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Research Article

Biochemical Patterns of Cardio-renal Biomarkers in Serum and Vitreous Humor of Rabbits after Chronic CO Exposure

Abstract

Carbon monoxide (CO) is a colorless gas that can cause cellular damage in exposed hosts depending on the levels inhaled. There is an increase in idiopathic diseases without a known cause. In Nigeria, this has led to a call for profiling of CO, a gas routinely inhaled by its population. This study was designed to assess the effect of chronic CO inhalation on vitreous and serum cardiorenal biochemical parameters. A total of twenty rabbits were divided into four groups. With the exception of control rabbits (air only), others were exposed daily to 200 ppm CO for 30 min for 10, 20, or 30 days. Five (5) rabbits constituted each of the four groups. At the 30 minutes after the final exposure, rabbits were euthanized mechanically and their vitreous humor and cardiac blood extracted using standard procedures. Serum and vitreous humor extracted were analyzed using ion selective electrode and enzymatic methods. The serum chemistry data revealed that pH, Na, non-ionized calcium (nCa), ionized calcium (Ca), total calcium (TCa), creatinine, lactate dehydrogenase (LDH), and creatine kinase concentrations were significantly raised ($p< 0.05$) as the duration of exposure increased. In contrast, uric acid (UA) concentrations were significantly decreased. The vitreous humor chemistry data revealed significant increases in creatinine, urea, LDH, and CK concentrations, whereas pH and concentrations of potassium, TCa, nCa, Ca, and UA were significantly decreased ($p< 0.05$). Thus, it may be possible to assess chronic CO poisoning by evaluating one or more biochemical alterations in the serum and vitreous humour.

Introduction

Carbon monoxide (CO) is a toxic gas produced from the incomplete combustion of organic materials. It is known to be a colorless/odorless non-irritant with a propensity to affect hosts mainly by induction of hypoxia. As an asphyxiant, it displaces/blocks oxygen from binding to hemoglobin, hence hampering transportation of oxygen in the body. Most impacted organs by hypoxia are the brain and heart, whereas the lungs, liver and spleen as less impacted [1].

Chronic CO poisoning is most often associated with inhalation of low levels of CO (i.e., < 2000 ppm) over time. While morbidity or mortality could result depending on the levels of CO inhaled, health status and age of the victim are also important factors. Routinely, Nigerians are exposed to varying degrees of CO due to a high demand for CO-producing machines/equipment. Poor power generation across Nigeria has created an acute shortage of electricity and so many homes and industries use generators as their steady source of power. Generating sets especially the single stroke type heavily patronized in Nigeria is known for increase production of CO. As such, these generators are the major source for potential ongoing CO exposures among Nigerian citizens.

Acute and chronic CO intoxication has been implicated in a handful of systemic pathologies [2-6]. Studies have shown that acute CO poisoning has a propensity to distort vital cardio-renal parameters [3]. The analyses of a variety of markers in the serum and vitreous humor that can provide insight into cardiac/renal functions reflect how chronic CO exposure could impart deleterious effects on renal\cardiac cells in an exposed host.

To build upon those earlier observations, the work reported here was undertaken to evaluate effects of chronic CO exposure on some important biochemical parameters related to function of cardiac and renal systems. Among the various markers used to evaluate any effect from chronic exposures to CO were measures of vitreous humor/serum pH, and levels of potassium, sodium, chloride, calcium profile, creatinine, urea, uric acid, creatine kinase and lactate dehydrogenase. For these studies, a

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rabbit model was employed as this model has previously been used in many studies to model human exposures to a wide variety of air pollutants [2,3,7,8].

Materials and Methods

Study area

The animal intoxication was carried out in the animal science laboratory of the Niger Delta University. Similarly, the biochemical analysis took place at the Chemical Pathology laboratory of the Niger Delta University Teaching Hospital, Okolobiri, Bayelsa State.

Animals

New Zealand white albino rabbits (male, 6-8-mo-of-age, 1.5-2.0 kg) were obtained from Imo State in Nigeria. Rabbits used were apparently healthy and active as confirmed and approved by a university veterinarian. Each was housed in an individual cage in a specific pathogen-free facility maintained at 25°C with a 60% relative humidity and a 12-hr light/dark cycle. All rabbits had *ad libitum* access to standard rabbit chow bought in Yenagoa, Bayelsa State and filtered water. Any rabbit showing signs or symptoms of illness prior to exposures were excluded from the research. Ultimately, a total of 20 rabbits were used for the exposures/analyses.

