Peer reviewed article

Prospective study of accidental carbon monoxide poisoning in 38 Swiss soldiers

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Summary

Background: Carbon monoxide (CO) poisoning is associated with a wide range of non-specific symptoms, whose time course and prognostic significance are ill defined.

Methods: We observed a large CO poisoning in a homogenous cohort of 38 male recruits and compared their symptoms with those of 46 unexposed controls from the same military unit. Incident and prevalent symptoms were assessed by sequential questionnaires.

Findings: Carboxyhaemoglobin (COHb) concentration extrapolated to the time of rescue was 30.4 ± 6.1%. Six recruits were initially unconscious, and five others were unable to get out of their sleeping bags without help. Dizziness was the most common symptom within the first two weeks and was reported in 92% of cases and 13% of controls, followed by headache (87% and 39%) and weakness (76% and 26%). Most symptoms were already present in the first hour, but vomiting, chest pain, and hearing disorders typically had a delayed onset. Headaches, cognitive impairment, and impaired vision were the slowest to resolve. After an initial maximum of 5.6 ± 2.9 symptoms ($p < 0.0001$ for the comparison with controls), cases reported 5.2 ± 2.5 symptoms at two days, 1.9 ± 2.3 symptoms at two weeks, and 1.3 ± 1.6 symptoms at one year ($p < 0.0001$ for decrease over time). Initial palpitations ($p = 0.002$) and visual changes ($p = 0.0003$) were independent predictors of a higher symptom score at one year.

Interpretation: In acute CO poisoning there are immediate and delayed symptoms suggesting different pathogenic mechanisms. Visual changes and palpitations are independent predictors of residual symptoms at one year.

Key words: carbon monoxide; poisoning; symptoms; immediate; delayed; carboxyhaemoglobin

Introduction

Carbon monoxide (CO) is a colourless, odourless, and non-irritating gas developing as a by-product of the incomplete combustion of carbon-containing fuels. Accidental CO-poisoning is responsible for approximately 40000 visits to the emergency department and about 600 deaths annually in the United States [1, 2]. Endogenous CO produced by the catabolism of haemoglobin acts as a physiologic relaxant for smooth muscle cells [3]. It has further been identified as a neurotransmitter and seems to confer cytoprotection against oxidative stress in hypoxic or inflammatory conditions [4]. Major sources of exogenous CO include motor vehicle exhaust fumes, defective heating systems, tobacco smoke, and methylene chloride [5]. The affinity of haemoglobin for CO is 200–250 times higher than for oxygen and carboxyhaemoglobin (COHb) is unable to transport oxygen. Carboxyhaemoglobin therefore accumulates during exposure to even relatively small CO concentrations, which results in a consecutive decrease of arterial oxygen transport capacity despite adequate partial pressure of oxygen. Furthermore, CO causes a shift of the oxygen-haemoglobin dissociation curve to the left resulting in impaired release of oxygen at the tissue level and thus cellular hypoxia [5–7]. Nevertheless, in experimental situations tissue hypoxia is only seen when COHb levels are very high (>70%). Thus, non-hypoxic mechanisms seem to contribute to the observed toxic effects [5, 6, 8]. Unfortunately, the clinical symptoms of CO poisoning including headache, nausea, dizziness, and weakness are non-specific and may be mistaken for viral illness in a considerable number of cases, especially since viral infection and CO poisoning both peak during the winter months [5, 6, 9]. On the other hand it may be very hard to determine whether a symptom in a patient exposed to CO is attributable to CO or not. Carboxyhaemoglobin levels often do not correlate with the severity of symptoms [5]. Furthermore, delayed onset of neuropsychiatric symptoms is known to occur in 2–30% of patients [5]. In this paper we present a quasi-experimental comparison of two groups of healthy young soldiers, of which one was accidentally exposed to an exogenous source of CO.

Samuel Henz has received funding for other studies by AstraZeneca and Pfizer, this study was not funded. Both authors declare that they have no conflicts of interest in this particular study.

Patients and methods

Patients and questionnaires

In October 2000, 38 male soldiers of the Swiss army were accidentally exposed to CO. The group was sleeping in a long stable directly adjacent to a small room in which a gasoline-powered generator (5 kW, 3000 U/min) was temporarily installed. One soldier was stationed outside as a guard. At 01:30 a.m. when he was unable to wake up a colleague for the change of guard, he gave alarm. The soldiers were immediately evacuated from the stable. Many needed help, but all comatose spontaneously regained consciousness within the next 15 minutes. Because of suspected CO poisoning all soldiers were transported to the five nearest local hospitals, where they arrived between 5:15 and 6:30 a.m. Soldiers, who had been comatose were treated with nasal oxygen during the transport. In the hospital oxygen was administered by facemask to all men and they were observed for 6 to 24 hours depending on the severity of their symptoms. One patient was transferred to another hospital for hyperbaric oxygen treatment due to transient limb paresthesias.

