Status Epilepticus–Induced Hyperemia and Brain Tissue Hypoxia After Cardiac Arrest

Sang-Bae Ko, MD, PhD; Santiago Ortega-Gutierrez, MD; H. Alex Choi, MD; Jan Claassen, MD, PhD; Mary Presciutti, RN; J. Michael Schmidt, PhD; Neeraj Badjatia, MD, MS; Kiwon Lee, MD; Stephan A. Mayer, MD

Objective: To report changes of cerebral blood flow and metabolism associated with status epilepticus after cardiac arrest.

Design: Case report.

Setting: Neurological intensive care unit in a university hospital.


Main Outcome Measures: Changes of cerebral blood flow and metabolism.

Results: Repetitive electrographic seizure activity detected at the start of monitoring was associated with dramatic reductions in brain tissue oxygen tension and striking surges in cerebral blood flow and brain temperature. Intravenous lorazepam and levetiracetam administration resulted in immediate cessation of the seizures and these associated derangements. The lactate to pyruvate ratio was initially elevated and trended down after administration of anticonvulsants.

Conclusion: Brain multimodality monitoring is a feasible method for evaluating secondary brain injury associated with seizure activity after cardiac arrest.

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Neurovascular coupling is the phenomenon of tight regulatory balance between local cerebral blood flow (CBF) and oxygen supply to neural activity. Experimental studies have shown that during periods of increased metabolic demand, brief periods of inadequate perfusion can occur. One report, using optical recordings of intrinsic signals, showed that brain tissue oxygenation decreased 20 seconds before the onset of electrical seizure activity in a patient with repetitive seizures. However, optical recording of intrinsic signals methods only measure surrogates for brain oxygenation or cerebral blood volume by quantifying reflectance of specific light wavelength. In addition, it requires an open-skull window for signal detection, which limits its clinical applicability.

Real-time continuous measurement of brain physiological parameters is currently possible through multimodality monitoring (MMM). Continuous recording of cerebral physiology includes intracortical electroencephalography (ICE), partial brain tissue oxygen tension (PbtO2), and regional CBF, and microdialysis provides hourly measurements of extracellular metabolites such as glucose, lactate, and pyruvate. Although, MMM has been used mostly in comatose patients with severe traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage, its use is currently expanding to include patients with cardiac arrest and status epilepticus (SE).

In 2008, we expanded the use of MMM to cardiac arrest patients treated with therapeutic hypothermia. We herein describe changes in PbtO2, CBF, brain temperature, and microdialysis measurements that occurred in a patient with uncontrolled electrographic SE.

REPORT OF A CASE

An 85-year-old man with a history of congestive heart failure was found unresponsive by his neighbors. Cardiopulmonary resuscitation was initiated by emergency medical services within 10 minutes. Initial rhythm showed pulseless electrical activity; after 2 rounds of epinephrine and atropine administration, spontaneous cir-
calculation returned 25 minutes after the initial arrest. On admission to the neurointensive care unit in the absence of vasopressor support, blood pressure was 134/80 mm Hg; heart rate was 74 beats/min; and respiratory rate was 16 breaths/min. Hypothermia was immediately initiated using an intravascular cooling catheter (Alsius Icy Catheter; Zoll Circulation, Chelmsford, Massachusetts) and bladder temperature reached 33°C within 2 hours. On neurological examination, the patient was unresponsive to verbal or painful stimuli and pupils were 2 mm and bilaterally reactive with intact corneal reflexes. Occasional mild facial twitching was observed. Oculocephalic reflexes were absent. Limbs were flaccid with no grimace or withdrawal to pain.

After obtaining informed consent, MMM probes were placed in the right frontal lobe. Brain tissue oxygen was measured using a Clark-type probe (Licox system; Integra NeuroSciences, Plainsboro, New Jersey), intracranial pressure (ICP) was measured using a parenchymal monitor (Camino; Integra NeuroSciences), cerebral metabolism was monitored with a microdialysis catheter with 10-mm membrane length (CMA Microdialysis, Solna, Sweden), and CBF was assessed using a thermal diffusion microprobe (QFlow 400; Hemedex Inc, Cambridge, Massachusetts). Intracranial electroencephalography (EEG) recording was performed using an 8-contact, 1.32-mm-wide ICE electrode (Ad-Tech, Racine, Wisconsin). At 4:30 AM, at the start of monitoring, the initial PbtO2 was low at 7 mm Hg (normal, >20 mm Hg) and CBF was 38 mL/100 g/min. The initial lactate to pyruvate ratio was 52 (normal, <20), and the brain glucose level was reduced at 1.2 mmol/L (normal, >2.0 mmol/L).

Over the next 11 hours, a striking pattern of surging CBF associated with parallel reductions in PbtO2 was recorded (Figure 1). During CBF surges, concurrent increases in ICP (10 mm Hg) and brain temperature (0.2°C) were noted. At 11:45 AM, recording of surface and ICE EEG was started and showed repetitive electrographic seizures. Compressed spectral array analysis of digital EEG showed that the abnormal rhythmicity index and spectrum perfectly overlapped with increases in total power of EEG, suggesting that total power was a surrogate for electrical SE. Discrete electrographic seizures were consistently preceded (30 seconds) by reductions in PbtO2 (Figure 2). During interictal periods, PbtO2 returned to 22 to 25 mm Hg, which is a noncritical level, accompanied by a cessation of abnormal surges of CBF, ICP, and brain temperature.

