



## Brain Tissue Oxygenation in Brain Death

Sylvain Palmer and Mary Kay Bader

Mission Hospital and Regional Medical Center Mission Viejo, CA

### Abstract

**Introduction:** The value of brain tissue oxygenation (PbtO<sub>2</sub>) measurements in determining brain death is unknown.

**Methods:** Eleven of 72 patients who had brain tissue oxygen monitors placed experienced brain death. Admission diagnoses included six severe traumatic brain injuries, one multiple trauma with cardiac arrest, one brain tumor, one subarachnoid hemorrhage, one intracerebral hemorrhage, and one cerebral stroke. Eleven males and zero females were studied, with an average age of 26 years (range: 20–70 years). Nine patients had Glasgow Coma Scores (GCS) of 3 on admission, one patient had a GCS of 5, and one patient had a GCS of 15.

**Results:** Time from admission to declaration of brain death varied from 5 hours to 7 days; the most common interval was 1 or 2 days. Cerebral perfusion pressure (CPP) fell to 0 in eight patients, which indicated primary failure of cerebral perfusion. CPP stayed above 60 mmHg in three patients, indicating primary tissue failure, possibly of the cerebral microvasculature. PbtO<sub>2</sub> fell to 0 in all patients who experienced brain death, and all patients with PbtO<sub>2</sub> of 0 experienced brain death. None of the 61 patients who did not experience brain death had confirmed PbtO<sub>2</sub> readings of 0.

**Conclusion:** PbtO<sub>2</sub> can be successfully and accurately used as a bedside adjunctive test for brain death. The use of PbtO<sub>2</sub> as a sole confirmatory test for brain death in the setting of an appropriate clinical examination will require the evaluation of a larger number of patients to assess its sensitivity and specificity.

**Key Words:** Brain death; cerebral oxygen monitoring; traumatic brain injury; subarachnoid hemorrhage; neurosurgical critical care.

### \*Correspondence and reprint requests to:

Sylvain Palmer MD, FACS  
Mission Hospital and  
Regional Medical Center,  
Dept. of Neurosurgery,  
NSMA 26732 Crown Valley  
Parkway Suite 561  
Mission Viejo, CA, 92651.

E-mail:  
sylvainpalmer@cox.net

### Introduction

All of the established standards for the determination of brain death use clinical examination as the major criteria for establishing brain death, with the optional use of confirmatory radiological or neurodiagnostic testing (1,2). These confirmatory tests have traditionally included electroencephalography, cerebral angiography, nuclear cerebral flow studies, somatosensory or brain stem-evoked potentials and transcranial Doppler (TCD) ultrasonography. Diaz-Reganon et al. (3) recently reported that a ratio of the central venous oxygen saturation (SvO<sub>2</sub>)/jugular venous oxygen saturation (SjO<sub>2</sub>) was useful in predicting the lack of cerebral blood flow

in cases of suspected brain death. In 1996, van Santbrink et al. (4) reported that the moment of death can be accurately determined by brain tissue oxygenation. This article explores the use of brain tissue oxygenation (PbtO<sub>2</sub>) in raising the suspicion of brain death or as a confirmatory test for brain death.

### Methods

Mission Hospital and Regional Medical Center (MHRMC) is a level II trauma center accredited by the American College of Surgeons that serves a community of 500,000 people. One thousand trauma patients are seen each year, half of whom have sustained head injuries. MHRMC has an active



neurosurgical service with 1500 surgical cases each year. Protocols have been developed that integrate the American Association of Neurological Surgeons/Brain Trauma Foundation Guidelines for Managing Severe Head Injury and techniques for monitoring cerebral oxygenation to maintain optimal conditions for cerebral protection and recovery (5–7). Data are prospectively collected on all patients admitted to the surgical intensive care unit (ICU) with brain dysfunction requiring intracranial monitoring. Demographics as well as systemic and cerebral data points are captured and recorded for later study.