The largest group was brought to the Cantonal Hospital of St. Gallen, where one of the authors (S.H.) was responsible for their management and *ad hoc* created a questionnaire to assess onset, duration and severity of symptoms as well as potential risk factors for an unfavourable clinical course. All men, including those treated in the neighbouring hospitals were given the *first questionnaire* two days after the accident. In this they were asked about the following symptoms: *headache*, *nausea*, *vomiting*, *palpitation*, *chest pain*, *breathlessness*, *visual problems*, *hearing disturbances*, *dizziness*, *confusion*, *weakness*, *clumsiness*, *or "other symptoms"*. Furthermore, each patient was asked about his condition at the time of the alarm. Four conditions of increasing severity were offered: 0) ability to walk alone and to help colleagues, 1) ability to walk out of the stable but inability to help others, 2) consciousness but inability to get out of the building without help, and 3) unconsciousness. Patients were also asked about a history of asthma and cigarette smoking. At two weeks the soldiers were given a *second questionnaire* concerning the 12-day time-period since completion of the first questionnaire. At one year all cases were contacted by mail and asked to fill in a *third questionnaire* relating to the period of the last month and their present health condition. *Vomiting*, *palpitation*, *chest pain and breathlessness* were not assessed at this time-point; otherwise the questionnaire was identical. For the majority of the 38 exposed soldiers blood pressure, heart rate, temperature and the results of blood gas analyses on admission could be extracted from the hospital charts. Informed consent was obtained from all patients and all controls. The accidental nature of the study however did not allow acquiring formal approval by an ethics committee.

Controls

All 46 soldiers from a parallel military unit served as controls. They were of comparable age and had undergone an identical training during the past 3 months, but they had not been exposed to the exhaust of the generator. Two weeks after the accident they were asked to anonymously complete the same questionnaire as their exposed colleagues, thus giving a subjective view of their health status during the previous two weeks.

Data handling

Since patients and controls were asked to report on incidence, onset and duration of each symptom during the respective time periods, it was possible to differentiate between the incidence of each symptom within these time periods (ie 0 to 48 hours; 2 to 14 days, and month 12) and the prevalence at the following time-points: 0, 1, 2, 3, 6, and 12 hours, 1, 2, 3, 7, and 14 days, and at 1 year. Missing entries for incident symptoms were considered as the absence of the respective symptom. If the symptom was reported as incident but the data on onset and duration were incomplete, the average onset and duration in the cases with complete information were imputed for the graphical presentation of the prevalence data. All statistical analyses were performed with the raw data however. A symptom score was calculated by simply adding all reported symptoms at each time-point.

Blood gas analyses and carboxyhaemoglobin levels

For 17 patients an arterial blood gas sample was available without previous oxygen treatment. In 9 patients the blood gas analysis was performed while the patient was breathing oxygen by facemask. In 6 patients COHb levels were only available from venous blood samples. From the measured CO level (COa) we estimated the initial level (COi) using the time between the time of alarm (t1) and blood sampling (t2), the duration of oxygen therapy (dt) and the published half-lives (HL) for COHb during respiration with air (HLair = 5 hours) and 100% oxygen (HLox = 1 hour) respectively by the following equation:

$$COi = (COa / e^{-(\ln 2 / HLox) \times dt}) / (e^{-(\ln 2 / HLair) \times (t1-t2-dt)})$$

[5, 10].

Calculations were done assuming that all patients who had initially been comatose had received oxygen therapy for 30 minutes during transport, and that those for whom blood gas analysis was performed while receiving oxygen supplements in the hospital had been treated for 15 minutes. Carboxyhaemoglobin levels in venous and arterial blood samples were considered to be equivalent [11].

Sleeping location during exposure

Each mans exact sleeping location on the two sides of the long and narrow stable was reconstructed, and the approximate distance of each sleeping bag from the generator-room was expressed in meters. The soldiers were then grouped as having slept close to (1–5 meters; n = 14), at a medium distance (5–10 meters; n = 12), or distant (>10 meters; n = 12) from the generator.

Statistics

Statistical calculations were performed using the statistical package SAS (SAS Institute, Cary, NC USA). Continuous normally distributed data are presented as means and standard deviations and were compared with Student's t-test. If normality was questionable, medians and ranges are presented and the comparison was done using Wilcoxon's rank-sum test. Categorical variables were compared using Fisher's exact test. Multivariate linear regression was used to search for predictors of a higher COHb as well as a higher symptom-score at two weeks and one year. In a stepwise procedure, variables were included in the model if their p was <0.15, and they remained in the model if their p was <0.05. The time-course of the symptom-score in cases was analysed with a mixed-procedures model for repetitive data using an unrestricted covariance matrix and a restricted maximum likelihood estimate.

Results

Baseline characteristics

All 38 cases and 46 controls were male Caucasians. The age of the cases was 20.7 ± 1.3 years and 8 (21%) reported a history of asthma. Cases smoked a median of 15 (range 0–30), and controls 10 (0–60) cigarettes per day (table 1). In order to keep the questionnaire as simple as possible, age and co-morbidity of the control group was not explored. However male Swiss citizens must fulfil the first part of their military service (recruit school) between the age of nineteen and twenty-one years.

Table 1

Baseline characteristics, and blood gas analyses of cases at admission.

Baseline characteristics	
Age (years)	20.7 ± 1.3 (n = 38)
Sex (male)	100% (n = 38)
Smoking	68% (n = 38)
Haemodynamics	
Heart rate (bpm)	74.9 ± 12.8 (n = 27)
Systolic blood pressure (mm Hg)	135.0 ± 16.1 (n = 27)
Diastolic blood pressure (mm Hg)	72.2 ± 15.5 (n = 27)
Blood gas analyses	
Haemoglobin (g/L)	150.6 ± 6.5 (n = 26)
Arterial pH	7.42 ± 0.04 (n = 28)
Arterial pO_2 (mm Hg) *	113.2 ± 42.3 (n = 28)
Arterial pCO_2 (mm Hg)	38.0 ± 4.3 (n = 28)
COHb (%) †	14.2 ± 3.0 (n = 32)
Extrapolated COHb (%) †	30.4 ± 6.1 (n = 32)
Bicarbonate (mmol/L) ‡	25.0 ± 1.4 (n = 30)
Lactate (mmol/L)	1.1 ± 0.4 (n = 22)

Data are given as mean ± standard deviation. Abbreviations: pO_2 = partial pressure of oxygen, pCO_2 = partial pressure of carbon dioxide, COHb = carboxyhaemoglobin; for calculation of extrapolated COHb see text.
* oxygen administration in 9 cases. † venous samples in 6 cases. ‡ venous samples in 2 cases.

