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Effect of chelation therapy on arrhythmogenic and basal ECG parameters of lead exposed workers

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ABSTRACT

Lead exposure has etiological role on cardiovascular system diseases as hypertension, atherosclerosis, stroke, and arrhythmic events. In this study, we aimed to compare the basal and arrhythmogenic ECG parameters of lead exposed workers before and after chelation therapy and to evaluate the effect of acute change of blood lead levels on ECG. Fourty consecutive occupationally lead exposed workers were enrolled, demographic, blood, echocardiographic, and electrocardiographic data's were analyzed before and after chelation therapy. Pmax, P min, P Wave Dispersion, and QT Dispersion values which are arrhythmia predictors were significantly lower after chelation therapy compared to values before chelation therapy. Lead exposed workers are under the risk of ventricular and atrial arrythmias and chelation treatment has a positive effect on these parameters.

ARTICLE HISTORY

KEYWORDS

Arrythmia; chelation; ECG; lead exposure

Introduction

Environmental and occupational lead exposure is a serious health problem and cause harmful cardiovascular effects.[1] After removal of lead from gasoline, progress has been made in the battle with environmental exposure. But occupational lead exposure is still a major concern. There are more than 3 million workers in the United States who are potentially exposed to lead occupationally.[2] Lead is a very widely used metal because of its unique physical and chemical properties like softness, poor conductibility, and corrosion resistance. Lead is one of the most hazardous substance among all heavy metals.[3]

It has many side effects on human health as reduced fertility, anemia, and gastrointestinal side effects. Neurological side effects as diminished cognitive functions and neuropsychiatric side effects and lead encephalopathy are also well-known health problems.[4] Lead has also several side effects on cardiovascular system as hypertension, atherosclerosis, stroke, and arrhythmic events.[5–7]

Chelation therapy effectively reduces blood lead levels.[8] Also, chelation therapy has been widely used for atherosclerotic disease treatment over 50 years.[9]

Analysis of electrocardiographic parameters (QT interval, P wave duration, Tp-e time) revealed higher risk of atrial and ventricular arrhythmias in lead exposed workers compared with healthy adults.[10] Another study reported higher numbers of premature atrial and ventricular contractions in lead exposure group.[11]

Blood lead levels reflect recent exposure and up to 95% of lead accumulates in bone and bone lead undergoes a constant interchange with lead circulating in the blood and soft tissues.[12]

The aims of our study are as follows: comparing the arrhythmogenic ECG parameters of lead exposed workers before and after the chelation therapy and evaluating the effect of acute change of blood lead levels on ECG.

Materials and methods

Fourty consecutive occupationally lead exposed workers from battery industry were enrolled to study. Patients with known diseases that can affect ECG parameters as coronary artery diseases (2 patients), hypertension (6 patients), diabetes mellitus (2), left

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ventricular hypertrophy (1 patient) were excluded from study. This study was approved by the ethics committee of local hospital and was carried out according to the rules of the Helsinki Declaration (Ethical committee approval number: 29620911-771) and informed consent was obtained from all patients.

Chelation with edetate calcium disodium decision was given by the authorized physician. Demographic and clinic data were reported at admission and reevaluated after blood sample results (for evaluating the parameters which would affect ECG like calcium and potassium metabolism disorders and newly diagnosed Diabetes Mellitus [DM]).

Blood samples were drawn from antecubital veins at admission, after chelation was completed and when the authorized physician ordered.

Office blood pressure measurement was done according to 2018 ESC/ESH guidelines for the management of arterial hypertension guideline recommendations.[13]

Twelve lead ECG was recorded at a standard calibration after 5-minute resting (25 mm/s paper speed 10 mm/mV) (Nihon Kohden, Tokyo, Japan) at admission and after chelation therapy was completed. Basic and arrhythmogenic parameters were evaluated by two cardiologists and verified by another cardiologist who were blind to patient data. Heart rate, PR interval, QRS duration, P wave maximum duration (P max) and P wave minimum duration (P min), P wave dispersion (PWD), QT interval maximum duration (QT max), QT interval minimum duration (QT min), QT dispersion (QTD), corrected QT duration (cQT), T peak-T end duration (Tp-e) were analyzed.

