The assessment of QT intervals in acute carbon monoxide poisoning

Akut karbonmonoksit zehirlenmelerinde QT intervallerinin değerlendirilmesi

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ABSTRACT

Objective: Carbon monoxide (CO) poisoning is known to cause myocardial toxicity and life threatening arrhythmias. QT interval measured from electrocardiogram is an indirect measure of the heterogeneity of ventricular repolarization, which may contribute to ventricular arrhythmias. The purpose of the study was to investigate whether the carboxyhemoglobin (COHb) level may be related to the changes of QT, corrected QT (QTc), QT dispersion (QTd), corrected Qtd (QTdc) and cardiac enzymes during carbon monoxide poisoning.
Methods: We conducted an observational study; 104 patients who had been diagnosed with CO intoxication were included in the study. Measurement of QT, QTc, QTd and QTdc intervals were performed form electrocardiogram on admission, 24 and 48 hours after admission. Cardiac enzymes were measured at each time-point. The myocardial perfusion scan was determined in all patients 1 week after admission.
Results: The QT interval level in 24h was significantly higher than admission level (p<0.001), additionally QTc interval levels in 24h and 48h were significantly lower than admission levels (p<0.001 and p<0.001, respectively). Carboxyhemoglobin level only significantly correlated with QT intervals (r=-0.288 ; p=0.019), troponin T (r=-0.297; p=0.007), and creatine kinase MB levels (r=0.262; p=0.020). As a result of ROC analysis the QT interval level was significantly powerful parameter to predict COHb (p=0.022).
Conclusion: Our data indicate COHb level correlated with QT intervals and cardiac enzymes. Clinicians should possibly avoid QT prolonging drugs and carefully monitor the QT, QTc, QTdc intervals in patients at high risk of cardiac disability due to high levels of COHb after CO poisoning.
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Key words: Carbon monoxide poisoning, carboxyhemoglobin, QT intervals, predictive value of tests

ÖZET

Amaç: Karbonmonoksit zehirlenmelerinin miyokard toksisitesine ve ciddi aritmilere yol açtığı bilinmektedir. Elektrokardiyografide (EKG) ölçülen QT intervalleri, aritmilere neden olan ventrikül repolarizasyonundaki düzensizliğin bir göstergesidir. Bu çalışmanın amacı, karbonomonoksit zehirlenmelerinde, karboksihemoglobin seviyesinin (COHb) QT, düzeltilmiş QT (QTc), QT dispersiyonu (QTd), düzeltilmiş QTd (QTdc) intervallerindeki değişikliklerle ve kardiyak enzimlerle ilişkisi olup olmadığını araştırmaktır.
Yöntemler: Karbonmonoksit zehirlenmesi tanısı konan 104 olgu çalışma kapsamına alındı. QT, QTc, QTd ve QTdc intervallerinin ölçümü olguların hastaneye kabulünde, 24 saat ve 48 saat sonra yapıldı. Eş zamanlı kardiyak enzim ölçümleri yapıldı.
Bulgular: Gözlemsel çalışma QT intervalleri 24. saatte, kabuldeki değerlerine göre daha yüksek (p<0.001), QTc intervalleri ise 24 ve 48. saatlerde kabuldekine göre daha düşük bulundu (p<0.001, p<0.001). Karboksihemoglobin düzeyi sadece QT intervali (r=-0.288; p=0.019), troponin T (r=-0.297; p=0.007) ve kreatin kinaz MB (r=0.262; p=0.020) düzeyleri ile korelasyon gösterdi. ROC analizinde QT süresi COHb düzeyin anlamlı öngördürücüsü olarak bulundu (p=0.022).
Sonuç: Çalışmamız karboksihemoglobin düzeyinin QT intervalleri ve kardiyak enzimlerle korele olduğunu göstermiştir. Karbonmonoksit zehirlenmelerinde, yüksek COHb düzeylerine bağlı oluşabilecek kardiyak problemler göz önüne alınarak, yüksek riskli hastalarda QT, QTc, QTd, QTdc intervallerinin monitorize edilmesi ve QT uzamasına yol açabilecek ilaçlardan kaçınılması gerektiği sonucuna varılmıştır.
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Anahtar kelimeler: Karbonmonoksit zehirlenmesi, karboksihemoglobin, QT intervalleri, testlerin prediktif değeri