Time course of symptoms in cases

Six soldiers (16%) were initially unconscious, five others (13%) could be woken up but were unable to get out of their sleeping bags without help, and eight soldiers (21%) could leave the stable but were unable to help others. Within the first day the most prevalent symptoms were headache and dizziness, followed by nausea and a sensation of weakness. The prevalence of most symptoms peaked at two to three hours (figure 1).

Latency to onset and duration of symptoms in cases

The latency from the alarm to the onset of each symptom differed considerably. Clumsiness and visual disturbances were already present when the patient woke up from sleep or coma. Confusion, dizziness, weakness, headache, palpitations and shortness of breath were noted after a mean latency of 10 to 20 minutes; nausea and hearing impairment started within an hour, whereas vomiting and chest pain were late symptoms (figure 2).

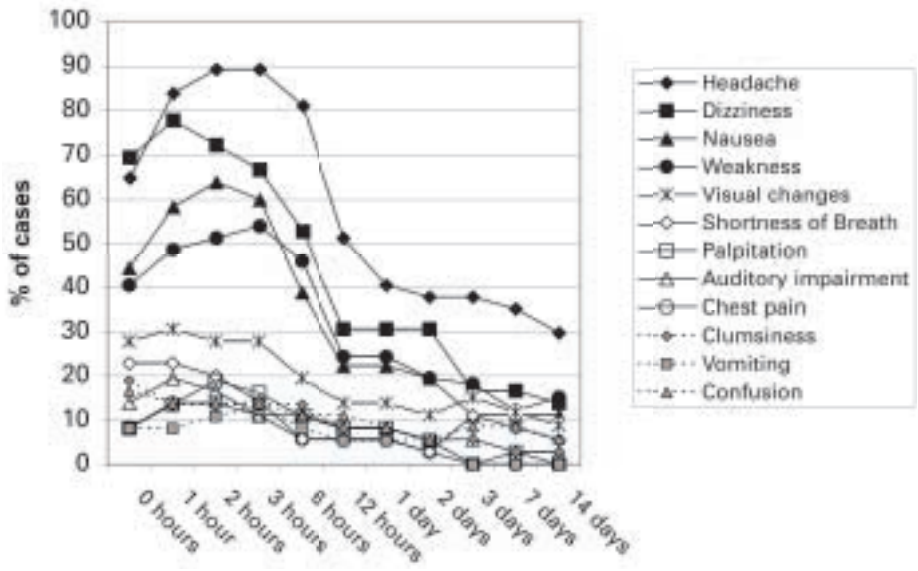
Individual symptoms also greatly differed in duration. Shivering was an early and quickly reversible, spontaneously reported symptom in two patients. Shortness of breath, chest pain, vomiting, palpitations and auditory impairment usually lasted less than 12 hours, whereas nausea, weakness, dizziness, and clumsiness generally lasted up to one day. Headaches, visual changes, and a sensation of confusion often persisted much longer (figure 3).

Differences between cases and controls: types of symptoms

Due to the variation within onset and duration of each symptom the prevalence changed considerably over time. For the comparison with controls

Figure 1

Point prevalence of individual symptoms in cases within two weeks.



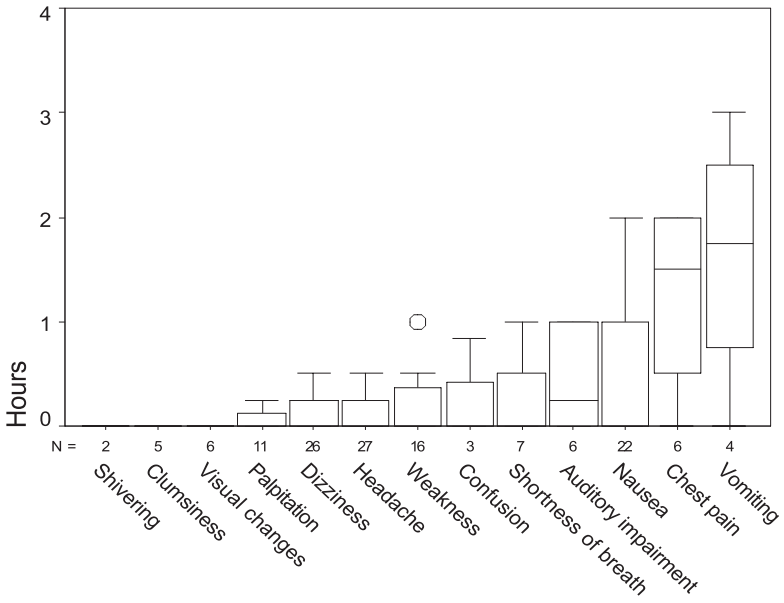


Figure 2

Latency time from alarm to start of each symptom (hours). Boxplots show 10th, 25th, 50th, 75th, and 90th percentiles as well as outliers (circle) but not extremes. N denotes the number of subjects who reported the latency.

