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Acute Isovolemic Anemia Does Not Impair Peripheral or Central Nerve Conduction

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Background: **Previous studies have found subtle slowing of responses in tests of addition and digit-symbol substitution during acute severe isovolemic anemia to a hemoglobin concentration of 5 g/dl in healthy unmedicated humans. In this study, the authors tested the hypothesis that such changes relate to the slowing of afferent neural traffic.**

Methods: **The median nerve was stimulated at the wrist in seven healthy unmedicated volunteers before and after induction of acute isovolemic anemia to a nadir hemoglobin concentration of 5.1 ± 0.3 g/dl (mean ± SD). Times for neural impulses to travel from the stimulus site to the brachial plexus, cervical spinal cord, and cerebral cortex were measured using somatosensory evoked potentials. Tests were repeated during acute anemia with the subject breathing oxygen. As a control for time and intrasubject variation, the testing was repeated on a separate day when anemia was not produced at times equivalent to those on the experimental day.**

Results: **Induced acute severe isovolemic anemia decreased nerve conduction latencies from the wrist to the contralateral cerebral cortex (*i.e.*, to the N20 peak) by 2.3 ± 1.6% compared with values at a mean hemoglobin concentration of 12.7 g/dl ($P < 0.01$). These decreased latencies were due solely to an increased peripheral conduction velocity, from the wrist to the brachial plexus ($P < 0.05$), and were not altered when subjects breathed oxygen ($P > 0.05$). Conduction velocity from the brachial plexus or cervical spinal cord to the cerebral cortex did not change with acute anemia ($P > 0.05$). Latencies did not differ on the control day among the times of testing (all $P > 0.05$), nor did they differ at baseline between the control and experimental days (all $P > 0.05$).**

Conclusion: **Somatosensory evoked potential latencies were not increased by acute severe isovolemic anemia, making it unlikely that the afferent portion of the neural system is responsible for slowing of cognitive responses previously observed during acute anemia. Because severe isovolemic anemia did not increase somatosensory evoked potential latencies, etiologies other than anemia should be sought if latencies are increased during intraoperative monitoring.**

THE lowest hemoglobin concentration that can maintain adequate oxygen delivery and tissue oxygenation varies among species.[1–3] Few data for humans have demonstrated the hemoglobin concentration or oxygen delivery that is inadequate to meet oxygen demand. We found no changes in systemic markers of inadequate oxygenation in 32 healthy unmedicated subjects at a hemoglobin concentration of 5 g/dl with an oxygen delivery of 10.7 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$ or in eight of these subjects in whom we produced a further reduction of oxygen delivery to 7.3 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$.[4,5]

Subsequently, we detected subtle deficits in cognitive function in healthy unmedicated individuals at similar hemoglobin concentrations[6] and were able to readily reverse these deficits with erythrocyte transfusion[6] or administration of oxygen.[7] Two of the tests used in those experiments, horizontal addition and digit-symbol substitution, showed a subtle slowing of the subjects' responses. However, those tests are not capable of defining the anatomic location of the deficit: whether it is related to dysfunction of the afferent, central, or efferent portions of the nervous system or muscle. We conducted the experiment described here as an initial effort to determine the location of the anemia-induced deficit. In this experiment, to test the hypothesis that the slowed response during acute anemia relates to the afferent portion of the nervous system, we recorded the somatosensory evoked potentials (SSEPs) and measured the latencies of various components of the response before and after induction of acute isovolemic anemia.

Methods

After approval by our institutional review board and informed consent of those participating, we studied seven paid adult volunteers who were without cardiovascular, pulmonary, or hepatic disease; did not smoke; were taking no medications; and weighed less than 80 kg. The weight requirement was imposed to avoid excessively long experimental days with potentially increased effects of time owing to the need to remove large quantities of blood to achieve the desired hemoglobin concentration.