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Introduction

Carbon monoxide (CO) poisoning is known to cause myocardial toxicity and life threatening arrhythmias (1-3). Ischemic chest pain and decreased exercise tolerance can also result. As CO binds with cardiac myoglobin, myocardial oxygen reserves are rapidly reduced (4). Carbon monoxide may cause papillary muscle dysfunction, abnormal ventricular wall motion, and mitral valve prolapse. The ventricular fibrillation threshold is lowered by CO, and atrial flutter, atrial fibrillation, premature ventricular tachycardia, and conduction system disturbances are also seen (5).

The QT interval has long been known to vary significantly between the individual 12 leads of the surface electrocardiogram (ECG) (6). A potential clinical application of this interlead difference was proposed in 1990 by Day and coworkers (7), who suggested that the interlead difference in QT interval might provide a measure of repolarization inhomogeneity, which they called "QT dispersion". Changes in heart rate play a major role in QT interval variation. The most common approaches use the correction, which divide QT by the square root (Bazett correction) or cube root (Fridericia correction) of the preceding RR interval. Corrected QT dispersion (QTdc) of ECG is an indirect measure of heterogeneity of ventricular repolarization, which may contribute to ventricular arrhythmias (8).

It was once commonly believed that the level of toxicity from carbon monoxide exposure was reflected in and paralleled by the level of carboxyhemoglobin in the victim's blood. However, studies over the past 30 years have demonstrated that this is not correct; the level of carboxyhemoglobin in the blood does not correlate precisely with either prognosis or clinical condition. We know that at levels of 25%, there may be ECG changes of ST segment depression, ischemia, atrial flutter, atrial fibrillation, premature ventricular tachycardia, and conduction system poisoning. Though the ECG changes in CO poisoning has been established, the knowledge on the extent of myocardial damage and diagnostic values for myocardial damage in the setting of CO poisoning are scarce and contradictive.

Our aim in this study was to investigate whether the carboxyhemoglobin (COHb) level may be related to changes of QT, corrected QT, corrected QT dispersion, and QT dispersion and to define the optimal CO cut-off values for presence of myocardial damage and repolarization abnormalities and cardiac enzymes during carbon monoxide poisoning.

Methods

The study was conducted between September 2006 and June 2007 at Anesthesiology Intensive Care Unit of the Eskişehir Osmangazi University hospital . One hundred and four patients, who had been diagnosed with carbon monoxide intoxication, were studied in this prospective study.

Carbon monoxide poisoning was confirmed in the patients by arterial blood gas analysis. Carboxyhemoglobin measurements were performed with a Rapidlab (Bayer) oximeter. Exclusion criteria included: any history of unconsciousness; the history of drugs administration that induced QT prolongation, affected the cardiac conduction system, in anyway, had arrhythmogenic properties, pregnancy; cardiac compromise diagnosed on the basis of chest pain or ischemic changes, and any evidence of bundle branch block on ECG.

This study was approved by the Institutional Review Board our institutes. Informed consent was obtained from all patient or their legal representatives.

After patients were taken to hospital, oxygen therapy was given. Patients inhaled oxygen through a tight-fitting mask and continued 100% oxygen therapy until they were asymptomatic and carboxyhemoglobin levels were below 10%.

QT interval measures

All 12-lead ECG's were performed at paper speed of 50 mm/s, and with standard lead positions (Nihon Kohden Cardiofax GEM, Japan). In each ECG lead the QT interval and QRS duration were measured in all patients. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, defined as the return T-P baseline. When U waves were present, the QT interval was measured to the nadir of the curve between T and U waves. The QT intervals for each lead were measured and corrected for heart rate (QTc) using Bazett's formula (QT/RR1/2). The QTdc is then the difference between the leads with the shortest and longest QTc intervals. Measurement of QT intervals was calculated on admission and at the ECGs at 24 hours and 72 hours after admission.

