BRAIN NATRIURETIC PEPTIDE (BNP) AS A BIOMARKER OF CARDIAC TOXICITY IN CASES OF ACUTE CARBON MONOXIDE POISONING

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ABSTRACT

Background: Acute carbon monoxide (CO) poisoning is a common toxicity emergency that leads in many occasions to morbidity and mortality. Acute myocardial injury is commonly observed among acute carbon monoxide poisoned patients and cardiac toxicity is found to be the cause of mortality in the majority of cases. Some studies recorded normal values of cardiac troponins in cases of acute CO poisoning with cardiac affection. Hence it is important to search for novel and sensitive biomarkers to diagnose cardiac ischemia in these cases. Brain natriuretic peptide (BNP) is a cardiac hormone which is produced mainly in the ventricular myocardium in response to myocardial hypoxia. **Aim:** The present study aims to investigate the value of BNP measurement in detection of cardiac toxicity in acute carbon monoxide poisoning. **Methods:** The present study was conducted on 42 patients with acute CO poisoning admitted to the Poison Control Centre of Ain Shams University hospitals (PCC-ASUH). Routine laboratory tests and ECG were done on admission in addition to determination of the level of BNP and determination of troponin I. **Results**: Analysis of the results showed that there is an increase in the levels of BNP in patients suffering from acute CO poisoning with high levels seen in those with ischemic changes recorded by ECG. **Conclusions**: The present study concluded that plasma BNP levels could be used as a specific reliable biomarker of cardiac toxicity in patients with acute CO poisoning.

Keywords: BNP; Acute CO poisoning; Cardiac toxicity; Troponin I

INTRODUCTION

Acute carbon monoxide (CO) poisoning is a common medical emergency and one of the leading causes of death due to poisoning. In survivors, morbidity persists following initial stabilization in nearly 40 percent of patients **(Rose et al., 2017; Hardy & Thom, 1994).**

Accidental poisoning is most seen during the winter months in cold climates. Potential exogenous sources of CO include fires, poorly functioning heating systems, improperly ventilated fuel-burning devices like kerosene heaters and charcoal grills and motor vehicles operating in areas with poor ventilation **(Thomassen et al., 2004).**

On the other hand, endogenous production of CO results from the breakdown of heme proteins by the enzyme heme oxygenase (HO) in the respiratory and cardiovascular systems **(Olson et al., 2012).**

CO has high affinity for hemoglobin, where they combine together forming carboxyhemoglobin (COHb). CO binds to the heme moiety of hemoglobin, generating a change that greatly decreases the ability of the other three oxygen binding sites to off-load oxygen to peripheral tissues. This causes impairment in tissue oxygen delivery causing tissue hypoxia **(Peers & Steele, 2012).**

In the heart, the resulting tissue hypoxia causes acute myocardial injury which is commonly observed in CO-poisoned patients and is associated with increased rate of long-term mortality. This acute myocardial injury is manifested clinically in the form of myocardial infarction, arrhythmia or heart failure **(Satran et al., 2005).** The manifestations of cardiac involvement in cases with CO poisoning also includes angina attack, cardiogenic shock and sudden death **(Kalay et al., 2007).** Cardiac toxicity is thought to be the cause of mortality in the majority of cases with acute CO poisoning **(Varon et al., 1999).**

Brain natriuretic peptide (BNP) is a cardiac hormone with systemic vasodilator effects as well as local cyto-protective and anti-proliferative properties **(Weidemann et al., 2008).** It is mainly produced in the ventricular myocardium with an additional production in both the atrial myocardium and the brain. It is induced in response to a variety of pathophysiological conditions one of which is myocardial hypoxia. Myocardial hypoxia is known to contribute to the increase in myocardial wall stretch and hypoperfusion which in turn stimulate stretch receptors leading to an increase in BNP production **(Alter et al., 2008).**

BNP is frequently used as a screening test in hospital and community checks to identify patients who might have heart failure and require further definitive investigations **(Ryding et al., 2009).**

The diagnosis of CO poisoning is mainly based on detailed history and meticulous physical examination in conjunction with an elevated level of carboxyhemoglobin **(Touger et al., 1995).** Patients are managed; after initial stabilization; with 100 percent oxygen via non-rebreathing face mask. Whereas patients with high risk for adverse outcomes are treated with hyperbaric oxygen. Those are identified having specific criteria one of which is cardiac ischemia. This raises the importance of diagnosis of cardiac ischemic affection in CO poisoned patients **(Huang et al., 2017; Hampson et al., 1995).**

