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Ventricular Arrhythmias in Patients with Acute Carbon Monoxide Poisoning are Associated with QT Dispersion

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Abstract

Background: Carbon monoxide (CO) poisoning has a direct myocardial toxicity and arrhythmogenic potential. QT dispersion (QTd), calculated from 12 lead ECG, is an index of heterogeneity of ventricular repolarization which may contribute to ventricular arrhythmias. The objective of the present study was to investigate QTd in patients of all grades of acute CO poisoning and its possible relation to ventricular arrhythmias and carboxyhemoglobin level. 1.2. Methods: A case-control study that included ten healthy non-smokers adult volunteers as control (Group I) in addition to thirty adult patients of both sexes suffering from acute CO poisoning admitted to Poison Control Center of Ain Shams University hospitals classified into three groups according to the symptoms and signs 9 Group II (mild toxicity) Group III (moderate toxicity) Group IV (severe toxicity)).

Measurements: Carboxyhemoglobin (COHB) level and 12 lead ECG were recorded on admission and at the time of discharge from each patient. This was done only once for the control subjects. QTd was defined as the difference between the greatest and the least QT intervals in any of the 12 leads.

Results: Mean COHB levels were significantly high in all patients on admission compared to the control group. They were higher in group IV than group III followed by group II. COHB levels decreased significantly on discharge time in all groups. On admission, cQTd durations were significantly increased in all CO-poisoned patients compared to Control group. They were higher in group IV than group III followed by group II. In all the tested groups, cQTd durations decreased significantly on discharge when compared with on admission durations. The patients who developed ventricular arrhythmias in the form of bigeminy and premature ectopic beats were mostly from group IV, showed higher cQTd durations compared with patients without arrhythmias. Moreover, cQTd durations were higher in patients with ventricular bigeminy than patients with premature ectopic beats. No correlation was found between COHB levels and cQTd durations of group IV.

Conclusion: This study showed that cQTd reversibly increased in all patients with various grades of acute CO poisoning. Development of ventricular bigeminy and premature ectopic beats especially in patients with severe poisoning was associated with higher cQTd. No correlation was found between the levels of COHB and the cQTd durations in the severe poisoning group. So cQTd determination could provide a potentially simple, cheap, non-invasive method of measuring the underlying dispersion of ventricular excitability, thus improving the diagnostic accuracy in a routine clinical setting.

Keywords: Poisoning; Carbon monoxide; Ventriculat arrhythmias; QT dispersion

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Introduction

Acute carbon monoxide (CO) poisoning is a common cause of toxicological morbidity and mortality and it is considered as one of the most lethal poisonings [1]. It is generally known to cause myocardial toxicity and life-threatening ventricular arrhythmias, which expose the patients to increased risk of sudden death [2,3]. This suggests that an appropriate diagnostic approach to identify patients at risk may help to prevent these events. Measuring changes in the duration of the QT interval and QT dispersion in the standard 12-leads Electrocardiogram (ECG) is currently a subject of growing interest [4]. The study of Eroglu et al. **[5]** showed that QTc dispersion was increased after CO poisoning. QT dispersion (QTd), first reported by Day et al. [6]**,** was defined as the difference between the maximum and minimum QT interval measurements among all the measured 12 leads on the standard ECG (QTd =QTmax-QTmin). Christov et al. [4] proposed the

Table 1: Demographic data and characteristics of acute carbon monoxide poisoned patients and control subjects.

	Control subjects (n=10)	CO poisoned patients (n=30)		
		Group II	Group III	Group IV
Sex (male/female) P	5/5	7/4	6/4	4/5
		> 0.05		
Age (year) (mean ± SD) p	27.4 ± 6.2	28.4 ± 5.9 > 0.05		
Duration of exposure (hours)	—	2.73 ± 1.04 (2-4)		
COHB % (on admission)	2.4±1.3	42.7 ± 2.24	27.7 ± 5.07	19.3 ± 5.18
cQTd (ms) (on admission)	12 ± 4.6	81 ± 4	65 ± 3.2	47 ± 4.2

p: >0.05 insignificant differences.

Table 2: Comparison of COHB % between different groups.

