Electrocardiographic Changes in Workers Occupationally Exposed to Lead

Rafał Poręba, M.D., Ph.D.,* Małgorzata Poręba, M.D., Ph.D.,†
Paweł Gać, M.D.,* Aleksandra Steinmetz-Beck, M.D., Ph.D.,*
Bogusław Beck, M.D., Ph.D.,* Witold Pilecki, M.D., Ph.D.,†
Ryszard Andrzejak, M.D., Ph.D.,* and Małgorzata Sobieszkańska, M.D., Ph.D.†

From the *Department of Internal Medicine, Occupational Diseases and Hypertension, Wrocław Medical University, Wrocław, Poland; and †Department of Pathophysiology, Wrocław Medical University, Wrocław, Poland

Background: The significance of heavy metals in pathogenesis of the circulatory system diseases remains unresolved. The aim of the study was to evaluate electrocardiographic changes in workers occupationally exposed to lead without clinical presentation of cardiac involvement.

Methods: A group of 60 smelters and refiners and 45 healthy men, as a control group, were enrolled. Twelve-lead electrocardiogram (ECG) and 24-hour Holter monitoring were performed. Further analysis included heart rate variability (HRV) in time and frequency domains and heart rate turbulence (HRT).

Results: Analysis of 12-lead ECG recordings revealed various pathologies in 27 out of 60 men occupationally exposed to lead. Twenty-four-hour ECG Holter monitoring showed the higher mean heart rate in copper smelters than in healthy subjects (85.8 ± 14.1 bpm vs 72.6 ± 9.2 bpm; $P < 0.05$) and more premature supraventricular and ventricular contractions (298 ± 235 vs 27 ± 45 ; $P < 0.05$ and 152 ± 138 vs 18 ± 18 ; $P < 0.05$, respectively). The majority of time domain and frequency domain HRV parameters were significantly lower, and the LF:HF ratio was higher when compared with the control group. Turbulence onset was abnormal in six copper smelters and turbulence slope in five men exposed to lead.

Conclusions: Electrocardiographic evaluation showed that various heart rhythm disorders were more frequent in metallurgists, as compared to the control group, and the decreased HRV and abnormal parameters of HRT were observed. Noninvasive electrocardiographic evaluation could be a valuable method of the early prediction of cardiovascular disorders in men occupationally exposed to lead.

Ann Noninvasive Electrocardiol 2011;16(1):33–40

exposure to lead; electrocardiographic changes; autonomic nervous system; cardiovascular risk

Due to the increase of pollution of the natural environment and the dynamic growth of the industry, the significance of heavy metals, including lead, in pathogenesis of the circulatory system disease remains to be a phenomenon intriguing numerous researchers. Significant number of researches deal with the problem of the harmful influence of lead on electrical impulse generating and conducting system of the heart, which may be reflected in the occurrence of heart rhythm disorders as well

as sino-atrial and atrioventricular blocks observed in electrocardiographic recordings.¹ Detailed processes related with influence posed by lead on creating electric impulse and cardiac conduction disturbances are not well known. They are most probably related with the influence of lead on the autonomic nervous system.

Electrocardiogram (ECG) Holter monitoring enables to obtain continuous recording of electric activity of the heart during the whole day or longer.

Address for correspondence: Rafał Poręba, M.D., Ph.D., Department of Internal Medicine, Occupational Diseases and Hypertension, Wrocław Medical University, Pasteur 4 Street, 50-367 Wrocław, Poland. Fax: +48713270954; E-mail: sogoood@poczta.onet.pl

Electrocardiographic measurement does not interfere with performing the actions related with everyday activity. It allows frequent revealing, the relation between changes in ECG, activity of the examined person, and reported symptoms. It is also known that the probability of identifying abnormalities in Holter monitoring is much higher than during the standard ECG examination. Moreover, ECG Holter monitoring allows evaluating heart rate variability (HRV) and heart rate turbulence (HRT), which can be used to evaluate the occurrence of adverse cardiovascular events after myocardial infarction (MI).^{2,3}

HRV is a useful, noninvasive measure of cardiovascular autonomic activity.^{4,5} Decreased HRV observed in patients after MI was probably related with an increased cardiovascular risk.^{6,7} HRT reflects a response of heart rate to premature ventricular contraction (PVC), and is most probably mediated via the baroreceptor reflex.^{2,8} It is a valuable method to predict mortality and sudden cardiac death following MI; however, other applications of this method are also possible.^{8–12}

The aim of the study was to evaluate electrocardiographic changes, including parameters of HRV and HRT, in the workers occupationally exposed to lead and without clinical presentation of cardiac involvement.