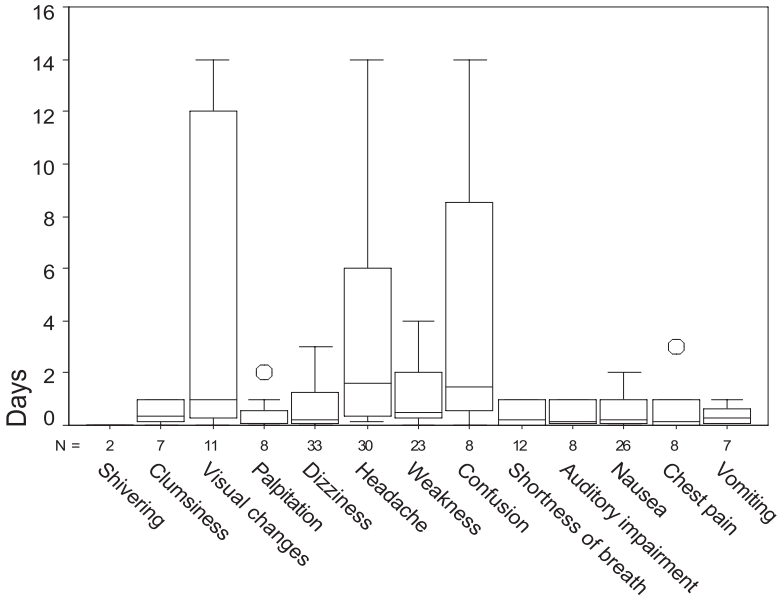


Figure 3

Duration of symptoms (days) excluding the time to onset. Boxplots show 10th, 25th, 50th, 75th, and 90th percentiles as well as outliers (circles) but not extremes. N denotes the number of subjects who reported the duration.

we therefore used the cumulative incidence of reported symptoms within two weeks after exposure. These incidence data are typically higher than the peak prevalence.

Dizziness had the highest incidence within the first two weeks following exposure (reported in 92% of cases and 13% of controls), followed by headache, weakness, nausea, breathlessness, chest pain, visual changes, confusion, palpitations, auditory symptoms, clumsiness, and vomiting (table 2).

Differences between cases and controls: number of symptoms

After an initial maximum of 5.6 ± 2.9 symptoms, cases reported on average 5.2 ± 2.5 symptoms at two days, 1.9 ± 2.3 symptoms at two weeks and 1.3 ± 1.6 symptoms at one year ($p < 0.0001$ for the decrease over time). Controls reported 1.7 ± 1.7 symptoms ($p < 0.0001$ for the comparison with the initial symptoms in cases).

Carboxyhaemoglobin levels

Arterial (n = 28) or venous (n = 6) blood gas samples were drawn 346 ± 57 minutes after the end of exposure. In 9 cases the samples were obtained shortly after the start of oxygen treatment. The mean uncorrected COHb level (n = 32) was 14.2 ± 3.0%. The mean extrapolated COHb level for the time of rescue was 30.4 ± 6.1% (table 1). The extrapolated COHb level was on average 1.1% higher for each package of cigarettes smoked per day (p = not significant [ns]), and 3% higher for each of the three degrees of increasing coma severity ($p < 0.001$). Yet there was no association between COHb levels and the type or number of other symptoms at any time point.

Contrary to our expectations, the highest COHb levels were not found in patients lying closest to the generator, rather the levels significantly increased by 0.5% for each meter further away from the generator (p = 0.007, adjusted for smok-

Table 2

Cumulative incidence of symptoms within two weeks after exposure in cases and controls.

Symptom	Cumulative Incidence		Odds Ratio	95% Confidence Interval	P Value
	Cases	Controls			
Dizziness	92%	13%	78	18–334	<0.0001
Headache	87%	39%	10	3.4–31	<0.0001
Weakness	76%	26%	9.1	3.4–25	<0.0001
Nausea	71%	15%	14	4.7–40	<0.0001
Shortness of breath	36%	11%	4.7	1.5–15	0.005
Chest pain	34%	15%	2.9	1.02–8.3	0.04
Visual changes	34%	7%	7.5	1.9–29	0.002
Confusion	29%	11%	3.3	1.04–11	0.04
Palpitations	24%	4%	6.8	1.4–34	0.009
Auditory disturbances	24%	2%	4.0	1.7–116	0.002
Clumsiness	24%	7%	4.4	1.1–18	0.03
Vomiting	18%	7%	3.2	0.8–14	0.09
Loss of consciousness	16%	0%			<0.0001

Table 3

Characteristics of soldiers reporting more than one symptom at one year.

Score 2 days	score 2 weeks	score 1 year	COHb	coma	smoker	residual symptoms after one year
8	*	6	44.4	3	Yes	headache, dizziness, weakness, clumsiness, fatigue, nausea
8	2	4	31.7	2	Yes	headache, visual changes, dizziness, nausea
9	8	3	*	1	Yes	headache, dizziness, nausea
6	3	3	26.6	0	Yes	headache, auditory disturbances, lack of energy
8	3	3	26.5	1	No	headache, dizziness, confusion
6	4	2	28.2	0	Yes	visual changes, auditory disturbances
9	8	2	29.6	1	Yes	confusion, reduced strength
6	4	2	21.7	0	Yes	headache, confusion
7	7	2	27.0	3	No	headache, confusion

The scores denote the added number of symptoms within the first two days, after two weeks, and after one year. COHb denotes extrapolated carboxyhaemoglobin levels. Coma is graded as follows: "0" = ability to walk alone and to help his colleagues, "1" = ability to walk out of the stable, but inability to help others, "2" = consciousness but inability to get out of the building without help, and "3" = unconsciousness.
* = data not available

ing). This effect however was lost after about 5 meters. If the soldiers were divided into three subgroups according to their distance from the CO source, it became evident that, compared to soldiers at the furthest end of the stable, COHb-levels were on average 6.3% lower in the group closest to the generator (p = 0.02), but only 1.8% lower (p = ns) for those sleeping in the middle section.

