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Current and Emerging Technology in G-LOC Detection: Noninvasive Monitoring of Cerebral Microcirculation Using Near Infrared

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G-induced loss of consciousness (G-LOC) has emerged as an important operational problem of high-performance aircraft. Since it appears that G-LOC will continue to be a problem, a requirement exists to detect its occurrence in pilots so that the aircraft may be placed on autopilot. One excellent method of detecting G-LOC physiologically, one would assume, would be based on the oxidative status of the brain. This determination can be made noninvasively with an Oxidative Metabolism Near-Infrared monitor using 4 wave lengths (OMNI-4). The OMNI-4 is capable of measuring the relative quantities in the brain of hemoglobin (Hb), oxygenated hemoglobin (HbO₂), blood volume (BV), and oxidative status of cytochrome c oxidase. This instrument was tested on subjects in the USAFSAM human-use centrifuge at +3, 4, and 5 G_z with onset rates of 1 G/s². Results showed changes within the brain, as expected, during increased G with reductions in Hb, BV, and HbO₂. Cytochrome c oxidase measurements were inconclusive. Immediately following G exposure, Hb, BV, and HbO₂ "overshoots" occurred suggesting vasodilation of the cerebral microcirculation. The use of OMNI-4 in the laboratory and its possible role as a detector of G-LOC in pilots are discussed including suggestions for future developments.

G-INDUCED LOSS of consciousness (G-LOC) has been blamed as the cause of several aircraft crashes and crew fatalities, and aircrew surveys have shown that G-LOC with recovery is not uncommon in today's high-performance aircraft. Any such incident must be considered potentially disastrous. While the incidence of G-LOC appears to be increasing *pari-passu* with improved aircraft maneuverability, other causes of loss of consciousness (hypoxia, hyperventilation, toxic fumes, incidental illness, etc.) may still occur. A system which detects incipient G-LOC could be

used to initiate an appropriate autopilot mode of flight until recovery of the pilot allowed him to regain control. Such a system of G-LOC detection must operate within a few seconds, be reliable (with no false positives or false negatives), and ideally should respond to LOC *per se*, rather than to one or other of the possible causative mechanisms.

Brain cells combine a high rate of oxygen utilization with relatively low energy reserves, so that a breakdown in O₂ supply leads within a few seconds to G-LOC. A monitor for impending G-LOC should, therefore, be addressed to cerebral oxygenation and, ideally, to the oxygen status of the cerebral nerve cells. Under normal conditions, glucose is the sole substrate for cerebral oxidative metabolism. The final step in the metabolic chain of redox reactions which leads to the production of carbon dioxide and water, with release of energy in the form of high energy phosphate bonds, occurs when cytochrome c oxidase (otherwise known as cytochrome *a₃*) reacts directly with molecular oxygen. This single reaction accounts for more than 90% of the tissue's O₂ utilization.

When light passes through biologic materials, absorption occurs at specific wavelengths determined by the molecular properties of the materials in the light path. In the visible part of the spectrum (400 to 650 nanometers), intense absorption due to hemoglobin and light loss caused by scattering prevents transmission over more than a few millimeters. In most of the infrared, certainly with wavelengths above 1300 nanometers (nm), the water present in tissue acts as an effective absorber of photons, again over a short distance. However, in the the near-infrared (NIR) range of 700-1300 nm, a significant amount of radiation can be transmitted through several centimeters of biological tissue. The hemoglobins, both oxygenated (HbO₂) and reduced (Hb), exhibit weak absorption activity throughout the NIR range. Hb has a peak at 760 nm which disappears upon oxygenation to HbO₂ and, conversely, HbO₂ has a broad