Between April 2001 and July 2002, 72 patients had Licox brain tissue oxygen monitors (Integra NeuroSciences, Plainsboro, NJ) placed for a variety of diagnoses. The Licox catheter is a polarographic Clark microcatheter. It measures a surface area of approximately 17 millimeters (2). All patients who are candidates for monitoring must first undergo a computerized axial tomography (CAT) scan. The patient is then transported to the operating room, where appropriate systemic monitoring begins. After an appropriate sterile preparation, any necessary definitive surgery is performed. This is followed by placement of an intraventricular fiberoptic intracranial pressure (ICP) monitor (Integra Neuro Sciences) or a fluid column intraventricular monitor (Codman). A bolt is placed through a separate twist drill access to secure a Licox intraparenchymal oxygen probe and a separate temperature probe (Integra Neuro Sciences).

Eleven of the 72 monitored patients later experienced brain death. Of these 11 patients, 5 were admitted with severe brain injury, 3 with subarachnoid hemorrhage (SAH) following aneurysm rupture, 1 with a brain tumor, 1 was admitted with an intracerebral hemorrhage, and 1 with a crush injury to the thorax. All 11 patients went to surgery. The patients with traumatic brain injuries (TBIs) went to surgery on the day of admission, whereas the patients with SAHs and the patient with the brain tumor went to surgery over the next several days. The Licox catheter was placed contralateral to the major pathology in the trauma cases and ipsilateral to the major pathology in the patients with SAHs and the patient with the brain tumor. There were 11 males and 0 females. The average age was 45.5 years (range: 20–70 years). Nine patients had Glasgow Coma Scores (GCS) of 3 on admission, one patient had a GCS of 5, and one patient had a GCS of 15 (brain tumor pre-operative state). Four of the 11 patients sustained cardiopulmonary arrests in the prehospital setting. Demographic data is displayed in Table 1.

Patient management for patients with severe TBIs and other patients with severe cerebral compromise included a standardized protocol (see Figure 1). All patients had intracranial intraventricular pressure monitors, PbtO<sub>2</sub> monitors, and brain temperature probes. Systemic monitors included arterial lines, pulmonary artery catheters, systemic temperature probes, heart rate monitors, electrocardiogram, continuous pulse oximetry, and end tidal carbon dioxide (CO<sub>2</sub>) monitors. Initial goals were to adjust mean arterial pressure with fluids and vasopressors to maintain cerebral perfusion pressure (CPP) greater than 60 to 70 mmHg. The CPP was then optimized for the individual patient based on PbtO<sub>2</sub> and ICP data. Interventions to lower ICP included cerebrospinal fluid drainage, enhancement of mean arterial pressure, intermittent

Table 1  
Demographic Data

Patient no.	Age	Date	GCS at admission	Reason for admission	Hours to PbtO <sub>2</sub> = 0
1	31	4/29/01	15	Brain tumor	101
2	37	6/3/01	3	Head trauma	0
3	70	6/19/01	5	Head trauma	19
4	51	7/8/01	3	SAH; Vfib on arrival; ruptured vertebral artery aneurysm	24
5	51	7/22/01	3	ICH	18
6	27	11/24/01	3	Multiple trauma	6
7	20	5/7/02	3	Crush injury to thorax; CPR for asystole at scene	37
8	53	6/17/02	3	SAH aneurysm; Vfib; arrest at home;	165
9	36	9/20/02	3	Severe TBI: torn L ICA; tied off L ICA	62
10	65	5/20/01	3	Head trauma	56
11	60	3/3/02	3	SAH Grade 5	35

Abbreviations: GCS, Glasgow Coma Score; SAH, subarachnoid hemorrhage; Vfib, ventricular fibrillation; ICH, intracerebral hemorrhage; TBI, traumatic brain injury; LICA, left internal carotid artery.

mannitol, propofol, and/or barbiturates. Hyperventilation to reduce ICP (defined as a PaCO<sub>2</sub> <35 mmHg) was only attempted if PbtO<sub>2</sub> was greater than 20 mmHg. Attempts to maintain PbtO<sub>2</sub> greater than 20 mmHg (normal: 20–40 mmHg) included increasing PaCO<sub>2</sub>, increasing hemoglobin, and increasing fraction-inspired oxygen (FIO<sub>2</sub>) and/or decreasing temperature, decreasing ICP, or decreasing cerebral metabolism with propofol/barbiturates.

Patient management for SAH prior to securing the aneurysm was a modification of the TBI protocol. The invasive monitors mentioned earlier were used. Prior to securing the aneurysm, systemic systolic blood pressure was maintained at less than 150 mmHg to reduce the risk of rebleeding. After securing the aneurysm, ICP and PbtO<sub>2</sub> management proceeded according to the standard protocol, with modifications for issues related to vasospasm.

