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Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation?

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Ducassé JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? Undersea Hyperbaric Med 1995; 22(1):9–15.—Twenty-six non-comatose patients with acute carbon monoxide (CO) poisoning were randomized into two groups. Both groups were treated as soon as possible and for 2 h, the first group by 100% normobaric oxygen (NBO) and the second by 100% hyperbaric oxygen. At the end of this period, patients treated by HBO had a significant improvement of their clinical and biological conditions compared with patients treated with NBO. Both groups then received the same NBO therapy for 10 h. At the end of this second period, carboxyhemoglobin level was normal in both groups. However, patients treated with NBO showed some clinical impairments, and 3 wk after onset had significantly more electroencephalogram abnormalities and a reduced cerebral blood flow reactivity to acetazolamide. We conclude that HBO reduces the time of initial recovery and the number of delayed functional abnormalities in non-comatose patients with acute CO poisoning. A practical scheme for the use of NBO and HBO in such patients is proposed.

carbon monoxide poisoning, randomized study, cerebral blood flow, hyperbaric oxygen therapy

Hyperbaric oxygen therapy is considered the most relevant treatment for comatose patients (1) and pregnant women (2) suffering from acute carbon monoxide (CO) poisoning, but remains a matter of controversy in non-comatose patients (3,4). This is mainly due to the lack of an accepted scale for assessing the severity of acute CO poisoning. Indeed, clinical signs correlate poorly with carboxyhemoglobin (HbCO) level, and neither the former nor the latter are predictive of the final outcome. For instance, the absence of coma is not fully predictive of a final and complete recovery (5). This could explain why the question has not so far been addressed by prospective, randomized clinical trials (6). As moderate CO poisoning is common in the South of France (7), we have the opportunity to include non-comatose patients in a randomized study to compare the effects on clinical and biological signs of either normobaric oxygen (NBO) or HBO therapies, applied as soon as possible. We also assessed the delayed effects of both treatments on

cerebral functions by electroencephalogram (EEG) recordings and cerebral flood flow (CBF) measurements.

PATIENTS AND METHODS

We studied 26 patients who were hospitalized in an intensive care unit (ICU) for moderate acute CO poisoning. The study procedure was a prospective, randomized, open, blinded evaluation. Criteria for inclusion were the following: acute exposure to CO for less than 12 h, age between 18 and 75, no pregnancy, Glasgow coma scale higher than 12, and elapsed time between discovery and hospitalization less than 2 h. Early clinical signs and normobaric oxygenation quality during medical transport were recorded. Informed consent was obtained before the study from the patients and, each time it was possible, from a relative as well, according to the principles outlined in the Declaration of Helsinki.

At admission (T = 0 h), a clinical examination included completion of the Glasgow coma scale and recording of clinical abnormalities. These included symptoms and signs of CO poisoning. As there is no rating scale for assessing the clinical condition of patients with CO poisoning, we quantified our data by toting up all the clinical abnormalities exhibited by each patient. The carboxyhemoglobin (HbCO) value was measured with air (21% O_2) by means of an automatic spectrophotometer with 7 specific wave lengths (Co-oxymeter Corning 2500). Chest radiography and electrocardiogram were also recorded.

Patients were then included in a therapeutic group according to a randomized list which was settled beforehand. The NBO group consisted of 13 patients (5 female, 8 male), mean age 31.6 ± 14.1, who were treated only by NBO according to the usual therapeutic scheme of the ICU in cases of slight CO intoxication. Oxygen was administered first through a facial mask at 100% for 6 h, then at 50% for the next 6 h. The HBO group consisted of 13 patients (7 female, 6 male), mean age 28.3 ± 13.6. In this group, patients first received HBO therapy (2.5 atm abs, 2 h) in a multiplace chamber, then 100% NBO during 4 h, and finally 50% NBO for 6 h.

Two hours after admission (T = 2 h), a second clinical examination and HbCO determination were performed. Twelve hours after admission (T = 12 h), patients underwent a third clinical examination and HbCO measurement, a chest x-ray, and an ECG. At each clinical examination, patients were classified for presence or absence of abnormal signs and symptoms, the number of which was noted for each patient.