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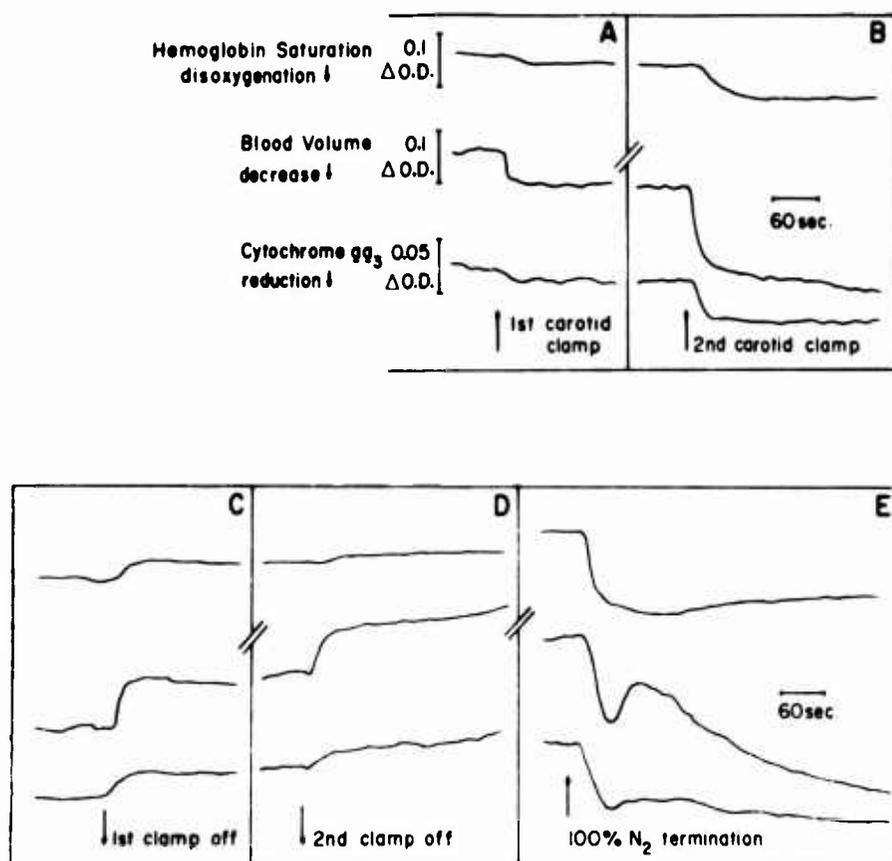


Fig. 1 Changes in hemoglobin saturation, cerebral blood volume and the redox status of cytochrome *c* oxidase after a period of transient ischemia in rat brain, and following termination with 100% N_2 . From (2) by permission of the American Heart Association, Inc.

band around 900 nm that is lacking in the Hb spectrum. Oxidized cytochrome *c* oxidase also has a weak absorption band in this range (780–870 nm) which disappears upon reduction. Changes in absorption at selected NIR wavelengths can, therefore, be used to determine changes in the oxidative status of Hb and cytochrome by means of algorithms that resolve the spectral contributions of each. This is the technique of multiwavelength near-infrared spectrophotometry (2).

This technique has been used to evaluate the *in-vivo* cerebral metabolism of rat brain (4) and Fig. 1, from this study, shows reduction of HbO_2 and cytochrome *c* oxidase following clamping of the two carotid arteries and terminal breathing of 100% nitrogen. These measurements were made across the brain through intact scalp and skull. For larger heads, a reflectance technique becomes more effective. In this approach light entry and pick up points are not arranged transcranially, but several cm apart on the skull. The NIR light penetrates scalp and skull, enters the brain and is diffusely reflected by the deeper white matter. The light emanating at the pick up point has interacted with the cells of the gray matter and the microvasculature serving them. In contrast, light reflecting back at the point of entry is scattered by skin and bone and does not contain much, if any, information on cerebral metabolism. It is, therefore, used as a reference signal in the instrumentation.