All the measurements were done after 500% magnification. Heart rate was measured manually from the surface ECG which was recorded after 5-minute resting period. P wave with maximum and minimum duration was determined with the help of compasses and calipers and rechecked with computerize method. Onset of P-wave is accepted as the initial deflection from the isoelectric baseline defined by the T-P segment and the offset of P-wave is accepted as the junction of the end of the P wave and its return to baseline.[14] PWD is calculated by subtracting P min value from P max as described in the literature.[15]

QT interval duration was calculated manually from the start of the Q wave to the end of the T wave. QT interval with maximum and minimum duration was determined with the help of compasses and calipers. QTD is calculated by subtracting QT min value from QT max value.

Corrected QT was calculated with Bazzett formula: QT interval (QT max)/$\sqrt{}$R–R cycle duration.[16]

For measuring T p-e we used the manual tangent method in lead V2 which gives the best and consistent results. T-peak is defined as the maximum positive or negative deflection of the T wave from the isoelectric line and T-end is defined as the intersection of the isoelectric line with the tangent to the downslope of the T wave.[17]

Echocardiographic evaluations were done by the same cardiologist on left lateral decubitus position according to American Society of Echocardiography (ASECHO) guidelines recommendations.[18] Left ventricle end diastolic diameter (LVEDD), left ventricle end-systolic diameter (LVESD), and left atrial diameter (LAD) were measured from apical 4 chamber view; systolic pulmonary artery pressure (sPAP) was calculated from tricuspid regurgitation peak wave velocity measured by continuous doppler and estimated right atrial pressure. Mitral E and A waves were also measured from apical 4 chamber view over mitral valve by pulse doppler. Ejection fractions were calculated by biplane Simpson method from apical four chamber view.

Statistical analyses

When the sample size was calculated based on 95% power by statistical method, 40 lead exposed patients treated with edetate calcium disodium were planned to be included in the study. Statistical analysis of the study was performed with SPSS Version 22.0 program (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for numerical variables were created. Paired sample T-test was used for normally distributed continuous variables. Kolmogorov-Smirnov test was used to determine normality. A p value less than 0.05 was accepted as significant. Fifteen patients were randomly selected from the study group. Measurements were repeated under the same basal conditions, and reproducibility of the ECG parameters were assessed according to the coefficient of variation between measurements. Mean intra-observer variability was 4.7% for ECG parameters.

Results

Baseline clinical characteristics and laboratory parameters of the study population are demonstrated in Table 1. All the patients were male workers. Mean age was 35.3 ± 8.93 years. Mean hemoglobin value, platelet count, neutrophil count, erythrocyte sedimentation rate, C-reactive protein, creatine, glucose, aspartate aminotransferase, alanine aminotransferase, uric acid,

Table 1. Demographic, blood and echocardiographic parameters of patients.

Parameter	Mean ± *SD*	Parameter	Mean ± *SD*
Age (years)	35.3 ± 8.97	BUN (mg/dl)	12.8 ± 3.2
Hemoglobin (g/dL)	14.89 ± 1.03	Blood Lead value (BT) (mcg/dL)	50.58 ± 5.06
WBC count (10^9/L)	6.41 ± 1.58	Blood Lead value (AT) (mcg/dL)	3.08 ± 0.51
Platelet count (10^9/L)	223 ± 35.44	SBP (mmHg)	120.4 ± 8.08
Neutrophil count (10^9/L)	3.56 ± 0.88	DBP (mmHg)	72.2 ± 5.24
ESR (mm/h)	5.44 ± 4.74	LVEDD (mm)	49.5 ± 1.59
CRP (g/L)	0.13 ± 0.48	LVESD (mmHg)	30.6 ± 4.21
Creatine (mg/dL)	0.83 ± 0.09	LVEF (%)	65.3 ± 1.64
Glucose (mg/dL)	83 (7.03)	sPAP (mmHg)	24.6 ± 4.25
AST (U/L)	18.8 (5.1)	LAD (mm)	33.5 ± 2.8
ALT (U/L)	22.5 (6.5)	E wave (mm/s)	78.6 ± 5.38
Uric acid (mg/dL)	5.21 (1.19)	A wave (mm/s)	59.1 ± 5.84

Abbreviations: WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic pressure; LVEF, left ventricle ejection fraction; LAD, left atrial diameter.

