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Some Biomarkers in Carbon Monoxide-Induced Cardiotoxicity

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Abstract

Background: Myocardial injury is a frequent consequence of carbon monoxide (CO) poisoning. Oxidative stress affection seems to be a relevant mechanism in the patho-physiology of patients with acute CO poisoning.

Methodology: Cardiovascular system examination and Electrocardiography (ECG) were performed for fifty CO intoxicated patients admitted to Poison Control Center, Ain Shams university Hospital for whom some oxidative stress indices have been investigated through the assessment of plasma level of malondialdehyde (MDA), superoxide dismutase (SOD) and nitric oxide (NO). Both cardiac enzymes; troponin I and beta natriuretic peptide (BNP) have been also assessed in addition to carboxyhemoglobin (COHb) levels. The investigated parameters were compared with those of 40 non-smoker healthy controls (comparable in terms of age and gender).

Results: ECG changes were present in 96% of patients, whereas only 4% had a normal ECG. In intoxicated patients, a statistical significant increase in plasma level of COHb level, MDA, NO, troponin I, and BNP peptide was reported compared to control individuals, while SOD enzyme was significantly decreased. BNP showed a significant positive correlation with COHb level and a negative correlation with SOD, while SOD showed a significant negative correlation with COHb level.

Conclusions and recommendations: Myocardial injury occurs frequently in patients hospitalized for CO poisoning. The oxidative stress indices are significantly affected after acute CO poisoning. We suggested that such affection could be partially mediated by CO. Patients admitted to the hospital with CO poisoning should have a baseline ECG and serial cardiac biomarkers.

Keywords: Carbon monoxide; Cardiotoxicity; Oxidative stress

Introduction

Carbon monoxide (CO) is a common cause of morbidity and the most common cause of mortality from poisoning in the United Kingdom [1] and the United States [2].

An Egyptian study performed by the Poison Control Center (PCC), Ain Shams University Hospitals in Cairo, showed that CO poisoning represented the 6th most frequent toxic exposure (2.28%) out of 25,555 cases admitted to PCC in 2004 [3].

CO induced myocardial damage is not completely understood as a clinical entity in terms of both pathophysiology and clinical features [4].

In carbon monoxide poisoned patients, an altered balance between reactive oxygen species and antioxidant levels has been reported [5]. Free radicals and oxidative stress are among factors involved in pathogenesis of acute carbon monoxide poisoning and particularly appear to have a role in carbon monoxide induced cardio-toxicity [6].

Carbon monoxide cardiotoxicity can be evaluated by various cardiac enzymes such as troponin I and beta natriuretic peptide [7,2].

Aim of the Work

The present study aimed at the detection of the cardiac effects of carbon monoxide toxicity through the estimation of cardiac biomarkers in "CO-exposed subjects", to report the oxidative stress effects on the heart of acute carbon monoxide poisoned patients and its relationship to cardiac biomarkers.

Methodology

This case control study was conducted in Poison Control Center, Ain Shams university Hospital, Cairo, Egypt. Patients with coronary artery disease or other known heart disease, patients with renal failure and individuals subjected to drugs or supplements with antioxidant effect as well as smoker subjects were excluded.

This study was conducted on 50 patients diagnosed as acute carbon monoxide poisoning according to medical history, examination, and/or COHb level>3% at the time of presentation.

They were 30 males and 20 females. Their age ranged between 15-45 years (26.5 ± 8.3 years). Apparently healthy 40 individuals, 20 males and 20 females, matched for age and sex were the control group.

Consent for examination was taken from these subjects.

On admission to the emergency department, blood samples were withdrawn from patients, after detailed clinical examination, to perform the following investigations; blood gases analysis, troponin I, BNP, SOD, MDA and (NO) synthase products (nitrate & nitrite) levels were measured. Baseline 12-lead ECGs were recorded with a paper speed of 25mm/s from each of the patients at the admission.

Arterial blood gases and Carboxyhemoglobin measurements were

performed using blood gas analyzer, Bayer 855. Carboxyhemoglobin Levels of 0-3% were accepted as normal values in non smoker patients.

Troponin I was estimated by microplate immunoenzymometric assay using The DRG° cTnI ELISA provided by Monobind Inc. Levels >1.3 ng/ml were accepted as indicating myocardial damage.

Malondialdehyde (MDA) was measured by spectrophotometric assay using BIOXYTECHÒ MDA-586™ provided by *Oxis*Research™ A Division of OXIS Health Products, Inc. levels<*3.5 µM=(n mol/ ml)* were accepted as normal values.

Superoxide dismutase (SOD) was measured by ELISA technique provided by *Oxis*Research™ A Division of OXIS Health Products, Inc. levels of >1.9 u/ml were accepted as normal values.

Serum nitrate nitrite concentration was determined using colorimetric assay kit provided by Cayman chemical company, USA. Levels 20-40 *n mol/ml* was accepted as normal values.

The quantitative determination of circulating troponin-I concentrations in human serum by microplate immunoenzymometric assay using The DRG° cTnI ELISA provided by Monobind Inc.

Beta natriuretic peptide (BNP) was measured in serum of all subjects by a competitive radioimmunoassay provided by DRG International Inc. levels of ≤ 10 pg/100 µl were accepted as normal values.

All data were collected, summarized, presented and analyzed using an appropriate Statistical Package Program (SPSS version, 17) (SPSS, Inc., Chicago, Illinois). Quantitative data were summarized as mean ± standard deviation. Qualitative data were summarized as number and percentage. Test of significance for qualitative data was Chi square test. Test of significance for quantitative data which are normally distributed for 2 groups was student (t) test, Pearson correlation coefficient between two continuous quantitative variables (r). In all tests the probability (P) was considered significant when p ≤ 0.05.