MATERIALS AND METHODS

Noninvasive measurements of cerebral metabolic parameters were made using the OMNI-4 monitor, for Oxidative

Metabolism Near-Infrared using 4 wavelengths¹. There are three basic parts to the system (Fig. 2): an optics unit which contains the four laser modules, reference photodiode and sample photomultiplier; an electronic control unit; and head mounted "optrodes" and fiber-optic bundles to conduct the near infrared energy to and from the subject's brain. Energy levels, it may be noted, are considerably less than that of normal sunlight, yet effective since the energy is narrow banded and pulsed. The instrument has been described previously (1) but, essentially, the four lasers are sequentially activated for 200 ns, a complete cycle taking 1.024 ms. Light reflected from the skin at the entry optrode is conducted to a reference photodiode, while energy transmitted through some 50 mm of brain tissue is collected by the exit optrode and led to the detector photomultiplier. Subsequently, the energy at each of the four wavelengths is preamplified, demodulated, amplified, expressed as logarithmic functions (since, according to the Beer-Lambert law, optical density is logarithmically related to light transmission), and placed in ratio to its appropriate reference level. The information is then processed according to algorithms, developed at Duke University Medical Center, to yield changes in the quantities of Hb and HbO_2 , and the oxidative status of cytochrome *c* oxidase. Additionally the sum of the Hb and HbO_2 signals is displayed as a measure of the volume of blood within the transilluminated field. Outputs are dis-

¹ The OMNI-4 is a second generation instrument developed under USAF contract F33615-82-D-0637, Task 47 by Dr. Jobsis and colleagues at Duke University Medical Center, Durham, NC.

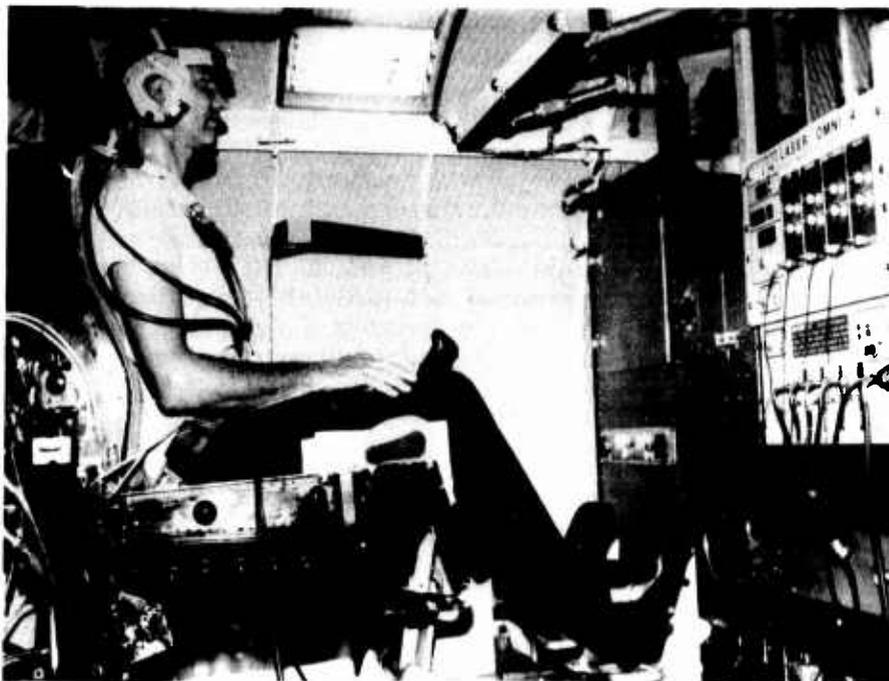
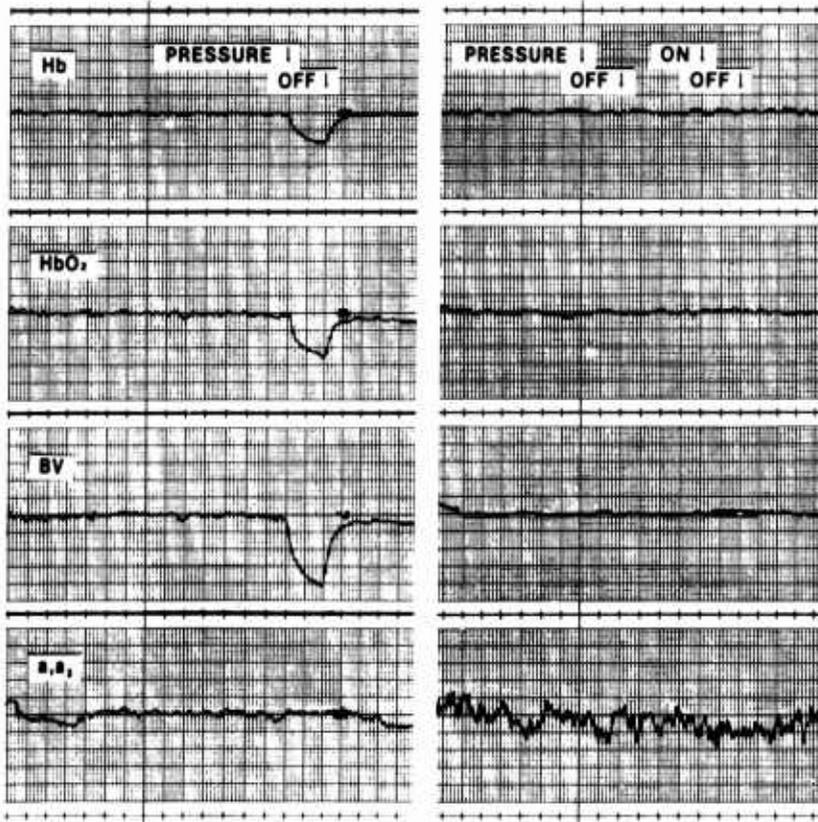


