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Myocardial findings in fatal carbon monoxide poisoning: a human and experimental morphometric study

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Abstract The aim of this study was to define the status of the myocardium in selected human cases of acute, fatal carbon monoxide intoxication and the myocardial changes in rats exposed to carbon monoxide in relation to the type of cardiac arrest and the effects of reoxygenation following pre-fatal CO intoxication. The human study consisted of 26 cases (17 accidental and 9 suicide) of acute, fatal CO intoxication, without evidence of obstructive coronary atherosclerosis or history of ischemic heart disease which were compared with 45 cases of fatal head trauma in subjects who died instantaneously (26 cases) or within 1–12 h (19 cases). Inhalation of a lethal dose of CO in rats was compared with sub-lethal doses plus reoxygenation with and without pre-treatment by a betablocker. In all human and experimental histological sections, changes were normalised per mm^2 area. In the human cases the myocardium did not show any ischemic types of changes or other lesions. Only in "three accidental" cases a few, small foci of coagulative myocytolysis were detected. In the case of spontaneous death in 31 rats following CO intoxication, no pathological myocardial changes were seen. Of the 15 "reoxygenated" rats, 2 of the 7 spontaneous deaths presented coagulative myocytolysis with 15 ± 6 foci and 381 ± 255 necrotic myocells. All the eight rats sacrificed at 3 h had coagulative myocytolysis with 5 ± 4 foci and 60 ± 47 myocells. Of the 24 reoxygenated rats pre-treated with a betablocker, 5 died spontaneously after a short survival and 2 of these showed 11 ± 9 foci and 21 ± 20 myocells. The 19 rats sacrificed after 3 h all presented coagulative myocytolysis with figures of 75 ± 43 and 356 ± 301 with 0.5 mg/kg of propranolol hydrochloride and 55 ± 45 and 253 ± 216 with 2 mg/kg, respectively.

Key words Carbon monoxide poisoning · Acute toxicity · Myocardial necrosis · Catecolamine myotoxicity · Coagulative myocytolysis

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Introduction

Carbon monoxide (CO) is classified toxicologically as a chemical asphyxiant and the pathogenetic mechanisms include binding to the heme prosthetic group of hemoproteins, altered dissociation of oxyhemoglobin (carbon monoxide hypoxia) and direct cytotoxic effects by inactivation of some cellular respiratory enzymes [1, 2]. Even if neurological manifestations prevail [1, 3], the heart is the other main target of CO intoxication. Clinical investigations have suggested that in individuals with pre-existing coronary disease, CO intoxication could precipitate cardiac symptoms and even lethal complications [3]. The frequent occurrence of cardiac disturbances during or after exposure to CO, such as increased frequency of anginal attacks, arrhythmia, and increased levels of cardiac enzymes, has led to a search for morphological changes that could be attributed to CO, especially because the myocardium has been shown to bind more CO than skeletal muscle [4, 5]. There is a decreased oxidative phosphorylation [6, 7] with a parallel decrease of heart rate, pulse pressure [8, 9, 10, 11] and increased coronary blood flow [8, 12] with a relative subendocardial underperfusion [13] whereby vasodilatation is the major response to CO hypoxia [14]. The cardiac electrical instability is not influenced by CO exposure in both normal and ischemic dog hearts, without any effect on coronary blood flow and

platelet aggregation [15], a finding which apparently contrasts with other studies both in animals and in human coronary artery disease [12, 16]. In this condition nonharmful CO doses may cause damage in these patients [17, 18, 19, 20] by aggravation of angina pectoris, reduced inotropic effect, abnormal electrocardiographic signs, impaired survival [21] and sudden death [22]. CO may make the endothelial cell relatively hypoxic, a powerful stimulus of prostacyclin (PGI_2) production, or less likely exert a direct toxic effect on the endothelial cells [23]. Furthermore, survivors of CO exposure may present a clinical pattern of ischemic heart disease [24, 25, 26] which can be recovered by hyperbaric oxygenation treatment [27, 28].