Results

Personal data

There was a non-significant difference between the exposed and control groups concerning the personal data (Table 1).

COHb levels in the study group

COHb level in the control group was <3% while in the study group, the COHb levels were increased. According to the COHb level, cases were classified into: Level 0: with COHb level > 3 % and <10 %, Level 1: with COHb level ≥ 10% and <20%, Level 2: with COHb level ≥ 20% and <25% and Level 3: with COHb level ≥ 25%.

Clinical results

Vital signs: There was a statistical significant difference in the heart rate, respiratory rate, systolicas well as diastolic blood pressure between the different groups (Table 2). Moreover, there was a statistical significant positive correlation between COHb level and changes in pulse and a negative correlation with both systolic and diastolic blood pressure (DBP) (Figures 1-4).

Cardiovascular manifestations: In the study group, 29 cases (58%) were complaining of dyspnea, 48 cases (96%) had palpitation, 25 cases (50%) had chest pain, and 48 cases (96%) had ECG changes in comparison to 5 cases (12.5%) in the control group with palpitation and ECG changes.

There was a statistically significant difference between the 2 studied groups concerning the palpitation and ECG changes (Table 3). Concerning ECG findings in the control group, no ECG changes were found except for sinus tachycardia in 5 subjects (12.5%). Whereas in the study group, the ECG findings were variable (Table 3 and Figure 5).

Concerning the ECG affection in the presented CO poisoned patients, 25% of study group with COHb level (0) had normal ECG, while 75% presented with tachycardia. 53.3% of study group with COHb level (3) had tachycardia, 20% presented with prolonged Q-T interval, 20% presented with prolonged Q-T interval & ST segment changes with inverted T wave and 20% presented with premature ventricular contractions (Tables 4 and 5).

Laboratory parameters: The parameters of arterial blood gases (ABG) of the CO poisoned subjects were statistically significant comparable to those of the control group (p<0.01**) (Table 6).

The laboratory parameters including (COHB), B-natriuretic peptide (BNP), troponin (cTnI), superoxide dismutase (SOD), malondialdehyde (MDA) and nitric oxide products (NO) were statistically significant different in the study group compared to the control group (Table 7).

Variable \ Group	Study group N= 50 Mean ± SD	Control group N= 40 Mean ± SD	p-value	Statistical significance
Pulse (Beat /min)	106.2 ± 10.6	78.5 ± 11.4	0.00	p<0.01** (HS)
Systolic BP (mmHg)	94.6 ± 8.1	115.2 ± 6.8	0.00	p<0.01** (HS)
Diastolic BP (mmHg)	64.5 ± 8.3	76.5 ± 7.3	0.00	p<0.01** (HS)
Temperature (ºC)	36.8 ± 0.23	37 ± 0.00	0.07	p>0.05 (NS)
Respiratory rate (cycle /min)	27.4 ± 7.09	12.4 ±1.05	0.00	p<0.01** (HS)

** (HS) = highly significant,(NS) = non significant
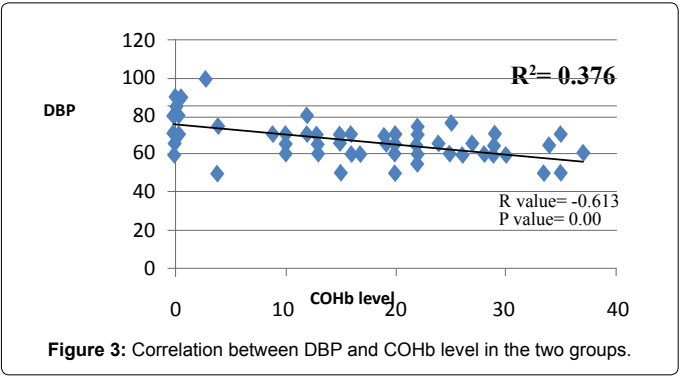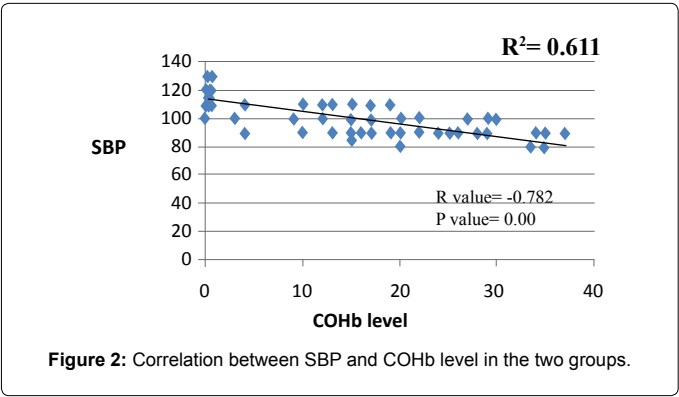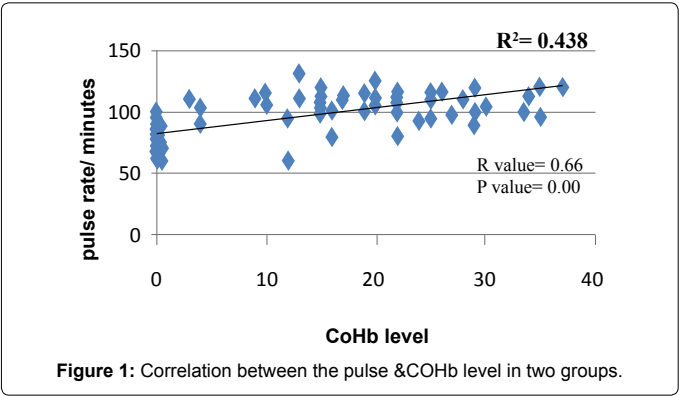**Table 2:** Vital signs among the study group and control group

