Cerebral oxygen metabolism during hypothermic circulatory arrest in humans

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Profound hypothermia with circulatory arrest is an important surgical adjuvant that allows protected cessation of cerebral blood flow for a brief period. In seven patients undergoing this procedure, continuous spectroscopic measurement of cerebral hemoglobin oxygen saturation was performed. Circulatory arrest at 18°C was associated with a significant progressive desaturation (p < 0.01) of residual cerebral hemoglobin. Arrest time varied based on operative complexity (range 10 to 65 minutes), and a negative linear correlation between arrest time (y) and oxygen saturation (x) was noted (y = —0.87x + 64). Five patients whose saturation remained above 35% had no neurological injury attributable to hypoxia. One patient (Hunt and Hess Grade 0) whose saturation fell below 35% had evidence of a global hypoxic injury at postmortem examination. Spectroscopically measured cerebral hemoglobin saturation (cerebral oximetry) may be used to monitor metabolic activity during circulatory arrest. Although the clinical utility of such monitoring cannot be established at this time, the potential may exist to prolong the safe duration of induced circulatory arrest for cerebral protection.

KEY WORDS • hypothermia • hypoxia • ischemia • circulatory arrest • cerebral aneurysm

Several centers have demonstrated renewed interest in using profound hypothermia with induced circulatory arrest as a surgical adjunct for the management of complex cerebrovascular disease. This practice allows temporary collapse of large aneurysmal sacs, control of the parent vessel, and transient neuronal protection from hypoxia. A major limitation of this adjunct is that cerebral oxygen delivery is completely stopped while cerebral oxygen metabolism (although greatly reduced by profound hypothermia) continues. Cerebral oxygen extraction during profound hypothermia has been demonstrated in animal models. The discrepancy between cerebral oxygen delivery and consumption during protected circulatory arrest limits the time period during which hypothermic neuronal protection is efficacious.

The period of “safe” circulatory arrest during profound hypothermia is apparently quite variable in both laboratory and clinical work. The determinants of safe arrest time in a given individual are poorly defined and traditional intraoperative monitoring paradigms are not capable of such determination.

Near-infrared light (650 to 1100 nm) is capable of penetrating human tissue to a depth of several centimeters. Because attenuation of this light in tissue is heavily dependent on the extent of hemoglobin oxygen binding, infrared transmission spectroscopy can be used to measure tissue hemoglobin oxygen saturation. This technology forms the basis of peripheral pulse oximetry, which is commonly used in clinical practice for monitoring arterial oxygen saturation.

Advances in optoelectronics have made it possible to perform infrared transmission spectroscopy on tissue below the level of the dermis, including the cerebral cortex. The spectra obtained can be used to measure hemoglobin oxygen saturation in the cerebral vasculature, which is primarily venous blood. This quantitative parameter, “cerebrovascular saturation,” is very sensitive to human cerebral hypoxia.

Because oxyhemoglobin and deoxyhemoglobin have unique absorption profiles in the near-infrared spectrum and these two molecules represent the significant tissue chromophores, a tissue content ratio of the two
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can be determined. The content ratio (oxyhemoglobin:deoxyhemoglobin) can be converted to the clinically recognizable parameter of percent hemoglobin oxygen saturation. An aggregate saturation of the hemoglobin is present in the arteries, veins, and capillaries of the brain, but measurement of oxygen saturation primarily represents cerebral venous saturation.

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Venous blood volume accounts for approximately 80% of total cerebral blood volume. This report describes the changes in human cerebrovascular saturation during profound cerebral cooling, circulatory arrest, and cerebral reperfusion. The measurements were made in seven patients during complex cerebral aneurysm repair.

Clinical Material and Methods

Patient Population

The seven patients ranged in age from 17 to 64 years (average 46 years). Five aneurysms were located in the posterior circulation, including two at the basilar tip, one midbasilar, one arising from the vertebral artery, and one from the posterior inferior cerebellar artery. The two aneurysms in the anterior circulation included a fusiform aneurysm of the M2 segment of the middle cerebral artery and a fusiform aneurysm of the distal internal carotid artery (ICA) including the bifurcation. Two patients presented with acute subarachnoid hemorrhage; both were in Hunt and Hess Grade III. One of these two patients rebled just prior to surgery and deteriorated to Grade IV.

Patients requiring the profound hypothermia protocol underwent extensive preoperative evaluation. Every patient underwent computerized tomography and magnetic resonance imaging of the brain, as well as four-vessel cerebral angiography. Five of the seven patients were subjected to further cerebral angiography, including superselective single intracranial vessel angiograms and vessel test occlusions. Every patient was evaluated by a cardiologist and had an electrocardiogram, rhythm strip, and echocardiogram preoperatively. Patients with cardiac symptoms and those over 50 years of age were given coronary angiograms. A preoperative coagulation profile, including a test of platelet function (Sona clot), was obtained in every case.