## Results

Time from admission to declaration of brain death varied from 5 hours to 7 days; the most common interval was 1 or 2 days. Hourly records, including mean arterial blood pressure, ICP, CPP, and PbtO<sub>2</sub>, were maintained and saved in Excel format. These records were then analyzed to evaluate for any similar patterns of progression. All patients eventually experienced PbtO<sub>2</sub> equal to 0. This was confirmed by the clinical examination whenever possible. The finding of PbtO<sub>2</sub> equal to 0 often preceded the actual clinical examination for brain death. Brain death was further confirmed on all patients with radionuclide brain scanning (Figure 1).

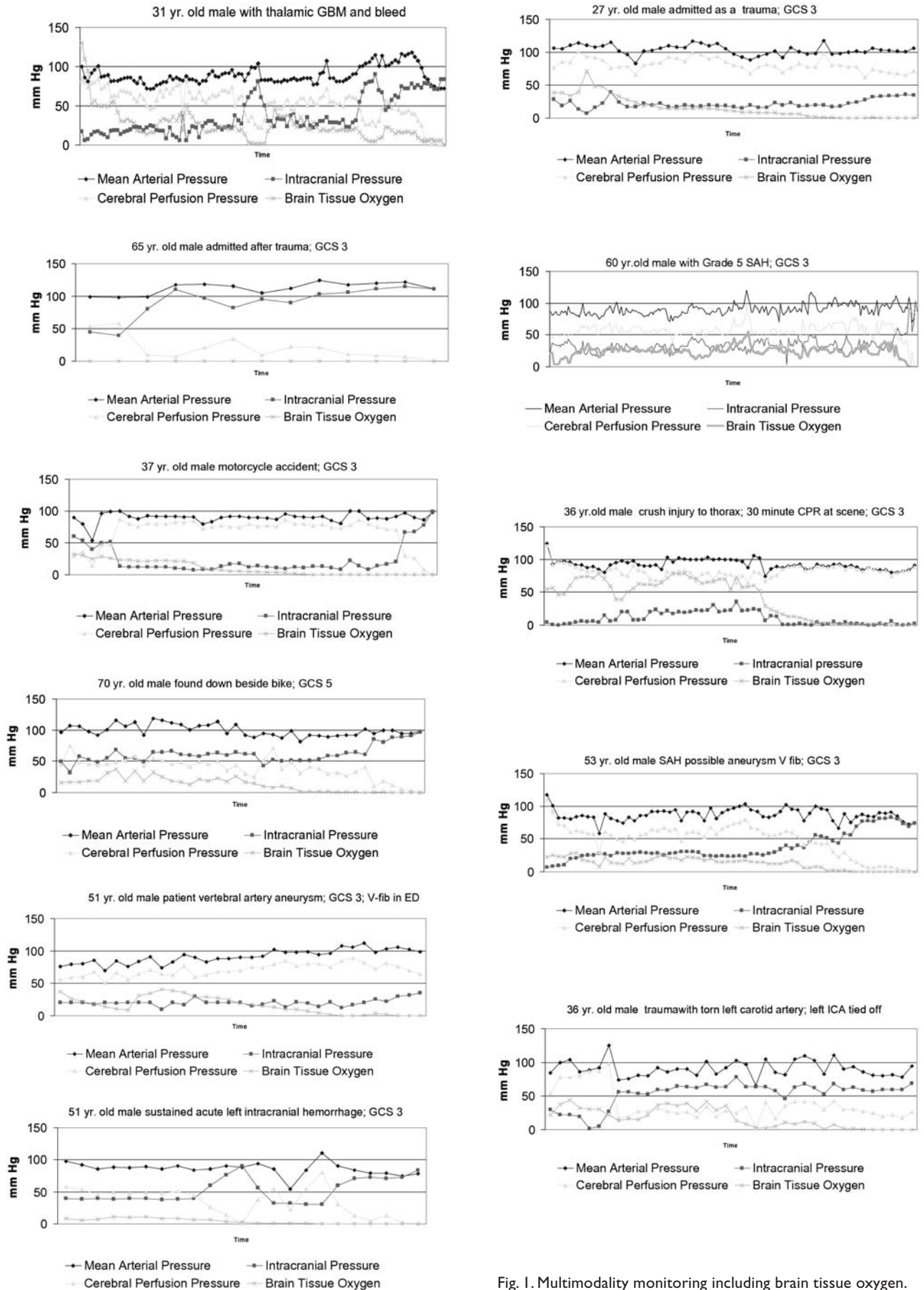


Fig. I. Multimodality monitoring including brain tissue oxygen.