Variable \ Group	Study group N= 50		Control group N= 40		Chi-Square	p-value	Statistical significance
	No	(%)	No	(%)			
Palpitation	48	96	5	12.5	52.8	0.00	p<0.01** (HS)
Normal ECG	2	4	35	78.5			
ECG changes	48	96	5	12.5	64.2		

** (HS) = highly significant
Table 3: Frequency of Palpitation and abnormal ECG in study group in comparison to control group

ECG changes \ Group	Study group No= 50
	(%)
Tachycardia	54%
ST segment changes with inverted T wave	24%
Prolonged Q-T interval	32%
Prolonged Q-T interval& ST segment changes with inverted T wave	6%
Premature ventricular contractions	6%

Table 4: Frequency of ECG changes among the study group.

Variable \ Group	Study group N= 50 Mean ± SD	Control group N= 40 Mean ± SD	p-value	Statistical significance
Age (years)	26.5 ± 8.3	25.5 ± 8.6	0.561	P >0.05(NS)
Sex (M/F)	30/20	20/20	0.568	p>0.05(NS)

(NS) = non significant.
Table 1: Personal data among the study group and control group

Figure 1: Correlation between the pulse &COHb level in two groups.

Figure 2: Correlation between SBP and COHb level in the two groups.

Figure 3: Correlation between DBP and COHb level in the two groups.

There was a statistical significant correlation between COHb level and BNP, SOD whereas, no significant correlation between COHb level and nitric oxide products (NO), troponin (cTnI) and malondialdehyde (MDA) (Table 8).

There was no significant correlation between NO products, malondialdehyde (MDA) and superoxide dismutase level (SOD) in the study group (Figures 6-8).

This study revealed that there was a statistical significant correlation between beta natriuretic peptide (BNP), superoxide dismutase (SOD) and malondialdehyde (MDA) whereas; there was no significant correlation between beta natriuretic peptide (BNP) and nitric oxide products (NO) (Figures 9-11).

Discussion

In our study, the male and female incidence ratio was 3:2 and males formed 60% of cases. This goes in agreement with many previous studies [7-10].

Carboxyhemoglobin levels tell us more about the degree of exposure than they do about how a poisoned victim will do in the short or long term [11]. Poor correlation between clinical presentations, and laboratory results could be related to the duration of exposure, the concentration of CO, or the amount and duration of supplemental oxygen administration prior to the blood sample withdrawing. Moreover, the level of CO in the tissues may have an equal or greater impact on the clinical status of the patient than does the blood level of CO [12].

Since, the relationship between carboxyhemoglobin levels and its toxic effects vary from person to person, we measured the carboxyhemoglobin (COHb) level base, and it was found to be significantly higher among patients with CO poisoning and these results are in agreement with Hampson and Hauff [13].

It was proven in previous studies that CO poisoning may affect the vital function; vital functions and heart rate [14,15] and, blood pressure [16,17]. In the present study, the heart rate, blood pressure and respiratory rate were affected, where CO intoxication resulted in cardiovascular manifestations e.g. dyspnea, palpitation, chest pain and ECG changes. The cardiovascular effects induced by CO poisoning may be due to decreased cardiac output caused by cellular hypoxia, binding of carbon monoxide with myoglobin, and diminished oxygen release. Studies in humans and animals have indicated that the threshold for induced ventricular fibrillation is lowered after exposure to carbon monoxide [18].

Figure 4: Correlation between temperature and COHb level in the two groups.
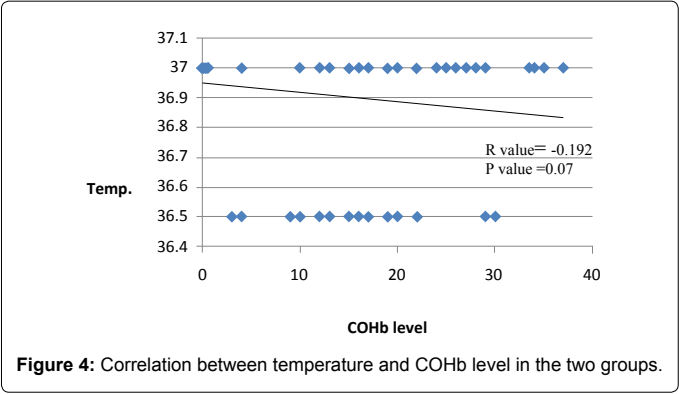
ECG \ COHb	Level (0) >3%, but <10%		Level (1) ≥10%, but<20%		Level (2) ≥20%, but<25%		Level (3) ≥25%	
	No	%	No	%	No	%	No	%
Normal ECG	1	25	0	0	1	10	0	0
Tachycardia	3	75	12	57.1	4	40	8	53.3
ST segment changes with inverted T wave	0	0	10	47.6	2	20	0	0
Prolonged Q-T interval	0	0	8	38	5	50	3	20
Prolonged Q-T interval, ST segment changes & inverted T wave	0	0	0	0	0	0	3	20
Premature ventricular contractions	0	0	0	0	0	0	3	20