MATERIAL AND METHODS

To the study, 60 men occupationally exposed to lead, smelters, and refiners, workers of copper smelter, were enrolled (group I). Control group consisted of 45 healthy men, administrative workers of the same industry (group II). In order to determine an influence of a single metal (lead) on electrocardiographic changes, a specific exclusion criteria has been used such as data on exposure to chemical substances delivered by foundry services. Persons working at the workplaces with exposure to compounds other than lead exceeding 0.2 of the maximum admissible concentrations were excluded. Men included in the study inhabited the same region, and their environmental exposure to metals was similar. Clinical data and characteristics of the occupational exposure are shown in Table 1. Any cardiovascular diseases, including arterial hypertension, diabetes mellitus, and coronary heart disease, were excluded in the examined subjects. Each subject gave written informed consent and the local ethics committee approved the study.

Blood samples were obtained by venipuncture from every man examined in the study. Concentration of lead in blood (Pb-B) was determined with atomic absorption spectrophotometry (SOLAAR M6, Thermo Elemental, Spectro-Lab, Warszawa, Poland). Zinc protoporphyrin (ZnPP) was evaluated by Piomelli method.¹³ Delta aminolevulinic acid in urine (ALA-U) was determined with the use of method described by Berko.¹⁴

Recordings of 12-lead ECG were collected in all of the men occupationally exposed to lead, as well in the controls. Corrected QT (QTc) analysis was performed with the help of Bazett's formula, and the ECG lead with longest QT period was chosen for analysis.

All the subjects underwent 24-hour Holter monitoring with HolCARD 24W (Aspel S.A., Zabierzow, Poland), three-channel registering device. The examined persons had a normal life activity, and they noted all performed activities in their diaries, also stating the hours of the night sleep. The examined persons were reminded to observe the hours of daily activity and night sleep. In order to properly prepare the ECG for subsequent analysis, the editing of automatic record was verified visually.

To evaluate cardiovascular autonomic function, HRV analysis from 24-hour Holter electrocardiographic recording, both in time and in frequency domains, separately for day (6:00–22:00) and for night (22:00–6:00) hours, was carried out. Time domain parameters: mRR (mean of RR), SDNN (standard deviation of all normal sinus RR intervals in ms), SDNNi (means of the standard deviations of all normal sinus RR intervals for all 5-min segments in ms), SDANN (standard deviation of the averaged normal sinus RR intervals for all 5-min segments), rMSSD (root-mean-square of successive normal sinus RR interval difference in ms), and pNN50 (the percentage of successive normal sinus RR intervals >50 ms in percent) were obtained. The following frequency domain variables were computed: ultra low frequency (ULF) power from 0 to 0.0033 Hz; very low frequency (VLF) power from 0.0033 Hz to 0.04 Hz; low frequency (LF) power from 0.04 to 0.15 Hz; high frequency (HF) power from 0.15 to 0.4 Hz. Also, LF/HF ratio was calculated. The fast Fourier transformation method was used to evaluate the power spectral density of the RR series in the studied periods. The time and frequency domain measures of HRV were analyzed by methods recommended by the Task Force of the European Society of Cardiology.⁴

Table 1. Clinical Data and Characteristics of the Occupational Exposition of the Study Groups (Group I = Men Occupationally Exposed to Lead; Group II = Control Group)

	Group I (n = 60)	Group II (n = 45)	P Value
Age (years)	52.71 ± 8.35	50.93 ± 6.54	NS
Height (m)	1.78 ± 0.09	1.75 ± 0.07	NS
Weight (kg)	82.66 ± 14.38	81.25 ± 12.48	NS
BMI (kg/m ²)	26.08 ± 4.36	26.53 ± 5.39	NS
Pb-B (μg/L)	242.11 ± 145.73	75.83 ± 30.82	<0.01
ZnPP (μg/dL in blood)	28.35 ± 12.42	16.83 ± 10.56	<0.05
ALA-U (mg/L)	4.47 ± 0.87	0.92 ± 0.67	<0.05
Total duration of exposition at work (years)	22.62 ± 6.32	0.00 ± 0.00	<0.05

ALA-U = concentration of delta aminolevulinic acid in urine; BMI = body mass index; Pb-B = lead concentration in whole blood; ZnPP = concentration of zinc protoporphyrin.