The diagnostic markers of cardiac toxicity in acute CO poisoning include electrocardiogram (ECG), creatine kinase (CK), creatine kinase-MB (CK-MB), and troponins. In addition, echocardiography and coronary angiography are recommended for patients with persistent signs of cardiac ischemia **(Kalay et al., 2007; Davutoglu et al., 2006).** Diagnostic investigations as CK, CK-MB are not clinically proved to be useful due to the fact that many factors can lead to an increase in their level, thus they are considered to be nonspecific markers **(Satran et al., 2005).**

Recent studies support the idea of using new biochemical indicators such as B-type natriuretic peptide (BNP) in

the diagnosis of cardiac toxicity. However, there are few studies in literature describing the relation between plasma BNP levels and cardiac toxicity in acute CO poisoning **(Yücel et al., 2016).**

The aim of the present study is to investigate the value of BNP measurement in detection of cardiac toxicity in acute carbon monoxide poisoning.

PATIENTS & METHODS

- Study design and setting

A case control study was conducted at the Poison Control Center of Ain Shams University hospitals (PCC-ASUH).

- Population and sample

Forty two patients with acute carbon monoxide toxicity admitted to the center between December 2016 and May 2017 were included in the study and compared to fifty age and sex-matched subjects.

The inclusion criterion for the study was acute carbon monoxide toxicity proved by history taking, meticulous examination and elevated level of carboxyhemoglobin (above 10%). Patients with history of cardiovascular or renal diseases were excluded from the study.

- Ethical issues

A valid informed consent was obtained from each patient as well as from each control subject or his guardian. In addition an approval of Faculty of Medicine Ain-Shams University Research Ethics Committee (FMASU REC) was obtained. In order to secure confidentiality, specimens were coded and anonymously stored.

- Study methods

All participants were subjected to the following

- An interviewed questionnaire including: demographic and occupational data (age, sex, occupation), intoxication data (source of carbon monoxide, duration of exposure and delay before seeking medical help) and clinical data (gastrointestinal symptoms such as nausea, vomiting and abdominal pain; cardiovascular symptoms such as chest pain and palpitations).
- Clinical examination including vital data (pulse, temperature, blood pressure and respiratory rate) and body systems examination.
- Investigations which included:
  - Electrocardiography (ECG) was done for each study subject and the results were recorded.
  - Laboratory investigations were done using arterial as well as venous samples. Samples were drawn on admission. Arterial blood samples were collected from each subject under complete aseptic precautions in a plastic disposable syringe and the levels of PO2, PCO2, pH, SO2, HCO3 were tested. Venous blood samples were collected under complete aseptic precautions by a heparinized plastic disposable syringe. Samples were spun then divided in two tubes. One was used for carboxyhaemoglobin (COHb) level determination and troponin I determination, while the other was stored at –80°C to be used for BNP level determination.
- Cardiac troponin I was tested in the plasma specimens by an antigen-antibody reaction. Qualitative detection was tested depending on the reaction of the troponin in the specimen (if present) with particles coated with anti-troponin I antibodies.
- BNP level was measured using enzyme immunoassay kit (Human pro-brain natriuretic peptide ELISA Kit)

Bioassay Technology Laboratory, Catalogue Number E3041Hu following the manufacturer's instructions.

- Statistical analysis

Statistical analysis was performed with IBM® SPSS® Statistics Version 20 for Windows. Continuous variables were presented as mean ± standard deviation (± SD), median and range values. Mann Whitney test was done to compare means of continuous variables between 2 independent groups as case and control. Categorical data were expressed as frequencies (n) and percentage (%). Correlation test was used to correlate between continuous variables. P-value ≤ 0.05 was considered significant.

RESULTS

- **Comparison between the study groups regarding personal, occupational and exposure history:**

Among the 92 participants in the present study, there were 42 cases and 50 controls. Personal, occupational and exposure history of both cases and controls are presented in table 1. It is clear that the 2 groups were matched for age, sex and occupation as proved by chi square test where there was no statistically significant difference between them. The source of exposure to CO was gas heaters in more than half of the cases (61.9%), charcoal heaters in 28.6%, and automobile exhaust in only 9.5% of the cases. The mean duration of exposure was 2.44±2.77 hours and the mean delay in seeking medical help was 7.17±10.88 hours after exposure.

