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CORRESPONDENCE



Extraction of an Embolus

TO THE EDITOR: We wish to point out that our letter to the editor in the September 5 issue¹ contained a description of clinical material from one patient that was also included in an article on a series of patients that was published shortly thereafter in *Stroke*.² Although asked, we failed to inform the editors of each journal of the other publication. We apologize for not providing this information.

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Hyperbaric Oxygen for Acute Carbon Monoxide Poisoning

TO THE EDITOR: The positive effect of hyperbaric-oxygen treatment on cognitive sequelae after carbon monoxide poisoning, reported by Weaver et al. (Oct. 3 issue),¹ has important implications for patients and their physicians. Since facilities for the administration of hyperbaric oxygen are usually available only at specialized centers, a broader indication for the use of such facilities would lead to an increase in time-consuming and costly transportation of patients, which is not without risk. Therefore, it is important to indicate which subgroup of patients will benefit most from hyperbaric-oxygen treatment.

The positive effect of hyperbaric-oxygen treatment in conscious patients has been suggested by Thom et al. in a report on an unblinded study.² However, in comatose patients on mechanical ventilation, a positive effect of hyperbaric oxygen treatment could never be demonstrated.³⁻⁵ In the study by Weaver et al., only 8 percent of the patients were intubated. Although the patients were stratified according to their age, whether they lost consciousness, and the interval between the end of exposure to carbon monoxide and the first chamber session, a subgroup analysis was not reported.

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TO THE EDITOR: A larger controlled trial by Scheinkestel et al.¹ showed no benefit of hyperbaric-oxygen therapy, and the patients in their study had more severe carbon monoxide poisoning than did the patients in the study by Weaver et al. Although Weaver

et al. cited that study, I think it merits greater consideration. One major difference between the two studies is the duration of normobaric-oxygen therapy (three days in the study by Scheinkestel et al.). An important unanswered question is whether protracted normobaric-oxygen therapy provides the same benefits as intermittent hyperbaric-oxygen therapy; I know of no reason why this should not be the case. Such an approach would avert the need for expensive and dangerous transfers of patients to centers with facilities for the administration of hyperbaric oxygen.

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1. Scheinkestel CD, Bailey M, Myles PS, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomized controlled clinical trial. *Med J Aust* 1999;170:203-10.

TO THE EDITOR: Weaver et al. recommend hyperbaric oxygenation for the treatment of acute carbon monoxide poisoning, regardless of its cause and severity. However, a larger randomized trial previously demonstrated that hyperbaric oxygenation was useless in patients with accidental, residential carbon monoxide poisoning who did not lose consciousness.¹ This finding was confirmed in later studies.² In addition, two hyperbaric-oxygenation sessions in comatose patients resulted in recovery rates at one month that were similar to the rates with one session.

It is noteworthy that in 31 percent of the patients in the study by Weaver et al., carbon monoxide intoxication was related to a suicide attempt. Obviously, in these cases, other gases were involved along with carbon monoxide. In addition, most such patients combine gas with drugs or alcohol intoxication, so there is no way to relate the symptoms specifically to carbon monoxide itself.

One also wonders about the clinical relevance of the cognitive tests used by Weaver et al. It is very likely that the suicidal persons had previously abnormal results of cognitive tests. Yet base-line information on abnormal cognitive tests is not provided. Given the heterogeneity of the population and the rather small sample, one cannot rule out an imbalance between the treatment groups with respect to abnormal results of cognitive tests, just as there was an imbalance with respect to cerebellar signs.

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TO THE EDITOR: We disagree with the claim by Weaver et al. that hyperbaric-oxygen therapy improves the outcome of carbon monoxide poisoning, for several reasons. First, the “battery” of six neuropsychological tests used by Weaver et al. was limited, since they failed to include measure of delayed memory, which is common after anoxia. Second, testing was undertaken at six weeks “to identify patients in whom delayed cognitive sequelae developed.” However, since no base-line measure was obtained immediately after the poisoning episode, any judgment about the development of impairment is impossible, nor can there be any assessment of differential recovery of function in the first six weeks (which might reasonably be expected). Third, there was no control group of subjects without poisoning, so regression to the mean cannot be ruled out as a factor in the differences noted.¹ Finally, the study did not evaluate activities of daily living or other measures of functional performance. Thus, the results of the study are unconvincing, both for methodologic reasons and because of the failure to demonstrate “real life” benefits of hyperbaric-oxygen treatment.