Outcome predictors

Follow-up information at one year was available for 25 persons. Eleven of them (44%) reported no symptoms at all, five (20%) reported one symptom (invariably intermittent headaches), four others (16%) had two symptoms, three persons (12%) had three, one (4%) had four symptoms, and another one (4%) reported six symptoms. Characteristics of the soldiers with more than one residual symptom at one year are presented in table 3. According to the information system of the Swiss army (PISA) all soldiers, who did not respond to the last questionnaire, were alive and still regular members of the army two years after the exposure.

In a multivariate regression model initial palpitations (p = 0.002) and visual disturbances (p = 0.0003) were independent predictors of a higher symptom score at one year. The presence or absence of visual symptoms was the better predictor for at least one late symptom other than headache with a sensitivity of 67% and a specificity of 87%, whereas the presence or absence of palpitations had a sensitivity of only 44% and a specificity of 80%.

Discussion

Carbon monoxide poisoning causes a wide spectrum of acute symptoms ranging from mild (constitutional symptoms similar to viral illness) to severe and even fatal disease (respiratory depression, coma, cerebral oedema) [5]. With 11 (29%) patients unconscious or unable to walk, the poisoning in our study is comparable to other large series in the literature [9, 12, 13]. The strength of our observation lies in the highly uniform cohort of otherwise healthy young men and the equally homogeneous control group, which converts this accidental exposure into a quasi-experimental study, in which the effects of CO exposure can be analysed without interference from other diseases. Since most patients could be sequentially assessed, starting only a few hours after exposure, we were able to prospectively evaluate the time course and the prognostic significance of each symptom.

The *time to onset* of each symptom varied considerably. Coma, the inability to walk, shivering, clumsiness and visual disturbances were invariably present from the very beginning, whereas auditory impairment, nausea and especially chest pain or vomiting often developed after a latency period of several hours. Although we cannot exclude that some more subtle symptoms were already present earlier but were only noted when more life-threatening symptoms diminished, these variable latencies to symptom onset are most likely due to different pathogenetic mechanisms. We postulate that early and rapidly reversible symptoms are more likely to be caused by direct toxic effects of CO or COHb-associated tissue hypoxia, whereas delayed symptoms may have other causes, such as brain oedema, localised vasomotor phenomena, secondary radical damage, or possibly psychological distress.

Coma or *the inability to move* was significantly correlated with higher COHb levels. These symptoms rapidly improved within a few minutes after rescue in all patients. Nonetheless given the long half-life of COHb (about five hours without oxygen therapy) neither the initial degree of coma nor this quick recovery can be explained by the degree of tissue oxygenation alone. From animal experiments we know that the cerebral metabolic rate for oxygen does not decrease below 90% of baseline until about 27% COHb is reached [14, 15]. Since many of our patients were below this level, cerebral oxygen supply should have been more than sufficient. In the 1940s, Drabkin et al. noted that dogs which received blood replacement to acutely produce 75% COHb showed none of the characteristic signs of anoxia as seen in dogs which inhale CO to the same level of saturation [16]. The non-haemoglobin bound fraction of CO thus must have anaesthetic properties beyond its ability to induce hypoxia. The quick resolution of this anaesthetic effect in our patients is an argument for a more rapid dissociation from its site of anaesthetic action than from haemoglobin. The cellular target of CO's anaesthetic action is not known. Potential candidates are intracellular haeme proteins, such as a recently described neuroglobin [17, 18]. Theoretically, CO may interfere with cellular respiration by binding to mitochondrial cytochrome c oxidase, but this is probably not clinically important since the affinity of cytochrome oxidase for CO is much lower than for oxygen [19]. Some researchers have also argued that CO may have direct neuropsychiatric effects by deranging dopaminergic and serotoninergic neural functions [20].

Muscle weakness could secondarily result from the same neurodepressive effects, but also from a direct binding of CO to myoglobin (Mb). Myoglobin is a respiratory haeme protein of muscle cells and has an even higher relative affinity for CO over oxygen than haemoglobin. Since functional Mb is required for maximal oxygen uptake by the muscle respiratory chain, muscle performance is reduced as CO binds to Mb [7]. A significant impairment of muscle oxidative phosophorylation is therefore already found at COHb levels between 20 and 40% [18]. This was the typical range in our patients, 76% of whom reported a feeling of weakness.

Other early symptoms were *clumsiness and visual disturbances*. Endogenous CO together with nitric oxide (NO) is a physiologic modulator of retinal signal transduction [21]. Visual disturbances could thus result from an overwhelming stimulation of this signalling pathway. In more severe intoxication retinal haemorrhage and papilloedema are common [22, 23]. However, deterioration of visual acuity can occur after several days and may respond to treatment with hyperbaric oxygen [24]. Similar to the brain the retina also contains high levels of neuroglobin [25]. Comparable to the role of Mb in muscle cells, this extravascular haeme protein may facilitate oxygen delivery to mitochondria and defend against oxidative stress [26]. Since neuroglobin has a high affinity for CO, intoxication could interfere with retinal oxygen delivery and antioxidative defence mechanisms [27].