To test our hypothesis that severe anemia decreases afferent nerve conduction velocity, we produced acute severe isovolemic anemia in the seven volunteers. A

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radial arterial and two peripheral venous cannulas were inserted in each subject after local anesthesia. After insertion of the cannulas, the subjects rested for 30 min before measurement of variables. The SSEPs (see below under SSEP Measurements) were recorded with the subject in a semisitting position before removal of any blood and twice after producing isovolemic anemia to a blood hemoglobin concentration of 5 g/dl by removal of aliquots of 450 ml blood into CPDA-1 collection bags (Baxter Healthcare Corporation, Deerfield, IL). Removal of each 450-ml blood aliquot required ≈ 10–15 min. Simultaneous with blood withdrawal, 5% human serum albumin (Baxter Healthcare, Glendale, CA) and the subject's own platelet-rich plasma (after separation from the erythrocytes of the removed blood) were warmed and infused intravenously in quantities 12 ± 3% (mean ± SD) greater than that of the removed blood to maintain isovolemia,[4,8] compensating for the extravascular distribution of albumin.[9] Tests at the baseline and nadir hemoglobin concentrations were conducted with the volunteer breathing room air. After the first test at the nadir hemoglobin concentration, a second test was performed with the volunteer fitted with a breathing mask through which oxygen was supplied at 15 l/min. The first test during anemia was always performed with the subject breathing room air to avoid any possible influence of increased Pa_{O_2} on subsequent tests. A 5-min equilibration period was allowed while the subject breathed the test gas before the SSEP was recorded. Arterial blood gas content and pH were measured during each test period. Following conclusion of the tests, all withdrawn erythrocytes were returned to each volunteer during the succeeding 12 h. There were no adverse events.

Each volunteer was studied twice. As a control for the effects of time and fatigue[10] and to examine intrasubject variation in the SSEP, on a different day, separated by at least 1 week from the experimental day, a "control" study was conducted. On this control day, the procedures were identical to those on the study day, except that an arterial cannula was not inserted and acute anemia was not produced. Tests on the control day were performed in an identical manner, at times similar to those performed during hemodilution studies. The dates of the two study days (experimental and control) were determined by the compatibility of volunteers' schedules with those of the research team.

SSEP Measurements

SSEPs were recorded by stimulating the median nerve at the wrist. The same wrist was stimulated on each of the two study days on the opposite side from the arm into which fluids were infused. Stimulus intensity was set slightly above that required to produce a minimal twitch of the short abductor muscle of thumb. Stimulation occurred at a rate of 5.1/s with a stimulus duration of 0.20 ms. A minimum of two trials, each consisting of 1,024 stimuli, were recorded to demonstrate reproducibility of the waveforms. Recording electrodes were placed after the skin was prepared (Nu-Prep; D. O. Weaver & Company, Aurora, CO) using a conductive adhesive paste (Elefix; Nihon-Kohden, Foothill Ranch, CA), gold-plated surface electrodes, and a 16-channel instrument (Nicolet Bravo EP-16; Nicolet Biomedical, Madison, WI). Impedance was assessed before and after each study and was always less than 5,000 Ω. Recordings were made between the following in accord with the recommendations of the American Clinical Neurophysiology Society[11]: contralateral and ipsilateral Erb point (brachial plexus); contralateral Erb point and the C5 spine; the contralateral Erb point and the ipsilateral C3'/C4'; and the ipsilateral C3'/C4' and the contralateral C3'/C4'. Filters were set at 30 and 2,500 Hz. Measurements were taken from the following locations and peaks: brachial plexus (Erb point; N9), cervical spine (N13), and cortex (N20 and P22). Interpeak latencies were measured or calculated from N9 to N20, N9 to N13, and N13 to N20 by the use of cursors applied by a blinded observer, who also measured the N20–P22 and N13 amplitudes and calculated the ratios of these amplitudes. The morphologic characteristics, latency, and amplitude of the SSEPs were also reviewed by an observer without regard to the conditions under which they had been recorded.

Data Analysis and Statistics

Before initiation of this study, there were no relevant data that could have been used for a power analysis to estimate the appropriate number of subjects to study. Consequently, the number of volunteers to be studied was determined by a power analysis, with a two-sided α of 0.05 and a power of 80% to detect a difference between the N20 latencies at hemoglobin concentrations of 5 and 13 g/dl, using the data obtained for the initial three volunteers. That analysis indicated that studying six volunteers would be sufficient. We studied seven volunteers in case one volunteer's data were uninterpretable.

