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The Contemporary Approach to Ischemic Brain Injury: Applying Existing Knowledge of Circulation, Temperature, and Glucose Management to Improve Clinical Outcomes

In the United States, ischemic brain injury is the fourth leading cause of death, and persistent neurologic deficits in stroke survivors account for the single largest cause of serious, long-term disability.[1,2] Origins of ischemic brain injury are diverse and include classic thrombotic or embolic stroke (ie, focal brain ischemia), prolonged systemic hypotension (ie, incomplete global ischemia), and cardiac arrest before resuscitation (ie, complete brain ischemia). These insults may occur spontaneously and unpredictably, or they may be related to clinical interventions (eg, surgery on the heart or cerebral vasculature). The prevention and treatment of brain ischemia depend on the nature of the insult.

In the current issue of *Mayo Clinic Proceedings*, 2 reports address various important aspects of contemporary prevention and treatment of ischemic brain injury, and they provide an opportunity to discuss best practices and the hope for improving patient outcomes. White et al[3] report on a patient who had a near-normal neurologic recovery after resuscitation from extreme-duration pulseless cardiac arrest followed by induced mild hypothermia, and Sui et al[4] discuss the association between glucose concentrations, stroke, and stroke outcomes.

In the June 2011 issue of *Mayo Clinic Proceedings*, White et al[5] reported on a 54-year-old man who had witnessed cardiac arrest, and a team of trained individuals started advanced cardiac life support almost immediately. (Artwork on the cover of this month's *Proceedings* pays homage to that patient, Dr Roger D. White, and the other health care professionals.) The patient had pulseless normothermic cardiac arrest for 96 minutes and not only survived but also awakened and recovered without measurable downstream neurologic deficits. The clinical experience of this patient received worldwide media attention,[6] and the patient has returned to employment (R. D. White, MD, oral communication, October 3, 2011).

In this month's *Proceedings,* White et al[3] report a second remarkable resuscitation and outcome that confirms that we need to reevaluate expectations for witnessed out-of-hospital cardiac arrest, provided best practices of resuscitation are used. This patient, a 61-year-old man, was pulseless for 63 minutes. The patient collapsed at home where he was alone with his wife, who called 911 emergency services. It is highly likely that the patient was, for all practical purposes, devoid of meaningful circulation and oxygen delivery to the brain for more than 9 minutes before emergency responders arrived and escalated the resuscitation effort. Effectiveness of cardiopulmonary resuscitation provided by trained emergency responders was eventually assessed at the scene by capnography. However, when the patient did not immediately awaken, total-body hypothermia was induced (in accordance with evidence-based guidelines), beginning at the scene and persisting thereafter. After an eventful hospital course, he was discharged to home to live independently. Mild memory loss is his only measurable neurologic deficit.

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Clearly these 2 cases challenge the old axiom that humans cannot be expected to survive a cardiac arrest lasting more than 5 or 6 minutes, especially when one considers that the second patient of White et al[3] experienced either frank circulatory arrest or a combination of profoundly inadequate circulation intermixed with arrest for more than 9 minutes before the arrival of emergency personnel. In the not-too-distant past, emergency responders would not have attempted resuscitation of the second patient because of concern that, although it may have been possible to re-

Address correspondence to William L. Lanier, MD, Department of Anesthesiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (lanier.william@mayo.edu).

suscitate the heart, the patient would eventually die in the hospital or be discharged from the hospital with a profound neurologic injury.[7,8] How can it be that success after more than 9 minutes of absent or profoundly diminished circulation met with success? We must look to the literature of experimental ischemia in animal models for insights.

In animal models of complete brain ischemia, the brain can tolerate 10 to 15 minutes of normothermic circulatory arrest without meaningful neurologic impairment (although there may be histological evidence of mild injury).[9] The laboratory animals used in these experiments tend to be extremely healthy, have optimal systemic physiology, and undergo a square-wave interruption of circulation followed by a near-square wave return to normal circulation and systemic physiology. Of note, the 2 nonhospitalized patients of White et al who survived after prolonged resuscitation from cardiac arrest were ambulating and neurologically intact until immediately before their collapse. Hence, they can be assumed to be virtually as physiologically optimal as the aforementioned laboratory animals at the onset of their collapse. This is in contrast to many hospitalized patients who are ill; have considerable aberrations of systemic circulation, blood oxygenation, and acid-base status before arrest; and retain compromised systemic physiology immediately after arrest has ended.