Headaches, nausea, and vomiting often developed with a latency period of several hours. This finding is in sharp contrast with the steadily declining blood and tissue contents of CO and requires other explanations than COHb levels. The similarity between CO intoxication and migraine is striking: Hampson & Hampson found no discriminating pattern in CO intoxication as opposed to other causes of headache [28]. Brain tissue is largely insensitive, but pain can be generated by cranial vessels or the dura mater [29]. In migraine the characteristic symptoms are preceded by a phase of increased cerebral blood flow, which

is then followed by oligaemia and depressed neuronal function [29]. In experimental CO intoxication cerebral blood flow also increases in order to correct for the degree of hypoxaemia [30]. This autoregulatory rise in cerebral blood flow is a consequence of vascular smooth muscle activation of calcium dependent potassium channels through CO, but seems to include mechanisms mediated by NO [31, 32]. Nitric oxide can induce delayed, slowly developing activation of central trigeminal neurons in an experimental model of migraine [33]. The often late onset of headache and nausea in our patients could therefore be caused by similar vascular and humoral mechanisms as in migraine. Brain oedema, which in fatal cases can progress for up to 48 hours [34], may aggravate these symptoms in severe CO intoxication.

Delayed neuropsychiatric symptoms after apparent recovery from acute CO intoxication are estimated to occur in 2 to 30% of victims and have been reported 3 to 240 days after exposure [5]. Mimura et al. described the long-term follow-up of 156 patients after severe CO poisoning in a mine [35]. Most patients reported memory deficits, followed by irritability, headaches, insomnia, and limb pain. Many patients also showed personality changes and extrapyramidal movement disorders. In our series nine patients (36% of those for whom information was available) reported persistent neuropsychiatric symptoms other than headaches after one year. All of these had also been symptomatic at two days and two weeks (table 3). Annane et al. reported dizziness before admission and headaches upon hospital admission as significantly associated with persistent neurological symptoms after one month [36]. Given the almost invariable initial presence of these two symptoms, their positive predictive value is very low. Most other authors were unable to identify a clinical or laboratory parameter, which could predict the occurrence of late sequelae [5]. We found initial palpitations ($p = 0.002$) or visual disturbances ($p = 0.0003$) to be independent predictors of residual neuropsychiatric symptoms after one year. The presence of visual symptoms was the best single predictor for at least one late neuropsychological symptom (other than headache) after one year. It had a sensitivity of 67% and a specificity of 87%.

Several explanations for these delayed neuropsychological symptoms have been proposed. In diffusion MRI reversible white matter-lesions, especially in the basal ganglia, can be observed during acute CO intoxication [37, 38]. Despite a global increase in cerebral blood-flow during CO intoxication [39], SPECT-studies typically demonstrate regional hypoperfusion in the basal ganglia and brain cortex during the reoxygenation phase [40]. Carbon monoxide induces oxidative damage including brain lipid peroxidation and polymorphonuclear leukocyte sequestration in the cerebral vasculature [41]. Nitric oxide induced by CO is at least partially responsible for these events [41]. Apoptotic cell death was found in some animal models of CO intoxication [42]. CO poisoning also causes elevations of the excitatory amino acid glutamate and dopamine in rats [42]. In experimental CO poisoning, the elevation of glutamate has been linked to a delayed type of amnesia: loss of neurons in the hippocampus of mice and loss of glutamate-dependent cells in the inner ear of rats [18, 43]. One may therefore speculate that in addition to hypoxia inhomogeneous perfusion and a cascade of oxidative and neuroexcitatory events following CO intoxication could confer a higher vulnerability to predisposed brain regions.

Chest pain started after a median of 90 minutes and rarely lasted more than two days. Carbon monoxide acts as a physiologic relaxant for vascular smooth muscle cells including coronary arteries [44]. This effect is also mediated by NO [45]. At first we would therefore consider myocardial ischaemia an unlikely explanation of chest pain, especially among very young trained soldiers. Nevertheless, chronic professional CO exposure is an independent risk factor for mortality from ischaemic heart disease [46], and in patients with chronic coronary disease CO increases the likelihood of angina [47–49]. Moreover, several patients with normal coronaries have been described with acute myocardial infarction in acute CO intoxication [50–52]. In CO poisoning a sharp reduction in total peripheral arterial resistance and a lability of blood pressure is found in humans [53]. The combination of coronary steal phenomena due to hypotension, decreased oxygen transporting capacity of the blood due to CO-Hb, decreased intracellular oxygen utilization due to CO-myoglobin, impaired mitochondrial function [54, 55] together with increased cardiac output to correct for whole body hypoxaemia may lead to myocardial ischaemia. Increased sympathetic tone (eg resulting from panic in our patients) may increase myocardial oxygen demand, and hyperventilation could provoke coronary spasms both of which may aggravate myocardial ischaemia. Indeed inhomogeneous venous myocardial oxygen saturation was found in a canine model of CO exposure [44] suggesting heterogeneous oxygen consumption and possibly regional myocardial ischaemia.

Our main goal was to describe the time course and prognostic significance of each symptom in acute CO-intoxication. Nevertheless, the unexpected finding of 0.5% higher extrapolated COHb each meter further away from the generator merits a comment. This effect was most pronounced within the first five meters from the generator and suggests a causal role for the convection of hot exhausts in the room. Since the extraction of CO from inspired air is nearly complete, the persons, who first came in contact with the gas, ie those lying further away, may have served as biological sinks and may thus have partially protected their colleagues.

Study limitations

The questionnaire was created within hours after the arrival of the soldiers in the emergency room in order to prospectively evaluate symptoms of CO exposure. The collection of clinical data such as the duration of oxygen therapy was, however, done retrospectively and is therefore incomplete. The advantage of this very homogeneous population has a drawback: the degree to which one can generalise beyond a population of young men is questionable. Since the symptoms of our patients were very similar to those of other studies, which included persons of both genders and a larger age-range, broader validity is however to be expected.