	Group I (n=10)	Group II (n=10)	Group III (n=10)	Group IV (n=10)	LSD
COHB (%) on admission	2.4 ± 1.3	19.3 ± 5.18	27.7 ± 5.07	42.7 ± 2.24	3.47
COHB (%) on discharge		2.06 ± 0.6	2.98 ± 0.67	3.28 ± 1.37	0.96
p		< 0.05	< 0.05	< 0.05	

n= number of individuals.
LSD: Least Significant Difference.
p: < 0.05 significant difference.

Table 3: Comparison of cQTd between different groups on admission and on discharge.

	Group I (n=10)	Group II (n=10)	Group III (n=10)	Group IV (n=10)	LSD
cQTd (ms) on admission	12 ± 4.6	47 ± 4.2	65 ± 3.2	81 ± 4	3.54
cQTd (ms) on discharge		15 ± 4.7	15 ± 3.84	17 ± 5.24	9.26
p		< 0.05	< 0.05	< 0.05	

use of QTd measurement, a noninvasive ECG parameter, as an index of the in homogeneity of myocardial repolarization, which is known to favor the development of ventricular arrhythmias. Also, it could be applied as a potential prognostic tool in the detection of future ventricular arrhythmia and death. The aim of the present study was to investigate QT dispersion in patients with all grades of acute carbon monoxide poisoning and its possible relation to ventricular arrhythmias and carboxyhemoglobin level.

Methods

Ten healthy non-smokers adult volunteers were included in the study as a control group (Group I) in addition to thirty adult patients of both sexes suffering from acute CO poisoning, admitted to Poison Control Center, Ain Shams University hospitals, Cairo, Egypt in the period between November 2016 and March 2017. Their ages ranged from 18 to 35 years (mean 28.4 ± 5.9). Young patients were selected, to avoid the influence of old age on the clinical course of CO poisoning and QT durations [7]. An informed written consent was obtained from patients participating in the study or from next of kin for those who were obtunded. CO poisoning was diagnosed based on a history of exposure, symptoms, signs and elevated COHB level of above 10%. These patients were divided into three groups of 10 patients each according to the signs and symptoms as described by Wallace as follows [8]:

Group II (mild toxicity) this group included patients suffering from headache, dizziness, weakness, nausea or malaise.

Group III (moderate toxicity) this group included patients suffering from confusion, lethargy, syncope, nystagmus or ataxia.

Group IV (severe toxicity) this group included patients suffering from coma, seizures, pulmonary edema, myocardial infarction, cardiac arrhythmias or cardiac arrest.

Exclusion Criteria

Patients were excluded from the study if they were smokers, had any condition that could influence QT duration measurement like: Electrocardiographic evidence of atrial fibrillation, flutter or bundle branch block, be receiving drugs influencing QT duration e.g. TCA, erythromycin, quinidine etc., history or signs of coronary heart disease, systemic hypertension or pregnancy.

Study Parameters

• Venous blood samples were withdrawn from each patient enrolled in the study immediately after admission to the hospital for measurement of carboxyhemoglobin level (COHB %) by blood gas co-oximetry [8,9]. This was repeated every six hours for assessing the effect of treatment until discharge time. One sample was taken from each of the control subjects.

• Baseline 12 lead electrocardiogram was recorded at a paper speed of 25 mm/s and standardization of 1.0 mV/cm from each patient on admission and at the time of discharge from the hospital. It was done only once for the control subjects.

Measurement of QTC Intervals and Calculation of QT Dispersion

QT dispersion was calculated in all the patients of CO poisoning as well as the control subjects, as described by [10]. R-R and QT intervals were measured in the 12 leads. The QT intervals were measured in each lead from beginning of the depolarization of QRS complex to the end of the T wave. Each measurement was taken

Table 4: The on-admission cQTd in patients without ventricular arrhythmias and those with ventricular arrhythmias.

	Patients without Ventricular arrhythmias (n=12)	Patients with Ventricular arrhythmias (n=18)	p
cQTd (ms)	53 ± 8.9	73 ± 11.8	< 0.05

Table 5: The on-admission cQTd in patients with ventricular premature beats and those with ventricular bigeminy.