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1. Kim H. Regression of lateral asymmetry scores toward the mean. *Cortex* 1994;30:331-41.

TO THE EDITOR: Weaver et al. hypothesize that one of the mechanisms by which hyperbaric-oxygen therapy reduces cognitive sequelae in patients with acute carbon monoxide poisoning could be preservation of mitochondrial ATP production, since their patients benefited from the therapy even in the presence of nearly normal levels of carboxyhemoglobin. In support of this mechanism in humans, we report data from six patients with acute carbon monoxide intoxication (mean [\pm SD] carboxyhemoglobin level, 22 ± 6 percent). Peripheral-blood lymphocytes were obtained from the patients before and 3 and 10 days after they received hyperbaric-oxygen therapy. We measured oxygen consumption and the activity of complexes III and IV of the mitochondrial respiratory chain (both of which contain cytochromes, a target for carbon monoxide),¹ using standard procedures.²

There was a marked inhibition of enzyme activity before the administration of hyperbaric oxygen, which was still clearly decreased 3 days after treatment (and in some patients even 10 days after treatment), despite already normal carboxyhemoglobin levels (Fig. 1). The decreases in the activity of complexes III and IV were accompanied by a reduction in the maximal rate of mitochondrial oxygen consumption, both in the absence and in the presence of substrates.

These findings and our previous data in humans³ also argue for subcellular mechanisms in hyperbar-

ic-oxygen therapy, distinct from elevated carboxyhemoglobin levels. However, the slow recovery of mitochondrial-respiratory-chain function suggests that other therapeutic approaches, in addition to hyperbaric-oxygen therapy, may be useful in some mitochondrial-respiratory-chain deficiencies.⁴

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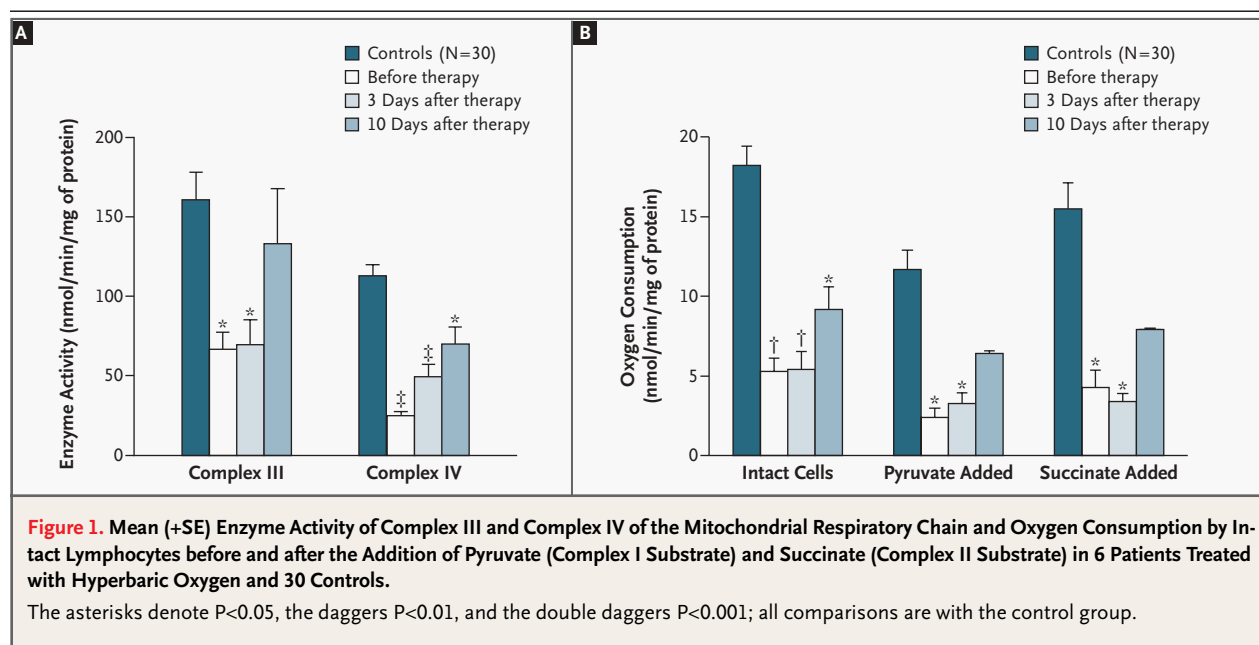
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THE AUTHORS REPLY: Dr. de Pont and colleagues ask for subgroup data. Our study was underpowered for post hoc subgroup analyses, and subgroup data could therefore be misleading.¹