Table (1): Personal, occupational and exposure history of the study groups

Variables	**Cases (n=42)**	**Control (n=50)**	**X^2**	**p-value**
Age Categories*				
< 25years	20(47.6%)	24 (48%)	0.001	1.00
≥ 25 years	22(52.4%)	26 (52%)		
Sex				
Male	29 (69%)	30 (60%)	0.812	0.392
Female	13 (31%)	20 (40%)		
Occupation				
Worker	20	22		
Employee	4	4	0.395	0.941
Student	11	16		
None	7	8		
Sources of exposure Charcoal	12(28.6%)	-	-	-
Gas Heater	26(61.9%)	-	-	-
Automobile Exhaust	4 (9.5%)	-	-	-
Duration of exposure (hours) Mean ± SD	2.44±2.77	-	-	-
Delay after exposure (hours) Mean ± SD	7.17±10.88	-	-	-

***Mean age = 27.1±12.2**

- **Comparison between the study groups regarding clinic-pathological findings:**

Table 2 shows the clinical findings of the study groups. The majority of cases presented with vomiting (61.9%) followed by chest pain (31%) and shock (23.8%). Regarding ECG findings, there was a statistically significant difference between groups as proved by X^2 test ($p < 0.01$). Among cases of CO poisoning, 21.4% had ischemic changes and 35.7% had sinus tachycardia.

Regarding the vital signs, the mean differences in systolic and diastolic blood pressure, pulse and respiratory rate were statistically significant between groups ($p < 0.01$), where systolic and diastolic blood pressure were lower among acute CO poisoning cases, pulse and respiratory rate were higher among them. However, differences in body temperature were not statistically significant between groups ($p > 0.05$).

Table (2): Clinical findings of the study groups

Variables	**Cases (n=42)**	**Control (n=50)**	**Test of significance**	**p-value**
Presenting symptoms				
Vomiting	26 (61.9%)	-	-	-
Chest pain	13 (31%)	-	-	-
Shock	10 (23.8%)	-	-	-
Palpitation	0 (0%)	-	-	-
ECG findings				
Normal	16 (38.1%)	50 (100%)		
Ischemia	9 (21.4%)	0 (0%)	X^2= 43.146	0.0001*
Sinus tachycardia	15 (35.7%)	0 (0%)		
Sinus bradycardia	2 (4.8%)	0 (0%)		
Vital signs	**Mean ± SD**	**Mean ± SD**		
Systolic blood pressure	108.93±20.94	117.60±10.11	t = -2.592	0.011
Diastolic blood pressure	70.24±12.97	76.20±6.11	t = -2.893	0.005**
Pulse	102.12±16.46	84.96±5.84	t = 6.879	0.0001**
Body temperature	36.98±0.33	36.97±0.24	t = 0.07	0.944
Respiratory rate	22.12±8.849	16.68±1.66	t = 4.262	0.0001**

*** There is a statistically significant difference between groups at 0.01 level by X^2 test.**
**** The mean difference is significant at 0.01 level by independent variable t-test.**

- **Comparison between the study groups regarding laboratory data:**

The level of COHb and BNP were found to be increased among cases compared to the control group with statistically significant difference between them ($p < 0.01$). In addition, the mean differences in pH, PO_2, HCO_3, and SaO_2 were statistically significant between groups ($p < 0.01$), where pH, PO_2 and SaO_2 were lower among acute CO poisoning cases, while HCO_3 was higher among those cases. However, differences in PCO_2 level were not statistically significant between groups ($p > 0.05$). Moreover, Troponin-I showed statistically significant difference between groups ($p < 0.01$) where it was positive in 61.9% of cases compared to 0% in control group. Those findings are illustrated in table 3.

Table (3): Comparison between the study groups regarding the laboratory findings.