Cardiac enzymes

On admission to the emergency department, blood samples were obtained from patients; troponin T, creatine kinase, and creatine kinase-MB (CK-MB) levels were measured in anticoagulant tubes. Creatine kinase, and CK-MB levels were determined using Thermo kits, Konelab (Thermo Clinical Labsystem, Finland). Levels <220 U/L for creatine kinase and <20 U/L for CK-MB were accepted as normal values. Troponin T was studied with immunoassay method using monoclonal antibodies (Enzymum Test System ES 300; Boehringer Mannheim, Mannheim, Germany). Levels >0.1 µg/ml were accepted as indicating myocardial damage. Measurements were repeated at 24 and 48 hours after admission. An intensivist blinded to patient status performed all measurements and analyses.

Statistical analysis

A prospective statistical analysis plan before beginning the statistical work was developed, and statistical analyses were performed using Statistica 7.0 (StatSoft, Inc. Tulsa, OK, USA) statistical software. Results are presented as mean±SD, median (min-max) values unless otherwise indicated. Normality distribution of the variables was tested using the one sample Kolmogorov-Smirnov test. Three different measurements were evaluated by repeated measures analysis of variance.

ANOVA test, and then Bonferroni post-hoc tests were used when the significance difference was obtained. Spearman correlation analysis was used to examine the relationships between COHb levels and demographical/clinical variables. Area under the curve (AUC) of the receiver operating characteristic (ROC) curve was used to assess the predictive power of the variables for COHb. A plot of true positive rate against false positive rate was made and the AUC was measured. The thresholds for different COHb levels were calculated and

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optimal thresholds were selected (COHb> 21% for QT interval, COHb> 31% for troponin T, and CK-MB levels). The sensitivity and specificity rates of the variables were estimated by cut off points. The AUC is a measure of the overall discriminatory power of the prognostic variable. A value of 1.0 indicates perfect discrimination, a value of 0.5 equals random prediction and a value of lower than 0.5 indicates no discriminative power. The relationships between COHb level with troponin T, CK-MB, and duration of QT, QTd, QTc and QTdc intervals were examined by Spearman correlation analysis.

A p value <0.05 was considered statistically significance.

Results

All poisoning occurred at home and were caused by improper combustion of coal or wood in inadequately ventilated stoves. Nausea, vomiting and headache were the most common symptoms in both groups. Demographic and clinic characteristics of the patients are presented in Table 1.

The QT, QTd, QTc and QTcd interval levels on admission, at 24th, and 48th hours are shown in Figure 1. The QT interval level at 24h was significantly higher than admission level (p<0.001), additionally QTc interval levels at 24th and 48th hours were significantly lower than admission levels (p<0.001 and p<0.001, respectively). There were no significant differences in other interval levels between the measurement times (p>0.05 for all). The QTdc interval was abnormally prolonged in 4 patients who died during follow-up.

Carboxyhemoglobin level only significantly correlated with QT intervals (r=-0.288; p=0.019), troponin T (r=-0.297 ; p=0.007), and CK-MB (r=0.262 ; p=0.020). There was no correlation between COHb and lactate dehydrogenase levels (p>0.05).

To define optimal decision thresholds for QT interval, troponin T, and CK-MB levels based on COHb levels in patients, ROC curve analysis was performed. We determined COHb thresholds for QT interval, troponin T, and CK-MB levels (COHb>21%, COHb>31%, and COHb>31%, respectively), (Fig. 2). Cut-off values, predictive accuracies, and AUCs for each variable are shown in Table 2. The QT interval level had significant AUC=0.650 (p=0.022) with optimal cut-off point ≤356 ms, and at this cut-off point, the sensitivity rate was 57.1% and the specificity rate was 77.3%. The troponin T level had significant AUC=0.676 (p=0.015) with optimal cut-off point was >0.054 ng/ml, and at this cut-off point, the sensitivity rate was 40.9% and the specificity rate was 96.7%. The CK-MB level had significant AUC=0.644 (p=0.037) with optimal cut-off point >36 U/L, and at this cut-off point, the sensitivity rate was 52.0% and the specificity rate was 80.0%.