Within the first 24 h after admission, an EEG recording was obtained. About 3 wk after poisoning, a second EEG recording was performed (n = 18). The recordings were classified as follows: class I included recordings with regular temporospatial distribution of alpha waves and with or without watchfulness alterations; class II included recordings with impairments such as sporadic presence of theta waves, or presence at rest of focuses of theta or delta waves, or both.

Cerebral blood flow was assessed in 10 patients (4 HBO, 6 NBO) and in 10 normal volunteers, paired for age and sex, using single-photon-emission tomography (Tomomatic 64, Medimatic) and i.v. injection of 2,200 Mbq of xenon 133 as described previously (8). A first measurement was performed at rest (eyes closed, quiet darkened room). One hour later, a second measurement was done, 10 min after injection of 1 g acetazolamide, a potent cerebral vasodilator. For each exam the data collection lasted 4 min. Data were obtained from 3 parallel transverse slices and centered 1, 5, and 9 cm above the orbito-meatal plane. From these data, quantitative maps were constructed. Mean values were calculated for each slice, for each hemisphere in slice 2 (5 cm above the orbito-meatal

plane), and in the prefrontal, premotor, insular, and parietotemporal cortical regions and two subcortical regions for each hemisphere. An index of interhemispheric asymmetry [IA = (lCBF-rCBF)/[(lCBF + rCBF)/2] × 100] was calculated for each left (l) and right (r) region of interest. A focal asymmetry was considered to exist when IA was ≥10. Reactivity to acetazolamide was taken as the percent difference in CBF between the two measurements.

Statistical analysis was based on Student's t test, Wilcoxon signed-rank, and Mann-Whitney non-parametric test.

RESULTS

Before admission, the pattern of early clinical signs or symptoms that motivated an emergency call was the same in the two groups (Table 1). During medical transport, 25 patients received O_2. This administration, which lasted 50 min on average with a mean O_2 flow of 12.4 liter/min, was not statistically different between the NBO and HBO groups.

At hospital admission, the Glasgow coma scale was 15 for all patients except one, for whom it was 14. Two patients (one in each group) were completely free of any clinical abnormality even though they had an increased HbCO ratio. In the other 24 patients, 48 clinical abnormalities were noted without statistical difference between the two groups. The CO poisoning was confirmed biologically by the HbCO ratio (23.4 ± 7.3% in the NBO group and 23.5 ± 9.8% in the HBO group, without statistical difference between the two groups). No statistical correlation was found between the number of clinical abnormalities and the HbCO level in a patient.

After 2 h of NBO or HBO treatment (T = 2 h), clinical status became normal in 15 patients, but 11 patients (9 NBO group 2 HBO group, $\chi^2 = 7.72$; $P < 0.01$) still showed clinical abnormalities (Table 2). At T = 12 h, no patient in the HBO group had abnormal clinical findings whereas 5 patients in the NBO group still showed clinical impairment ($\chi^2 = 6.19$, $P < 0.05$). For ethical reasons, two of these patients were given an HBO session

Table 1: Clinical Signs and Symptoms of Acute Moderate CO Poisoning in Patients Before Their Inclusion in NBO or HBO Groups

	NBO	HBO
Before admission		
Loss of consciousness	9	8
Headache	8	8
Nausea	8	5
Asthenia	3	6
Vertigo	4	2
Others	2	3
At admission		
Reflex impairment	8	9
Headache	6	7
Tremor	3	2
Skin signs	4	3
Vertigo	3	–
Others	1	2

Table 2: Clinical Signs and Symptoms at T = 2 h and T = 12 h

	NBO	HBO
Clinical abnormalities at T = 2 h		
Reflex impairment	3	1
Headache	5	1
Asthenia	1	–
Clinical abnormalities at T = 12 h		
Moderate pulmonary edema	3	–
Headache	2	–

immediately after Hour 12. At the end of the session, they were asymptomatic. All 26 patients were discharged from the hospital without abnormal clinical findings. None returned later with complaints. No adverse effects of HBO was observed in our patients.