Variables	Cases (n=42)	Control (n=50)	Test of significance	p-value
	Mean± SD	Mean± SD		
COHb (%)	21.37±8.19	3.48±2.73	t = 14.528	0.0001*
BNP pg/mL	1408.93±903.43	7.52±5.38	t = 10.980	0.0001*
pH	7.32±0.10	7.40±0.02	t = -5.746	0.0001*
PO_2 mmHg	71.65±10.37	92.92±3.81	t = -13.472	0.0001*
PCO_2 mmHg	38.00±8.34	40.12±1.84	t = -1.750	0.08
HCO_3 mEq/L	19.47±3.97	25.00±1.49	t = -9.116	0.0001*
SaO_2 %	92.36±4.33	96.28±1.29	t = -6.088	0.0001*
Troponin-I	**n (%)**	**n (%)**	X^2=43.146	0.0001**
Positive	26 (61.9%)	0 (0%)		
Negative	16(38.1%)	50 (100%)		

*** The mean difference is significant at 0.01 level by independent variable t-test.**
**** There is a statistically significant difference between groups at 0.01 level by X^2 test.**

- **The relation between measured BNP level and ECG findings among cases of CO poisoning:**

There was a statistically significant difference in the mean BNP levels between subjects with different ECG findings as determined by one-way ANOVA (F = 7.96, p = 0.0001). LSD post hoc test revealed that the BNP level was significantly higher in patients with ischemic ECG findings (2080.00±739.39 pg/ml, p = 0.0001) and sinus tachycardia (1756.00±825.18 pg/ml, p = 0.001) compared to normal (770.94±655.95 pg/ml). There was no statistically significant difference in BNP level between ischemic and sinus tachycardia patients (p = 0.303), sinus tachycardia and sinus bradycardia (p = 0.126), or between normal and sinus bradycardia patients (p = 0.830). Those findings are illustrated in table 4.

Table (4): One-Way ANOVA and Post Hoc Multiple Comparison test for BNP level according to ECG findings among acute CO poisoning cases

ECG Findings	n	Mean BNP (in pg/ml)	F	p-value	Post hoc test
Normal[1]	16	770.94±655.95	7.96	0.0001*	1-2 (p = 0.0001) 1-3 (p = 0.001) 2-4 (p = 0.045)
Ischemic[2]	9	2080.00±739.39			
Sinus tachycardia[3]	15	1756.00±825.18			
Sinus bradycardia[4]	2	890.00±438.41			

*** The mean difference is significant at 0.01 level.**

- **The relation between measured BNP level and Troponin I results:**

The mean BNP level was found to be significantly higher in patients with positive Troponin-I (p<0.001) as shown in table 5.

Table (5): BNP level in relation to Troponin-I among acute CO poisoning cases

Variables		BNP pg/ml (Mean± SD)	t-test	p-value
Troponin-I	Positive	1801.54±812.15	-4.283	0.0001*
	Negative	770.94±655.95		

* The mean difference is significant at 0.01 level.

- **Correlation between measured BNP serum level and COHb level among cases of CO poisoning:**

There is a positive correlation between COHb level and the BNP level (r = 0.786, p < 0.01) as shown in **figure (1).**

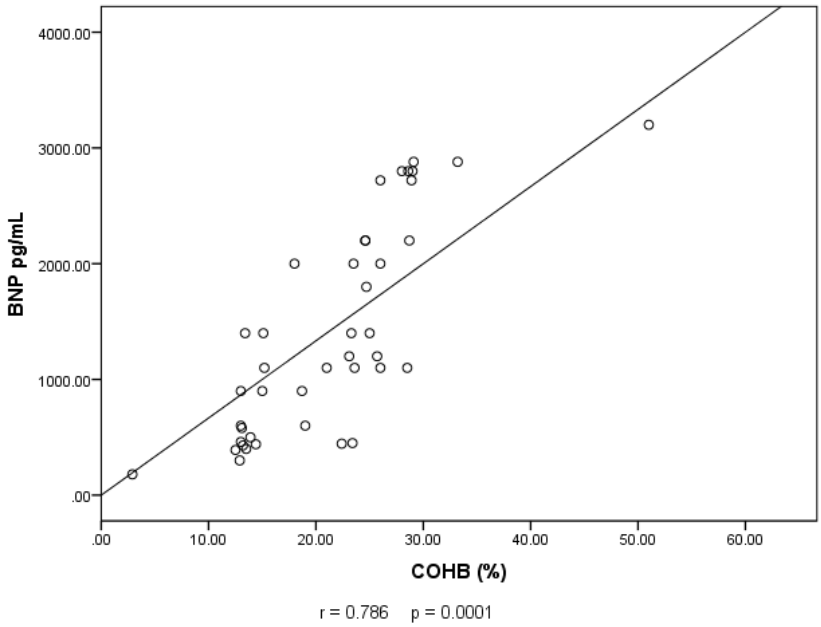

Figure (1): Correlation between serum BNP and COHb level

- **Correlation between measured BNP level and recorded data among cases of CO poisoning:**

There is a negative correlation between the BNP level and the delay in seeking medical advice (r = -0.348, p < 0.05) as shown in table 6.