Despite many studies, the relationship between CO hypoxia and myocardial morphological changes is still unclear both in humans and in experimental models. In human cases, myocardial fiber degeneration, focal necrosis, haemorrhages, mainly scattered in the subendocardium of interventricular septum and papillary muscles without any possibility to discriminate ischemic versus CO lesions, have been described [29, 30, 31]. In animals exposed to chronic carbon monoxide treatment, focal myocardial necrosis associated with lymphocytic, plasmacellular and histiocytic infiltrates and moderate increase of interstitial collagen [32], or early interstitial edema with partial separation of the intercalated discs in acute intoxication [33] have been described. By electron microscopy, focal "myofibrillar" necrosis, degenerative mitochondrial changes (e.g. swelling, cristolysis, mitochondrial fusion, loss of limiting membrane), separation of intercalated discs, intra- and extracellular edema and increased lipid droplets have been reported [34].

The aim of this study was to define the status of the myocardium in selected human cases of acute, fatal carbon monoxide intoxication, the myocardial changes in rats exposed to carbon monoxide in relation to the type of cardiac arrest and the effects of reoxygenation following pre-fatal CO intoxication.

Material and methods

The experimental procedures followed the "Principles of laboratory animal care" (NIH publication No. 85–23, revised 1985) and were approved by the local ethical committee for animal experiments.

Human studies

A total of 26 cases of fatal acute carbon monoxide intoxication were studied. In 17 cases the intoxication was an accidental event while 9 were suicide cases. All died without resuscitation attempts of any type. Only cases with normal coronary arteries or minor atherosclerotic lesions with minor luminal stenosis (< 50%) were included. No changes in other organs were observed at autopsy.

The control group consisted of 45 cases of instantaneous death (26 cases) or death within 1–12 h (19 cases) following head trauma (Table 1).

In all cases the heart was weighed and inspected and any gross alterations were examined histologically. The subepicardial coronary arteries and their main branches were cross-sectioned at 3 mm intervals and any segment with pathological changes was processed for histology. From the whole anterior wall of the left ventricle, 2–4 samples were taken, fixed in 10% buffered formalin and embedded in paraffin. The histology sections were routinely stained by hematoxylin-eosin.

Experimental studies

A total of 88 male albino rats with a body weight of 230–250 g (Harlan, Italy) were kept under standard conditions (MIL Morini diet; water ad libitum, room temperature 25 °C, alternate cycles of light and dark of 12 h) for 7 days. All animals were anesthetised with chloral hydrate 400 mg/kg i.p. (Carlo Erba, Italy) , a basal electrocardiogram was recorded for 10 min (Electrocardiograph Powerlab, Varese, Italy) and a blood sample (heparin) was taken from the abdominal aorta. The time course of the experiment was 3 h. The heart was removed, immersed in buffered formaldehyde solution (10%) and processed for histological examination. The histology sections were stained by hematoxylin-eosin. The following groups were studied:

1. Control group: 5 animals

2. CO group: 31 rats were placed in an 8 l, airtight metabolic container. CO (2%) was administered at a constant flow of 0.34 l/min. The ECG was continuously recorded up to death of the animal. In this group the heart was removed and divided into two superior and inferior parts, one placed in buffered formalin and the other in glutaraldehyde for ultrastructural studies.

3. CO + reoxygenation: A total of 15 rats were treated as in the previous "CO group" until a stable status of bradycardia, lasting 3 min was reached. Then, the animals were reoxygenated by exposure to normal air and an ECG was recorded every 30 min for 3 h.

4. CO + reoxygenation + betablocker: Before CO intoxication, 24 rats were pre-treated with i.v. propranolol hydrochloride (RBI, Amersham, Italy) at a dose of 0.5 mg/kg in 11 and 2 mg/kg in 13 animals. The control group consisted of five rats in which 2 mg/kg propranolol was administered.