One difference from experiments in laboratory animals is that neither patient described by White et al would have had square-wave return of normal blood pressure during prolonged cardiopulmonary resuscitation, but clearly they did not require it to prevent brain injury. The reason for this may be as follows: With cardiac arrest, cerebral oxygen consumption decreases due to a decrease in the electrical activity of the brain.[10] In response to autoregulatory vasodilation and the effects of brain carbon dioxide accumulation, the brain would have received an increased fraction of cardiac output during chest compressions. Hence, it is likely that, during optimal cardiopulmonary resuscitation, even though the patient may have had little or no palpable pulse, there was still sufficient oxygen delivery and metabolite elimination to keep the brain from becoming further injured. The fact that in both cases emergency responders were able to record normal or near-normal end-expired carbon dioxide partial pressures,[3,5] but minimal metabolic acidosis (R. D. White, MD, oral communication, October 3, 2011), confirmed that blood was circulating throughout the body and performing at the blood vessel/tissue interface.

In recent years, research in animal models discovered that temperature reductions of as little as 1ºC can improve neurologic outcome after cerebral ischemia.[11] Specifically, temperature reductions that do not measurably affect supply-demand metabolism dramatically affect outcomes, even when hypothermia is introduced after cessation of the ischemic insult.[9,12] These observations have been confirmed in human trials of resuscitation from out-of-hospital ventricular fibrillation in which temperature reductions to 32°C to 34°C, begun shortly after resuscitation, and lasting 12 to 24 hours, have been demonstrated to improve outcomes.[13] On the basis of the available data, Holzer and Behringer[14] have calculated that a mere 6 patients must undergo hypothermic therapy to benefit 1 patient. Induced hypothermia has, since 2003, been a routine treatment for comatose survivors of out-of-hospital cardiac arrest.[13] In the 2 reports by White et al, only the second patient, ie, the one who had the longer initial period of suboptimal or absent cerebral circulation, received treatment with hypothermia. Perhaps this treatment contributed to a good neurologic outcome.

Independent of the reasons for success in the 2 reports by White et al, these patient experiences cause us to rethink the upper limits of optimal outcomes when relatively healthy patients suddenly experience cardiac arrest.

In another article in the current issue of *Proceedings,* Sui et al[4] report on stroke rates and outcomes in a series of 43,933 men who were assessed at a preventive medical examination program at a single medical institution during a 31-year period. None of the men had a history of diabetes mellitus or hypoglycemia, and the database accounted for 702,928 person-years of exposure. Fasting plasma glucose concentrations of 110 mg/dL or greater at the time of medical assessment were associated with a greater risk of fatal, nonfatal, and total stroke events. This report is an important addition to a large and growing body of research in humans that links hyperglycemia to the risk of a stroke and the severity of neurologic injury once a stroke has occurred.

The basis of the association between hyperglycemia and stroke incidence and outcome is likely as follows: Hyperglycemia, whether a prequel or component of diabetes mellitus, is known to correlate long-term with vasculopathies involving the central nervous system and the onset of stroke.[2,15,16] As reported by Sui et al,[4] the worse the hyperglycemia, the greater the risk of stroke downstream. If brain ischemia occurs, elevated blood and brain glucose concentrations at the time of ischemia should exacerbate ischemic neurologic injury, turning subclinical injury into clinically apparent injury, and mild clinical injury into potentially debilitating or mortal injury.[17] This exacerbating effect is believed to result from greater intracellular lactic acidosis during ischemia plus hyperglycemia, which in turn augments preexisting physiologic processes that are injurious to the brain. It is the glucose that is locked into brain cells at the time of injury that is critical to lactic acidosis and worse injury. Hyperglycemia that has completely resolved before an ischemic insult, or hyperglycemia that

has begun only after an insult has completely ended, has no effect on outcome.[17]

Although issues of glucose timing and outcome can be clearly elucidated in animal models, correlating glucose timing and outcome is more problematic in human observational studies.[17-19] In the report by Sui et al,[4] years elapsed between measurement of blood glucose concentrations and determination of definitive neurologic outcomes. Although the authors demonstrated that small incremental increases in blood glucose concentrations correlated with a higher incidence of stroke and worse stroke outcomes, for this to be a cause-and-effect relationship, one must infer that early hyperglycemia in otherwise nondiabetic patients predicts chronic glucose intolerance and the consequences of that glucose intolerance. Others have attempted to elucidate the glucose/stroke-outcome relationship by comparing glucose concentrations at the time of stroke evolution with eventual patient outcomes.[17,18] A major criticism of these investigations has been the inability to distinguish between hyperglycemia exacerbating ischemic brain injury or worse brain-injury-in-evolution causing a more severe stress-induced hyperglycemia. (Note: Mechanistically, these 2 processes are not mutually exclusive.[17])