After two weeks of acclimatization, the rabbits were randomly allocated into four groups. The first group was designated controls that were to be exposed to air only (n = 5). The remaining three groups of rabbits were to be exposed daily whole-body to CO for 30 min for 10, 20, or 30 days (n = 5/group) [9]. All animals were exposed in a CO chamber. The source of the CO was a portal Sumac generating set. All CO levels were constantly monitored using a Carbon Monoxide Meter Gasman-CO (PCE Instrument, UK). Exposure levels were never greater than 200 ppm in the chamber. This level was selected based on earlier studies of Goldstein [10] and Struttmann et al. [11], wherein 200 ppm was found to reflect CO concentration that will not lead to immediate mortality and morbidity

At 30th minutes after the final exposure, CO-treated rabbits and their matched controls were euthanized mechanically. Bio-samples (i.e., vitreous humor and blood) were then collected for analyses (see below).

All protocols were approved by the Ethics Committee of the Bayelsa State Ministry of Health and adhered to the Animal Welfare Act of 1985 of the United States of America for research and Institutional Animal Care and Use Committee (IACUC) protocols [12].

Collection of vitreous humor

Vitreous humor samples were collected by the method of by Coe [13]. In brief, within 30 min of euthanization, samples were collected by insertion of a 27-G needle into the cantus of the eye and ≈ 1 ml was then retrieved into a plane tube. Only clear liquid free of any tissue contaminants/fragments was acceptable foranalyses. Each isolated vitreous samples was centrifuged at 2050 rpm (10 min, 25°C) and resultant supernatants were collected for the analyses.

Collection of cardiac blood

At necropsy, blood samples were collected from the heart using the method of by Ness [14]. In brief, within 30 min of euthanization, samples were collected by insertion of a 27-G into the left side of the chest, through the diaphragm, from the top of the sternum. Blood was then slowly withdrawn into a plane tube. The samples were allowed to clot at room temperature and then serum was collected by centrifugation at 2000 rpm for ten minutes at 25°C for use in biochemical analyses. Any supernatants containing lysed blood were rejected.

Bio-analyses

An ion-selective electrode (ISE) (Analyzer ISE 4000, France) was used for measures of vitreous and serum pH and selected electrolytes (e.g., sodium, potassium, chloride, calcium [total, ionized, non-ionized calcium forms]).Urea levels in each material were estimated using adiacetyl monoxime method [15]. Creatinine levels were evaluated using a Jaffes method [15]. Sample CreatineKinase (CK-NAP) and lactate dehydrogenase (LDH-P) activity were assayed using an AGAPPE System (AGAPPE Diagnostics, Bern, Switzerland).

Statistical analyses

All data are reported as means ± Standard Deviation. A one-way analysis of variance (ANOVA) followed by a Fisher's Least Significant Difference (LSD)*post-hoc* test was used to compare values for each biomarker across the study groups. All data were analyzed by Statistical Package for Social Sciences program v.18-21 (SPSS Inc., Chicago, IL).

Results

Table 1 shows a multiple comparison of serum electrolytes (Mean ± SD) in the four groups of the chronic CO intoxication using one way-Anova (LSD's post hoc test). Serum sodium, ionized calcium, non-ionized calcium and total calcium significantly increased ($p < 0.05$) as the days and duration of chronic CO exposures increases. On the contrary, serum pH significantly increased ($p < 0.05$) at the 10th day of CO Intoxication and later significantly declined ($p< 0.05$) as the days and duration of chronic CO exposures increases.

Table 2 shows a multiple comparison of some vitreous electrolytes (Mean ± SD) in the four groups of the chronic CO intoxication using one way-Anova (LSD's post hoc test). Vitreous potassium, pH, ionized calcium, non-ionized calcium and total calcium significantly decreased ($p < 0.05$) as the days and duration of chronic CO exposures increases.

