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Effects of oxidative stress on blood pressure and electrocardiogram findings in workers with occupational exposure to lead

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Abstract

Objective: To observe the correlation between the oxidative stress index and cardiovascular system damage in a population with lead exposure.

Methods: Two populations (144 manufacturing workers and 94 administrators) from a lead–acid battery manufacturer in Shandong Province in China were recruited. The blood lead level, oxidative stress index, blood pressure, electrocardiogram findings, and their correlations were analyzed in both groups.

Results: The blood lead level was significantly higher in manufacturing workers than administrators (254.34 vs. 65.32 μg/L, respectively). The differences in the oxidative stress index, serum total superoxide dismutase (T-SOD) concentration, and malondialdehyde (MDA) concentration between the two populations were statistically significant. The rates of abnormal blood pressure and electrocardiogram findings were significantly higher in manufacturing workers than administrators. Workers with middle- and high-dose lead exposure had lower T-SOD and higher MDA concentrations than those with low-dose lead exposure. Significant correlations were found between the blood lead level and the MDA concentration, systolic pressure, diastolic pressure, and electrocardiogram findings. Linear multiple regression analysis showed that T-SOD was negatively associated with blood lead, electrocardiogram findings, and MDA.

Conclusion: Lead exposure can lead to oxidative stress, increased blood pressure, and abnormal electrocardiogram findings and may impact cardiovascular diseases through oxidative stress.

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Introduction

The heavy metal lead is a common occupational and environmental pollutant, and damage caused by lead exposure is still a major public health problem. In 2004, the possible carcinogen grade of inorganic lead was promoted from Group 2B to 2A by the International Cancer Research Institute.[1] Lead can damage the nervous system, cardiovascular system, circulatory system, urinary system, reproductive system, and other organs and systems. Heavy metal contaminants are considered strong toxic substances. Induced oxidative stress plays a key role in the pathogenicity of heavy metal contaminants.[2–5] Heavy metal compounds participate in a Fenton-like reaction to produce more reactive oxygen species (ROS), which induce oxidative stress.[6] In 1965, Wills[7] discovered that lead toxicity was associated with oxidative stress. Additionally, epidemiological studies have revealed toxic effects of lead on the cardiovascular system.[8–11] As the levels of *in vivo* lead exposure biomarkers (such as blood lead and bone lead) increase, the risk of cardiovascular diseases such as hypertension, coronary heart disease, and atherosclerosis also increase. Likewise, the mortality of these cardiovascular diseases rises. Youdim et al.[12] and Stehbens[13] found that oxidative stress was involved in many pathological processes of cardiovascular diseases. The lead–acid battery industry consumes the largest amount of lead. At present, the lead–acid battery industry in China is ranked first in the world in terms of production, consumption, and even export volume. During the manufacture of lead–acid batteries, lead can enter the body of workers through the mouth or nose or by skin contact, resulting in an elevated blood lead concentration. In the present study, we explored the relationship between oxidative stress and cardiovascular system injury in lead-exposed workers by measuring the blood lead concentration, serum total superoxide dismutase (T-SOD) concentration, malondialdehyde (MDA) concentration, blood pressure, and electrocardiogram (ECG) findings. The results of this study may contribute to the identification of oxidative stress lead-exposed workers with cardiovascular system injury. The findings will provide a theoretical basis for the prevention and treatment of cardiovascular toxicity by lead exposure.

Materials and methods

Participants

Manufacturing workers and administrators in a lead–acid battery manufacturing enterprise in Shandong Province in China were recruited by random cluster sampling, and all of the participants had been working in that company for more than 6 months. Subjects who had been treated with deleading agents and/or had upper respiratory tract infections during the first 3 weeks and those with a history of respiratory diseases were excluded. No subjects had abnormal ECG findings during the pre-job

physical examination. The administrators were assigned to the control group and the manufacturing workers were assigned to the lead-exposed group. This study was approved by the ethics committee of Shandong Academy of Medical Sciences, and written consent was obtained from all subjects after they had been informed of the importance of the study.