For analysis of HRT, turbulence onset (TO), reflecting the initial phase of sinus rhythm acceleration, and turbulence slope (TS), describing deceleration phase, were calculated according to the method described by Schmidt.² The HRT parameters were defined as normal, if TO was <0% and TS >2.5 ms/R-R interval. Persons were divided into three subgroups: both HRT parameters normal (HRT0), one of the parameters abnormal (HRT1), and both parameters abnormal (HRT2).

Quantitative variables were expressed as the mean ± standard deviation. Statistical analysis was performed using "STATISTICA PL 6.0" package (StatSoft, Krakow, Poland). Data distribution was confirmed by Shapiro-Wilk's W test. Considering the abnormal data distribution, Mann-Whitney test was performed. Qualitative data were expressed as percents. Qualitative nondependent variables were analysed by chi square test. P value equalling less than 0.05 was assumed as statistically significant. Relationships between the examined variables were tested by analyses of correlation and regression. Linear correlations were investigated with the use of Spearman's rank correlation coefficient. P value of <0.05 was considered statistically significant in all the cases.

RESULTS

Analysis of 12-lead ECG recordings revealed the following pathologies in 27 out of 60 (45%) men occupationally exposed to lead: incomplete and complete right bundle branch block, left anterior fascicular block, premature supraventricular contractions (PSVCs), PVCs, first-degree atrioventricular block, and prolonged QTc interval (QTc >440 ms). Changes in 12-lead ECGs are shown in Table 2.

None of the above-mentioned pathologies were detected in subjects from the control group. The mean QRS duration and the mean QTc duration were similar in both the groups (QRS duration was 80 ± 20 ms vs 80 ± 10 ms; QTc duration 410 ± 30 ms vs 420 ± 10 ms).

The 24-hour ECG Holter monitoring showed that the mean heart rate was significantly higher in copper smelters than in normal subjects (85.8 ± 14.1 bpm vs 72.6 ± 9.2 bpm; P < 0.05). There were statistically more numerous PSVCs and PVCs in men occupationally exposed to lead, as compared with the control group (298 ± 235 vs 27 ± 45; P < 0.05 and 152 ± 138 vs 18 ± 18; P < 0.05, respectively). The first-degree atrioventricular block was observed in seven metallurgists (11.7%). In two copper smelters (3.3%), the episodes of paroxysmal atrial fibrillation were present, and in seven

Table 2. Analysis of 12-Lead ECG Recordings in Men Occupationally Exposed to Lead

ECG Abnormalities	Number of Copper Smelters
Normal ECG	33
Incomplete right bundle branch block	4
Complete right bundle branch block	1
Left anterior fascicular block	6
Premature supraventricular contractions	7
Premature ventricular contractions	3
First-degree atrioventricular block	4
Prolonged corrected QTc (>440 ms)	2

men occupationally exposed to lead (11.7%), the episodes of supraventricular tachycardia were observed. These episodes were excluded from HRV and HRT analysis. None of those findings were observed in the normal subjects. Other pathologies in copper smelters included: bigeminy in six men (10%), trigeminy in four men (6.7%), and couplets in five copper smelters (8.3%). Those disturbances were not detected within the control group. Analysis of ST-T changes in the study group revealed an inverted T wave in four men (6.7%), and a depressed ST segment (>1 mm) in two copper smelters (3.3%). None of such abnormalities were noted within the control group.

In case of people occupationally exposed to lead, the majority of variables of time domain and frequency domain HRV were significantly lower, and the LF:HF ratio was considerably higher when compared with a group of healthy men, both during the day and at night (Tables 3 and 4). In men occupationally exposed to lead, negative linear correlations were found between blood lead level and HRV parameters: between Pb-B and rMSSD ($r = -0.44$; $P < 0.05$), between Pb-B and SDANN ($r = -0.42$; $P < 0.05$), and between Pb-B and HF ($r = -0.57$; $P < 0.05$).