Table 5: Frequency of ECG changes with different COHb levels in the study group
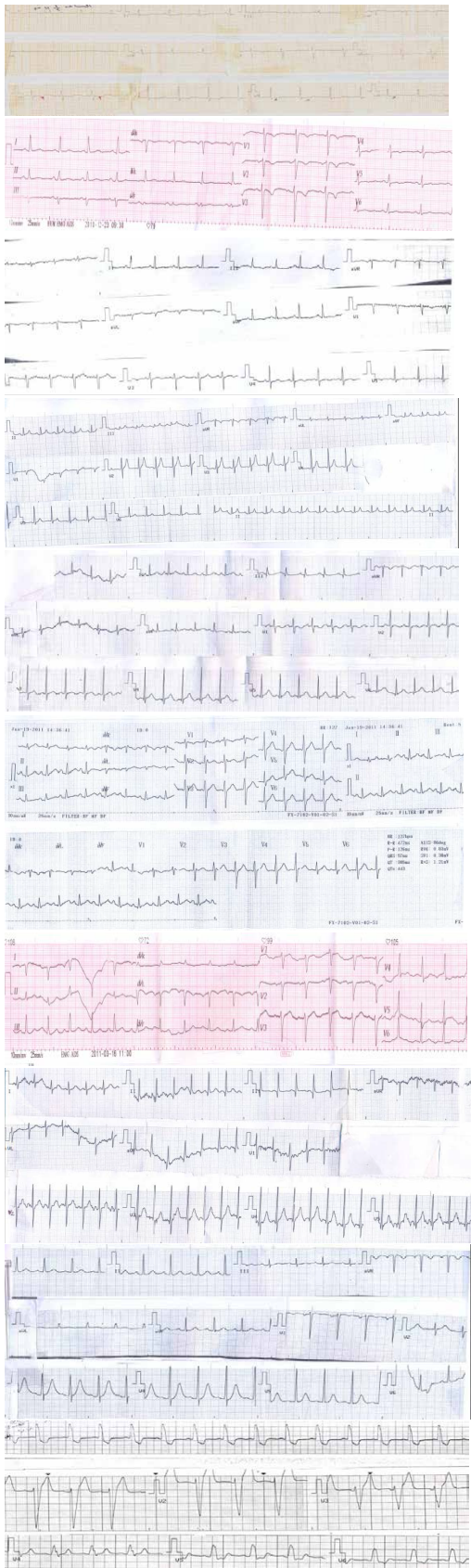
Figure 5: Examples of ECG alterations caused by CO exposure.

Group / Variable	Study group No= 50 Mean ± SD	Control group No= 40 Mean ± SD	t-test	p-value	Statistical significance
PH	7.30 ± 0.072	7.38 ± 0.03	5.9	0.00	$p<0.01$** (HS)
PCO2 mmHg	31.5 ± 8.4	37.8 ± 2.7	4.3	0.00	$p<0.01$** (HS)
PO2 mmHg	62.2 ± 22.1	97.5 ± 1.4	9.8	0.00	$p<0.01$** (HS)
SO2 %	84 ± 10.4	98 .8 ± 1.01	8.7	0.00	$p<0.01$** (HS)
HCO3 Mmol/l	16.1 ± 5.08	23.2 ± 1.1	8.5	0.00	$p<0.01$** (HS)

** (HS) = highly significant

Table 6: Mean ±SD levels of Arterial blood gases parameters among study group and control group.

Group / Variable	Study group Mean ±SD	Control group Mean ±SD	p-value	Statistical significance
COHb %	19.7 ± 8.3	0.4 ± 0.188	0.00	$p<0.01$** (HS)
BNP pg/100 µl	39.12± 32.27	0	0.00	$p<0.01$** (HS)
cTnI ng/ml	0.838 ± 0.77	0.28 ± 0.17	0.00	$p<0.01$** (HS)
SOD u/ml	1.9 ± 0.706	2.4 ± 0.551	0.00	$p<0.01$** (HS)
MDA µM	5.08 ± 3.2	1.2 ± 1.1	0.001	$p<0.01$** (HS)
NO µM	55. 1 ± 39 .9	38 .8 ± 21.3	0.025	$p<0.05$* (S)