Each participant was asked to complete a questionnaire regarding personal characteristics (sex, age, height, weight, and residence area), lifestyle (smoking and drinking), and occupational history (history in the current business, seniority, and use of protective equipment).

Sampling

After the participants underwent an overnight fast, blood specimens were collected for analysis. Five milliliters of blood mixed with heparin was sampled for determination of the blood lead concentration. Another 5 mL of blood with no anticoagulant reagents was centrifuged at a speed of 3500 rpm, and the upper serum was packed and stored at −80°C to analyze the oxidation effect of the subjects.

Measurement of blood lead concentration and oxidative stress index

The blood lead concentration was analyzed by graphite furnace atomic absorption spectrometry as previously described.[14] An T-SOD detection kit (hydroxylamine method) was used to determine the serum T-SOD activity (Nanjing Jiancheng Bioengineering Institute, Nanjing, China), and an MDA determination kit (thiobarbituric acid method) was used to determine the serum MDA concentration (Nanjing Jiancheng Bioengineering Institute).

Cardiovascular indicators

A mercury sphygmomanometer was used to measure blood pressure. After resting for at least 5 minutes, each participant's blood pressure was measured three times, at 5-minute intervals, by the tail-cuff method on the upper left arm with the participant in a sitting position.

The ECG examination was performed using a Japanese photoelectric 9020P automatic ECG analyzer. After resting for at least 5 minutes, the participant was connected to 12 ECG leads (18 ECG leads if necessary) in the supine position to collect ECG data. All ECG findings were reviewed by three cardiovascular specialists. Previously established ECG diagnostic criteria were used.[15]

Statistical methods

IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Wilcoxon rank sum test was applied to analyze numeration data, including age, working years, blood lead concentration, and oxidative damage biomarkers. Associations between variables were determined using Spearman's rho (rank) correlation analysis. A multivariate logistic regression model was built to analyze the association of the blood lead concentration with oxidative damage indices and cardiovascular damage indices.

Results

Demographic, occupational, and lifestyle characteristics of study subjects

The demographic and occupational characteristics of the subjects are shown in Table 1. We investigated 146 lead-exposed workers and 95 controls, and 2 lead-exposed worker and 1 controls did not complete the questionnaire. The lead-exposed group comprised 112 men (77.8%) and 32 women

Table 1. Demographic characteristics and occupational histories of participants.

	Control group (n = 94)	Lead-exposed group (n = 144)	P value
Age, years	42.2 ± 7.8	37.7 ± 8.2	0.049
Sex			
Men	67 (71.3)	112 (77.8)	0.256
Smoking status			
Yes	25 (26.6)	51 (35.4)	0.154
Alcohol drinker			
Yes	21 (22.3)	39 (27.1)	0.410
Work years	7.7 ± 3.7	4.3 ± 2.5	<0.001

Data are expressed as mean ± standard deviation or n (%).

Table 2. Oxidative stress, electrocardiogram findings, and blood pressure in control and lead-exposed groups in the lead–acid battery production industry.

	Control group (n = 94)	Lead-exposed group (n = 144)	P value
Blood lead, μg/L	65.3 ± 37.3	254.3 ± 120.1	<0.001
T-SOD, U/mL	48.4 ± 15.7	13.1 ± 5.1	<0.001
MDA, μmol/L	4.1 ± 0.7	6.7 ± 0.8	<0.001
Systolic pressure, mmHg	116.8 ± 10.1	121.4 ± 9.9	0.005
Diastolic pressure, mmHg	76.2 ± 7.3	79.8 ± 7.8	0.039
Abnormal electrocardiogram	14 (14.9)	43 (29.9)	0.008

Data are expressed as mean ± standard deviation or n (%). T-SOD, serum total superoxide dismutase; MDA, malondialdehyde.

(22.2%) with a mean age of 37.7 years and mean exposure period of 4.3 years. The control group comprised 67 men (71.3%) and 27 women (28.7%) with a mean age of 42.2 years and mean exposure period of 7.7 years.