Operative Procedure

The details of perioperative patient management and the use of a femoral-femoral bypass for cooling and cerebral or cardiac arrest have been previously described. All patients had peripheral arterial line and Swan-Ganz catheters inserted prior to anesthesia. Anesthesia was induced with an intravenous injection of thiopental (2 to 3 mg/kg), sufentanil (1 to 3 mg/kg), lidocaine (1.5 mg/kg), and the muscle relaxant vecuronium (0.15 mg/kg). A standard anesthetic maintenance regimen was used in all patients, consisting of isoflurane (0.5 to 1 vol%), sufentanil (0.3 to 0.5 μg/kg/hr), thiopental (0.1 to 0.2 mg/kg/min), and vecuronium (titrated to no twitch response on a neuromuscular blockade monitor). The patient’s temperature was allowed to decrease passively to 32° to 33°C. After adequate surgical exposure and dissection, systemic heparinization was achieved with a heparin loading dose (3 mg/kg) followed by small boluses to maintain an activated clotting time of at least 450 seconds. The femoral-femoral bypass was performed and the patient’s temperature (tympnic) was allowed to reach 17°C. An average temperature of 28 ± 3°C, spontaneous asystole occurred. The average elapsed time for cooling was 43 ± 22 minutes. During reperfusion, the patient’s temperature was gradually increased to 37°C. Cardiac activity was seen at approximately 28°C. Anticoagulation was reversed using protamine sulfate.

Spectroscopic Measurement

Prior to surgery in each case, a two-channel, multiple wavelength, tissue infrared spectrometer* was placed. The optoelectronic-patient interface was placed on the patient’s shaved scalp in the region of the middle frontal gyrus on the nonoperated side, using customized fiber-optic cables and photodiodes on miniaturized printed circuit boards configured in a sealed unit. This hardware has been described in detail elsewhere.

Optical coupling to the scalp was protected from ambient light with an adhesive shield. The light source had a 0.5-mm diameter, and two receivers were placed 1.0 and 2.7 cm from the center of the light source. The configuration of the infrared source and receiver mounted in this fashion has been shown to measure light attenuation in the human cerebrovascular compartment.

Infrared transmission attenuation at five wavelengths (650, 726, 750, 803, and 840 nm) was measured and updated at 3.0-msec intervals. Attenuation at each wavelength w was analyzed according to the Beer-Lambert law: In I(w)0/In I(w) = ∑n=1→N ao(w)sjo C0(s). In this expression, I(w)0 represents the intensity of transmitted light at wavelength w, I(w) represents the intensity of the incident light at wavelength w, a represents the molar extinction coefficient of oxyhemoglobin or hemoglobin, C represents the concentration of the molecule in the tissue, and s represents the photon pathlength in the tissue. Tissue photon pathlength is not directly measurable with current clinical technology, and this variable is treated as a constant over the narrow wavelength band of 650 to 900 nm. The near-infrared scattering profile of fresh brain over this wavelength band is relatively flat.

Spectroscopic measurements made during passive cooling, active cooling, circulatory arrest, and reperfusion were divided into 3-minute epochs. There were a total of 33 measurements (Fig. 1). The 3-minute epochs at the end of passive cooling, active cooling, and circulatory arrest and immediately following reperfusion were considered representative of these major intraoperative phases and were statistically compared by analysis of variance.

Cerebrovascular saturation measurements were stored every 5.5 seconds during patient cooling, circu-

* Tissue infrared spectrometer, INVOS Model 2910, manufactured by Somanetics, Troy, Michigan.
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Results

No significant difference was found between cerebrovascular saturation measurements during passive cooling, active cooling, and reperfusion (Fig. 2). There was a significant difference (p < 0.01) between each of the above conditions and circulatory arrest. This difference demonstrated desaturation during circulatory arrest and resaturation during reperfusion.

The duration of circulatory arrest varied from 10 to 65 minutes and had a negative linear correlation with cerebrovascular saturation (seven cases, r = −0.87, s = 7) (Fig. 3). The smallest drop in saturation recorded was 15%. At the opposite extreme, in one patient cerebrovascular saturation fell to 30% after 45 minutes of circulatory arrest, and in another saturation fell to, but not below, 34% after 65 minutes of arrest. These two patients with prolonged circulatory arrest periods (45 and 65 minutes) had a poor outcome. The first was in Grade IV going into surgery and the outcome may not be related to the duration of circulatory arrest. The second, however, was in Grade 0 preoperatively. This patient required extensive reconstruction of the ICA bifurcation during clipping, resulting in a prolonged period of cardiac arrest. Postoperatively the patient failed to regain consciousness, and an electroencephalogram (EEG) was consistent with profound encephalopathy. Postmortem examination revealed the immediate cause of neurological deterioration to be a 1.0 × 0.5-cm pontine hemorrhage, but in addition cellular changes consistent with diffuse cerebral ischemia were observed.