Dr. Finnerty incorrectly suggests that our results differ from those in a previous report² because our



patients were less severely poisoned. In fact, 80 percent of our patients (121 of 152) (vs. 73 percent²) met criteria used for severe poisoning. Dr. Finnerty also proposes that three days of normobaric-oxygen therapy should be equivalent to intermittent hyperbaric-oxygen therapy, yet the rate of cognitive sequelae was 25 percent with hyperbaric-oxygen therapy in our study, whereas it was 70 percent with normobaric-oxygen therapy in the study by Scheinkestel et al.² Finally, our 132 medical transfers were carried out without adverse events.

It is not easy to compare our results with previous findings,³ because our study was different with respect to blinding, the definition of sequelae, neuropsychological testing, the patient population, and the dose and frequency of hyperbaric-oxygen treatment. Apparently overlooking our inclusion and exclusion criteria, Raphael et al. incorrectly assert that we recommend hyperbaric-oxygen therapy regardless of the cause or severity of carbon monoxide poisoning.³ They claim that the 31 percent rate of attempted suicide in our study confounds the results, because they expect cognitive function to be abnormal before carbon monoxide poisoning in patients who attempt suicide. If they are correct, the higher proportion of suicide attempts in the hyperbaric-oxygen group (36 percent, as compared with 26 percent in the normobaric-oxygen group)³ should have resulted in an increased rate of cognitive sequelae in the hyperbaric-oxygen group. However, we found a reduced rate of cognitive sequelae in the hyperbaric-oxygen group. We reanalyzed our data and found a lower, though statistically insignificant, rate of cognitive sequelae among patients who had attempted suicide (28 percent [13 of 47 patients]) than among

those who had been accidentally poisoned (39 percent [41 of 105])—the opposite of their expectation.

Dr. Isbister and colleagues correctly identify the absence of delayed-memory tests in our study. However, the tests we used detect impairments due to hypoxia. Since we found impairments with less sensitive cognitive measures, our results may underestimate cognitive dysfunction. Isbister et al. claim that base-line cognitive measures are necessary, and they appear to overlook the power of between-group comparisons in randomized clinical trials.¹ Furthermore, on the basis of comparisons of our patients with normal matched control subjects,⁴ “regression to the mean” did not bias our results. Scores for activities of daily living and other functional scores, as well as “real life” benefits, are reported and discussed in our article.

We thank Dr. Cardellach and colleagues for sharing their data that support the concept of mitochondrial dysfunction due to carbon monoxide poisoning.

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Aspirin, Clopidogrel, or Both for Secondary Prevention of Coronary Disease

TO THE EDITOR: Gaspoz et al. (June 6 issue)¹ present an interesting perspective on the problem of escalating health care costs. Their comparison between the cost effectiveness of aspirin and that of clopidogrel is commendable, given the increasing focus by the public on the costs of newer drugs. In their analysis, the authors' assumptions about the costs of the drugs do not take into consideration future costs that would be expected to be lower for both brand-name and generic versions of clopidogrel.

Estimates of the cost of developing a new drug vary, with some figures as high as \$800 million.² The need to recoup these expenses is one of many reasons for the price of new drugs. Without the marketing of new drugs, it is doubtful whether lower-priced generic versions would become available once the patents had expired; if they did not, the public would be deprived of therapeutically superior medications. Clopidogrel has been shown to be more effective than aspirin alone in reducing the in-