Table (6): Correlation between serum BNP level and age, exposure history and blood gases

	BNP	
	r	**p-value**
Age	0.088	0.579
Duration of exposure	0.036	0.822
Delay in hours	-0.348	0.024*
PO_2 in mmHg	-0.033	0.835
PCO_2 in mmHg	0.27	0.084
HCO_3 in mEq/L	0.024	0.88
SaO_2%	-0.157	0.319

***significant negative correlation at 0.05 level.**

DISCUSSION

Acute carbon monoxide poisoning is an important environmental health problem and a serious medical emergency with high mortality rate **(Weaver, 1999).** In the present study, the most common sources of exposure were gas and charcoal heaters accounting to nearly 90% of cases. This finding is consistent with **Hampson (2016)** who found that defective heaters and defective ventilation with heaters usage are the most common non-fire exogenous sources of CO exposure.

In the present study, 31% of patients presented with chest pain. In addition, ECG findings showed ischemic changes in 21% of patients and abnormalities in heart rate in 40% of patients. Moreover, the measured levels of BNP showed significant elevation in cases when compared to controls; and troponin I was detected in nearly 62% of cases but in none of the controls. These findings are in accordance with **Satran et al. (2005)** who reported that acute myocardial injury is commonly seen in acute CO poisoned patients. They recorded evidence of myocardial ischemia (diagnosed by both ECG changes and elevated levels of cardiac biomarkers) in one third of the 230 patients they studied.

Koylo et al. (2011) stated that hypoxia is the main cause of mortality caused by acute CO poisoning; and they emphasized that the clinical presentation of acute CO poisoning varies with severity where severe symptoms often correlate with the measured level of COHb. They added that the patient is usually asymptomatic with levels that are less than 10% and death is likely to occur in levels above 60%. In the present study, there was a statistically significant difference in the measured level of COHb between the two study groups being higher among cases of CO poisoning. In addition, the measured levels of oxygen partial pressure (PO_2) and oxygen saturation (SO_2) in patients denoted different levels of hypoxia.

Myocardial infarction is reported by several studies to be the most common cardiac complication leading to death after acute CO poisoning.

The assessment of cardiac troponins is considered the mainstay for the diagnosis of myocardial injuries. However, some studies recorded normal values of cardiac troponins in cases of acute CO poisoning with cardiac affection. Hence it is important to search for novel and sensitive biomarkers to diagnose cardiac ischemia **(Li et al., 2015; Unal et al., 2007; Aslan et al., 2005).** BNP is a cardiac biomarker that is secreted in a variety of occasions with myocardial stress **(Henry et al., 2006).**

In the present study, the level of both cardiac biomarkers namely troponin I and BNP were measured. The level of BNP was found to be significantly higher in cases with positive troponin I. In addition, there was a positive correlation between the measured level of BNP and COHb among patients. This finding is in accordance to **Davutoglu et al (2006)** who recorded similar findings and reported a statistically positive correlation between the level of BNP and COHb. In addition, **Yücel et al (2016)** reported a statistically positive correlation between the level of BNP and the level of troponin I.

The threshold value of the increased serum level of BNP for cardiac affection is postulated to be 100 pg/mL in literature **(Maurellet et al., 2008).** In the present study, all patients

had measured serum levels of BNP greater than 100 pg/mL whereas 38% of them had normal values of troponin I. This highlights the value of BNP level determination over troponin I determination.

The present study recorded a significant increase in BNP level in cases with ischemic ECG changes and those with sinus tachycardia. **Karakiliç et al. (2016)** detected a significant positive correlation between measured BNP level and the degree of cardiac involvement and the ischemic ECG changes in patients with poisoning by cardiotoxic drugs.