Discussion

This study of 104 patients with carbon monoxide poisoning demonstrated the use of non-invasive assessment of dispersion ventricular repolarization by use of QT dispersion. The QTc interval levels at 24th and 48th hours were significantly lower than admission levels. Carboxyhemoglobin level significantly correlated with QT interval duration, troponin T, and CK-MB levels.

Carbon monoxide poisoning is associated with myocardial depression, partly because of hypoxic stress, the mitochondrial bond of CO with cytochrome a3, and a link with myocardial myoglobin. The link to myoglobin may play a major role in myocardial depression associated with intoxication by CO, given the significant role that myoglobin has on the intracellular diffusion of oxygen.

The blocking of the function of myoglobin is associated with a reduction in the uptake of oxygen and a reduction in the production of ATP by cardiac muscle. The possible cardiac toxic effects of CO include atrial flutter, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and myocardial ischemia. It has been shown without ambiguity that at 5.0% COHb, there is a reduction of oxygen binding and a consecutive reduction in the physical capacity under conditions of maximum exertion in young adults in good health. Tissue hypoxia resulting from a large COHb load, in clinical terms, has the greatest influence on the heart, and CO binding to hemoproteins, including cytochrome, myoglobin and guanylate cyclase, contributes to the clinical syndrome (9, 10).

Overt signs of toxic effects usually appear at COHb levels of 15 to 20%, and a level of 25% is the index of severe poisoning, which may lead to a sudden loss of consciousness. Recent studies have indicated that exposure to low concentrations of

Table 1. Demographic and clinical characteristics of the patients at admission

Parameters	Carbon monoxide intoxication (n=104)
Age, years	41.9±18.2
Sex, M/F	65/35
Troponin T, ng/ml	0.04±0.10
COHb, %	26.6±10.3
CK, U/L	172.9±369.6
CK-MB, U/L	34.5±25.0
LDH, U/L	278.3±170.0

Data are expressed as Mean±SD and number/percentage

CK – creatine kinase, COHb – carboxyhemoglobin, LDH – lactate dehydrogenase

Table 2. Calculated cut-off, sensitivity, specificity, and AUC values of parameters for thresholds in ICU admission

Variables	Threshold for COHb (%)	Cut-off	Sensitivity (%)	Specificity (%)	AUC (95% confidence Interval)	p
QT interval, ms	21	≤356	57.1	70.4	0.650 (0.524-0.776)	0.022
TroponinT, ng/ml	31	>0.054	40.9	96.7	0.676 (0.529-0.824)	0.015
CK-MB, U/L	31	>36	52.0	80.0	0.644 (0.510-0.774)	0.037

AUC - area under the curve, CK – creatine kinase, ICU - intensive care unit

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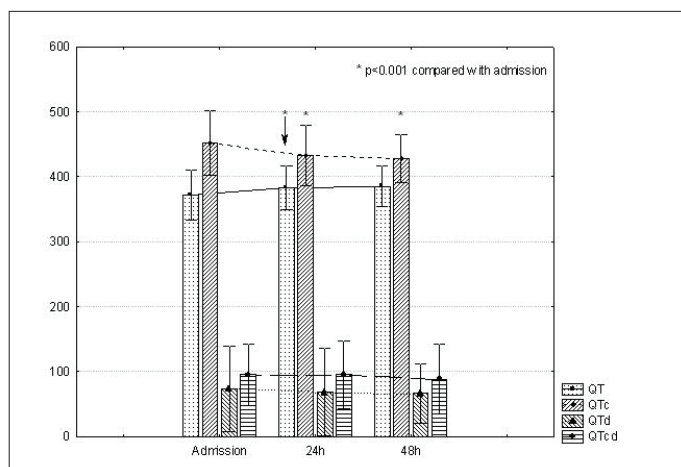Carbon monoxide and QT intervals

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Figure 1. QT (ANOVA F=6.742; p=0.003), QTc (ANOVA F=5.202; p=0.010), QTd (ANOVA F=1.649; p=0.204), and QTcd (ANOVA F=1.546; p=0.225) interval levels at admission, 24, and 48 hours after admission

ROC curve for QT interval (ms) AUC=0.650 (%95 CI:0.524-0.776); p=0.022.