Table 3 shows a multiple comparison of some serum renal biomarkers (Mean ± SD) of the four groups of chronic CO intoxication using one way-Anova (LSD's post hoc test). Serum uric acid significantly decreased ($p < 0.05$) as the days and

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Table 1: A Multiple Comparison of Serum Electrolytes on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
Sodium µmol/l	136.75 ± 3.40	145.50 ± 8.78 ^{a}	133.50 ± 4.21 ^{b}	146.75 ± 2.02 ^{ac}	1.48	0.27
Potassium µmol/l	5.05 ± 0.84	6.53 ± 2.48	5.46 ± 0.53	4.64 ± 0.11	6.13	0.01
Chloride µmol/l	97.00 ± 4.69	95.98± 3.73	89.55 ± 7.03	90.68 ± 5.97	1.84	0.19
pH	7.45 ± 0.04	7.65 ± 0.05 ^{a}	7.55 ± 0.05 ^{ab}	7.23 ± 0.05 ^{abc}	60.27	0.00
Calcium µmol/l	1.21 ± 0.09	1.14 ± 0.17	1.34 ± 0.03 ^{b}	1.43 ± 0.05 ^{ab}	6.91	0.01
nCalcium µmol/l	1.20 ± 0.02	1.30 ± 0.16	1.45 ± 0.01 ^{ab}	1.30 ± 0.07 ^{c}	5.56	0.01
Total Calcium µmol/l	2.17 ± 0.13	2.35 ± 0.32	2.94 ± 0.04 ^{ab}	2.63 ± 0.05 ^{abc}	14.72	0.000

Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

Table 2: A Multiple Comparison of Vitreous Electrolytes on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
Sodium µmol/l	140.00 ± 3.74	140.95 ± 12.38	132.35 ± 4.86	131.23 ± 3.09	2.04	0.16
Potassium µmol/l	6.15 ± 0.56	4.66 ± 0.37 ^{a}	4.97 ± 0.70 ^{a}	4.24 ± 0.41 *a*	9.69	0.00
Chloride µmol/l	104.75 ± 4.03	105.00 ± 3.92	99.60 ±9.52	103.65 ±4.82	0.69	0.58
pH	7.86 ± 0.05	7.59 ± 0.02	7.77 ± 0.07 ^{a}	7.23 ± 0.05 ^{a}	2.75	0.09
Calcium µmol/l	1.34 ± 0.05	1.19 ± 0.18 ^{a}	1.15 ± 0.10 ^{a}	1.16 ± 0.05 ^{abc}	30.41	0.00
nCalcium µmol/l	1.59 ± 0.09	1.40 ± 0.12	1.36 ± 0.05 ^{ab}	1.07 ± 0.02 ^{abc}	52.86	0.00
Total Calcium µmol/l	3.08 ± 0.19	3.07 ± 0.07 ^{a}	2.71 ± 0.14 ^{ab}	2.07 ± 0.08 ^{abc}	120.35	0.00

Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

Table 3: A Multiple Comparison of Serum Renal Biomarkers on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
Creatinine (µmol/L)	68.02 ± 10.01	72.32± 9.01	74.22 ± 12.04	90.01 ± 13.22 ^{a}	0.52	0.48
Urea (mmol/L)	4.02± 1.73	4.80 ± 0.91	5.00 ± 1.22	5.80 ± 0.71	0.72	0.56
Uric Acid (µmol/L)	74.25 ± 18.01	59.00 ± 6.02	45.01 ± 7.00 ^{a}	30.06 ± 6.24 ^{ab}	12.36	0.00

Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

duration of chronic CO exposures increases. However, serum creatinine exhibited significant increase (p < 0.05), whereas urea did not show significant change.

Table 4 shows a multiple comparison of some vitreous renal biomarkers (Mean ± SD) of the four groups of the chronic CO intoxication using one way-Anova (LSD's post hoc test). Vitreous uric acid significantly decreased (p < 0.05) as the days and duration of chronic CO exposures increases. On the contrary, vitreous creatinine and urea exhibited a significant increase (p < 0.05) as days and duration of chronic CO exposures increases.

Table 5 shows a multiple comparison of some serum cardiac biomarkers and glucose (Mean ± SD) of the four groups of chronic CO intoxication using one way-Anova (post hoc test-LSD). The serum creatine kinase, and lactate dehydrogenase significantly increased (p < 0.05) as the days and duration of chronic CO exposures increases.

Table 6 shows a multiple comparison of some vitreous cardiac biomarkers and glucose (Mean ± SD) of the four groups of chronic CO intoxication using one way-Anova (post hoc test-LSD). The vitreous creatine kinase and lactate dehydrogenase significantly increased (p < 0.05) as the days and duration of chronic CO exposures increases.