Table 2. Comparison of ECG parameters before and after chelation therapy.

	Mean ± *SD* (BCT)	**Mean ± *SD* (ACT)**	*p* value
HR (beat per minute)	75.45 ± 8.9	76.4 ± 10.2	0.576
PR interval (ms)	159.62 ± 18.06	158.90 ± 15.95	0.699
QRS duration (ms)	92.77 ± 6.16	92.10 ± 6.60	0.567
Pmax (ms)	114.6 ± 7.42	108.3 ± 5.69	<0.001
Pmin (ms)	90 ± 4.96	86.1 ± 7.39	0.019
PWD (ms)	26.6 ± 7.95	22.2 ± 6.87	0.003
QTmax (ms)	369.05 ± 23.32	370.85 ± 28.9	0.706
QTmin (ms)	343.65 ± 19.52	350.65 ± 30.37	0.134
QTD (ms)	25.65 ± 10.95	20.45 ± 12.53	0.002
cQT (ms)	412.6 ± 7.98	415.75 ± 14.06	0.226
Tp-e (ms)	75 ± 6.16	75.6 ± 10.75	0.636
Tp-e/QT (ms)	0.2 ± 0.02	0.2 ± 0.04	0.623

Abbreviations: HR, Heart rate (beat per minute); BCT, before chelation therapy; ACT, after chelation therapy; cQT, corrected QT interval; PWD, P wave dispersion, QTD, QT interval dispersion; Tp-e, T peak-T end duration.

and blood urea nitrogen were all in normal range. Mean blood lead value before chelation therapy was 50.58 ± 5.06 mcg/dL and it was 3.08 ± 0.51 mcg/dL after chelation therapy.

Mean systolic blood pressure (120.4 ± 8.08 mmHg) and diastolic pressure (72.2 ± 5.24 mmHg) measurements were in normal range.

The echocardiographic parameters LVEDD, LVESD, LVEF, sPAP, LAD, E wave, and A wave were also in normal range.

There was not a significant difference in mean heart rate before and after chelation therapy (75.45 ± 8.9 vs 76.4 ± 10.2, respectively; *p*: 0.576).

When the arrhythmogenic surface ECG parameters were compared Pmax (114.6 ± 7.42 ms vs 108.3 ± 5.69 ms, $p < 0.001$), Pmin (90 ± 4.96 ms vs. 86.1 ± 7.39 ms, p: 0.019), PWD (26.6 ± 7.95 ms vs 22.2 ± 6.87 ms, p: 0.003), and QTD (25.65 ± 10.95 ms vs 20.45 ± 12.53 ms, *p*: 0.002) values were significantly lower after chelation therapy compared to values before chelation therapy.

There was not a significant difference in terms of HR, PR interval, QRS duration, QT max, QT min, cQT, Tp-e, and Tp-e/QT between before chelation treatment and after chelation treatment (Table 2).

Table 3. Correlation between blood lead levels and proarrhythmic ECG findings.

	Blood lead levels (BCT)	
	r	*p* value
P max	0.575	<0.001
P min	0.447	0.004
PWD	0.532	<0.001
QTD	0.303	0.057

Abbreviations: BCT, Before chelation therapy; PWD, P wave dispersion, QTD, QT interval dispersion.

Blood lead levels were positively correlated with Pmax ($r = 0.575$, $p < 0.001$), Pmin ($r = 0.447$, $p = 0.004$), and PWD ($r = 0.535$, $p < 0.001$). The correlation between blood lead levels and QTD was not statistically significant ($r = 0.303$, $p = 0.507$) (Table 3 and Figure 1).