Fig. 2 The OMNI-4 monitor mounted in the gondola of the USAFSAM human centrifuge.

played on digital volt-meters and recorded in analog form on a strip chart recorder.

Initial specifications for OMNI-4 had called for the optrodes to be mounted within an aircrew helmet (HGU-26), but preliminary centrifuge studies disclosed problems of stray light ingress, inaccessibility of the optrodes, variable optrode pressure and optrode motion under G. The op-

trodes were remounted on a lightweight head harness (designed for supporting the Hewlett-Packard ear oximeter) using a block of Vinyl Polysiloxane dental registration material (Express; 3M). Also mounted within this block was an aluminum bracket which could be rigidly bolted to a dental bite plate (formed from the same registration material) to eliminate optrode motion in certain experiments.



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Fig. 3 The effect of applying downwards pressure on the optrode assembly with it unsupported (left-handed panel) and when clamped to a fitted dental bite plate (right panel). Gain settings are $1\frac{1}{4}$ for full scale deflection except for the second cytochrome c oxidase trace (a,a) which was recorded at 5 x gain. Time in seconds is shown above the Hb trace.

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RESULTS

Control centrifuge runs in which the optrodes were rigidly clamped across a stack of white card discs (to simulate the NIR absorption of skull and brain tissue) showed that the instrumentation system was insensitive to acceleration, *per se*, at least up to 9 G. However, despite the lighter weight head mount assembly, motion artifacts were still observed, particularly in the blood signal channels, during the onset and offset of acceleration and in other maneuvers which involved head motion. These artifacts were only eliminated when the optrode assembly was rigidly attached to a plate clamped between the subject's teeth and previously molded to his dental profile.

Fig. 3 shows that, in the absence of the bite plate (left-hand panel), downwards pressure on the optrode mount caused outputs which disappeared with the bite plate *in situ* (right-hand panel). Similarly, offsets noted during changing acceleration were also abolished, leaving only signals which could be accounted for physiologically.

Fig. 4 illustrates centrifuge runs at +3, 4, and 5 +G_z using a 1 G·s⁻¹ onset rate with the subject (DG) sitting relaxed and unprotected. Reading from the top, downwards, the traces show applied acceleration, a single channel electrocardiogram (ECG), beat by beat heart rate (HR), the quantities of reduced hemoglobin (Hb) and oxyhemoglobin (HbO₂) in brain tissue, and cerebral blood volume (BV). Acceleration at all three levels investigated produced a tachycardia, falls in Hb and HbO₂, and a prompt reduction in blood volume. At +3G_z, the HR and BV changes were mirror images with, respectively, peak and trough occurring 8 s following attainment of plateau acceleration. Partial recovery then occurred to new values which were maintained until return to 1 G. Hb and HbO₂ signals responded differentially in that Hb fell, but returned to baseline during continued G stress and thereafter showed a rebound increase, while HbO₂ fell more sharply initially and continued to decline at a slower rate, full recovery being delayed until well after return to normal gravity. These post acceleration over- and undershoots, with the return to normal of blood