There was no significant difference in sex, smoking habits, or drinking habits between the control group and lead-exposed group. Participants in the control group tended to be older than those in the lead-exposed group ($P = 0.049$) and had more exposure years ($P < 0.01$).

Blood lead level and oxidative stress index

The blood lead levels in the two groups are shown in Table 2. The mean blood lead level in the lead-exposed group was significantly higher than that in the control group (254.3 ± 120.1 vs. 65.3 ± 37.3 μg/L, respectively; $P < 0.01$). The T-SOD activity was significantly lower and the MDA concentration was significantly higher in the lead-exposed group than control group ($P < 0.01$ for both) (Table 2).

Comparison of blood pressure and ECG findings between the two populations

The mean blood pressures in the lead-exposed group and control group are shown in Table 2. The systolic and diastolic blood pressures were 121.4 ± 9.9 and 79.8 ± 7.8 mmHg, respectively, in the lead-exposed group and 116.8 ± 10.1 and 76.2 ± 7.3 mmHg, respectively, in the

control group. Statistical analysis showed that both the systolic and diastolic blood pressures were significantly higher in the lead-exposed group than control group ($P < 0.05$ for both).

In total, 43 (29.9%) participants in the lead-exposed group had abnormal ECG findings, including 10 (6.9%) with sinus arrhythmia, 5 (3.5%) with premature beats, 4 (2.8%) with incomplete bundle branch block, 12 (8.3%) with a low T wave or bidirectional T wave, 6 (4.2%) with a prolonged Q-T interval, and 6 (4.2%) with other abnormalities. Fourteen (14.9%) participants in the control group had abnormal ECG findings, including 4 (4.3%) with sinus arrhythmia, 2 (2.2%) with premature beats, 3 (3.2%) with incomplete bundle branch block, 4 (4.3%) with a low T wave or bidirectional T wave, and 1 (1.1%) with a prolonged Q-T interval. The rate of ECG abnormalities was significantly higher in the lead-exposed group than control group ($P < 0.01$) (Table 2).

There was no significant difference in the systolic blood pressure, diastolic blood pressure, or abnormal ECG findings between men and women (Table 3).

Different doses of lead exposure were defined according to the blood lead level: low-dose exposure, <100 μg/L; middle-dose exposure, 100 to 400 μg/L; and high-dose exposure, >400 μg/L.[16] Workers with middle- and high-dose lead exposure had lower T-SOD concentrations and higher MDA concentrations than workers with low-dose lead exposure ($P < 0.05$ for both). The systolic and diastolic blood pressures increased as the dose of lead exposure increased ($P < 0.01$ for both) (Table 4).

Table 3. Electrocardiogram abnormalities and blood pressures in lead-exposed women and men in the lead–acid battery production industry.

	Men (n = 112)	Women (n = 32)	P value
Systolic pressure, mmHg	124.1 ± 12.4	120.4 ± 9.3	0.393
Diastolic pressure, mmHg	80.7 ± 8.4	76.9 ± 7.6	0.127
Abnormal electrocardiogram	35 (14.9)	8 (29.9)	0.662

Data are expressed as mean ± standard deviation or n (%).

Table 4. Oxidative stress, electrocardiogram abnormalities, and blood pressure among workers in the lead–acid battery production industry according to doses of lead exposure.

	Low-dose exposure (n = 96)	Middle-dose exposure (n = 132)	High-dose exposure (n = 10)	P value
T-SOD, U/mL	42.8 ± 17.3	17.0 ± 14.7	8.2 ± 0.8	<0.001
MDA, μmol/L	4.4 ± 1.0	6.4 ± 1.1	7.1 ± 0.8	<0.001
Systolic pressure, mmHg	116.5 ± 10.2	121.4 ± 9.4	124.1 ± 16.7	<0.001
Diastolic pressure, mmHg	76.6 ± 7.7	79.4 ± 7.4	82.5 ± 10.7	0.008
Abnormal electrocardiogram	13 (13.5)	39 (29.5)	5 (50.0)	0.003

Data are expressed as mean ± standard deviation or n (%). T-SOD, serum total superoxide dismutase; MDA, malondialdehyde.