Discussion

According to our best knowledge, this is the first study demonstrating the effect of chelation therapy on proarrhythmogenic ECG parameters of occupationally lead exposed workers.

Our study indicated that acute fall in blood lead after chelation therapy decreased P max, P min, PWD, and QTD significantly. ECG of a lead exposed patient before and after chelation therapy is presented as Figure 2.

Lead has no biological function in the body and has toxic effects on all the tissues. Nervous system is the mostly effected system. At very high doses, lead toxicity can cause encephalopathy and death while lower doses can cause impaired cognitive development, irreversible neuronal damage, and increased violent behavior.[19–21] Lead poising can cause anemia by interfering heme synthesis, many gastrointestinal

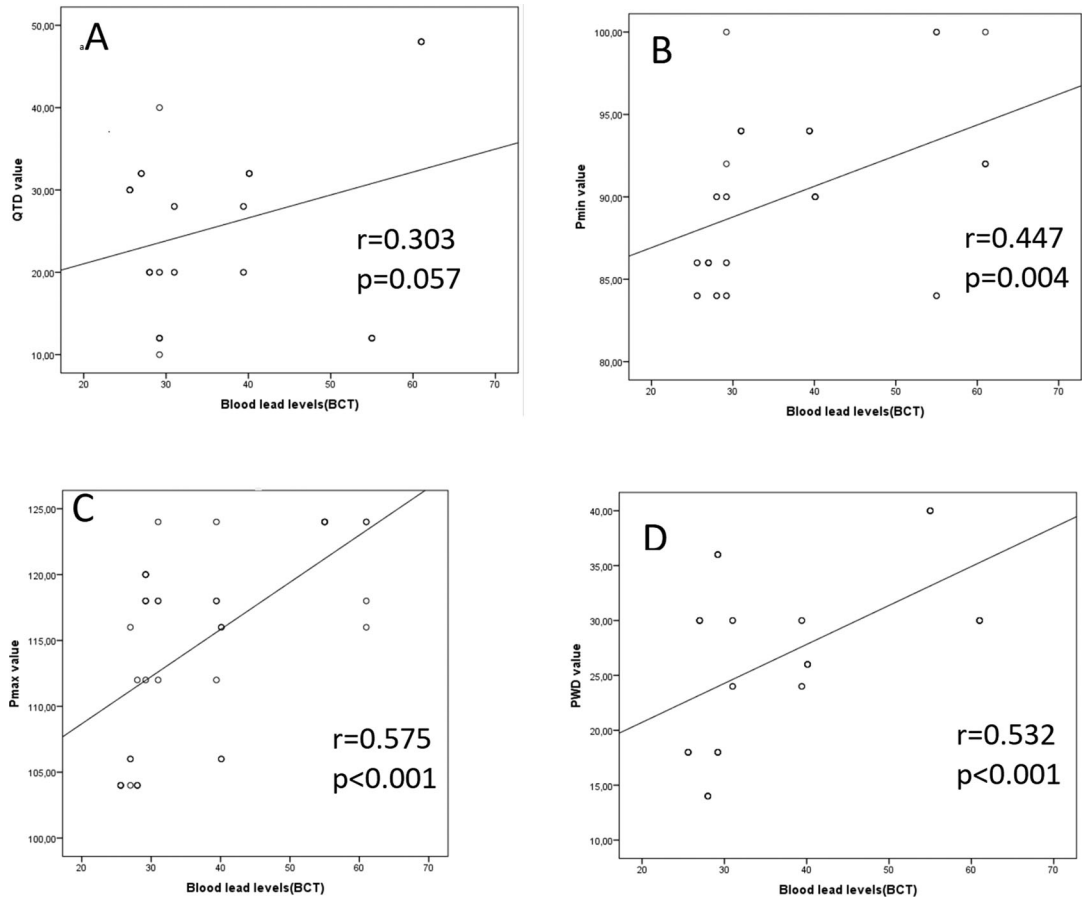

Figure 1. (A) Correlation between blood lead levels and QT interval dispersion; (B) correlation between blood lead levels and P wave min; (C) correlation between blood lead levels and P wave max; (D) correlation between blood lead levels and P wave dispersion.