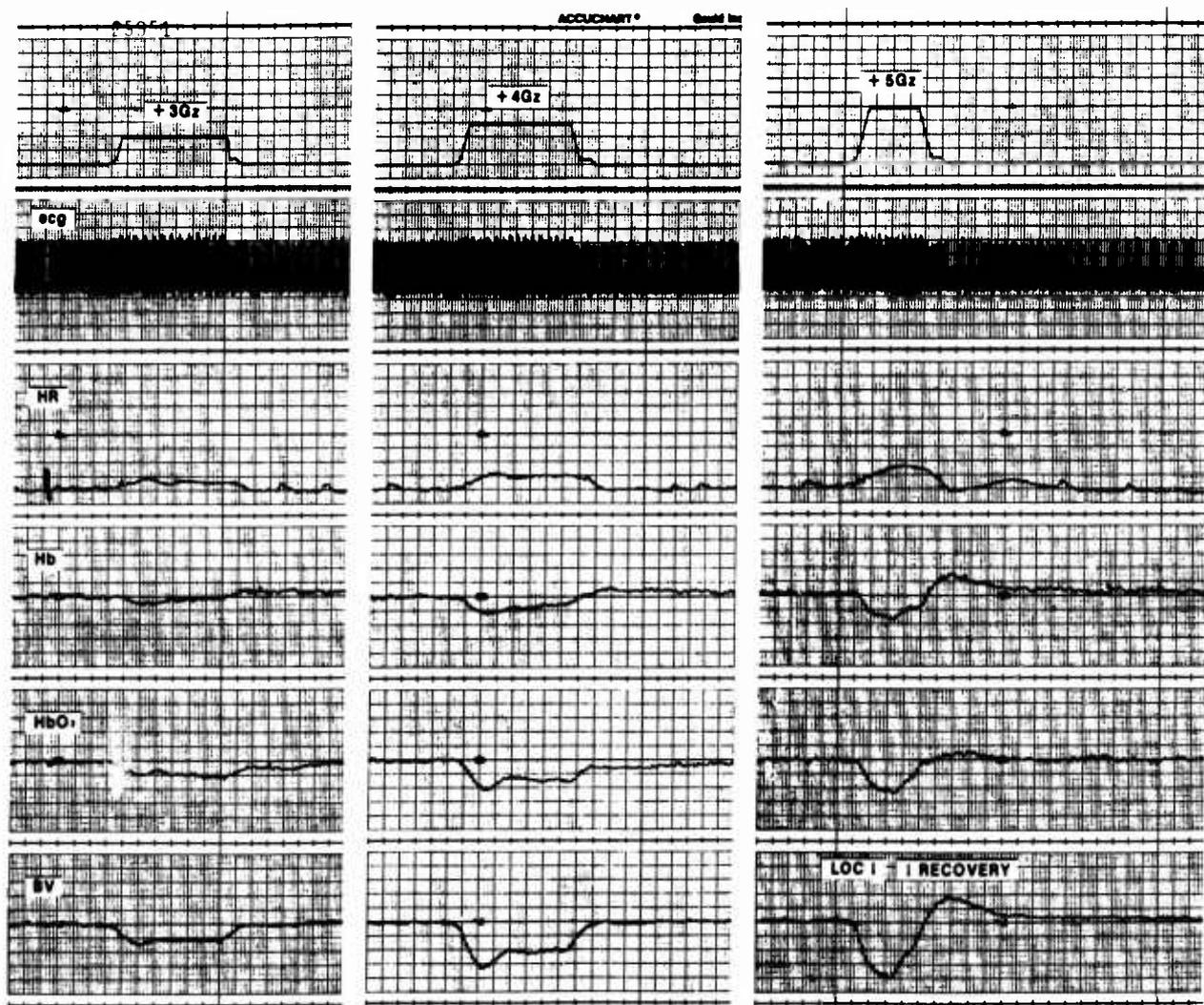


Fig. 4 Effect of +G_z acceleration on electrocardiogram, heart rate, Hb and HbO₂ concentrations in brain tissue and cerebral microcirculation blood volume. Gain settings for the OMNI-4 outputs were 1 1/4 for full scale deflection and time in seconds is given below the accelerometer record. The onset of loss of consciousness G-LOC at +5G_z was determined from a videorecording of the subject.

volume, suggest the development of arterial oxygen desaturation during the acceleration exposure, presumably due to ventilation-perfusion inequalities induced within the lungs.

Similar changes (Fig. 4, center panel), though of greater magnitude, were seen at +4G_z, recovery to normal of Hb and HbO₂ signals being still incomplete 45 s after return to 1 G. The lowest blood volume value was seen 7 s after reaching plateau acceleration. The HbO₂ signal shows several phases—a rapid initial fall, partial recovery and further progressive fall during the G stress, with slow recovery to control levels thereafter. This appears to be a combination of blood volume changes (presumably secondary to fluctuations in arterial blood pressure at head level), decreased cerebral blood flow with enhanced oxygen uptake, and the more gradual development of arterial oxygen desaturation.

At +5G_z (Fig. 4, right hand panel), the subject lost consciousness, but involuntarily retained his grip on the "enabling" switch and only released this, and so stopped the centrifuge, upon regaining consciousness while still at +5G_z. G-LOC was not immediately apparent to the medical monitor, but, from a subsequent study of the recorded videotape it was possible to time its onset as indicated on the blood volume record. The blood traces initially showed similar changes to those seen at the lower levels of acceleration, a trough in blood volume occurring 8.5 s after reaching plateau acceleration and recovery well on the way before the centrifuge was stopped. However, in contrast to the earlier runs, return to normal gravity was followed by a pronounced overshoot in blood volume, mainly contributed by the Hb signal, though HbO₂ also rose above its control level. This observation suggests that postischemic vasodilation had occurred within the cerebral microcirculation.

