnormal distribution variables and as mean ± standard deviation in normal distribution variables. Comparisons between groups were performed using the Mann–Whitney test and Student t test. Fisher exact tests were used to analyze the correlation between categorical variables. To calculate the relative correlation of the hs-CRP value, standardized coefficients (b) and 95% CIs were obtained using linear regression models. Univariate and stepwise linear regression analyses were used. The following factors were investigated: PM_{10}, SO₂, NOₓ, CO, O₃, PM_{2.5}, age, PD duration, serum Cr level, white blood cell count (WBC), nPNA, serum albumin, serum total IS, serum total PCS, residual renal function test, intact parathyroid hormone level (iPTH), blood aluminum (Al) level, diabetes mellitus (DM), coronary artery disease (CAD), and hypertension. All the nominal variables in linear regression were transformed into dummy coding. Missing data was approached with listwise deletion. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 12.0 for Windows (SPSS Inc, Chicago, IL). A P value of <0.05 was considered statistically significant.

**RESULTS**

**Patient Characteristics**

A total of 175 patients from a single PD center were enrolled in this study. Fourteen patients received APD and 161 patients received CAPD. Table 1 lists the characteristics of the study subjects (mean age, 50 years). Of all patients, 125 were women and 78 patients showed anuria. Furthermore, the daily exchange volume was 9.85 L. The median hs-CRP level was 2.8 mg/L (range, 1.2–7.6 mg/L). Fifteen patients (8.5%) were habitual users of tobacco. The median concentration of PM_{10} was 49.1 μg/m³; SO₂, 5.2 ppb; NOₓ, 20.1 ppb; CO, 0.53 ppm; O₃, 28.7 ppb; and PM_{2.5}, 29.6 μg/m³. The causes of ESRD were diabetic nephropathy (n = 21), polycystic kidney disease (n = 1), glomerular disease (n = 79), malignant hypertension (n = 15), obstructive nephropathy (n = 3), lupus nephritis (n = 4), gouty nephropathy (n = 2), tubulointerstitial disease (n = 2), and unknown factors (n = 48).

**Factors Associated With hs-CRP Level in Patients With PD**

The correlation between CO and hs-CRP was revealed in Figure 1 (r = 0.16, P = 0.03). To further investigate the correlation between inflammation (hs-CRP ≥10 mg/L) and the 6 air pollutants, we categorized the levels into high and low levels according to each pollutant’s median value and analyzed the results with the linear trend for ordinal variables analysis. The median value of PM_{10} was 49.1 μg/m³; SO₂, 5.2 ppb; NOₓ, 20.1 ppb; CO, 0.53 ppm; O₃, 28.7 ppb; and PM_{2.5}, 29.6 μg/m³. Table 2 shows that among the 6 air pollutants, a high level
of CO was significantly (P = 0.04) associated with a high level of hs-CRP (≥10 mg/L); however, all the other pollutants did not show a significant association (P > 0.05). In this study, 75 patients lived in the area of higher level of CO and other 100 patients lived with contrary condition. Thirty patients had inflammation status. Except for gender, no related clinical variables were different between these 2 groups (Table 3).

To further clarify the factors associated with hs-CRP level in our study patients, we used univariate and multivariate linear regression "stepwise" methods, for analyses. PM10, SO2, NO2, CO, O3, PM2.5, age, PD duration, serum Cr level, WBC, nPNA, serum albumin level, serum total IS, serum total PCS, residual renal function test, iPTH, blood Al level, DM, CAD, and hypertension were investigated as clinical variables. Table 4 revealed that in univariate linear regression, the environmental CO level (β: 0.16, 95% CI [0.91, 21.27]), blood Al level (β: 0.16, 95% CI [0.17, 3.91]), and blood WBC (β: 0.24, 95% CI [0.51, 1.98]) were positively associated with hs-CRP and serum albumin levels (β: −0.22, 95% CI [−12.95, −2.78]), and log nPNA (β: −0.24, 95% CI [−50.47, −12.75]) was negatively associated with hs-CRP level. Except for CO, the other air pollutants were not associated with hs-CRP level (P > 0.05). Furthermore, in the "stepwise" model of linear regression, after adjustment for related factors, blood WBC (β: 0.28, 95% CI [0.73, 2.12]) and CO level (β: 0.17, 95% CI [2.54, 21.27]) were positively associated with hs-CRP and serum albumin levels (β: −0.25, 95% CI [−13.51, −3.93]), and log nPNA (β: −0.18, 95% CI [−17.25, −2.33]) was negatively associated with hs-CRP level. However, serum IS and PCS levels were not significantly associated with hs-CRP level (P > 0.05).

**DISCUSSION**

In this study, we have shown that after adjustment for related risk factors, the level of the air pollutant CO was significantly positively associated with the level of the inflammation marker hs-CRP in PD patients.