At T = 2 h, NBO patients had statistically ($P < 0.002$) high values of HbCO (6.4 ± 4.5%) than HBO patients (1.9 ± 1.2%). At T = 12 h, no marked impairment persisted: HbCO levels were low and not statistically different between NBO (1.2 ± 0.2) and HBO (1.2 ± 0.6) groups.

We found no statistical difference between the two groups in the 26 EEG recordings obtained within the first 24 h after admission (Table 3). An average of 21 days later, 18 patients (10 from NBO and 8 from HBO) were recorded again, and a difference between the two groups was noted. The eight patients treated by HBO were all in class I, whereas four treated by NBO were assigned to class I and six to class II (Wilcoxon, $P < 0.02$). There was no correlation between the clinical abnormalities at T = 12 h and either the first EEG signs or the EEG signs at Day 21.

At rest, mean CBF values in the mid slice were quite similar in normal subjects (63.4 ± 13.7 ml · 100 g^{-1} · min^{-1}), in patients treated with HBO (64.6 ± 17.5 ml · 100 g^{-1} · min^{-1}), and in patients treated with NBO (63.8 ± 11.8 ml · 100 g^{-1} · min^{-1}). However, Fig. 1 shows that the reactivity to acetazolamide, which did not differ significantly in normal subjects (50.8 ± 11.0%) and in patients treated with HBO (44.8 ± 25.9%), was lower in patients treated by NBO (33.4 ± 18.1%). This trend to a cerebrovascular hyporeactivity in the NBO group was shown to be significant by a Man-Whitney non-parametric test. In a few cases (three NBO subjects, one HBO), a focal asymmetry was observed in either one cortical or subcortical region of interest. Finally, we failed to demonstrate any significant differences between groups with regard to the perfusion of the basal nuclei (subcortical regions).

Table 3: EEG Recordings

	T = 24 Hours		T = 21 Days	
EEG	NBO, $n = 13$	HBO, $n = 13$	NBO, $n = 10$	HBO, $n = 8$
Class I	5	9	4	8
Class II	8	4	6	0
	NS		Wilcoxon: $P \leq 0.02$	

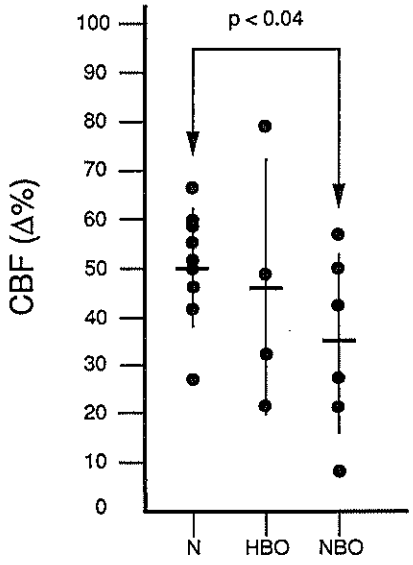

FIG. 1—CBF reactivity to acetazolamide in normal subjects (*N*) and in patients with moderate CO poisoning treated by NBO or by HBO (significant on Mann-Whitney test).

DISCUSSION

Our randomized study shows that early treatment with HBO reduces significantly the time of biological and clinical recovery in non-comatose patients with CO poisoning, compared to NBO treatment. In the first randomized study published on this topic, Raphaël et al. (3) failed to find evidence of this early effect of HBO because they undertook the treatment with HBO as late as 5.3 or 6.4 h after rescue and because they studied their patients 3 wk after NBO or HBO treatment. Concerning the HbCO decrease, our results were probably obtained because we started the treatment with HBO as soon as possible (mean time from rescue: 53 min). At this time, the HbCO values were 23–24% in both groups. Thus we were able to show differences in HbCO levels between the two groups immediately after the HBO session or 2 h of NBO therapy, but such a difference was not observed at T = 12 h. A significant effect of HBO on HbCO level was also found by Raphaël et al. (3) after treatment that began 5 or 6 h after the end of exposure. At this time, the HbCO levels in their patients, calculated according to their reported initial HbCO values (21.3–25.5%) and the known CO elimination half times, were probably lower than 5%. After a 6-h treatment they found a significant difference between HbCO levels in their HBO group (1.1 ± 0.8%) and in their NBO group (1.5 ± 1.1%). Yet, even though HBO is as effective on HbCO decrease in patients with CO poisoning as in normal young volunteers (9), the longer the time between removal from CO exposure and beginning of O_2 therapy, the weaker the effects of this therapy on HbCO elimination.