Toxicological analysis

Blood samples were taken from the abdominal aorta of all animals, heparinized and sealed for analysis. Carboxyhemoglobin (COHb),

Table 1 Human fatal acute carbon monoxide intoxication cases and control cases: main characteristics (*M* male, *F* female, *COHb* carboxyhemoglobin)

Source	*n*	Gender		Age (years)	Heart weight (g)	Survival (min)	COHb (%)
		M	F				
CO intoxication	26	20	6	48 ± 16	375 ± 71	–	
Accidental	17	12	5	54 ± 14	394 ± 77	–	64.8–87.9
Suicide	9	8	1	35 ± 11	338 ± 38	–	65.2–88.3
Head trauma	45	37	8	42 ± 17	364 ± 47	< 5 min–12 h	–
Instantaneous death	26	20	6	42 ± 18	362 ± 44	< 5 min	–
Rapid death	19	17	2	42 ± 17	367 ± 53	1–12 h	–

Table 2 Human fatal acute carbon monoxide intoxication cases and control cases: frequency and extent of coagulative myocytolysis

Source	*n*	Coagulative myocytolysis (100 mm^2)		
		Present	Foci	Myocell
CO intoxication	26	3	1.3 ± 0.9	5.4 ± 4.0
Accidental	17	3	1.3 ± 0.9	5.4 ± 4.0
Suicide	9	–	–	–
Head trauma	45	9	10 ± 18	23 ± 31
Instantaneous death (< 5 min)	26	1	0.5	35
Rapid death (1–12 h)	19	8	12 ± 18	21 ± 33

oxyhemoglobin (HbO_2) and methemoglobin (MetHb) levels were measured in triplicate with the use of a spectrophotometer (Spectracomp 601, Carlo Erba, Milan), calibrated for rat blood [35].

Quantitative analysis

An image analyser (Vidas, Zeiss) was used to measure histological sections and the total area was calculated in pixels and converted to mm^2 by a calibration procedure using a reference system. Myocardial changes were counted in terms of the number of foci and of myocells and normalized to 100 mm^2.

Statistical analysis

Data are expressed as mean values ± one standard deviation. Student's *t*-test for paired or unpaired data or non-parametric Mann-Whitney or Wilcoxon tests for skewed variables or one-way analysis of variance and post hoc Scheffe's test for continuous variables and χ^2-test for discrete variables were used to assess whether differences were statistically significant. Linear regression analysis was used to determine the presence of correlation between continuous variables. A probability value of $p < 0.05$ was considered significant.

Definitions

In previous reports, three different forms of myocardial cell death were distinguished in relation to the contraction cycle [36, 37, 38, 39, 40]. One is myocell death in an irreversible relaxation phase, typical of infarct or ischemic monofocal necrosis. This is characterised by early stretching with elongation of sarcomeres and nuclei by the intraventricular pressure (paradoxical bulging of a myocardium in flaccid paralysis; atonic death) followed within 6 h by polymorphonuclear leukocyte infiltration. The second form is the opposite pattern with microfocal myocell death in irreversible hypercontraction with rupture in anomalous cross-bands of the myofibrillar apparatus (tetanic death). This rhexis is most likely due to the action of the cyclic contractility of the surrounding myocardium on rigid, hypercontracted elements. The repair process is carried out by macrophagic monocytes. The third is lysis of the myofibrils and their progressive disappearance with intramyocellular edema (failing death). No cellular reaction has been observed. The first type of damage has been defined as "infarct necrosis" rather than the classic term "coagulation necrosis" since no coagulation occurs at any time. For the second, usually called" contraction band necrosis", the term "coagulative myocytolysis" was adopted since different forms of contraction band exist. This lesion is pathognomonic of catecholamine myotoxicity. The third "colliquative myocytolysis" follows a progressive loss of function seen in congestive heart failure [36].

Reoxygenation means a return to breathing normal air after severe CO intoxication. The "lumen reduction" at the site of a plaque was measured as a percentage of the lumen diameter in relation to the normal one [36]. Survival is the period of time from the onset of the terminal episode or beginning of an experiment and death.