The Shapiro–Wilk test was used to test for normal distribution of the results. Paired comparisons were performed within-day for baseline, hemoglobin concentration of 5 g/dl while breathing room air, and hemoglobin concentration of 5 g/dl with breathing oxygen, and between study and control days by Student paired *t* test or, if the data were not normally distributed, by Wilcoxon signed-rank test. Statistical significance was accepted at $P \leq 0.05$ for all tests. Data are presented as mean ± SD or as median and interquartile range.

Results

The volunteers (five women, two men) were 30.1 ± 5.5 yr old, 1.67 ± 0.12 m tall, weighed 64.0 ± 9.8 kg, and had

Table 1. Baseline Latencies on Control and Experimental Days

Peak	Latency (ms)		
	Control Day	Experimental Day	*P*
N9	10.41 ± 1.02	10.37 ± 0.83	0.60
N13	13.40 ± 1.17	13.26 ± 1.08	0.52
N20	19.63 ± 1.00	19.70 ± 0.83	0.54
P22	22.47 ± 1.12	22.37 ± 1.21	0.61

Data are mean ± SD for seven volunteers.

an estimated body surface area of 1.74 ± 0.18 m^2. Hemodilution reduced the hemoglobin concentration from 12.7 ± 1.5 to 5.1 ± 0.3 g/dl. The time from the SSEP at baseline to the last SSEP was 197 ± 26 min.

The within-person variations of all latencies were small. Baseline SSEP latencies from the wrist to all measured points did not differ between control and experimental days (table 1). The differences in baseline latencies between these days were 0.4 ± 2.0% for N9, 1.0 ± 4.2% for N13, 0.4 ± 1.5% for N20, and 0.4 ± 2.2% for P22. When calculated without respect to sign, the differences were 1.4 ± 1.1% for N9, 3.2 ± 2.7% for N13, 1.2 ± 0.8% for N20, and 1.6 ± 1.5% for P22. Of the paired values, 93% were within 4% of each other (fig. 1); only two pairs had differences that exceeded 4%. Similarly, on the control day, latencies from the wrist to all measured points for baseline and the time equivalent to that after hemodilution on the experimental day did not differ (all $P > 0.05$). The differences were 1.2 ± 1.6% for N9, 0.7 ± 2.7% for N13, 0.2 ± 1.4% for N20, and 0.2 ± 0.9% for P22. When calculated without respect to sign, the differences were 1.8 ± 0.6% for N9, 2.4 ± 1.1% for N13, 1.0 ± 0.9% for N20, and 0.7 ± 0.5% for P22. Of the paired values, 96% were within 3% of each other (fig. 1), with only one pair having a greater difference.

None of the nerve conduction times differed from one another on the control day (all $P > 0.05$; fig. 2). Conduction time from the wrist to the contralateral cortex (N20 and P22) decreased at a hemoglobin concentration of 5.1 g/dl compared with that at a hemoglobin concentration of 12.7 g/dl. The latency was 2.3 ± 1.6% shorter (conduction was faster) ($P < 0.01$) to the N20 potential and 2.1 ± 1.2% shorter ($P < 0.005$) to the P22 potential. This decreased latency was due solely to the changes in the periphery. The conduction time from the wrist to

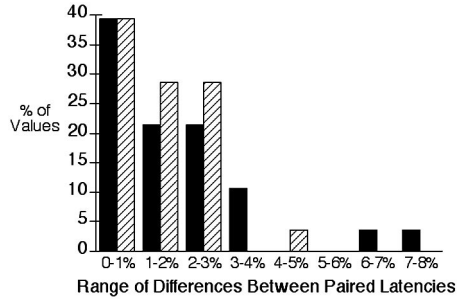

Fig. 1. Histogram of the distribution of absolute differences in all baseline latencies between the control and hemodilution days (*solid bars*) and between two measurements (baseline and a time equivalent to a hemoglobin concentration of 5 g/dl on the hemodilution day) on the control day (*striped bars*) for all volunteers.