** (HS) = highly significant. *(S) = significant.

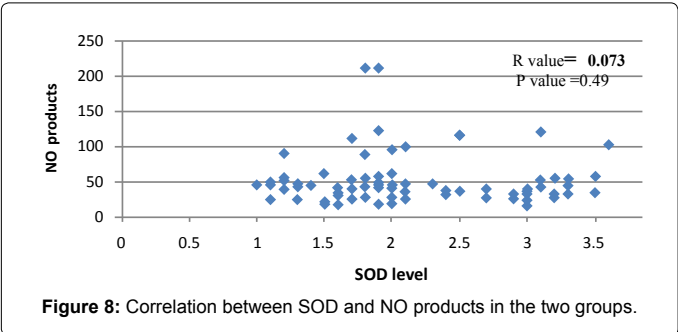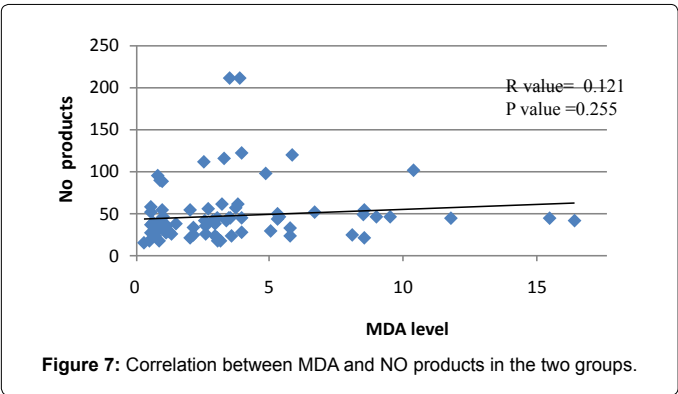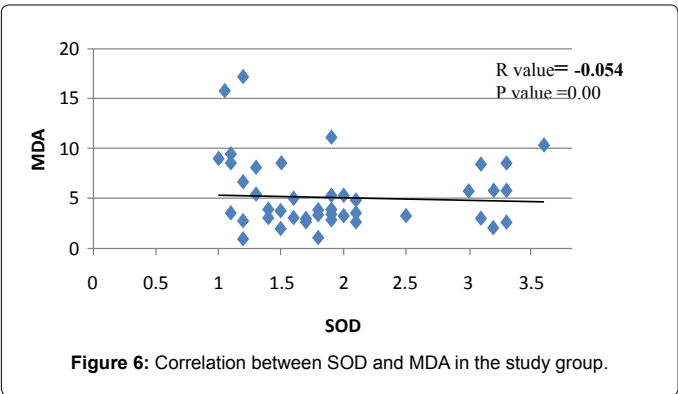**Table 7:** Mean ±SD of Laboratory parameters study.

Palpitation due to tachycardia is the most common complaint among cardio circulatory changes after acute CO exposure. Tachycardia is usually considered as a compensatory response to systemic hypoxemia and decreased cardiac systolic function. Chest discomfort or pain can result from myocardial ischemia or necrosis in the presence and in the absence of coronary artery disease. Shortness of breath and low blood pressure can be symptoms of cardiac dysfunction [19].

The present study demonstrated that mild and moderate abnormalities in myocardial functions (arrhythmic cardiac events) may occur in patients with CO poisoning with the following percentages: tachycardia (54%), ST changes with inverted T wave (24%), prolonged QT interval (32%), prolonged QT interval and ST segment changes with inverted T wave (6%) and premature ventricular contractions (6%). These findings agreed with Satran et al. [2] and Dallas et al. [20].

ECG changes according to the COHb levels, tachycardia was reported in: (75%) of level 0, (57%) of level 1, (40%) of level 2 and (53%) of level 3 while, ST segment changes with inverted T wave was detected in (47%) of level 1 and (20%) of level 2. However, prolonged QT interval was found in (38%) of level 1, (50%) of level 2 and (20%) of level 3, prolonged QT interval and ST segment changes with inverted T wave 3 and premature ventricular contractions were reported in (20%) of level 3.

ECG changes in cases of acute CO poisoning can be attributed to the direct toxic effect of CO on the heart or due to CO-induced depression of respiratory and central nervous systems causing cardiac affection [21].

Regarding the arterial blood gases, there was a statistically significant lower pH (acidosis), PO_2, PCO_2, SO_2 and HCO_3 levels in the CO poisoned group when compared to the control group. Our explanation for this lower PCO_2 levels in the studied cases was owing to the hyperventilation and tachypnea producing washing of CO_2 together with acidosis. Acidemia engendered by metabolic acidosis promptly triggers hyperventilation [22], furthermore hypoxia is detected by chemoreceptors in the carotid body. The function of these receptors

Figure 6: Correlation between SOD and MDA in the study group.

Figure 7: Correlation between MDA and NO products in the two groups.

Figure 8: Correlation between SOD and NO products in the two groups.

increases dramatically, so much so to override the signals from central chemoreceptors in the hypothalamus and causing hyperventilation [23]. Turner et al. and Cevik et al. [8,24], came to the same conclusion. However, Gorman et al. [25] stated that poisoned patients usually have normal blood gases, and have few if any systemic markers of hypoxia. The presence of metabolic acidosis may be attributed to the combination of hypoxia, inhibition of cellular respiration and increase metabolic demand [26].

Cardiac troponins are markers of all heart muscle damage, not just myocardial infarction. Other conditions that directly or indirectly lead to heart muscle damage can also increase troponin levels [27]. The current study showed that cardiac troponin (I) was significantly higher in CO poisoned patients compared to control group with no significant correlation between COHb level and cardiac troponin (I). On the same base, Henry et al. [7], documented that carbon monoxide poisoning can also be accompanied by release of troponin due to hypoxic cardiotoxic effects. Cardiac injury occurred in about one third of severe CO poisoning cases, and troponin screening was appropriate in these patients.

In the present study, B-natriuretic peptide (-which is a sensitive marker to identify cardiac dysfunction-) was significantly higher in CO poisoned patients with a significant positive correlation with COHb level. This goes in agreement with many studies [28-30].

Our study reported that there was a link between CO exposures and oxidative stress. Acute CO poisoned patients presented with increased (NO), oxidative stress marker (MDA) with decreased antioxidant status (SOD) in comparison to the control with a significant negative correlation with COHb level. (MDA) and (SOD) was valuable indicator for CO induced- oxidative stress. Although (NO) products were significantly higher in CO poisoned patients; there were no significant correlations between these (NO) products as well as COHb level, BNP level, plasma concentration of (SOD), or plasma concentration of (MDA).

These results are in line with Thom et al. [31]. However they could not find significant correlations between MDA, SOD and NO concentration.