Results

Human studies

In the cases with fatal carbon monoxide intoxication, the age ($p < 0.002$) and heart weight ($p < 0.05$) were significantly less in suicides. The myocardium did not show any ischemic type of changes or other lesions. Only in "three accidental" cases were a few, small foci of coagulative myocytolysis detected. The frequency and extent of this lesion was significantly less than those seen in controls with a survival between 1–12 h (Table 2).

Animal studies

Morphology findings

In the 31 rats where death was within 4–9 min following CO intoxication (range COHb 63.6%–88.6%) no pathological myocardial changes were seen. As in the control group, the myocardial cells appeared to be in the relaxation phase of the contractile cycle, a condition more clearly documented by electron microscopy (Fig. 1). Myocells never showed stretching with elongation of sarcom-

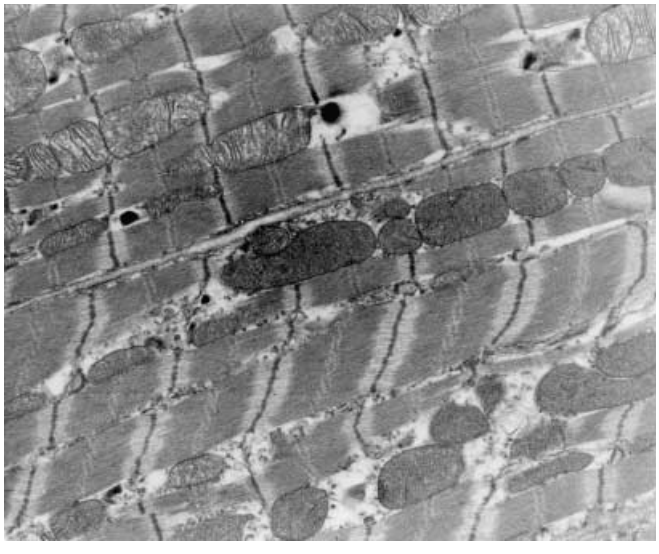

Fig. 1 Fatal CO intoxication in rats. Ultrastructural view of a normal, relaxed myocardium (TEM × 7000)

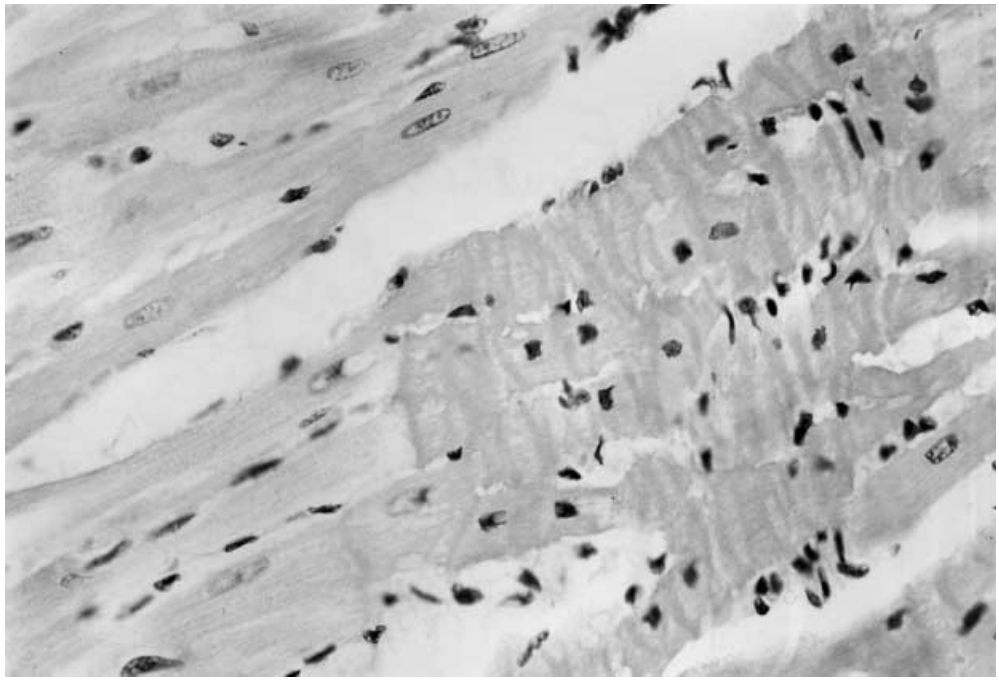

Fig. 2 CO + reoxygenation group. Coagulative myocytolysis, visible as dark bands spanning some myofibres (H & E × 400)