Of the remaining five patients, four had an excellent outcome and returned to premorbid levels of activity. One patient had a good outcome with a mild new left hemiparesis.

Discussion

Measurement Methodology

It is firmly established that near-infrared light penetrates human tissue to a depth of several centimeters.9,27,34 This light is attenuated during transmission through tissue by both scattering and absorption. Absorption is due primarily to the few molecules in human tissue that absorb near-infrared light, including hemoglobin, oxyhemoglobin, and cytochrome aa3.13,25,36 Because cerebral hemoglobin content is approximately 600 mg/100 gm tissue and is several orders of magnitude higher than cytochrome aa3 content, hemoglobin accounts for the majority of absorption events. Transmission attenuation, therefore, can be used to quantify changes in hemoglobin oxygen saturation in cerebral tissue. Using a pulse-gated signal from a distal appendage, the primarily arterial oxyhemoglobin signal can be correlated with measured arterial saturation. This is the basis of pulse oximetry.

Transmission measurements through deeper tissues including the scalp, skull, and brain are possible.9,14 Several investigators have reported direct transillumination spectroscopy of the adult human cerebrum.8,16,35 Recently, the concept of diffuse transmission spectroscopy has been adapted for generating cerebral transmission spectra. This involves the use of a single infrared point source and one or more diode receivers placed 1 cm or more from the source.17-19,27 In this arrangement, light propagates along a high probability course into the tissue of interest and then back to the sur-
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The existence of an optimum temperature is demonstrable. The neurological tolerance of baboons to hypothermic circulatory arrest is worse at 10°C and at 15°C (RS Zimmerman, et al., unpublished data). An
 Progressive Hypothermia and Cerebrovascular Saturation

Cerebrovascular saturation did not change significantly during progressive cooling in these patients. Assuming that metabolic demand for oxygen decreases during hypothermia, one might expect an increase in cerebral venous saturation and therefore in cerebrovascular saturation. The fact that this did not occur in the group as a whole demonstrates intact oxygen delivery, or oxygen metabolism coupling. Metabolic autoregulation is known to be preserved during hypothermia in humans. 

Reperfusion and Cerebrovascular Saturation

Reperfusion following circulatory arrest is a critical event because it re-establishes oxygen delivery to the brain and usually begins the rewarming process. It is known that the rewarming period is a high-risk time for brain injury because metabolic needs may outstrip oxygen delivery at various temperatures, both regionally and globally. In our patients saturation rapidly returned to near baseline levels. However, due to the temperature dependence of both hemoglobin oxygen affinity and cerebral metabolic demand, this return to baseline saturation may not prevent episodes of tissue hypoxia during rewarming. In addition, following arrest, the tissue may be abnormal with exhausted homeostatic reserves, absent ionic gradients, and decompartmentalized neurotransmitters; any of these phenomena may increase metabolic demand from baseline.

In two patients the return of saturation to pre-arrest levels was delayed by several minutes despite the fact that postarrest patient temperature and cerebral oxygen delivery were similar to the pre-arrest levels. This delay was not related to prolonged arrest (less than 40 minutes in both patients) but may represent an increased metabolic rate of oxygen, as expected following hypoxia.

Patient Management Implications

Noninvasive cerebral hemoglobin saturation (cerebral oximetry) can be used to monitor the oxygen reserve of cells during circulatory arrest. Assuming that oxygen available from this reserve is necessary for cellular integrity, then monitoring it may allow arrest time to be tailored to prevent hypoxic injury.

One management paradigm recently employed in a patient not included in this series was to reperfuse the brain after 33 minutes of arrest, when cerebrovascular saturation had dropped to 45%. Reperfusion lasted 5 minutes and circulatory arrest was then reintroduced for 12 minutes to finish the operation. At the end of the second arrest period, saturation had dropped to 54%. The total arrest time was 52 minutes and the patient made a complete recovery, returning to pre-morbid activity levels.

Although cerebral oximetry is potentially clinically useful in monitoring cerebral oxygen saturation and thus indirectly cerebral metabolism, not enough data exist to recommend its routine use for evaluating the safety of controlled circulatory arrest. As clinical experience with such real-time measurements increases, it is hoped that a management strategy extending the safe time limit of adjuvant hypothermic circulatory arrest will be established. Used in this fashion, cerebral oximetry may prolong the duration of safe circulatory arrest in humans.

Conclusions

In seven patients undergoing elective hypothermic circulatory arrest for aneurysm repair, ongoing cerebral oxygen metabolism was identified. This metabolic activity is consistent with animal data. Oxygen is supplied by an oxyhemoglobin reserve in the microcirculation, which may be directly monitored by infrared spectroscopy. A negative linear correlation between residual hemoglobin saturation and duration of arrest was observed, and a lower limit of desaturation may exist at 30%. Continuous monitoring of such cerebral saturation may allow for management strategies that extend the safe time limit of adjuvant hypothermic circulatory arrest.

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