In contrast to our results Hara et al. [32] found that extracellular levels of the oxidative NO products decreased during exposure to CO poisoning. Following reoxygenation, the NO products levels gradually recovered to the control values.
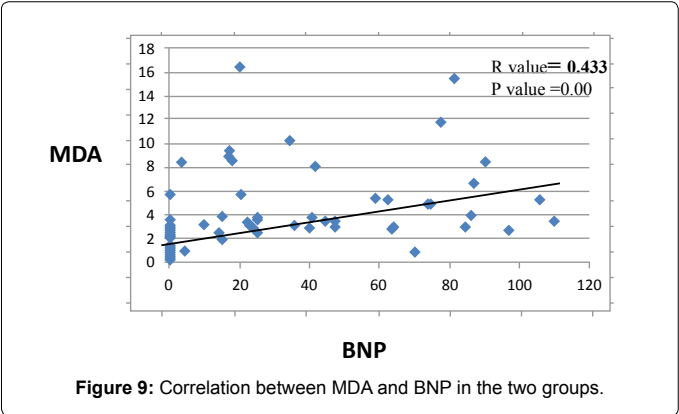
Gorman et al. [33] reported that CO induced nitric oxide synthetase (NOS) and hemeoxygenase (HO) and hence increased intracellular levels of both NO and CO. CO not only increased NO levels but was responsible for the potent oxidant production, peroxynitrite, being deposited in vascular walls. This was seen together with membrane lipid peroxidation [34,25].
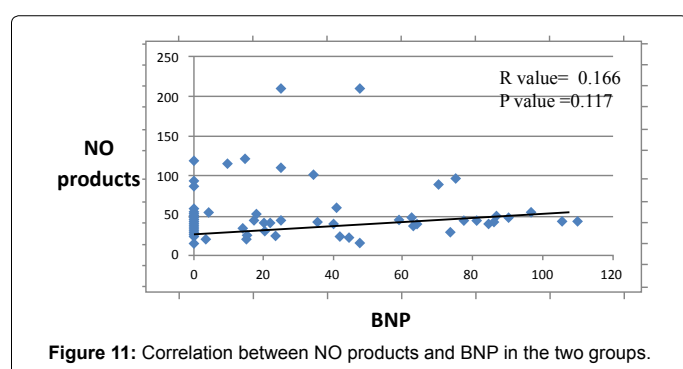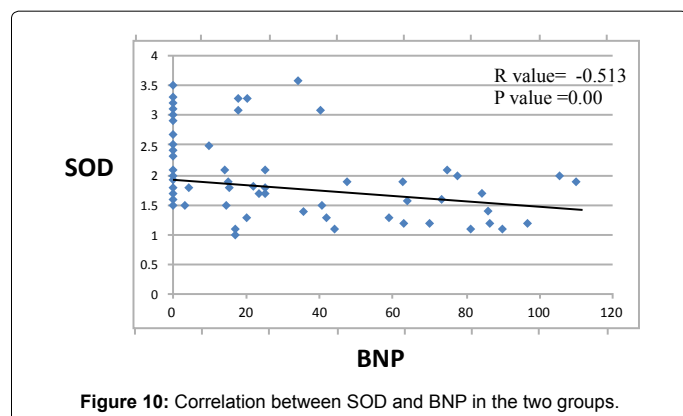
The release of (NO) from platelets and endothelial cells, which forms the free radical (NO) products, peroxynitrite, can further inactivate mitochondrial enzymes and damage the vascular endothelium. The end result was membrane lipid peroxidation [35].

COHb in the study group			
	r value	p value	Statistical significance
MDA	-0.12	0.234	p>0.05 (NS)
BNP	0 .40	0.00	p<0.00** (HS)
SOD	-0.35	0.001	p<0.001**(HS)
NO	0.16	0.115	p>0.05 (NS)
cTnI	-0.27	0.854	p>0.05 (NS)

(NS) = non significant,** (HS) = highly significant

Table 8: Pearson correlation coefficient between COHb levels and different laboratory parameters in the study group.

Figure 9: Correlation between MDA and BNP in the two groups.

Figure 10: Correlation between SOD and BNP in the two groups.

Figure 11: Correlation between NO products and BNP in the two groups.

The current study indicate that (MDA) (as a marker of oxidative stress), showed a highly statistical significant difference in CO poisoned patients compared to control group. There was no significant correlation between (MDA) and COHb level, or SOD. Results were in-line with Miro et al. [36], Thom et al. [37] and Guan et al. [38].

The heart is protected against oxidative stress by various antioxidants, including the SOD system. Moreover decrease in SOD, was accompanied by an increase in lipid peroxidation which is a sign of destruction in cells [6].

The current study showed that superoxide dismutase (one of antioxidant parameters) was highly significantly decreased in CO poisoned patients compared to control group together with a significant negative correlation with COHb level. But the study didn't find any significant correlation between plasma concentration of (SOD) and (MDA) and NO products.

Our results were in agreement with Webber et al. [39], Piantaosi et al. [40], Hamed et al. [41] and Kavakli [5]. However it is in partially agreement with those of Patel et al. [42], who described the effects of exposure of isolated perfused rat hearts to CO; they found that the SOD was decreased by superoxide derivative.

Inhibition of superoxide dismutase and elevation of malodialdehyde, nitric oxide products levels were possible mechanisms of CO induced cardio-toxicity [5].

This study revealed that there was a statistical significant negative correlation between BNP and SOD, with a statistical significant positive correlation with MDA whereas; there was no significant correlation with NO products. Our results suggested that oxidative stress may contribute to the pathogenesis of CO cardiotoxicity.