	Patients with Ventricular premature beats (n=12)	Patients with ventricular bigeminy (n=6)	P	CL
cQTd (ms)	67 ± 10.2	84 ± 2.8	< 0.05	7.9

Table 6: Pearson's correlation between cQTd and COHB% in patients with severe Carbon monoxide poisoning on admission.

	cQTd (ms)	COHB level (%)	r	P
Group IV (n=10)	81 ± 4.1	42.7 ± 2.2	0.4	> 0.05

r: correlation coefficient.
p: > 0.05 insignificant difference

as the mean value of 2 to 3 consecutive RR and QT intervals. The difference between the greatest and the least QT intervals on any of the 12 leads were considered QT dispersion (QTd). QT dispersion was corrected in accordance with the heart rate using Bazett's formula (corrected QTd (cQTd) = QTd/ √ R-R interval) in milliseconds [11]. This traditional correction procedure is intended to obviate the dependence of QT interval on heart rate. In the case of interfering premature complexes, the lead concerned was not included in the subsequent analysis. Ventricular arrhythmias were analyzed and its relationship to QTd was observed.

Statistical Analysis

The results were expressed as mean ± SD and statistically analyzed using Graph Pad Instat program version 3.05 for Windows XP. One-way Analysis Of Variance (ANOVA) was performed for multiple comparisons between the different studied groups while student "t" test was used to compare two groups. Pearson's correlation was done to determine the correlation between COHB % levels with cQTd. A value of $p < 0.05$ was considered statistically significant [12].

Results

As regards demographic criteria**,** there was an insignificant difference in age and sex distribution between the patients and control group. All poisoning occurred at home and were caused by burning of charcoal, wood, kerosene, or natural gas for heating and cooking or inadequately ventilated bathroom heater. Estimated duration of exposure to CO ranged from 2-4 hours. The duration of stay at hospital ranged between 1-10 days. None of the patients in the present study died (Table 1).

Concerning COHB levels, ANOVA one-way analysis showed that they were significantly increased in all patients on admission compared with the control group. By applying Least Significant Difference (LSD) the increase was more in group IV (patients with severe poisoning) than group III (patients with moderate poisoning) followed by group II (patients with mild poisoning). While't' test compared on admission and discharge COHB levels showed a significant decrease in the level in all tested groups (Table 2).

As regards cQTd durations, on admission ANOVA one-way analysis showed a significant increase of the durations in all patients compared with the control group. By applying LSD, cQTd was significantly greater in group IV than group III followed by group II. Student't' test compared cQTd in all the tested groups between the on admission and the on-discharge times and showed significant decrease of the durations in all tested groups (Table 3).

While as regards the occurrence of ventricular arrhythmia, three patients from group II, five patients from group III and four patients from group IV had got Ventricular Premature Beats (VPBs), and six patients from group IV had ventricular bigeminy. The cQTd was significantly higher in 18 patients with ventricular arrhythmia than 12 patients without Tables 4 and 5. By applying LSD, cQTd durations were significantly higher in patients with ventricular bigeminy than those who had VPBs (Table 5).

Pearson's correlation between the COHB% level and cQTd durations in severely acute CO intoxicated patients (group IV) was insignificant (Table 6).

Discussion

Acute CO poisoning is considered an important health problem. Ventricular arrhythmias are a frequent consequence of it [1,2]. In a previous study done by [13] there was a significant increase in frequency and severity of ventricular arrhythmia in patients with coronary artery disease who exposed to CO and this may explain increased sudden death rates associated with the toxicity. Since QT dispersion (QTd) is used as an indirect, simple and noninvasive measure of heterogeneity of ventricular repolarization that contributes to ventricular arrhythmias in patients with myocardial ischemia, after myocardial infarction and drug arrhythmogenicity [14-16], so, the present study is designed to investigate the QTd durations in patients with acute CO poisoning and to find its relation to the ventricular arrhythmias and COHB level.

[7,17] found that the frequency of toxic myocardial injury and number of deaths were significantly higher in the group of CO intoxicated patients older than 60 years. Moreover, [16] examined QTd of the elderly group and they noticed a significant increase as compared to the younger group with a positive correlation between QTd and age.

The present study showed that COHB levels were significantly higher on admission in all poisoned patients as compared with the control group and they were higher in patients with severe poisoning than those with moderate followed by mild poisoning**.** These results are in accordance with [18,9]. WHO reported that most cases of CO poisoning demonstrated an elevated blood COHB% concentration. Moreover, in all tested groups the COHB levels significantly decreased on discharge when compared with on admission levels, this could be explained according to [19] who postulated that treatment with high flow oxygen decreases the circulating COHB half-life from 4-5 hours on room air to less than 1 hour at 100% oxygen.