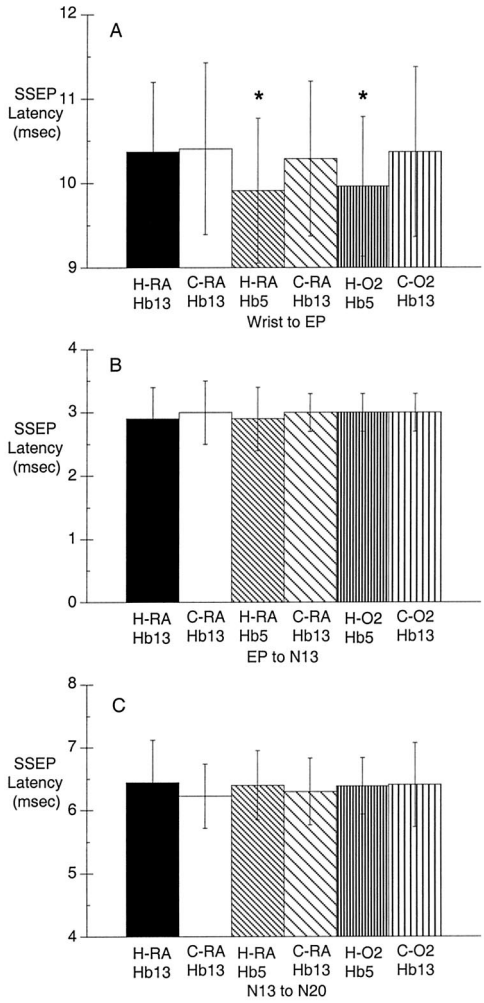

Fig. 2. Latencies of somatosensory evoked potential (SSEP) components in healthy unmedicated humans before and after isovolemic hemodilution from hemoglobin concentrations of 12.7 g/dl (Hb13) to 5.1 g/dl (Hb5). Stimulation was applied at the wrist. EP = Erb point (brachial plexus); N13 = cervical spine; N20 = cerebral cortex; H = hemodilution day; C = control day; RA = breathing air; O2 = breathing oxygen. Data are mean ± SD. (*A*) Conduction velocity from the wrist to the Erb point was decreased by acute isovolemic hemodilution compared with the subjects' normal hemoglobin concentrations. Breathing oxygen did not alter the latency during severe isovolemic anemia compared with breathing room air. Latency was not altered at any time during the control day. *Statistically significant difference ($P < 0.05$) compared with data from baseline at that recording site. (*B*) Conduction velocity from the Erb point to the cervical spinal cord was unaffected by reduction of the hemoglobin concentration to 5.1 g/dl ($P > 0.8$). Breathing oxygen did not alter the latency during severe isovolemic anemia ($P > 0.7$). Latency was not altered at any time during the control day. (*C*) Conduction velocity from the cervical spinal cord to the cerebral cortex was unaffected by reduction of the hemoglobin concentration to 5.1 g/dl ($P > 0.8$). Breathing oxygen did not alter the latency during severe isovolemic anemia ($P > 0.9$). Latency was not altered at any time during the control day.

the brachial plexus (Erb point; N9) decreased by 4.4 ± 1.3% ($P < 0.0001$; fig. 2), whereas the interpeak latency from the Erb point or the cervical spinal cord (N13) to the cerebral cortex (N20 and P22) did not change (all $P > 0.5$; fig. 2). Conduction times did not differ when the subjects breathed oxygen (Pa_{O_2} of 421 ± 62 mmHg in the four volunteers in whom it was measured; technical problems precluded measurement of Pa_{O_2} in the other three volunteers) compared with when the volunteers breathed room air at a hemoglobin concentration of 5.1 g/dl (all $P > 0.05$; fig. 2).

The ratio of the N20–P22 amplitude to the N13 amplitude did not change ($P > 0.2$) when breathing air at a hemoglobin concentration of 5.1 g/dl (216% [101–255%]) compared with the ratio at a hemoglobin concentration of 12.7 g/dl (202% [133–330%]). Similarly, breathing oxygen at a hemoglobin concentration of 5.1 g/dl did not change ($P > 0.8$) the amplitude ratio of the N20–P22 to N13 (148% [109–328%]) peaks. The morphology characteristics of the responses also remained unchanged.

Discussion

The major finding of this study is that acute severe isovolemic anemia did not increase afferent nerve conduction time from the periphery to the cerebral cortex. The conduction time was decreased in the arm, and it was unchanged from the brachial plexus and the cervical spinal cord to the cerebral cortex. Thus, our data do not support the hypothesis that slowing of afferent conduction was responsible for the previously noted slowing of human responses in tests of addition and digit-symbol substitution[6,7] during similarly acute severe isovolemic anemia.