This was also proven by Scheubel et al. [43]. They stated that in situations with lowered antioxidant defense, the combination of NO and enhanced mitochondrial superoxide anion formation results in a slowly developing, irreversible depression of myocardial mitochondrial respiratory function, probably via peroxynitrite formation. Although this sequence has not yet been analyzed in failing myocardium, enhanced NO formation in failing myocardium has been documented.

Likewise, Lu et al. [44], found that BNP level was increased in patients with heart failure. They stressed that oxidative stress was increased and contributed to cardiac failure. They stated that the increased myocardial oxidative stress may arise from several sources, including mitochondrial electron transport leakage, increases of lipid peroxidation, NO synthase, or decreased antioxidant expression (such as SOD).

Wattel et al. [45], explored the functional effects of CO on isolated perfused rat hearts, found that the (NO) products, peroxynitrite, level was increased. They stated that the mechanism of cardiac toxicity could be explained by nitros active stress due to peroxynitrite formation but without increases NO formation. They concluded that NO pathways were incriminated in endothelium dysfunction seemed to trigger coronary vasoconstriction and increased of cardiac function.

Conclusion

The present study provides evidence that acute exposure to CO directly influences the occurrence of arrhythmic cardiac events. Beta natriuretic peptide was a valuable marker for its early detection. Also, this study provided evidence that there was a link between CO exposures and oxidative stress. Inhibition of superoxide dismutase and elevation of malodialdehyde, and nitric oxide products levels were possible mechanisms of CO induced cardio-toxicity.

References

1. Durmaz E, Laurence S, Roden P, Carruthers S (1999) Carbon monoxide poisoning and hyperbaric oxygen therapy. Br J Nurs 8: 1067-1072.

2. Satran D, Henry CR, Adkinson C, Nicholson CI, Bracha Y, et al. (2005) Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. J Am Coll Cardiol 45: 1513-1516.

3. Gamalludin HA, El-Seddawy AH, Sakr AH et al. (2005) Evaluation of the magnitude of acute poisoning problem through analysis of cases recieved at Poison Control Center Ain Shams University Hospitals during 2004. PCC, Ain Shams University Hospitals, Cairo, Egypt.

4. Teksam M, Casey SO, Michel E, Liu H, Truwit CL (2002) Diffusion-weighted MR imaging findings in carbon monoxide poisoning. Neuroradiology 44: 109-113.

5. Kavakli HS, Erel O, Delice O, Gormez G, Isikoglu S, et al. (2011) Oxidative stress increases in carbon monoxide poisoning patients. Hum Exp Toxicol 30: 160-164.

6. Wang F, He Q, Sun Y, Dai X, Yang XP (2010) Female adult mouse cardiomyocytes are protected against oxidative stress. Hypertension 55: 1172-1178.

7. Henry CR, Satran D, Lindgren B, Adkinson C, Nicholson CI, et al. (2006) Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning. JAMA 295: 398-402.

8. Turner M, Esaw M, Clark RJ (1999) Carbon monoxide poisoning treated with hyperbaric oxygen: metabolic acidosis as a predictor of treatment requirements. J Accid Emerg Med 16: 96-98.

9. Brvar M, Mozina H, Osredkar J, Mozina M, Noc M, et al. (2004) S100B protein in carbon monoxide poisoning: a pilot study. Resuscitation 61: 357-360.

10. Homer CD, Engelhart DA, Lavins ES, Jenkins AJ (2005) Carbon monoxide-related deaths in a metropolitan county in the USA: an 11-year study. Forensic Sci Int 149: 159-165.

11. Jasper BW, Hopkins RO, Duker HV, Weaver LK (2005) Affective outcome

following carbon monoxide poisoning: a prospective longitudinal study. Cogn Behav Neurol 18: 127-134.

12. Nikkanen H, Skolnik A (2011) Diagnosis and management of carbon monoxide poisoning in the emergency department. Emerg Med Pract 13: 1-14.

13. Hampson NB, Hauff NM (2008) Carboxyhemoglobin levels in carbon monoxide poisoning: do they correlate with the clinical picture? Am J Emerg Med 26: 665-669.

14. Aslan S, Uzkeser M, Seven B, Gundogdu F, Acemoglu H, et al. (2006) The evaluation of myocardial damage in 83 young adults with carbon monoxide poisoning in the East Anatolia region in Turkey. Hum Exp Toxicol 25: 439-446.

15. Hampson NB, Zmaeff JL (2001) Outcome of patients experiencing cardiac arrest with carbon monoxide poisoning treated with hyperbaric oxygen. Ann Emerg Med 38: 36-41.

16. Chamberland DL, Wilson BD, Weaver LK (2004) Transient cardiac dysfunction in acute carbon monoxide poisoning. Am J Med 117: 623-625.

17. Cevik Y, Tanriverdi F, Delice O (2010) Reversible increases in QT dispersion and P wave dispersion during carbon monoxide intoxication. Hong Kong Journal of Emerg Med 17: 441-450.

18. Grant M, Clay B (2002) Accidental carbon monoxide poisoning with severe cardiorespiratory compromise in 2 children. Am J Crit Care 11: 128-131.

19. Jang WI, Park JH (2010) Transient left ventricular systolic dysfunction associated with carbon monoxide toxicity. J Cardiovasc Ultrasound 18: 12-15.

20. Dallas ML, Yang Z, Boyle JP, Boycott HE, Scragg JL, et al. (2012) Carbon monoxide induces cardiac arrhythmia via induction of the late Na+ current. Am J Respir Crit Care Med 186: 648-656.