Acknowledgment: For assistance with data collection we are indebted to the military physician, David Simonett, MD, and to the chiefs of the medical departments of our neighbouring hospitals: Paul-Josef Hangartner, MD, Altstätten, Urs Trümpler, MD, Wil, Yves Crippa, MD, Grabs, and Jürg Winnewisser, MD, Wattwil. We further thank Renato L. Galeazzi, MD, Professor of Medicine, St. Gallen, and Karl Schimke, St. Gallen, for helpful remarks concerning the manuscript.

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References

1 Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002;347:1057–67.
2 Geehr EC, Salluzzo R, Bosco S, Braaten J, Wahl T, Wallenkampf V. Emergency health impact of a severe storm. Am J Emerg Med 1989;7:598–604.
3 Ryter SW, Morse D, Choi AM. Carbon Monoxide: To boldly go where NO has gone before. Sci STKE 2004;2004(230):RE6.
4 Sarady JK, Zuckerbraun BS, Bilban M, Wagner O, Usheva A, Liu F, et al. Carbon monoxide protection against endotoxic shock involves reciprocal effects on iNOS in the lung and liver. FASEB J 2004;854–6.
5 Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998;339:1603–8.
6 Tomaszewski C. Carbon Monoxide. In: Goldfrank LR FN, Lewin NA, Weisman RS, Howland MA, Hoffmann RS, editors. Goldfrank's toxicologic emergencies. 5th ed. Norwalk: Appleton&Lange; 1994. p. 1199–210.
7 Weaver LK. Carbon monoxide poisoning. Crit Care Clin 1999;15:297–317.
8 Gorman D, Drewry A, Huang YL, Sames C. The clinical toxicology of carbon monoxide. Toxicology 2003;187:25–38.
9 Ely EW, Moorehead B, Haponik EF. Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning. Am J Med 1995;98: 145–55.
10 Weaver LK, Howe S, Hopkins R, Chan KJ. Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure. Chest 2000;117:801–8.
11 Touger M, Gallagher EJ, Tyrell J. Relationship between venous and arterial carboxyhemoglobin levels in patients with suspected carbon monoxide poisoning. Ann Emerg Med 1995;25: 481–3.
12 Burney RE, Wu SC, Nemiroff MJ. Mass carbon monoxide poisoning: clinical effects and results of treatment in 184 victims. Ann Emerg Med 1982;11:394–9.
13 Myers RA, Snyder SK, Emhoff TA. Subacute sequelae of carbon monoxide poisoning. Ann Emerg Med 1985;14:1163–7.
14 Doblar DD, Santiago TV, Edelman NH. Correlation between ventilatory and cerebrovascular responses to inhalation of CO. J Appl Physiol 1977;43:455–62.
15 Langston P, Gorman D, Runciman W, Upton R. The effect of carbon monoxide on oxygen metabolism in the brains of awake sheep. Toxicology 1996;114:223–32.
16 Drabkin DL, Lewey FH, Bellet S, Ehrich WH. The effect of replacement of normal blood by erythrocytes saturated with carbon monoxide. Am J Med Sci 1943;205:755–6.
17 Burmester T, Weich B, Reinhardt S, Hankeln T. A vertebrate globin expressed in the brain. Nature 2000;407:520–3.
18 Raub JA, Benignus VA. Carbon monoxide and the nervous system. Neurosci Biobehav Rev 2002;26:925–40.
19 Caughey WS. Carbon monoxide bonding in hemeproteins. Ann N Y Acad Sci 1970;174:148–53.
20 Muraoka M, Hayakawa H, Kagaya A, Kojima T, Yamawaki S. Effects of carbon monoxide exposure on serotonergic neuronal systems in rat brain. Life Sci 1998;62:2101–8.
21 Cao L, Blute TA, Eldred WD. Localization of heme oxygenase-2 and modulation of cGMP levels by carbon monoxide and/or nitric oxide in the retina. Vis Neurosci 2000;17:319–29.
22 Ferguson LS, Burke MJ, Choromokos EA. Carbon monoxide retinopathy. Arch Ophthalmol 1985;103:66–7.
23 Kelley JS, Sophocleus GJ. Retinal hemorrhages in subacute carbon monoxide poisoning. Exposures in homes with blocked furnace flues. JAMA 1978;239:1515–7.
24 Ersanli D, Yildiz S, Togrol E, Ay H, Qyrdedi T. Visual loss as a late complication of carbon monoxide poisoning and its successful treatment with hyperbaric oxygen therapy. Swiss Med Wkly 2004;134:650–5.
25 Schmidt M, Giessl A, Laufs T, Hankeln T, Wolfrum U, Burmester T. How does the eye breathe? Evidence for neuroglobin-mediated oxygen supply in the mammalian retina. J Biol Chem 2003;278:1932–5.
26 Herold S, Fago A, Weber RE, Dewilde S, Moens L. Reactivity Studies of the Fe(III) and Fe(II)NO Forms of Human Neuroglobin Reveal a Potential Role against Oxidative Stress. J Biol Chem 2004;279:22841–7.
27 Pesce A, Dewilde S, Nardini M, Moens L, Ascenzi P, Hankeln T, et al. The human brain hexacoordinated neuroglobin three-dimensional structure. Micron 2004;35:63–5.
28 Hampson NB, Hampson LA. Characteristics of headache associated with acute carbon monoxide poisoning. Headache 2002; 42:220–3.
29 Wood AJJ. Migraine – current understanding and treatment. N Engl J Med 2002;346:257–70.
30 Mendelman A, Zarchin N, Meilin S, Guggenheimer-Furman E, Thom SR, Mayevsky A. Blood flow and ionic responses in the awake brain due to carbon monoxide. Neurol Res 2002;24:765–72.
31 Xi Q, Tcheranova D, Parfenova H, Horowitz B, Leffler CW, Jaggar JH. Carbon monoxide activates KCa channels in newborn arteriole smooth muscle cells by increasing apparent Ca2+ sensitivity of alpha-subunits. Am J Physiol Heart Circ Physiol 2004;286:H610–8.
32 Meilin S, Rogatsky GG, Thom SR, Zarchin N, Guggenheimer-Furman E, Mayevsky A. Effects of carbon monoxide on the brain may be mediated by nitric oxide. J Appl Physiol 1996;81:1078–83.
33 Koulchitsky SV, Fischer MJ, De Col R, Schlechtweg P, Messlinger K. Biphasic response to nitric oxide of spinal trigeminal neurons with meningeal input in rat – possible implications for the pathophysiology of headaches. J Neurophysiol 2004 Apr 28.
34 Hawkins M, Harrison J, Charters P. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. Br J Anaesth 2000;84:584–6.