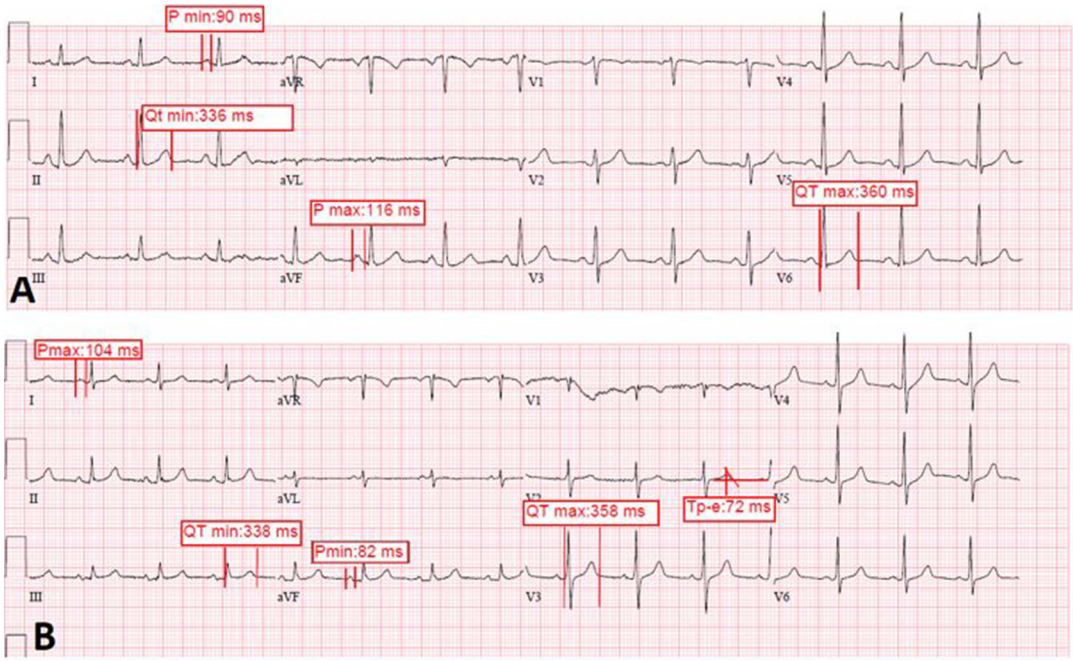

Figure 2. (A) ECG of a lead exposed patient before chelation theraphy (PWD: 116-90 = 26 ms; QTD: 360-336 = 24 ms); (B) ECG of the same patient after chelation theraphy (PWD: 104-82: 22 ms; QTD: 358-338: 20 ms).

symptoms as weight loss, abdominal pain, nausea, vomiting, and constipation.[2,22] Excessive exposure to lead may cause acute or chronic nephrotoxic effects.[23]

The effects of lead poisoning on the heart began to be reported in the early 19th century.[24] Many studies revealed the effect of lead exposure on hypertension, left ventricular hypertrophy, diastolic dysfunction, and reduced ejection fraction.[5,25,26] Cardiovascular morbidity, mortality, and stroke is also increased in lead exposure.[7] Possible mechanism for atherosclerosis is increased blood pressure, reactive oxygen radicals, inflammation, altered lipid metabolism, and endothelial dysfunction caused by lead exposure.[27–29]

The effect of lead exposure on ECG parameters is also documented in the literature. Decreased heart rate variation,[11] prolonged QT,[30] increased heart rate, corrected QT and QRS intervals and with increased risk of intraventricular and AV conduction defects,[31] abnormal QRS-T angle,[32] prolonged Pmin, Pmax, PWD, QTmax, QTd, Tp-e interval[10] were found to be related with lead exposure. But in all these studies comparisons were between lead exposed group and controls. One of the valuable aspects of our study is that the same patients' basal and proarrhythmic ECG parameters were extensively compared with high blood lead values and low blood lead values after chelation therapy. So, the effect of confounding factors was eliminated.