It is well known that cardiovascular disease (CVD) is the leading cause of death in patients with ESRD, and chronic inflammation is a risk factor correlated with CVD. Inflammation is highly prevalent in the PD population. When estimated by CRP level with different cutoff values and assay sensitivities, the prevalence of inflammation varied between 12% and 65%. The causes of inflammation in PD patients are multifactorial, primarily systemic infection, glucose in the dialysate, peritonitis, malnutrition, residual renal function, and accumulation uremic toxins. Bergstrom showed an important association between increased CRP level and increased mortality in hemodialysis patients. A number of other studies reported a similar association between increased CRP level and increased mortality in both hemodialysis and PD patients. Herzig et al showed in a study of 50 PD patients that an increased CRP level was associated with an increased risk of acute myocardial infarction. Wang et al also pointed out that an increased CRP level predicts mortality in cardiovascular death independent of other clinical, cardiovascular, dialysis, nutritional, and biochemical parameters. Iseki et al reported that in a 5-year follow-up study, a CRP level of 10 mg/L or higher was associated with a 3-fold increased mortality in PD patients. An increased CRP level has also been associated with poor outcomes in PD patients.
shown to predict cardiovascular events in PD patients independent of other traditional and nontraditional risk factors.

Interestingly, several studies have revealed that air pollution is associated with systemic inflammation. The most common air pollutants are PM, Pb, SO2, NO2, O3, and CO. In addition, air pollution has been associated with increased incidence of and mortality from CAD. In a large population and long follow-up study of 6 US cities (Harvard Six Cities study), a significant association was noted between air pollution and mortality after adjustment for smoking, particularly in cities where pollutant levels were highest. An extended follow-up of the Harvard Six Cities study showed that cardiovascular and lung cancer mortality rates were each positively associated with fine particulate air pollution (PM2.5).

To our knowledge, reports on the association between inflammation and air pollution in PD patients are limited. In this study, we found that the CO level is positively associated with the level of hs-CRP after adjustment for related risk factors. CO is a colorless, odorless, and tasteless gas that is slightly lighter than air. It occurs in various natural and artificial environments. However, with increasing industrialization and urbanization, CO is chiefly emitted from the exhaust of internal combustion engines and industrial production, as well as from incomplete combustion of various other fuels. CO is toxic to

### TABLE 2. Linear Trend for Ordinal Variables Analysis of Air Pollutants and hs-CRP

| Pollutant | Low* hs-CRP < 10 mg/L | High† hs-CRP ≥ 10 mg/L | P for trend |
|-----------|-----------------------|------------------------|------------|
| PM10      | 70                    | 75                     | 0.13       |
| SO2       | 88                    | 57                     | 0.28       |
| NO2       | 89                    | 56                     | 0.13       |
| CO        | 88                    | 57                     | 0.04       |
| O3        | 77                    | 68                     | 0.33       |
| PM2.5     | 97                    | 48                     | 0.28       |

CO = environmental carbon monoxide, hs-CRP = high-sensitivity C-reactive protein, NO2 = environmental nitrogen dioxide, O3 = environmental ozone, PM10 = environmental particulate matter with aerodynamic diameter <10 μm, PM2.5 = environmental particulate matter with aerodynamic diameter <2.5 μm, SO2 = environmental sulfur dioxide.

* Level lower than the median level of each air pollutant.
† Level higher than or equal to the median level of each air pollutant.

### TABLE 3. Comparison of Patients With Low and High-Environmental CO Exposure

| Low CO (n = 100) | High CO (n = 75) | P |
|------------------|------------------|---|
| Age              | 49.37 ± 10.23    | 50.42 ± 11.66 | 0.53 |
| Smoking          | 8                | 7              | 0.48 |
| CVD              | 3                | 0              | 0.18 |
| Hypertension     | 5               | 33             | 0.51 |
| DM               | 14               | 7              | 0.24 |
| HBV              | 10               | 7              | 0.54 |
| HCV              | 1                | 1              | 0.11 |
| BSA, m²          | 1.57 ± 0.153     | 1.58 ± 0.17    | 0.60 |
| PD duration, mo  | 58 ± 38.2        | 67.92 ± 42.26  | 0.11 |
| Residual renal function | 2.1 (0–10.7) | 1.5 (0–8.9) | 0.49 |
| Sex (M/F)        | 22/78            | 28/47          | 0.02 |
| CT ratio         | 0.50 ± 0.06      | 0.50 ± 0.071   | 0.64 |
| Serum Cr, mg/dl  | 11.37 ± 2.86     | 11.54 ± 2.60   | 0.67 |
| WBC, ×10³/L      | 7.64 ± 2.54      | 7.64 ± 2.12    | 0.99 |
| AL, µg/L         | 0.8 (0.2–1.27)   | 0.8 (0.4–1.3)  | 0.31 |
| iPTH, pg/dL      | 126 (63.2–361)   | 249 (63.2–550) | 0.31 |
| Albumin, g/L     | 4.05 ± 0.34      | 4.10 ± 0.34    | 0.29 |
| nPNA, g/kg/d     | 1.02 ± 0.19      | 1.02 ± 0.245   | 0.88 |
| KT/V P           | 2.01 ± 0.40      | 2.05 ± 0.40    | 0.48 |
| KT/V K           | 0.055 (0–0.28)   | 0.03 (0–0.21)  | 0.99 |
| CCr K, L/wk/1.73 m² | 2.55 (0–12.3) | 1.69 (0–9.74) | 0.99 |
| CCr P, L/wk/1.73 m² | 50.56 ± 12.05 | 52.43 ± 11.11 | 0.28 |