In men occupationally exposed to lead, the mean TO and TS values equalled: $0.097 \pm 0.02\%$, and 15.4 ± 12.7 ms/R-R interval, respectively. According to the definition, the mean TO exceeded the limits ($>0\%$) in six copper smelters (10%). The mean TS was abnormal (<2.5 ms/RR interval) in five men occupationally exposed to lead (8.3%). Simultaneous occurrence of pathological TO and

TS values was not observed in any of the examined metallurgists. To HRT0 subgroup, 49 subjects (81.7%) were included, to HRT1–11 individuals (18.3%), none of the participants of the study met the HRT2 group criteria. In the majority of control subjects, TO and TS values could not be calculated due to the absence of the required PVCs number.

A multifactorial stepwise reverse regression analysis, taking into account principal anthropologic parameters (age, body height and weight, body mass index) and toxicological parameters (Pb-B, ZnPP, ALA-U), yielded the following model:

$$rMSSD = 82.63 - 0.06 \text{ Pb} - B - 0.77 \text{ BMI} \pm 6.57$$

Appropriate determination of the model was confirmed by values of determination coefficient ($R^2 = 79.34$), P value of the model ($P < 0.001$), P value for Pb-B ($P < 0.01$), and P value for BMI ($P < 0.05$). The obtained model demonstrated that higher blood lead level and a higher BMI represented independent risk factors of the decreased HRV (expressed as decreased values of rMSSD) in the group of persons chronically exposed to lead.

DISCUSSION

Epidemiological and experimental researches indicate a negative influence of lead on the circulatory system. Prolonged exposure to lead may result in atherosclerosis and arterial hypertension. Lead may cause atherosclerosis through its influence on lipid metabolism disturbances and by decreasing activity of antioxidant enzymes.^{15,16} On

Table 3. Time-Domain HRV Analysis for Day Activity Hours (6:00–22:00) and Night Resting Hours (22:00–6:00) in Men Occupationally Exposed to Lead and Healthy Subjects. Results Are Given as Mean $\pm$ Standard Deviation

	6:00–22:00			22:00–6:00		
	Copper Smelters	Control Group	P Value	Copper Smelters	Control Group	P Value
mRR (ms)	845.31 $\pm$ 214.97	860.37 $\pm$ 328.53	NS	875.84 $\pm$ 432.79	896.37 $\pm$ 214.91	NS
SDNN (ms)	69.32 $\pm$ 25.23	75.31 $\pm$ 16.27	NS	59.59 $\pm$ 28.35	63.61 $\pm$ 33.42	NS
SDNNi (ms)	50.45 $\pm$ 19.10	64.21 $\pm$ 12.86	<0.01	45.57 $\pm$ 22.29	52.76 $\pm$ 20.32	<0.05
SDANN (ms)	55.18 $\pm$ 19.38	69.47 $\pm$ 21.58	<0.01	50.74 $\pm$ 15.67	63.52 $\pm$ 20.68	<0.01
rMSSD (ms)	52.94 $\pm$ 21.58	79.42 $\pm$ 31.14	<0.01	37.12 $\pm$ 21.86	58.23 $\pm$ 26.52	<0.01
pNN50 (%)	5.36 $\pm$ 2.14	9.28 $\pm$ 4.51	<0.01	7.23 $\pm$ 3.59	12.50 $\pm$ 6.24	<0.01

mRR = mean of RR; SDNN = standard deviation of all normal sinus RR intervals; SDNNi = means of the standard deviations of all normal sinus RR intervals for all 5-minute segments; SDANN = standard deviation of the averaged normal sinus RR intervals for all 5-minute segments; rMSSD = root mean square of successive normal sinus RR interval difference; pNN50 = the percentage of successive normal sinus RR intervals >50 ms; NS = nonsignificant; P = statistical significance.