The clinical course of our patients paralleled the HbCO decrease, and HBO was more effective than NBO on clinical conditions at T = 2 h as well as at T = 12 h. These clinical effects of HBO can result from the decrease in the duration of O_2 privation due to a quick washout of CO. Indeed, it is well known that CO is eliminated from the body entirely by the lungs and that CO elimination becomes faster under O_2 (9,10). However, we found no correlation between the HbCO level and the number of clinical abnormalities in patients at any time. This, in part, could be because the HbCO level does not correlate with the patient's condition. The clinical assessment should perhaps include neuropsychologic tests, as suggested by Myers et al. (11). We think that clinical abnormalities

are somewhat independent of HbCO levels, as suggested by the patients of the NBO group exhibiting some abnormal signs at T = 12 h although their HbCO levels were normal. The small prognostic value of the HbCO level (11) suggested that the discharge of a patient after moderate CO intoxication should not be decided on the normalization of this parameter only (12).

An important aim of treating patients with moderate CO poisoning is to prevent possible delayed effects (13). Indeed, the delayed neurologic deficit is the most worrying outcome in patients with moderate poisoning (14). Its incidence has been assessed as 0.06–2.75% (15,16). However, Raphaël et al. (3) reported an incidence of more than 40% after their trial. The interval period varied from 1 wk to 1 mo. in the majority of cases (with an average of 23 days) but was as long as 47 days (17). The causes and mechanisms of the delayed syndrome are not fully understood, but one can assume, first, that this syndrome would result from foci of incomplete detoxification in the brain and, second, that these foci could be detected by means of functional laboratory tests, even though they are clinically undetectable.

To test this assumption, we used two independent laboratory tests, i.e., EEG recording, because it is available in most hospitals, and CBF measurement because it has recently been shown to be altered in delayed CO sequelae (18,19). These tests were performed about 3 wk after poisoning. Patients treated with NBO were shown to have more frequent EEG and CBF focal abnormalities than patients treated by HBO. Their CBF reactivity to acetazolamide was also significantly reduced. As for the HBO group, we cannot make conclusions about CBF reactivity because of the small size and the large standard deviation of the sample. In the whole group, CBF at rest was not reduced, in contrast to the finding of Lee et al. (18) and Shimosegawa et al. (19), but this can be explained by the fact that our patients were clinically normal, whereas theirs were severely impaired. Our results suggest that an early HBO treatment could reduce the number of delayed syndromes in patients with moderate CO poisoning. However, as our patients were free of any clinical sign of delayed syndrome, EEG and CBF abnormalities could be considered risk factors of such a syndrome. An additional factor (for instance a mild hypoxia) would be necessary in these patients to induce delayed clinical signs.

As a practical consequence, complete clinical recovery at T = 12 h and fewer delayed laboratory test abnormalities in our HBO group show the value of treating patients suffering moderate CO poisoning by HBO as early as possible, whatever the modalities of the intoxication. Some patients of the NBO group were free of clinical abnormalities after 2 h of O_2 (4/13) and at the end of the therapeutic regimen (8/13). Thus, when a hyperbaric facility is not available immediately, pure O_2 can be administered for a few hours under careful clinical supervision. However, because of the remaining clinical abnormalities in more than one-third of patients at T = 12 h and because of the persistence of EEG and CBF abnormalities at 3 wk in our NBO group, we propose to treat with HBO all the patients who did not fully recover clinically 2 h after breathing pure O_2.

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