Discussion

Chronic carbon monoxide (CO) poisoning is the inhalation of low quantity of CO over a long duration. Both acute and chronic inhalations of CO are known to be deleterious to the body. The picture of cardiorenal biochemical biomarkers occasioned by stead and repetitive inhalation of low concentration of CO over the durations is the quest for this research.

This study showed that potassium concentration did not show significant increase (p > 0.05) in the serum, whereas significant decrease (p < 0.05) in the vitreous (Tables 1,2). The relationship between potassium concentrations in the serum

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Table 4: A Multiple Comparison of Vitreous Renal Biomarkers on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
Creatinine (μmol/L)	41.75 ± 9.07	48.75 ±4.86	62.25 ± 4.57 ^{ab}	80.50 ± 8.23 ^{abc}	23.96	0.00
Urea (mmol/L)	3.93 ± 0.22	4.05 ± 0.51	4.43 ± 0.51	6.25 ± 0.60 ^{abc}	020.16	0.00
Uric Acid (μmol/L)	56.50 ±5.80	55.00 ±7.79	44.00 ±7.44 ^{ab}	27.50 ± 4.36 ^{abc}	16.99	0.00

Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

Table 5: A Multiple Comparison of Serum Cardiac Biomarkers and Glucose on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
CK (U/L)	301.75 ± 80.43	539.00 ± 53.28 ^{a}	575.00± 132.29^{a}	1031.75± 160.87 ^{abc}	28.32	00.00
LDH (U/L)	243.75± 44.42	400.25 ± 72.09	527.75 ± 98.01^{a}	830.75± 224.90 ^{abc}	14.75	0.00

Legend: CK = Creatinine kinase; LDH = Lactate Dehydrogenase.
Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

Table 6: A Multiple Comparison of Vitreous Cardiac Biomarkers and Glucose on the Basis of Duration of Chronic CO Intoxication.

Parameters	Control	Duration of CO Exposure				
		Day 10	Day 20	Day 30	f-value	p-value
CK (U/L)	907.75 ± 221.76	922.50± 429.76	1237.50± 110.87	1480.73 ± 374.48 ^{ab}	3.17	0.06
LDH (U/L)	562.22 ±160.08	1025.00 ± 170.78 ^{a}	1100.00 ± 316.23 ^{a}	1225.00 ± 263.00 ^{a}	7.03	0.01

Legend: CK = Creatinine kinase; LDH = Lactate Dehydrogenase.
Symbols- *a*: P < 0.05 vs control, *b*: P < 0.05 vs Day 10, *c*: P < 0.05 vs Day 20
Data are expressed as mean ± SD; Significant at 0.05 Confidence (p < 0.05)
Concentration of acute CO intoxication= ≤ 200 pm

and the vitreous is not clearly established scientifically, but the serum potassium constantly supplies the vitreous with potassium [16]. This is strictly regulated by the ATPase pump. The decrease as observed in the vitreous could be as a result of the inactivity of the ATPase pump due to hypoxic inhibitory capacity of chronic CO intoxication. Hence, this finding could be useful in the diagnosis of chronic CO poisoning.

The current study also revealed that chronic CO poisoning elicited a significant decline in both serum and vitreous humor pH values, resulting in acidosis. The decrease in pH could be due to a production of acids from enzymes triggered by a presence of too much CO in the blood. Normally, carbon dioxide (CO_2) plays a crucial role in the activity of carbonic anhydrase [17]. In CO poisoning, the supply of CO_2 is altered due to carboxyhemoglobin formation. This in turn affects the bicarbonate production cycle which helps to main blood pH.

Another finding of the current study was a significant increase in levels of ionized calcium (Ca), non-ionized calcium and total calcium in the serum - and the reverse situation in the vitreous humor. The noted significant increase in serum Ca could be due to cardiac muscular contractions. This would be in keeping with the fact that one of the most impacted organs from CO poisoning is the heart [1]. Cardiotoxicity is known to provoke a release of calcium [18]. It is well accepted that intracellular calcium release from sarcoplasmic reticulum (SR) is required for cardiac muscle contraction and excitation [18]. Hence, the perturbation of Ca signaling occasioned by the toxicity of chronic CO could be a result of cardiac hypertrophy [18,19]. Acidotic environments created by a CO-induced hypoxia could cause hypercalcemia. Acidosis decreases binding of Ca to albumin; this, in turn, results in increases in the proportion of plasma Ca to its the free-ionized form [19]. The decrease in vitreous Ca could be as a result of a compromised regulatory mechanism especially the pumps, as many of these pumps are vulnerable to toxicity from alterations in local potassium levels [20].