Table 4. Frequency-Domain HRV Analysis for Day Activity Hours (6:00–22:00) and Night Resting Hours (22:00–6:00) in Men Occupationally Exposed to Lead and Healthy Subjects. Results Are Given as Mean $\pm$ Standard Deviation

	6:00–22:00		P Value	22:00–6:00		P Value
	Copper Smelters	Control Group		Copper Smelters	Control Group	
ULF (ms ²)	6396.82 $\pm$ 1132.40	7468.49 $\pm$ 1376.56	<0.01	6175.80 $\pm$ 1740.36	7187.74 $\pm$ 1552.99	<0.05
VLF (ms ²)	775.04 $\pm$ 132.71	994.36 $\pm$ 316.84	<0.01	678.69 $\pm$ 67.63	845.56 $\pm$ 224.10	<0.01
LF (ms ²)	643.63 $\pm$ 204.77	957.30 $\pm$ 268.39	<0.01	414.12 $\pm$ 104.65	843.97 $\pm$ 206.33	<0.01
HF (ms ²)	325.75 $\pm$ 210.42	622.01 $\pm$ 336.89	<0.01	240.74 $\pm$ 125.10	575.22 $\pm$ 268.10	<0.01
LF:HF	1.98 $\pm$ 0.97	1.54 $\pm$ 0.89	<0.05	1.72 $\pm$ 0.78	1.47 $\pm$ 0.72	<0.05

ULF = ultra low frequency; VLF = very low frequency; HF = high frequency; LF = low frequency; LF:HF = LF/HF ratio; P = statistical significance.

the other hand, lead can cause arterial hypertension by adverse influence on central and peripheral regulation of arterial pressure by nervous system, hormonal regulation mechanisms, in particular the renin-angiotensin system, and the reactivity of blood vessel walls to pressive factors.^{17–21} Despite the widely discussed atherosclerotic and hypertensive influence posed by lead, this metal may also cause morphological lesions in myocardium and affect cardiac function through its influence on contractility and electric activity of the heart.

In the present study, we aimed to determine the influence of chronic, occupational exposure to lead on electric impulses generating and conduction within the heart by the evaluation of changes in resting ECG and in Holter monitoring. The average lead concentration in blood of metallurgists equalled $242.11 \pm 145.73 \mu\text{g/L}$, while concentrations of zinc erythrocyte protoporphyrins and ALA-U were in normal range. Therefore, a group of metallurgists chronically exposed to lead compounds, yet in a degree allowed for population occupationally exposed to the activity of this metal (normal blood lead concentration in people occupationally exposed to this metal equals up to $500 \mu\text{g/L}$), has been examined. Such a selection of the examined group enabled to evaluate the influence of early cardiac lesions induced by lead on heart pacemaker and conduction system.

Analysis of the 12-lead resting ECG revealed, in men occupationally exposed to lead, the occurrence of cardiac rhythm disorders, atrioventricular and intraventricular conduction disturbances, and prolonged QTc interval. Such pathologies were not observed in resting ECGs taken in the control group. Monitoring ECG with Holter method

also confirmed that dysrhythmia, and atrioventricular conduction disorders was found considerably more frequently in the group of men occupationally exposed to lead than in the control group. Results of our research are compliant with the observations of the other authors. They revealed that the influence of lead on impulse generating and impulse conduction in the heart may result in changes within electrocardiographic recordings, such as sinus bradycardia, atrioventricular blocks, ventricular repolarization disorders, ectopic atrial rhythm, multifocal ventricular premature contractions, left bundle branch block, and changed T-wave morphology.^{1,22–24} The first three pathologies were observed in patients chronically exposed to lead, whereas remaining ones were related with cases of acute lead poisoning, very rare currently. Reverse of changes in electrocardiographic recordings after the use of chelation therapy is an interesting phenomenon, although it did not occur in every case.²⁵ Another changes were observed in ECG of experimental animals, depending on the lead dose. With exposure to lead in slight concentrations, disturbances in atrioventricular conduction were observed.²² In case of greater exposure, a prolongation in PR distance, shortening QT distance, and reverse of T wave were observed.²⁶