Different doses of lead exposure were defined according to the blood lead level: low-dose exposure, <100 μg/L; middle-dose exposure, 100–400 μg/L; and high-dose exposure, >400 μg/L.

Table 5. Correlations of blood lead level with oxidative damage indices and cardiovascular damage indices.

Parameters	T-SOD	MDA	Systolic pressure	Diastolic pressure	Electrocardiogram
Blood lead	−0.659[b]	0.690[b]	0.246[b]	0.239[b]	0.229[b]
T-SOD	–	–	−0.126 (0.053)	−0.134[a]	−0.058 (0.374)
MDA	–	–	0.163[b]	0.151[b]	0.162[b]

Analysis was performed using Pearson's test. T-SOD, serum total superoxide dismutase; MDA, malondialdehyde.
[a]Correlation coefficient significant at $P < 0.05$.
[b]Correlation coefficient significant at $P < 0.001$.

Table 6. Regression analysis between blood lead and oxidative damage indices and cardiovascular damage indices.

Parameters	T-SOD	MDA	Systolic pressure	Diastolic pressure	Electrocardiogram
Blood lead	−0.343[b]	0.395[b]	0.076	0.074	0.011[a]
T-SOD	–	–	−0.082	−0.024	−0.095
MDA	–	–	0.106	0.127	0.082

Analysis was performed using a univariate regression method. T-SOD, serum total superoxide dismutase; MDA, malondialdehyde.
[a]Standard regression coefficient β significant at $P < 0.05$.
[b]Standard regression coefficient β significant at $P < 0.001$.

Correlation and regression analyses between blood lead level and oxidative and cardiovascular damage indices

Table 5 shows positive correlations between the blood lead level and MDA concentration ($r = 0.690$, $P < 0.01$), systolic blood pressure ($r = 0.246$, $P < 0.01$), diastolic blood pressure ($r = 0.239$, $P < 0.01$), and ECG findings ($r = 0.229$, $P < 0.01$). A negative correlation coefficient was found between the blood lead level and T-SOD concentration ($r = -0.659$, $P < 0.01$). There were significant correlations between the T-SOD concentration and diastolic blood pressure ($r = -0.134$, $P < 0.05$) and between the MDA concentration and systolic blood pressure ($r = 0.163$, $P < 0.01$), diastolic blood pressure ($r = 0.151$, $P < 0.01$), and ECG findings ($r = 0.162$, $P < 0.01$).

Table 6 shows the regression analysis between the blood lead level and oxidative damage indices and cardiovascular damage indices. The linear multiple regression analysis showed that the T-SOD concentration was negatively associated with the blood lead level ($\beta = -0.343$, $P < 0.01$) and ECG findings ($\beta = 0.11$, $P < 0.05$) and that the MDA concentration was positively associated with the blood lead level ($\beta = 0.395$, $P < 0.01$).

Discussion

The mechanism of lead toxicity mainly involves oxidative damage, the ion competition mechanism, apoptosis, and genetic damage. Many studies have shown that oxidative damage plays an important role in lead toxicity, which may explain the various toxic effects of lead.[17–20] We found significant associations of changes in blood pressure and ECG findings with the MDA and T-SOD concentrations in both the lead-exposed group and control group. The oxidative stress index increased as the

blood lead concentration increased. Significant correlations were also found between the blood lead level, T-SOD, MDA, blood pressures, and abnormal ECG findings.