21. Blumenthal I (2001) Carbon monoxide poisoning. J R Soc Med 94: 270-272.

22. Wiederseiner JM, Muser J, Lutz T, Hulter HN, Krapf R (2004) Acute metabolic acidosis: characterization and diagnosis of the disorder and the plasma potassium response. J Am Soc Nephrol 15: 1589-1596.

23. West JB (2008) Respiratory Physiology: The Essentials (8th ed.) La Jolla: Wolters Kluwer Lippincott Williams & Wilkins 88-89.

24. Cevik AA, Unluoglu I, Yanturali S, Kalkan S, Sahin A (2006) Interrelation between the Poisoning Severity Score, carboxyhaemoglobin levels and in-hospital clinical course of carbon monoxide poisoning. Int J Clin Pract 60: 1558-1564.

25. Gorman D, Drewry A, Huang YL, Sames C (2003) The clinical toxicology of carbon monoxide. Toxicology 187: 25-38.

26. Kao LW, Nañagas KA (2004) Carbon monoxide poisoning. Emerg Med Clin North Am 22: 985-1018.

27. Tsai SH, Chu SJ, Hsu CW, Cheng SM, Yang SP (2008) Use and interpretation of cardiac troponins in the ED. Am J Emerg Med 26: 331-341.

28. Pach D, Gawlikowski T, Targosz D, Groszek B, Wilimowska J (2005) B-type natriuretic peptide plasma concentration in acutely poisoned patients. Przegl Lek 62: 465-467.

29. Davutoglu V, Gunay N, Kocoglu H, Gunay NE, Yildirim C, et al. (2006) Serum levels of NT-ProBNP as an early cardiac marker of carbon monoxide poisoning. Inhal Toxicol 18: 155-158.

30. Kalay N, Ozdogru I, Cetinkaya Y, Eryol NK, Dogan A, et al. (2007) Cardiovascular effects of carbon monoxide poisoning. Am J Cardiol 99: 322-324.

31. Thom SR, Fisher D, Zhang J, Bhopale VM, Cameron B, et al. (2004) Neuronal nitric oxide synthase and N-methyl-D-aspartate neurons in experimental carbon monoxide poisoning. Toxicol Appl Pharmacol 194: 280-295.

32. Hara S, Mukai T, Kurosaki K, Kuriiwa F, Endo T (2003) Characterization of suppression of nitric oxide production by carbon monoxide poisoning in the striatum of free-moving rats, as determined by in vivo brain microdialysis. Brain Res 979: 27-36.

33. Gorman D, Huang YL, Williams C (2002) A narcotic dose of carbon monoxide induces neuronal haeme oxygenase and nitric oxide synthetase in sheep. Toxicology 179: 79-84.

34. Thom SR, Fisher D, Manevich Y (2001) Roles for platelet-activating factor and *NO-derived oxidants causing neutrophil adherence after CO poisoning. Am J Physiol Heart Circ Physiol 281: H923-H930.

35. Mehta M, Das S, Singh S (2007) Carbon Monoxide Poisoning. MJAFI 63: 362-365.

36. Miró O, Alonso JR, Casademont J, Jarreta D, Urbano-Márquez A, et al. (1999) Oxidative damage on lymphocyte membranes is increased in patients suffering from acute carbon monoxide poisoning. Toxicol Lett 110: 219-223.

37. Thom SR, Bhopale VM, Han ST, Clark JM, Hardy KR (2006) Intravascular neutrophil activation due to carbon monoxide poisoning. Am J Respir Crit Care Med 174: 1239-1248.

38. Guan L, Zhang YL, Wen T, Wang XF, Zhu MX, et al. (2011) Dynamic changes of heme oxygenase-1 in the hippocampus of rats after acute carbon monoxide poisoning. Arch Environ Contam Toxicol 60: 165-172.

39. Webber DS, Lopez I, Korsak RA, Hirota S, Acuna D, et al. (2005) Limiting iron availability confers neuroprotection from chronic mild carbon monoxide exposure in the developing auditory system of the rat. J Neurosci Res 80: 620-633.

40. Piantadosi CA, Carraway MS, Suliman HB (2006) Carbon monoxide, oxidative stress, and mitochondrial permeability pore transition. Free Radic Biol Med 40: 1332-1339.

41. Hamed S, Brenner B, Aharon A, Daoud D, Roguin A (2009) Nitric oxide and superoxide dismutase modulate endothelial progenitor cell function in type 2 diabetes mellitus. Cardiovasc Diabetol 8: 56.

42. Patel AP, Moody AJ, Sneyd JR, Handy RD (2004) Carbon monoxide exposure in rat heart: evidence for two modes of toxicity. Biochem Biophys Res Commun 321: 241-246.

43. Scheubel RJ, Tostlebe M, Simm A, Rohrbach S, Prondzinsky R, et al. (2002) Dysfunction of mitochondrial respiratory chain complex I in human failing myocardium is not due to disturbed mitochondrial gene expression. J Am Coll Cardiol 40: 2174-2181.

44. Lu Z, Xu X, Hu X, Lee S, Traverse JH, et al. (2010) Oxidative stress regulates left ventricular PDE5 expression in the failing heart. Circulation 121: 1474-1483.

45. Wattel F, Favory R, Lancel S, Neviere R, Mathieu D (2006) Carbon monoxide and the heart: unequivocal effects?. Bull Acad Natl Med 190: 1961-1974.