A prolonged P wave duration is a sign of abnormal conduction and excitability in the atriums. PWD shows the inhomogeneity of atrial conduction and it can be caused by irregularities between conduction system of atrium and abnormal intracellular or intercellular factors such as deteriorated membrane structures such as connexins, ion channels, or regulatory proteins.[33,34] Increased P max and PWD are predictors of atrial fibrillation.[35] QTD reflects regional variation in ventricular repolarization, which represents an electrophysiological substrate for arrhythmias.[36] Many publications have shown association between QTD and cardiovascular mortality and arrythmia.[36,37]

Possible mechanisms accused for these arrhythmogenic changes are effect of lead on autonomic system, increased plasma norepinephrine and c-AMP production in heart, effect on cardiac excitability, and deterioration of cell membrane function because of calcium like effects of lead.[38–41] Lead has also morphological effects on heart like fibrosis, degeneration and necrosis, mononuclear cell infiltration.[42] In an autopsy series, children who died from lead poisoning revealed myocarditis characterized with interstitial fibrosis.[43] Blood lead levels are about acute exposure but lead accumulates in many body parts especially in bones and there is a continuous turnover between bones and blood. Cheng et al found bone lead levels were associated with heart rate, cQT, and QRS interval while blood lead levels had not a relation. Bone lead levels are a marker of chronic exposure while blood lead levels show acute exposure. So, the findings of Cheng et al can be interpreted as these ECG changes are not because of blood lead's effect on cellular mechanisms as we mentioned before but a consequence of chronic morphological changes. In our study P max, P min, PWD, and QTD were significantly changed after chelation therapy, but there was not a significant change in QTmax, QTmin, heart rate, cQT, and Tp-e which were shown to be associated with lead exposure. We can speculate that Pmax, Pmin, PWD, and QTD changed because of cellular mechanism of lead (on autonomous system, acting like calcium ions or altering enzymes and hormones) while the rest ECG parameters were associated with chronic myocardial changes.

Chelation therapy is also used for cardiovascular disease treatment. The effect of chelation therapy on cardiovascular system is controversial. There are contradictory data on literature.[44,45] Possible mechanism advocated about the effect on cardiovascular system are decalcification of coronary plaques, decreasing platelet aggregation and free oxygen radicals, vasodilation, effect on parathormone, lipid and iron metabolism.[46–48] We do not have enough data about the effect of chelation on ECG parameters.

Best of our knowledge, our study is first study evaluating basic and arrhythmogenic ECG parameters extensively in the same patient group while blood lead levels were high and normal, unlike many studies comparing ECG parameters of different patients. So, we could eliminate many confounders.

Our study should be interpreted with some limitations. The study population were all male workers occupationally exposed to high lead levels without comorbidities so the study results cannot be generalized to whole population with comorbidities.

We compared biochemical parameters which could affect ECG like calcium, magnesium, potassium etc. But despite enough data in the literature chelation could have some effect on ECG.

We do not have data about cardiovascular and arrhythmic events because lack of long-term follow up.

Only blood lead levels which shows acute exposure were evaluated, bone lead levels which best shows chronic exposure were not taken into consideration.

Conclusions

Our study has shown that some proarrhythmic ECG parameters, whose prolongation is an indicator of arrhythmia, are shortened by chelation therapy.

Lead exposed workers are under the risk of ventricular and atrial arrythmias and chelation treatment has potential to reduce arrythmia.

However, lead has acute and chronic effects on heart like all body parts. For understanding the actual mechanism of effect of lead on arrythmia and effect of chelation therapy, experimental trials and multicenter prospective trials with long-term follow up are needed.

Disclosure statement

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