Two contemporary studies have attempted to overcome these glucose-timing issues in humans. McGirt et al[20] compared operative-day, preoperative glucose concentrations to outcomes after carotid endarterectomy surgery. Increased glucose concentrations were associated with small, but statistically significant, increases in perioperative stroke or transient ischemic attacks, myocardial infarction, and death. Patients with operative day glucose concentrations greater than 200 mg/dL were more likely to experience stroke or transient ischemic attacks (by 2.8-fold), myocardial infarction (4.3-fold), or death (3.3-fold). These effects were independent of previous cardiac disease, diabetes mellitus, or other identifiable comorbidities. Pasternak et al[19] correlated blood glucose concentration at the time of cerebral aneurysm clipping surgery (an intervention that carries a risk of transient cerebral ischemic insults) and 3-month neurologic outcome. Glucose concentrations of 129 mg/dL or higher at the time of clip placement were associated with impairment of psychometric tests, and concentrations of 152 mg/dL or higher were associated with worse functional outcome by the National Institutes of Health Stroke Scale (but not other metrics of gross function). Hyperglycemia did not affect mortality rates.

What is missing from the collective data in humans is that no study to date has had adequate statistical power, produced meaningful glucose reduction, and used the most sensitive end points of injury (eg, as identified by Pasternak et al[19]) to determine the relationship between acute reduction of glucose concentrations with insulin and neurologic outcome after anticipated cerebral ischemia (eg, high-risk cerebrovascular surgery) or stroke in evolution.[18,21] Mortality rate, although commonly used as an end point for glycemic control in populations of patients having primary disease processes not involving the central nervous system, is a poor surrogate for the testing of psychometric function and other survivable ischemic neurologic deficits.[19] The promise of benefit from insulin is enticing. Studies in animal models clearly demonstrate that insulin treatment of existing hyperglycemia is effective in attenuating ischemic neurologic injury.[17] This insulin benefit is demonstrated with hyperglycemia resulting from diabetes mellitus or other causes.[17,22] The beneficial effect is due to a simultaneous reduction in both blood and brain glucose concentrations (and a lesser brain lactic acidosis) plus a glucose-independent beneficial effect of insulin on the ischemic brain.[17,22]

The ideal target blood glucose concentration for the human ischemic brain—identified by Pasternak et al[19] as in the range of less than 129 to less than 152 mg/dL, depending on the end point (ie, values similar to those found in earlier investigations[17])—is open to debate until there are definitive prospective randomized trials of insulin treatment in humans. Currently, it is not appropriate to extrapolate from outcome studies in nonneurologic patients to the setting of human brain ischemia. This is because the risk-to-benefit profile of glucose management in the ischemic brain should be more sensitive to treatment (ie, the outcome for the ischemic brain is likely far more susceptible to glucose modulation than many other disease entities).[17,19,20] Surrogate markers of neurologic outcome (metabolic markers, electrophysiologic changes), whether in animal models or humans, should not be used to dictate clinical care in humans because such markers have, in general, been proven to be inaccurate in predicting anatomic and functional postischemic neurologic outcomes (eg, with anesthetics, mild hypothermia, and carbohydrate loading). However, it *is* appropriate to defer to the recent American Diabetes Association recommendation for maximum glucose concentrations for patients in the intensive care unit—ie, no glucose measurement greater than 180 mg/dL—as this guideline takes into account the maximum allowable glucose for a variety of outcomes.[23]

During the past half-century, exhaustive research and immense capital have been expended to identify highly sophisticated "magic bullet" drugs targeted to specific receptors, channels, and genes that will, in a wide variety of settings, improve postischemic neurologic outcome. Collectively, these efforts have met with disappointing returns on investment.[24] Ironically, some of the most promising therapies and therapeutic concepts today involve inexpensive, widely accessible approaches to patient care that have been available for decades. There is great promise

in improving outcomes after cerebral ischemia by lessening the periods the brain is deprived of oxygen-rich blood flow, manipulating body temperature expeditiously, and closely monitoring and managing blood glucose concentrations. Although more research is needed in each of these 3 areas—eg, to improve the delivery of optimal cardiopulmonary resuscitation, discover which patients will benefit most from induced hypothermia, and conduct prospective randomized trials of glucose control in humans—there is still ample opportunity to improve patient outcomes simply by having health care professionals more effectively apply existing knowledge.

William L. Lanier, MD
Jeffrey J. Pasternak, MD
Department of Anesthesiology
Mayo Clinic
Rochester, MN

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