After analysis of EEG and MMM data, 1000 mg of levetiracetam and 4 mg of lorazepam were administered.
intravenously at 3:52 PM (Figure 1, arrow) and the sei-

sures were terminated. After cessation of the seizures, the

lactate to pyruvate ratio decreased from levels higher than

60 to levels of 40 to 45, and the brain glucose level in-

creased from between 1.2 to 2.2 mmol/L to more than 3

mmol/L. Subsequently, EEG showed intermittent orga-

nized bursts of synchronized delta activity without defi-

nite ictal discharges. After 24 hours of hypothermia treat-

ment, the patient was slowly rewarmed, which provoked

episodes of increased ICP (>20 mm Hg) treated with man-

nitol. On day 2, the patient was declared clinically brain
dead.

COMMENT

To the best of our knowledge, this is the first descrip-
tion of dynamic PbtO2 and CBF changes in a human pa-
tient with SE. Using intracortical EEG, we were able to
identify ongoing SE. Dramatic reductions in PbtO2 and
surges in CBF, compatible with increased metabolic de-
mand out of proportion to CBF increase, were seen dur-
ing SE. This phenomenon between brain metabolism and
CBF has been observed in animal models of SE.2-6,9 Our
data confirm that neurovascular coupling was pre-
served in our patient and was triggered by an initial pe-

rior of relative tissue oxygen hypoxia. During normal
brain activation, this is characterized by a brief “initial
dip” in brain tissue oxygenation that rapidly normalizes
as CBF increases to meet metabolic requirements.10 In
pathological states such as SE, our findings confirm that
critical brain tissue hypoxia can persist for periods as long
as 2 hours, despite demand-related increases in CBF.2,5,11

Interestingly, our time-locked data show that PbtO2
began to drop about 30 seconds prior to the onset of elec-
trographic seizure activity (Figure 2), which is similar
to the reported time difference (20 seconds) using opti-
cal recording of intrinsic signals in a patient with repeti-
tive partial seizures.6 The reason for this is unclear, but
a few potential physiologic explanations should be con-
templated. First, the initial surge in electrical activity suf-
ficient to induce increased cerebral oxygen metabolism
might not be robust enough for detection by ICE.6 Al-
though ICE is superior to scalp EEG for detecting elec-
trographic seizures,12 it might not be sensitive for de-
tecting less synchronized focal dendritic activity of a small
number of neurons. Second, brain hypoxia might be a
prerequisite for the compensatory CBF surge. In animal
studies, CBF does not change until PbtO2 drops below a
certain level, which triggers CBF to increase with a cer-
tain time gap, similar to our data.13 Third, but less likely,
the time gap might be caused by the small difference in probe location. The measured distance between the Clark-type probe and the thermal diffusion probe was 22.7 mm, and the ICE was located directly adjacent to the CBF probe. If seizures started near the Clark-type probe and propagated toward the thermal diffusion probe, the time lag may be explained by the distance between the probes. However, considering the distance and the time lag between the 2 probes (about 30 seconds), the calculated propagation velocity is too slow to be considered seizure activity (44 mm/min).

Complementary to the hemodynamic data, hourly microdialysis measurements show additional evidence for metabolic distress as a consequence of seizures. Sustained elevation and resolution of an increased lactate to pyruvate ratio after the ictal period has been reported after SE. Generally, an increased lactate level is an indicator of ischemia, and a decreased pyruvate level is regarded as a sign of perturbed metabolic activity, indicating an impaired glycolytic pathway. Although it is not clear which is more important in a patient with SE, both an increase of lactate level and a decrease of pyruvate level might be equally meaningful in this patient. In addition, brain temperature also increased with the elevation of CBF, although the absolute degree of change was small (0.2°C). Increased heat production is regarded as an indicator of an increase in local cerebral metabolism during ictal clusters.

As displayed in Figure 1, PbtO2 levels were initially very low, at around 7 mm Hg, and then tended to fluctuate between 7 and 23 mm Hg prior to stabilizing at a level of 25 mm Hg after the termination of seizures. We think that the initial low PbtO2 values were associated with continuous seizure activity, given the striking temporal relationship between increased total EEG power and critically reduced PbtO2 later on. Our patient showed a sustained elevation of ICP after rewarming, suggesting massive ischemic injury and cytotoxic brain edema. Given the apparent association between seizures and poor outcome in cardiac arrest patients who undergo hypothermia treatment, our data provide a clear example of how uncontrolled seizures may precipitate brain tissue hypoxia and energy failure in a reperfused human brain.

The main limitation of this study is that it is a report from a single patient. However, a total of 17 episodes of ictal events repeated with the same pattern of changes in physiological variables. In addition, the distance between the probes of CBF and PbtO2 could have potentially contributed to the time gap between PbtO2 and CBF. Despite these limitations, this report strongly suggests that a period of relative hypoxia and metabolic distress occurs during SE in humans resuscitated from cardiac arrest, even in the presence of hypothermic therapy.

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Correspondence: Stephan A. Mayer, MD, Division of Neurocritical Care, Department of Neurology, Columbia University College of Physicians and Surgeons, Milstein Hospital Bldg 8 Center, 177 Fort Washington Ave, New York, NY 10032 (sam14@columbia.edu).

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REFERENCES