Table 3 Experimental acute carbon monoxide intoxication in rats: main characteristics

Source	No. of rats	Survival (min)	Coagulative myocytolysis (100mm^2)		
			Present	Foci	Myocells
Control group					
Sacrificed	5	–	–	–	–
CO intoxication	31	7 ± 1	–	–	–
CO + reoxygenation	15				
Spontaneous death	7	7 ± 1	2	15 ± 6	381 ± 255
Sacrificed	8	180	8	5 ± 4	60 ± 47
CO+reoxyg.+β-block (0.5 mg/kg)	11				
Spontaneous death	1	–[a]	–	–	–
Sacrificed	10	180	10	75 ± 43	356 ± 301
CO+reoxyg.+β-block (2 mg/kg)	13				
Spontaneous death	4	37 ± 6	2	11 ± 9	21 ± 20
Sacrificed	9	180	9	55 ± 45	253 ± 216
Control group (β-block 2 mg/kg)					
Sacrificed	5	180	5	37 ± 5	492 ± 59

[a] 40 s survival

eres and nuclei or the opposite pattern of hypercontraction with extremely short sarcomeres and markedly thickened Z-lines.

Of the 15 "reoxygenated" rats, 7 died spontaneously (range COHb 10%–19.1%) with a survival time similar to the previous group, while 8 were sacrificed after 3 h of breathing normal air (range COHb 1.2%–5.7%). Of the seven spontaneous deaths, two animals presented coagulative myocytolysis (contraction band necrosis) with 15 ± 6 foci (range 2–49) and 381 ± 255 necrotic myocells (range 91–838). All the eight rats sacrificed after 3 h had coagulative myocytolysis with 5 ± 4 foci and 60 ± 47 myocells (Fig. 2).

Of the 24 reoxygenated rats pretreated with a beta-blocker, 5 died spontaneously after a short survival (COHb 17%–35.2%) and 2 of these showed 11 ± 9 foci and 21 ± 20 myocells. The 19 rats sacrificed after 3 h (range COHb 1%–9.2%) all presented coagulative myocytolysis with figures of 75 ± 43 and 356 ± 301 with 0.5 mg/kg of propranolol hydrochloride and 55 ± 45 and 253 ± 216 with 2 mg/kg respectively. In the subgroup treated with 2 mg/kg propranolol without CO intoxication, and sacrificed at 3 h, all five rats had this form of lesion with 37 ± 5 foci and 492 ± 59 myocells (Table 3).

Electrocardiography findings

In all groups the basal ECG showed a basal sinus rhythm with a frequency ranging from 371 ± 49 to 379 ± 24 beat/min. The control group presented a sinus rhythm with an average frequency of 372 ± 134 beat/min. The ECG changes were as follows:

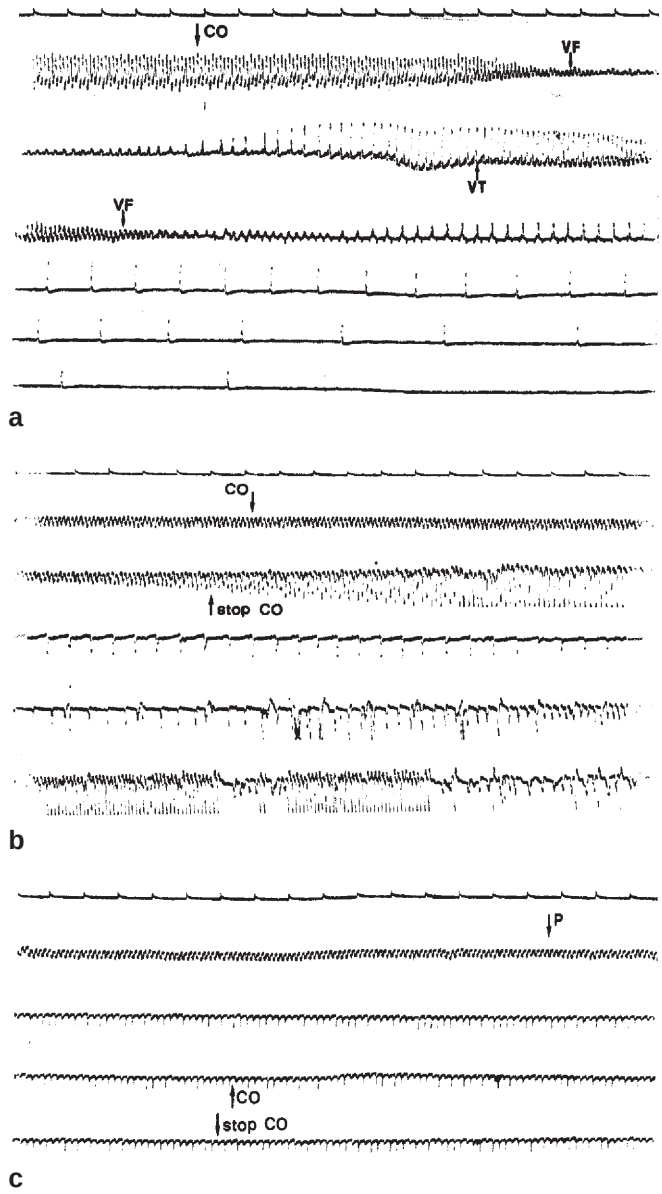

Fig. 3 **a** CO group: the ECG presented an early tachycardia followed by short episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF). Subsequently persistent and worsening bradycardia ending in asystole **b** CO + reoxygenation group: episodes of bradycardia alternated with episodes of ventricular tachycardia **c** CO + reoxygenation + betablocker: following propranolol somministration (P) the ECG showed lower heart rates which was not modified by CO intoxication

1. CO group: 62% of the 31 rats had episodes of ventricular tachycardia, 9.5% episodes of ventricular fibrillation and 28.5% showed an immediate bradycardia. The latter, ending in asystole, was the ECG pattern following ventricular tachycardia or ventricular fibrillation in all rats (Fig. 3a). Along with bradycardia all rats had an atrio-ventricular block of first and second Luciani-Weckenbach types and in seven a total block preceded the cardiac arrest in asystole.

2. CO + reoxygenation group: The ECG changes were similar to the previous group until reoxygenation started and then 80% of the 15 rats showed progressive bradycardia associated with 1st and 2nd Luciani-Weckenbach AV block. In 20% of the rats there was a normal ECG. In seven rats episodes of bradycardia alternated with episode of ventricular tachycardia immediately after reoxygenation. Subsequently there was a normal rhythm often associated with premature beats and bigeminism (Fig. 3b).

3. CO + reoxygenation + betablocker: Following propranolol administration, a significant ($p < 0.001$) reduction in frequency (basal 379 ± 24 vs 337 ± 34) which was not modified by CO intoxication could be observed (Fig. 3c). After reoxygenation there was a further reduction in frequency (259 ± 6). Only 2 of the 24 rats had 2 episodes of asystole and in 3, bradycardia was associated with 1st degree atrio-ventricular block. Ventricular tachycardia, premature beats and ventricular fibrillation were never observed.