35 Mimura K, Harada M, Sumiyoshi S, et al. [Long-term follow-up study on sequelae of carbon monoxide poisoning; serial investigation 33 years after poisoning]. Seishin Shinkeigaku Zasshi 1999;101:592–618.
36 Annane D, Chevret S, Jars-Guincestre C, Chillet P, Elkharrat D, Gajdos P, et al. Prognostic factors in unintentional mild carbon monoxide poisoning. Intensive Care Med 2001;27: 1776–81.
37 Sener RN. Acute carbon monoxide poisoning: diffusion MR imaging findings. AJNR Am J Neuroradiol 2003;24:1475–7.
38 Kim JH, Chang KH, Song IC, Kim KH, Kwon BJ, Kim HC, et al. Delayed encephalopathy of acute carbon monoxide intoxication: diffusivity of cerebral white matter lesions. AJNR Am J Neuroradiol 2003;24:1592–7.
39 Fiumana E, Parfenova H, Jaggar JH, Leffler CW. Carbon monoxide mediates vasodilator effects of glutamate in isolated pressurized cerebral arterioles of newborn pigs. Am J Physiol Heart Circ Physiol 2003;284:H1073–9.
40 Wu CI, Changlai SP, Huang WS, Tsai CH, Lee CC, Kao CH. Usefulness of 99mTc ethyl cysteinate dimer brain SPECT to detect abnormal regional cerebral blood flow in patients with acute carbon monoxide poisoning. Nucl Med Commun 2003;24:1185–8.
41 Ischiropoulos H, Beers MF, Ohnishi ST, Fisher D, Garner SE, Thom SR. Nitric oxide production and perivascular nitration in brain after carbon monoxide poisoning in the rat. J Clin Invest 1996;97:2260–7.
42 Piantadosi CA, Zhang J, Levin ED, Folz RJ, Schmechel DE. Apoptosis and delayed neuronal damage after carbon monoxide poisoning in the rat. Exp Neurol 1997;147:103–14.
43 Liu Y, Fechter LD. MK-801 protects against carbon monoxide-induced hearing loss. Toxicol Appl Pharmacol 1995;132:196–202.
44 Zhu N, Weiss HR. Myocardial venous O_2 saturation becomes more heterogeneous during hypoxic and carbon monoxide hypoxia. Microvasc Res 1995;49:253–67.
45 Maulik N, Engelman DT, Watanabe M, Engelman RM, Rousou JA, Flack JE 3rd, et al. Nitric oxide/carbon monoxide. A molecular switch for myocardial preservation during ischemia. Circulation 1996;94(9 Suppl):II398–406.
46 Koskela RS, Mutanen P, Sorsa JA, Klockars M. Factors predictive of ischemic heart disease mortality in foundry workers exposed to carbon monoxide. Am J Epidemiol 2000;152:628–32.
47 Kleinman MT, Leaf DA, Kelly E, Caiozzo V, Osann K, O'Niell T. Urban angina in the mountains: effects of carbon monoxide and mild hypoxemia on subjects with chronic stable angina. Arch Environ Health 1998;53:388–97.
48 Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, et al. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. N Engl J Med 1989;321:1426–32.
49 Elsasser S, Mall T, Grossenbacher M, Zuber M, Perruchoud AP, Ritz R. Influence of carbon monoxide (CO) on the early course of acute myocardial infarction. Intensive Care Med 1995;21: 716–22.
50 Lee D, Hsu TL, Chen CH, Wang SP, Chang MS. Myocardial infarction with normal coronary artery after carbon monoxide exposure: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 1996;57:355–9.
51 Marius-Nunez AL. Myocardial infarction with normal coronary arteries after acute exposure to carbon monoxide. Chest 1990;97:491–4.
52 Tritapepe L, Macchiarelli G, Rocco M, Scopinaro F, Schillaci O, Martuscelli E, et al. Functional and ultrastructural evidence of myocardial stunning after acute carbon monoxide poisoning. Crit Care Med 1998;26:797–801.
53 Penney DG. Hemodynamic response to carbon monoxide. Environ Health Perspect 1988;77:121–30.
54 Gandini C, Castoldi AF, Candura SM, Locatelli C, Butera R, Priori S, et al. Carbon monoxide cardiotoxicity. J Toxicol Clin Toxicol 2001;39:35–44.
55 Gandini C, Castoldi AF, Candura SM, Priori S, Locatelli C, Butera R, et al. Cardiac damage in pediatric carbon monoxide poisoning. J Toxicol Clin Toxicol 2001;39:45–51.