We found in the periphery that conduction velocity not only did not decrease but it actually increased by 4.4% (*i.e.*, latency decreased), whereas central (spinal cord to cortex) conduction time was unchanged. The most likely explanation of the increased wrist to brachial plexus conduction velocity is a change in limb temperature. Peripheral nerve conduction velocity varies directly with limb subcutaneous and near-nerve temperature, increasing from 1.3 to 2.4 $m \cdot s^{-1} \cdot °C^{-1}$.[12–23] Although we did not measure limb temperature in our subjects, we previously found that subcutaneous arm temperature increased by 1.8–2.4°C in other subjects for whom we performed isovolemic hemodilution in the same manner[24] (Hopf HW, Weiskopf RB, Viele MK, *et al.*, unpublished data). The 4.4% decrease in conduction time of the median nerve in our subjects when the hemoglobin concentration was 5 g/dl represents a latency change of an estimated 1.8–2.4%/°C or conduction velocity changes of an estimated 1.3–1.8 $m \cdot s^{-1} \cdot °C^{-1}$. These values thus correspond closely with the reported altered latency or conduction velocity in sensory fibers of the human median nerve of 2.2%/°C,[13] 1.4 $m \cdot s^{-1} \cdot °C^{-1}$,[17] 1.5 $m \cdot s^{-1} \cdot °C^{-1}$,[18] and 2 $m \cdot s^{-1} \cdot °C^{-1}$.[22]

It is possible that anemia-induced slowing did occur but was overshadowed by temperature-induced changes. However, we are unaware of other data for humans regarding SSEP or peripheral nerve conduction latency during acute severe isovolemic anemia. Nerve conduction has been evaluated in uncontrolled studies of patients with various diseases associated with chronic anemia, but the results were confounded by other effects of the underlying diseases. For example, megaloblastic anemia not only produces changes in SSEP but also is associated with nerve degeneration. End-stage renal disease is associated with impaired peripheral[25–27] and central[25] conduction. Treatment with dialysis or administration of erythropoietin to increase the hemoglobin concentration from 6.6–8 to 12–13 g/dl has yielded inconsistent effects on the SSEP. Suppiej *et al.*[28] found no change in N9 latency after erythropoietin increased the hemoglobin concentration from 6.6 to 10.9 g/dl. Arbus *et al.*[29] noted a lesser median nerve conduction velocity in children with end-stage renal disease than in normal children, but the deficit was unchanged with chronic dialysis. However, in the eight children in whom it was measured immediately after dialysis, median nerve velocity returned to normal, suggesting a metabolic rather than an anemia-induced decrement of conduction velocity. On the other hand, Jebsen *et al.*[30] noted a correlation between decreasing renal function and decreasing peripheral nerve conduction velocity, with an improvement by chronic dialysis. Di Paolo *et al.*[26] noted that median nerve conduction velocity improved following renal transplantation in 16 patients, returning to a value not different from normal. The rapidity of the change suggested that the conduction deficit was a result of "uremic toxins," although the time of and data for such early improvement were not supplied.[26]

Hypoxic hypoxia can alter nerve conduction. Severe hypoxic hypoxia in anesthetized dogs, produced by breathing oxygen (4.5%), decreased peripheral nerve conduction velocity.[31] Less severe hypoxia in conscious humans breathing oxygen (11%), resulting in an end-tidal P_{O_2} of 48 mmHg, did not change latency of the cortical responses to posterior tibial nerve or peroneal nerve stimulation.[32] The degree of hypoxia in that study should have resulted in an oxyhemoglobin saturation of ≈ 80–85%, which would have reduced arterial oxygen content by less than half the fraction that we reduced it in our volunteers.

If increased peripheral latencies had been induced by anemia but remained undetected, any anemia-induced changes should have been reversed by improved oxygenation when the subjects breathed oxygen while their hemoglobin concentration was 5 g/dl. We found no such

change, suggesting that anemia was not responsible for the decreased peripheral latencies. We previously found that breathing oxygen reverses cognitive deficits induced by anemia,[7] similar to the deficit reversal resulting from transfusing erythrocytes.[6] The absence of changes in latency of any of the other SSEP components when breathing oxygen at a hemoglobin concentration of 5 g/dl similarly argues against the occurrence of any anemia-induced changes in these latencies.