Al = aluminum, BSA = body surface areas, CCr K = normalized renal creatinine clearance, CCr P = normalized peritoneal creatinine clearance, Cr = creatinine, CT = cardiothoracic, CVD = cardiovascular disease, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, hs-CRP = high-sensitivity C-reactive protein, iPTH = intact parathyroid hormone, KT/V K = renal KT/V, KT/V P = peritoneal KT/V, nPNA = normalized protein nitrogen appearance, PD = peritoneal dialysis, WBC = white blood cell counts. Low CO exposure: level lower than or equal the level of median (0.53 ppm) of environmental CO level. High CO exposure: level higher than the level of median (0.53 ppm) of environmental CO level. Residual renal function presented as: (normalized renal urea nitrogen clearance + CCr P K)/2.
TABLE 4. Linear Regression Analysis Between Clinical Variables and hs-CRP Level (N=175)

| Univariate Linear Regression β (95% CI) | P | Stepwise Linear Regression β (95% CI) | P |
|----------------------------------------|---|--------------------------------------|---|
| PM$_{10}$                              | -0.01 (-0.25, 0.20) | 0.83 | 
| SO$_2$                                 | 0.03 (-0.93, 1.46)  | 0.66 |
| NO$_2$                                 | 0.13 (-0.04, 0.83)  | 0.07 |
| CO                                     | 0.16 (0.91, 21.27)  | 0.03 | 0.17 (2.54, 21.27) | 0.01 |
| O$_3$                                  | -0.09 (-1.02, 0.23) | 0.21 |
| PM$_{2.5}$                             | 0.03 (-0.35, 0.58)  | 0.63 |
| Age                                    | 0.13 (-0.01, 0.31)  | 0.07 |
| Cr                                     | -0.03 (-0.8, 0.51)  | 0.64 |
| WBC                                    | 0.24 (0.51, 1.98)   | 0.001 | 0.28 (0.73, 2.12) | <0.001 |
| Log nPNA                               | -0.24 (-50.47, -12.75) | 0.001 | -0.18 (-17.25, -2.33) | 0.009 |
| Albumin                                | -0.22 (-12.95, -2.78) | 0.003 | -0.25 (-13.51, -3.93) | <0.001 |
| Log iPTH                                | -0.02 (-3.51, 2.64) | 0.78 |
| Al                                     | 0.16 (0.17, 3.91)   | 0.03 |
| IS                                     | -0.04 (-0.13, 0.07) | 0.57 |
| PCS                                    | -0.12 (-0.19, 0.01) | 0.10 |
| Duration                               | 0.07 (-0.02, 0.06)  | 0.32 |
| Residual renal function$^1$            | -0.11 (-0.26, 0.03) | 0.14 |
| DM                                     | 0.10 (-1.58, 9.33)  | 0.16 |
| CAD                                    | -0.05 (-18.55, 8.89) | 0.48 |
| HTN                                    | -0.008 (-3.78, 3.39) | 0.91 |
| Smoking                                | 0.09 (-2.41, 10.27) | 0.22 |

Initially, univariate linear regression analysis was performed to identify the variables associated with hs-CRP levels in 175 patients. WBC, blood Al, environmental CO, albumin, and nPNA were found to be associated with hs-CRP levels. In a further analysis with stepwise linear regression, WBC, albumin, nPNA, and CO were found to be positively correlated with hs-CRP levels. The environmental CO level was positively correlated with hs-CRP levels. In our study, we found that in PD patients, the environmental CO level was positively correlated with hs-CRP level. This result agrees with the findings of the studies cited above.

CONCLUSION

In conclusion, this cross-sectional study shows that in patients with PD, the environmental CO level is associated with the level of hs-CRP. Further studies are required to clarify the role of environmental air pollutants in inflammation and related comorbidities in PD patients.

Limitations

This study has several limitations. Among them is the cross-sectional nature of the observation and that the study group is predominantly represented by women. In our PD center, the patients themselves choose between PD and HD. Considering the working environment and home-care conditions, most women chose PD. On the contrary, according to the limitations in technology and information on indoor air quality, we used the previous 1-year average air quality published by the Environmental Protection Administration Executive Yuan, Taiwan to represent the air quality of the patients’ living areas.

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