DISCUSSION

It will be noted that no scales have been indicated on the OMNI-4 outputs. Each of these is based upon an algorithm which weights changes in optical density measured at each of the four NIR wavelengths. It is possible to scale the records only in terms of "variations of density" (or $\frac{1}{d}$, commonly referred to as "Vanders") caused by changes in the quantities of the relevant chromophores present within the illuminated tissue. As the length of the effective light path is unknown, absolute values for Hb, HbO₂, or cytochrome c oxidase cannot be determined. In Fig. 4, $\frac{1}{d}$, or a 10-fold variation in the computed concentration, is equal to full scale deflection for each of the blood channels. The only technique currently available for quantifying these changes is to determine the "total labile signal" obtained under extreme conditions, as for example, from going from a hypoxic, hypercapnic gas mixture to 100% nitrogen (Fig. 1), an obvious impossibility with human subjects. However, in other studies, the change from breathing a 95% O₂, 5% CO₂ mixture to a 9% O₂, 91% N₂ mixture produced about a 0.1 $\frac{1}{d}$ swing in Hb and HbO₂ levels in the same experimental subject using the same optrode configuration and placement. Greater changes were seen during +5G_z acceleration.

It is believed that this is the first time that direct measurements have been made of intracerebral blood oxygen and blood volume parameters during exposure of a human subject to acceleration. Neither are there any relevant ani-

mal data available for comparison. However, the changes in Hb, HbO₂ and blood volume signals are in accord with what would be predicted from changes in head-level blood pressure and arterial oxygen saturation known to take place during +G_z exposure in man. The blood volume changes are of particular interest as they contradict the notion of the skull as a closed and indistensible box. Presumably, a decrease in blood volume is compensated for by an increase in the intracerebral volume of cerebrospinal fluid. During the breathing of gas mixtures, the technique was sensitive enough to show up blood volume changes in phase with respiration and caused, presumably, by breathing through a regulator which offered greater than normal breathing resistance.