Another finding of this study was that there were significant increases in serum sodium due to the increasing periods of exposure to CO. Oddly; there was no effect on this endpoint in the vitreous humor. The biochemical bases for this induced hypernatremia could be three-fold, i.e., neurological, hypovolemia, and/or normovolemia [21]. The path utilized by CO could be neurological as CO is associated with neurons [21]. Also, CO could utilize the path of normovolemia by altering the capacity of anti-diuretic hormone (ADH) responsible for the regulation of extracellular and intracellular water composition. It is an established fact that CO affects the brain [1], ADH being a product of the brain could be affected, hence the hypernatremia observed.

Other renal biochemical parameters studied were urea, creatinine and uric acid. The result shows that chronic CO poisoning has a relationship with studied renal biomarkers

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both in the serum and vitreous humor (Tables 3,4). Urea and creatinine had been shown to be the most stable of the vitreous constituents tested in postmortem [22]. Also, both serum and vitreous urea and creatinine had been implicated in renal abnormalities [5,19]. Hence, the increase in concentrations of creatinine and urea is a pointer to the fact that renal dysfunction is a long term outcome of chronic inhalation of CO. The study agreed with Guy and Gil, [23] who attributed renal failure to acute CO exposure secondary to myoglobinuria. Another study stated again that the hallmark of severe carbon monoxide poisoning is renal failure. Blood urea nitrogen (BUN) and creatinine concentrations increased in acute renal failure secondary to myoglobinuria [24]. In the nutshell, the study had shown explicitly that pulsatile inhalation of CO could have a long term effect on the renal physiology.

The decrease in concentrations of serum and vitreous uric acid could be attributive to the toxicity potentials of CO on one hand and the anti-oxidant attribute of uric acid on the other hand. Uric acid formation is an enzymatic process which involves arrays of enzymes. The step wise process yields uric acids which are target in therapeutics and toxicology. A lot of chemicals could inhibit either of the enzymatic steps. The inhibitions usually result to a fall in concentration of uric acid. The fall as seen in this study could be the basis of hypouricaemia as observes in the blood and vitreous humor. This same mechanism is utilized by sevelamer and arrays of drugs for the management of renal dysfuction, arthritis and gout management by inhibiting uric acid pathway [25].

Alternatively, the decrease could also be seen from uric acid function as an anti-oxidant. Uric acid is a known marker of oxidative stress [26] and may have a potential therapeutic role as an antioxidant [27]. Like other strong reducing agents such as ascorbate, uric acid can also act as anti-oxidant. Hence the decrease could be due to the activity of uric acid as an antioxidant to free radicals generated from the ravaging CO concentrations. The findings of this study disagreed with that of Baillie *et al.* [28], that stated that exposures to acute CO resulted to hyperuricemia, though in high concentration.

Carbon monoxide is known to be deleterious to the myocardium [27]. The findings of this study showed a significant increase in the study cardiac markers both in the serum and vitreous (Tables 5,6). The increase seen could be due to the hypoxic effect of CO on the cardiac muscles. Carbon monoxide effect on myoglobin is a well-researched topic [18]. Myoglobin is closely knitted with the cardiac muscle; hence the assault on the cardiac muscle by the preferential binding of CO to the muscle cells will result to the denial of oxygen supply to the muscles. The insufficiency or almost absent supply of oxygen results to an assault with consequent release of cardiac enzymes to the blood. This study finding agreed that with of Whang and Choi [29] who also observed increases of serum creatine kinase and lactic dehydrogenase in carbon monoxide intoxicated patients relating it to cardiotoxicity of carbon monoxide. However, the work contradicted Davutoglu et *al*, [30], which stated that acute carbon monoxide (CO) poisoning may cause cardiotoxicity but troponin, CK, and CK-MB concentrations were not statistically significant between groups as observed in victims of carbon monoxide intoxication.

Conclusions

The study sought to assess the applicability of measuring vitreous humor and serum to reflect cardio-renal toxicities associated with chronic CO exposure. The data clearly showed that consistent (daily, up to 30 d) short-term exposures to CO could impart negative effects on renal and cardiac cells in a rabbit. If these translate up to human subjects in well-designed studies, then such profiles could potentially be used as diagnostics for chronic CO poisoning and subsequent management in preventing such intoxications among populations in Nigeria and elsewhere.

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Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content of this manuscript.

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