SOD is an important antioxidant enzyme *in vivo* and can clear superoxide free radicals and protect cells from oxidative damage. When the activity of T-SOD decreases, the body initiates a free radical and lipid peroxidation chain reaction that can cause corresponding physiological and biochemical reactions and even lead to oxidative damage of DNA, enzyme proteins, and biofilm, resulting in multi-system and multi-organ damage.[21] If the antioxidant system cannot remove excess free radicals in time, peroxidation will occur and MDA will be produced, which can cause cross-linking and polymerization of biological macromolecules and thus damage the body. Our study showed that the serum T-SOD level in the lead-exposed group was significantly lower than that in the control group ($P < 0.05$), while the MDA level was significantly higher. Previous studies have shown that lead exposure leads to oxidative stress in lead-exposed individuals.[22]

In recent years, increasingly more evidence has shown that oxidative stress and related oxidative damage are the main causes of vascular injury and may participate in the occurrence and development of hypertension.[23–25] Navas-Acien et al.[26] summarized previous research results and found a causal relationship between lead exposure and blood pressure; they also found that systolic blood pressure increased by 0.08 to 0.167 kPa for every doubling of the blood lead concentration. SOD is one of the most important antioxidant enzyme and plays a very important role in the oxidative stress cascade reaction; it is considered a common index with which to evaluate the degree of oxidative stress. With generation of H_2O_2 and O_2 under SOD disproportionation, O_2^- is eliminated. Under conditions of reduction of SOD, O_2^- bypasses the antioxidant enzyme defense system, leading to dysfunction of endothelial cells and thus increased blood pressure. In the present study, the systolic and diastolic blood pressures in the control group were significantly lower than those in the lead-exposed group. This result indicates increased blood pressure in lead-exposed workers. Our findings further showed that occupational exposure to lead was related to increases in systolic and diastolic blood pressure among the lead-exposed group. This result is consistent with a previous study.[27] It also confirmed the direct correlation between oxidative stress induced by lead exposure and hypertension.

The ECG is sensitive to slight structural and functional changes in the early stage of cardiovascular disease as confirmed by a large number of clinical studies.[26–28] Since 1903, when the ECG was invented by Willem Einthoven, the ECG has been widely used in the diagnosis of cardiovascular diseases and arrhythmias and has made great contributions to the prevention and treatment of cardiovascular diseases.[29] Increasingly more studies are showing that ECG abnormalities are an independent predictor of coronary heart disease[30] and contribute to cardiovascular risk assessment.[31] The purpose of this study was to analyze the possible effects of occupational lead exposure on the cardiovascular system and to emphasize the early subclinical response. Therefore, the rate of ECG abnormalities was used as an indicator of cardiovascular system health in workers exposed to lead. Nawrot and Staessen[9] found that low-level environmental exposure to lead can increase cardiovascular mortality.

The results of the present study showed a significant association between the blood lead level and rate of abnormal ECG findings in the lead-exposed group. The heart is an organ with high oxygen consumption, is extremely sensitive to oxidative reaction,

and is vulnerable to oxidative stress. As the blood lead level increases, lead-induced oxidative stress produces ROS, induces cell autophagy, damages endothelial cells, and causes cardiac hypertrophy.[32] In addition, ROS can induce mitochondrial damage, release pro-apoptotic proteins, activate the downstream proteins of the caspase family, and initiate cell apoptosis, thus causing cardiac cell damage.[33] Long-term exposure to excessive ROS can lead to myocardial cell hypertrophy, apoptosis, necrosis, and fibrosis, eventually causing excitation–contraction coupling disorder, arrhythmia, and myocardial remodeling.[34–36] These are important factors that induce cardiovascular system diseases.

Limitations

This study has several limitations. First, noise and sulfuric acid mist were not considered in our study. In addition, other factors such as the work performed by the control group during the fixed hours of the day and that performed by the lead-exposed group, many of whom probably also work during nights, were not considered in our study.

Conclusions

The current study has shown that lead exposure may result in reduced antioxidant enzymes and oxidative stress followed by high blood pressure and ECG abnormalities in lead–acid battery manufacturers. Lead exposure has a significant impact on the cardiovascular system, and oxidative stress is involved in the pathogenesis of cardiovascular diseases.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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