There are other possible explanations for the decreased peripheral latency found with severe isovolemic anemia. The small change we found, even though statistically significant, could represent nothing more than the random error in testing (*i.e.*, normal intertest variation). There are few data regarding the within-day and between-day reproducibility of SSEP latencies in healthy subjects. Henriksen,[21] quoted by Aminoff,[33] reported up to 7.5% variability of response, whereas Bleasel and Tuck[34] reported an interday coefficient of variation of 4.3% for conduction velocity of the sensory fibers of the median nerve of a single subject, with 54% of the variation attributed to temperature variation. To examine variation in our volunteers and to control for the possible effects of time, we measured latencies to all peaks on a second control day in the same volunteers without altering the volunteers' hemoglobin concentrations. Overall, both within-day and between-day responses had a high reproducibility. On the same day, 96% of responses were within 3% of one another. Comparing the two different days, 82% of the baseline values were within 3% of one another, and 93% of the values were within 4%. There were no differences in any baseline latency values between the 2 days, and for the N9 latencies, the nonstatistically different variation between the 2 days at baseline was 0.3 ± 1.9%.

Our failure to find decreased nerve conduction velocity in the afferent neural traffic from the wrist to the cortex indicates that the previously noted deficit[6] likely lies in central processing, efferent nerve conduction, or muscle. Conduction of median and ulnar nerve motor (efferent) fibers seems to be more sensitive to the depressive effects of ischemia than are the afferent fibers.[14,35] Furthermore, it seems unlikely that impaired muscle action is responsible for all the impairments we previously noted, as some of these involved immediate and delayed memory. This suggests that central processing, efferent conduction, or both are the likely candidates for these previously observed memory deficits. It should be noted that two of the tests with which we previously found anemia-induced deficits (digit-symbol substitution and horizontal addition) required visual rather than somatosensory input. It is possible that the visual afferent system is more sensitive to the effects of severe anemia than is the somatosensory system; however, data are lacking. Visual evoked responses are reportedly delayed in diseases associated with chronic anemia, but the underlying diseases are associated with neural damage. Finally, studies of uremic patients have suggested that the cognitive deficits noted clinically and by testing are associated with increased P300 latencies, suggesting an attention deficit.[36–39] Renal transplantation increased the hemoglobin concentration, decreased the creatinine and blood urea concentrations, and decreased the P300 latency to a value not different from that for a group of normal individuals.[38] However, patients treated with erythropoietin before transplantation increased their hemoglobin concentration from 7 to 9 g/dl and improved their P300 latency, but to a value that remained prolonged.[38,39] Furthermore, six patients with chronic anemia from gastrointestinal bleeding had normal P300 latencies,[38] casting doubt on the proposal that it is the anemia in renal failure that is responsible for the altered P300 latencies. Nevertheless, it is possible that a similar attention deficit is the explanation of our previous findings during acute severe isovolemic anemia.

SSEP latency was the prospective main outcome variable and the basis of the power analysis on which we based the required number of subjects to be studied. We used SSEP latencies rather than SSEP amplitudes because amplitudes are highly variable both within and between persons. Nevertheless, because synaptic failure may have occurred as a result of anemic hypoxia, we also examined both the absolute amplitude of the cortical component of the short-latency SSEP and the ratio of the cortical to the cervical N13 component. We found no evidence of central dysfunction.

Our results may also have potential clinical implications. SSEP monitoring is used during spinal, intracranial, and major vascular surgery. A number of factors may alter latency of evoked potentials; however, acute anemia *per se*, within the limits that we measured, is not one. If latencies are altered intraoperatively, it would seem prudent to examine other possibilities: direct neural damage; hypoperfusion, whether caused by hypotension, hypovolemia, or mechanical means; alteration of limb or core temperature; alteration of stimulating or recording electrode placement; or alterations of drug or anesthetic administration.[40]

In summary, we found that acute isovolemic reduction of the hemoglobin concentration to 5.1 ± 0.3 g/dl in unmedicated healthy humans does not slow the velocity of human peripheral or central nerve conduction. This would seem to place the site of the impairment noted in our previous studies of similar volunteers made similarly anemic in central processing (including "attention"), efferent neural traffic, or muscle.

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