Discussion

The search for early myocardial alterations constitutes an essential problem in the research of fatal CO poisoning [1]. The myocardial lesions reported in the literature [30, 34, 41, 42] pertain to chronic CO intoxication by sublethal doses. In our experiment the intoxication was lethal in less than 10 min and resulted in cardiac arrest in asystole following predominantly bradycardia. In our human cases the length of the survival period was not demonstrable by the circumstances surrounding death. Nevertheless, the myocardial lesions in the human cases were identical to those observed in the rats. Most of the myocardial cells were in the relaxation phase of the contraction cycle, the unique changes being ultrastructural anoxic-like alterations of some mitochondria in rats. The lack of differences between accidental and suicide death, excludes the effect of any possible emotional factor in the latter. Myofibrillar degeneration has even been observed in suicide victims and in ischemic heart disease patients whose basic feelings were helplessness or hopelessness [43]. Intense emotion is a common denominator of these psychological states in which a loss of balance, between sympathetic and parasympathetic modulation may produce tachycardia and ventricular fibrillation, bradycardia or asystole [36].

Foci of coagulative myocytolysis or contraction band necrosis were found after reoxygenation. This lesion is typical of catecholamine myotoxicity [37], is not related to ischemia and is demonstrable in several human conditions and experimental models, including ischemic heart disease [38] and associated to malignant arrhythmia. It can be defined as a morphofunctional and biochemical pattern in contrast to the ischemic necrosis. On that basis we speculate that this lesion found in chronic or sublethal CO intoxication is the result of an adrenergic overstimulation to counteract the loss of contractility rather than to anoxia or direct CO action on myocardial cells. A view supported by electrocardiographic signs of arrhythmia following reoxygenation and prevented by a betablocker.

This view is in agreement with the observation that nicotine, a promoter of an adrenergic response, and not CO in smoking is the cause of myocardial stiffness by increase of myocardial fibrosis [44] as result of coagulative myocytolysis. The same mechanism can explain the linkage between CO intoxication and ischemic heart disease [45, 46] since the major complication, i.e. malignant arrhythmia/ventricular fibrillation, is linked with adrenergic stress [37]. On the other hand another main complication, i.e. congestive heart failure, may occur following CO intoxication [47]. The latter may ensue in different conditions by a primary, still unknown, metabolic disorder in which the adrenergic system seems to play a role [39]. Again, the question is whether eccentric cardiomegaly with longer myocells and without an increase of their volume [48, 49, 50, 51], a finding observed in congestive failure following any cardiac disease [36], is due to CO as a promoter of myocell growth [52, 53, 54, 55] or to adrenergic stimulation.

Two last points need to be emphasised. Firstly, the basic differences between reoxygenation following CO intoxication and reperfusion or reflow injury [40]. Despite a common catecholamine-type of damage associated with malignant arrhythmia, prevented by betablocking, reperfusion injury presents a characteristic, massive interstitial hemorrhage plus microcirculatory platelet-fibrin aggregates, never seen in reoxygenation. The second point concerns the effect of propranolol on the myocardium of the rat. In previous [56] and in recent experiments (unpublished results) in dogs by coronary occlusion lasting from 18–60 min or repeated occlusions for a few minutes, it was possible to document and quantify an increasing extent of coagulative myocytolysis in both the ischemic and non ischemic areas. Propranolol prevented this lesion and ventricular fibrillation. In the present experiment in rats, propranolol per se induced coagulative myocytolysis, the extent of which was similar to that obtained by reoxygenation, but prevented the arrhythmic dysfunction. These contradictory findings need further investigation to ascertain a possible different neurogenic control in the two species. The action of noradrenaline primarily mediated through alpha-receptors, involves the hemodynamic abnormalities (cardiac output, minute and stroke work, increase in left ventricular end-diastolic pressure, peripheral resistance) while when mediated by beta receptors produces myocardial morphologic changes [57].

Finally, we were unable to confirm any microcirculatory alteration within the myocardium, including the leukocytic sequestration described in the brain [58].

In conclusion:

1. Acute lethal CO intoxication causes bradycardia ending in cardiac arrest by asystole without evidence of related myocardial damage.

2. Reoxygenation determines a necrosis typical of catecholamine myotoxicity without interstitial hemorrhage, characteristic of reperfusion injury.

3. Morphologic lesions described in CO intoxication are most likely due to adrenergic stress following reoxygenation rather than a direct action of CO or related anoxia on myocardial cells.

4. No morphologic differentiation exists between accidental and suicide CO intoxication.

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