It was noticed that the severity of poisoning was concordant with the observed levels of COHB this was in accordance with the study of [20] who observed that the severity of symptoms correlates roughly with its COHB levels. However, [21] mentioned that such a fixed relation between the level and clinical features and outcome doesn't always occur. Furthermore [19,22-24] stated that COHB levels are valuable only for confirming CO exposure but do not correlate well with symptoms, cannot be used to stratify severity of poisoning and

do not predict prognosis or sequel. These studies did not report the time elapsed to measurement and whether or not oxygen has been given and COHB level strongly depends on both factors.

In the present study, CO intoxication resulted in significant increase of cQTd as compared to the control group. The cQTd was significantly greater in severely intoxicated followed by moderately and mildly intoxicated patients. And in all groups, cQTd was highest at the time of admission and it decreased on discharge time.

Similar observations have been made earlier by [25-27]. WHO found an increase in cQT and cQTd intervals in patients suffering from mild to moderate acute CO poisoning. They were treated with high-flow oxygen and supportive medical therapy with complete resolution later after elimination of COHB.

The association may be explained at the cellular level by a previously reported experimental animal studies done by [28,29]. WHO induced hypoxia and hypercapnia, and both have been shown to increase cQTd. As CO known to impair oxygen delivery and oxygen utilization by the myocardial muscles through high-affinity binding to hemoglobin with the displacement of oxygen and leftward shift of oxyhemoglobin dissociation curve decreasing the availability of oxygen to the already hypoxic tissues. Also, it binds to cardiac myoglobin resulting in myocardial depression and hypotension which exacerbate the tissue hypoxia. In addition, it binds to certain cytochromes which play a critical role in meeting cellular energy requirements [30], so tissue hypoxia resulted from COHB load, lead to disturbance of myocardial repolarization which is measured by cQTd. The reduction in cQTd in all patients after treatment could be explained by COHB clearance by using 100% inspired O2 that reduces the CO half-life elimination from 4-6 hours to 40 minutes [19,31].

The cQTd were significantly higher in patients with ventricular arrhythmias than patients without. Also, it was found that they were significantly higher in patients with ventricular bigeminy than patients with premature ectopic beats. Previously this relation between cQTd and the occurrence of ventricular arrhythmia in patients with acute CO poisoning had been noticed by [25]. WHO described a case history of profound, reversible, increased cQTd with ventricular ectopic beats after acute CO poisoning. This simply illustrated that the reduced threshold for arrhythmia in acute CO poisoning might be due to inhomogeneous repolarization of the ventricles that could be assessed by increased cQTd.

In an attempt to elucidate the mechanism of ventricular arrhythmias, Antzelevitch and Belardinelli, proposed that hypoxia leads to preferential prolongation of the myocardial cell action potential, thus prolonging the cQTd interval, and resulted in prolongation of the vulnerable period and thereby enhanced susceptibility to reentry ventricular arrhythmias. Although increased cQTd have been reported to contribute to ventricular tachycardia and ventricular fibrillation in various cardiovascular diseases, none of the ECGs showed these types of arrhythmias in the patients of this study. This could be explained by the younger age of the patients and absence of cardiac diseases which might lower the arrhythmogenic potential.

In the present study, no correlation was found between COHB% level and cQTd in severely intoxicated patients who showed the maximum increase in cQTd durations and all of them developed ventricular arrhythmias. This was in accordance with Gurkan et al. [26]. So COHB level cannot be used to predict the occurrence of ventricular arrhythmias.

Conclusion and Recommendations

The results of the present study demonstrated reversible disturbance of myocardial repolarization in all patients of various grades of acute CO poisoning, as manifested by significant increase of cQTd. All patients with severe poisoning developed ventricular bigeminy and ventricular premature ectopic beats which were associated with higher cQTd duration than patients without, no correlation was found between the levels of COHB and the cQTd durations in the severe poisoning group. So, it is recommended to calculate and use cQTd duration as a simple, noninvasive screening broadly accessible, easily repeatable/applied, and affordable procedure, to identify patients at greatest risk of ventricular arrhythmia after acute CO poisoning thus improving the diagnostic accuracy in a routine clinical setting.

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