Mechanisms of the influence of lead on electrical impulse conduction in the heart are not precisely known. They are most probably related with the influence of lead on the autonomous nervous system. The available reports provide an equivocal explanation of the influence this metal poses on the autonomic nervous system. According to Niu et al., lead does not result in vegetative dysfunction.²⁷ Nonetheless, majority of authors emphasize its

influence on the occurrence of autonomic dysregulation. It is more often stated that lead decreases parasympathetic activity.^{28–30} Only a small number of researches indicate disadvantageous influence of this metal on the sympathetic nervous system.³¹ Our current, as well as previous researches indicate the lowered HRV in persons occupationally exposed to lead, mainly resulting from the decreased tension in the parasympathetic nervous system.³² Time domain analysis and frequency domain analysis of the HRV, performed separately for the hours of daily activity as well as night's sleep, revealed that the values of examined parameters were lower in subjects occupationally exposed to lead than in normal men. Significantly lower values of time domain analysis parameters, such as rMSSD and pNN50, indirectly proving the tension of the vagus nerve, may indicate a decreased tension of the parasympathetic nervous system in metallurgists. Frequency domain analysis of HRV, performed within the same time segments as time domain analysis, carried out to obtain a more definite evaluation concerning both components of the autonomic system, proved that in persons occupationally exposed to lead, all examined parameters were considerably lower than in normal men, both during the day and at night. The above-mentioned differences in frequency of HRV analysis (ULF, VLF, and LF) support the notion of decreased tension of the sympathetic system in people exposed to the activity of lead. Significantly lower HF value in metallurgists, proving the smaller tension of the parasympathetic part of the autonomic system in these people, with smaller tension of the sympathetic part of the autonomic system coexisting in case of these people confirms the suspicion related with the fact that lowered HRV in metallurgists is not a consequence of increased activity of the sympathetic nervous system. Significant increase of the LF:HF relation in men occupationally exposed to lead, assisting the above-mentioned phenomena, may indirectly prove another level of sympathetic-parasympathetic balance within this group of the examined persons.

As it is known, abnormal cardiac autonomic function may be an important contributor to the pathophysiology of vascular disease, heart failure, and myocardial ischemia and their consequences, including sudden cardiac death. In patients with MI, depressed SDNN, the parameter of HRV time domain analysis, and left ventricle ejection fraction both independently predict cardiac death.³³ Simi-

larly, in patients after stroke, the decreased HRV predicted a poor outcome.³⁴ Imbalance in cardiac autonomic innervation may be crucial for the generation of cardiac arrhythmias and reduced HRV can be associated with increased mortality.^{35,36}

Choudhury and Leyva. reported the link between HRV and endothelial dysfunction. They showed that endogenous nitric oxide (NO) can augment vagal control of the heart rate in humans.³⁷ The reduced activity of NO is the main hallmark of endothelial dysfunction, and NO deficiency may result in autonomic and baroreflex dysfunction, which causes a reduction in the vagal component of HRV.^{38,39} Therefore, the endothelial function and autonomic function seem to be closely connected. In many pathological states, such as heart failure, arterial hypertension, diabetes, and hypercholesterolemia, and in cigarette smoking, the abnormal generation or function of NO was reported. These conditions are also associated with autonomic and endothelial dysfunction.⁴⁰ Thus, the depressed HRV may reflect accelerated endothelial dysfunction and progression of the disease.⁴¹ In our previous reports, we have noted the endothelial dysfunction in men occupationally exposed to lead, which may be important in the aspect of the present study.⁴²

HRT, describing the short-term fluctuation in sinus cycle length that promotes PVCs, has a proven clinical significance based on its ability to predict mortality and sudden cardiac death following MI.² HRT reflects a change in the length of the sinus cycle in baroreceptor responses to hemodynamic fluctuations after premature ventricular beat. Impaired baroreflex regulation in cases of blunted HRT was experimentally and clinically confirmed.^{8,9} In the present study, we made an attempt to apply HRT analysis in men occupationally exposed to lead. However, a limitation of our observations is that there is insufficient amount of data (we observed abnormal TO or TS level only in case of 11 copper-smelters) to state, whether this approach could be routinely used in clinical practice.

CONCLUSIONS

Electrocardiographic evaluation showed that heart rhythm disorders, atrioventricular, and intraventricular conduction disorders were observed more frequently within the examined group of smelters and refiners, compared to the subjects not exposed to lead. What is more, decreased HRV

and improper parameters of heart rhythm turbulences were more common within the examined workers. Electrocardiographic noninvasive evaluation, including Holter monitoring, HRV, and HRT analysis, could be a method facilitating prediction of early-phase cardiovascular disorders, as well as monitoring them in men occupationally exposed to lead.

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