The Hb and HbO₂ measured could come from blood within the skin, bone, or brain tissue lying in the NIR path. The skin contribution was eliminated by applying sufficient pressure to the optrodes to cause an obvious reactive hyperemia upon their removal, and studies have shown that, in the cat, the skull contributes no more than 5% of the signal (3). Other animal studies from the same laboratory suggest the normal resting contribution to blood volume as being 75% Hb and 25% HbO₂ (Jöbsis, personal communication) so that the technique appears to be biased toward the venous end of the cerebral microcirculation, so yielding information which should correlate well with cerebral oxygen sufficiency.

Taken together, the three blood traces show that there is considerably less blood in the brain during acceleration (at least in the forebrain) and that there is proportionately less HbO₂. This is suggestive of a reduction in cerebral blood flow, again in accord with published data. Furthermore, both the rate of disappearance of the blood and the eventual level achieved are greater the higher the G-level, and other measures which could be developed to predict or confirm the development of G-LOC.

While cytochrome c oxidase changes were recorded during acceleration, they have not been illustrated because they were either small, lost in noise, or occurred in a direction other than expected. In other situations—the breathing of hypoxic or hyperoxic gas mixtures, Valsalva maneuvers, presyncope from exposure to lower body negative pressure—and using the identical instrumentation, interpretable changes in the redox status of cytochrome c oxidase were observed. Possible explanations for the anomalous behavior of this channel during acceleration exposure are: a physical shift in brain position under the optrodes; the removal of Hb and HbO₂ allows more brain tissue, and hence more oxidized cytochrome, to be visualized; the "saving" of neurons in the observed field by their being switched off to reduce oxygen consumption; or G-LOC being due to a lack of glucose substrate rather than oxygen. Two technical features of the methodology also contribute to the problem: there is much less cytochrome present than hemoglobin and a 10 × gain is needed for its detection; and cytochrome c oxidase absorbs in the NIR only in its oxidized form. Thus, the presence of reduced cytochrome c oxidase can only be inferred from the reduction in absorption previously caused by it when in its oxidized state. This problem does not occur with hemoglobin as both Hb and HbO₂ give distinctive absorption spectra. Finally, the algorithm used for estimating cytochrome c oxidase may need to be modified for human use. Obviously, further studies are needed in this area.

FUTURE DEVELOPMENTS

Non-invasive multiwavelength NIR spectrophotometry has been demonstrated to be practicable in human subjects exposed to centrifugal acceleration, and has been shown to yield data relating to Hb, HbO₂, and blood volume changes within the cerebral microcirculation which could possibly be used to determine incipient G-LOC in aircrew. Specific areas which will need further development include the following:

1. The continuous pressure needed to exsanguinate skin beneath the optodes must be avoided, possibly by using intermittent pressure or by application only during periods of G stress.

2. Movement artifacts must be eliminated, possibly by using larger or multiple optodes, or skin mounted detectors.

3. The weight of all man-mounted components must be reduced, though this should prove relatively simple with helmet mounted NIR sources and solid state detectors.

4. Quantification of the signal outputs is desirable, and could be achieved, at least in part, by the use of a greater number of NIR wavelengths. For example, it should be possible to obtain Hb oxygen saturation as a percentage from within the cerebral microcirculation by use of six discrete wavebands within the NIR spectrum. An even greater number would allow redundancy and give improved resolution.

5. The paradoxical behavior of the cytochrome c oxidase signal needs further study during acceleration and in other

stresses which are known to influence cerebral oxygen sufficiency, both in man and in animals.

6. More measurements need to be made in human subjects during varied acceleration exposures—differing rates of onset, simulated air combat, etc.—and the records analyzed for derivatives which might be used as evidence for, or predictors of, loss of consciousness.

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The voluntary informed consent of the subjects used in this study was obtained in accordance with AFR 169-3. All subjects have passed medical examinations required for centrifuge exposure.

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