The cause of cardiac damage was investigated by various studies and it was concluded to be due to two mechanisms. The first mechanism is the ischemic damage caused by the binding of CO to the heme moiety in place of oxygen. While the second is the direct toxic damage caused by the effects of CO on tissues. CO was found to directly damage the mitochondria which leads to inhibition of cytochrome C oxidase and a decrease in the level of glutathione. This in turn induces anaerobic metabolism which results in hypoxia, lactic acidosis and apoptosis in the cardiac myocytes and during the apoptotic process, enzymes are induced which cause endothelial damage (Kaya et al., 2016; Weaver, 2009; Taskiran et al, 2007; Thom et al., 2000).

Goetze et al. (2004) suggested that acute myocardial hypoxia causes a rapid increase in cardiac BNP gene transcription, and increase in the plasma level of BNP. This supports the findings of the present study where CO intoxication is known to cause tissue hypoxia. Another study that could add value to BNP determination is the one performed by **Wang et al. (2004)** which suggested that a single determination of increase in the level of BNP in cases with cardiac affection is suggestive of future development of cardiovascular outcomes.

Reyding et al (2009), Bethell et al (2008) and Güneş et al. (2008) concluded that the increase in serum level of BNP is related to the severity and prognosis of patients with cardiac affection. In the present study, the measured serum level of BNP in patient ranged from 180-3200 pg/mL with a mean level of 1409 pg/mL. Similar findings were observed by **Gugli et al. (2007)** who categorized the elevated levels of serum BNP into mild elevation (500-1000 pg/mL), moderate elevation (2000-3000 pg/mL) and high elevation (4000-20,000 pg mL) and emphasized that this high BNP elevation is determined by renal dysfunction rather than isolated cardiac problems.

CONCLUSIONS

In light of the findings of the present study, it is concluded that plasma BNP levels could be used as a specific reliable biomarker of cardiac toxicity in patients with acute CO poisoning.

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البيتيدات الناتريوريتية الدماغية كمؤشر للسمية القلبية الناجمة عن التسمم الحاد بأول أكسيد الكربون

التسمم الحاد بغاز أول أكسيد الكربون من حالات التسمم الشائعة التى قد تؤدي في كثير من الأحيان إلى المرض والوفاة. ويؤدى التسمم بغاز أول أكسيد الكربون إلى إصابة عضلة القلب فى كثير من الحالات لتسببه فى حدوث نقص حاد فى تروية القلب، ويُعتقد أن إصابة القلب هي السبب الرئيسى للوفاة فى أغلب الحالات. تعتبر التروبونينات القلبية من المؤشرات المعملية الهامة التى تشخص إصابة عضلة القلب ولكن بعض الدراسات قد سجلت قيم طبيعية للتروبنينات القلبية في حالات إصابة القلب عند المرضى المصابين بالتسمم الحاد بأول أكسيد الكربون. لذا تتجه الأبحاث الحديثة للبحث عن مؤشرات جديدة وأكثر حساسية لتشخيص نقص تروية القلب في حالات التسمم الحاد بأول أكسيد الكربون. وتعتبر البيتيدات الناتريوريتية الدماغية هى نوع من أنواع الهرمونات التى تنتج بشكل رئيسي في عضلة القلب البطيني إستجابة لنقص الأكسجين. وتهدف هذه الدراسة إلى التحقق من قيمة قياس البيتيدات الناتريوريتية الدماغية في الكشف عن إصابة القلب في حالات التسمم الحاد بأول أكسيد الكربون. وقد أجريت الدراسة الحالية على 42 مريضا يعانون من التسمم الحاد بأول أكسيد الكربون والذين تم إستقبالهم وعلاجهم بمركز علاج التسمم بمستشفيات جامعة عين شمس. وتم إجراء الفحوصات المعملية الروتينية ورسم القلب عند الدخول بالإضافة إلى قياس مستوى البيتيدات الناتريوريتية الدماغية والكشف عن التروبونين فى بلازما الدم. وأظهرت النتائج أن هناك زيادة في مستويات البيتيدات الناتريوريتية الدماغية في المرضى الذين يعانون من التسمم الحاد بأول أكسيد الكربون مع ارتفاع هذه المستويات فى المرضى الذين سجلوا تغيرات فى رسم القلب تشير إلى وجود نقص فى تروية القلب. وخلصت الدراسة إلى أن مستويات البيتيدات الناتريوريتية الدماغية فى بلازما الدم ويمكن أن تستخدم كمؤشر محدد وموثوق لتشخيص إصابة عضلة القلب في المرضى الذين يعانون من التسمم الحاد بأول أكسيد الكربون.