ROC curve for Troponin (ng/ml) AUC=0.676 (%95 CI: 0.529-0.824); p=0.015.

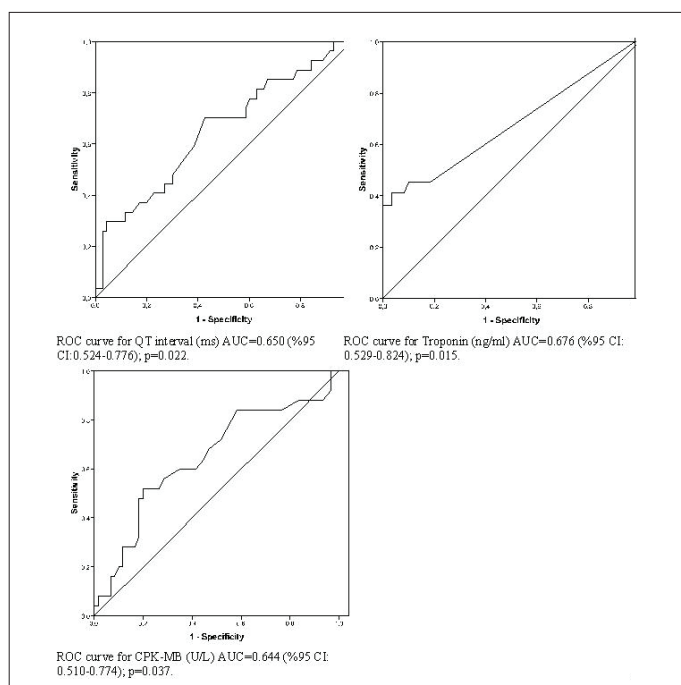ROC curve for CPK-MB (U/L) AUC=0.644 (%95 CI: 0.510-0.774); p=0.037.

Figure 2. ROC curves for QT interval, troponin T and CK-MB
CK - creatine kinase

carbon monoxide have a direct adverse effect on the heart, exacerbating myocardial ischemia, and facilitating ventricular arrhythmias in patients with coronary heart disease (1, 2, 11). In contrast with previous studies on the effects of COHb in patients with ischemic heart disease (11, 12), only few studies have considered this issue in healthy subjects. However the results of those studies are controversial. Turner and McNicol (13) did not find a significant effect CO exposure on cardiovascular performance, whereas Aronow and Cassidy (14) found that increased concentrations of COHb impaired exercise performance in 10 normal middle-aged men. Neither study measured ischemic ECG changes during exercise. In the light of this controversial data on the healthy population, we decided to analyze the dispersion of QT interval duration in patients with acute carbon

monoxide poisoning and to compare it with different COHb levels. In this study, we demonstrated that carboxyhemoglobin at levels of 21%, there were ECG changes of QT intervals.

Several studies have shown the importance of inhomogeneous myocardial repolarization in the genesis of ventricular arrhythmias. The difference between maximum and minimum QT intervals on standard 12 lead ECG (QT dispersion) has been proposed as a non-invasive measure of the degree of homogeneity in myocardial repolarization, which might be a significant predictor of serious arrhythmias and cardiac mortality in humans (15, 16). Although increased QTdc has been reported to contribute to ventricular arrhythmias in various cardiovascular diseases, in some studies the ECGs have shown ventricular arrhythmia in CO-intoxicated patients.

Conclusion

The results of the present study demonstrate that COHb level correlated with QT intervals and cardiac enzymes. Clinicians should possibly avoid QT prolonging drugs and carefully monitor the QT, QTc, QTdc intervals in patients at high risk of cardiac disability due to high levels of COHb after CO poisoning.

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