The most common pattern observed in the graphs of ICU data was an increase of ICP to equal mean arterial pressure (eight patients). One other patient had ICP of 60 mmHg (approaching mean arterial pressure) with a very low CPP (20 mmHg). It is clear that as ICP approached mean arterial pressure in these patients, the CPP progressively fell, leading to failure of blood and oxygen delivery to the brain and, therefore, a critical fall in the  $PbtO_2$ . At the time of brain death, the  $PbtO_2$  was 0 in all eight patients.

A second pattern, observed in three patients, was that of a normal or elevated ICP with a maintained CPP greater than 60 mmHg. In these patients, the  $PbtO_2$  fell to 0, even with an apparently adequate perfusion pressure. One patient had a very low ICP (<5 mmHg). Mean arterial pressure and CPP were well-maintained, but  $PbtO_2$  progressively deteriorated, eventually falling to 0 at the time of brain death. This patient had sustained a crush injury to the thorax and was administered cardiopulmonary resuscitation (CPR) for 30 minutes in the prehospital setting, possibly resulting in anoxic brain injury. The patient underwent bilateral craniectomies soon after admission to the hospital and was placed on appropriate monitors.

Another patient sustained ventricular fibrillation with CPR and defibrillation in the prehospital setting. This also may have led to anoxic brain injury with irreversible injury to the cerebral parenchyma as well as failure of the microvasculature of the brain, leading to progressive ischemia, a fall in  $PbtO_2$ , and brain death. The lack of oxygenation of the brain is not a failure of the delivery system and, therefore, must represent end organ failure of the brain at the capillary or tissue level. It is unclear whether cerebral vasospasm plays a role in this failure of the microvasculature. Cerebral anoxia or other irreversible metabolic injury to the parenchyma may result in end organ failure and the inability to deliver or use oxygen at the tissue level.

Regardless of the pattern of failure, all 11 patients had  $PbtO_2$  measurements of 0 at the time of brain death (Table 1). Nuclear medicine cerebral flow studies were performed on all patients, and lack of flow to the brain was confirmed. In each patient with a  $PbtO_2$  of 0, the patient progressed to clinical brain death according to established guidelines (8). In this group of 11 patients, all patients with  $PbtO_2$  of 0 went on to experience brain death. Of 76 patients, any patient who experienced brain death had confirmed  $PbtO_2$  readings of 0. This represents a specificity and sensitivity of 100%, but the numbers are too small to be generalized.

## Conclusion

Modern techniques in intensive care medicine required a redefinition of death. Our current ability to support vital functions even after functional recovery is impossible has clouded the traditional view of cardiopulmonary death. A definition was needed that encompasses a lack of cerebral viability (9). The need for death criteria in the face of continued cardiopulmonary function is paramount in organ donation as well as legal issues concerning succession, inheritance, insurance, and criminality (1,10). The limitations to unnecessary costs of supportive care in the face of clinical patient nonviability is also an issue of fiscal responsibility.

In 1959, Mollaret and Goulon introduced the concept of brain death as "coma depasse" (11,12). They described 26 comatose patients with total loss of brain stem reflexes and respirations with no activity on electroencephalogram. In 1968, the concept of brain death was formalized by the Harvard Medical School Ad Hoc Committee to Examine the Definition of Brain Death (13). Key points stated the coma had to be of a known etiology, there had to be total unresponsiveness, and there had to be an absence of breathing. At the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom (1976), brain death was defined as the irreversible loss of all brain stem reflexes (14). The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1981) further clarified death into two components: (a) the irreversible cessation of heart and lung function and (b) the irreversible loss of all brain function. They defined brain death as coma that was irreversible and of known cause. There had to be a total loss of cerebral and brain stem function as well as a 24-hour confirmation period, and they recommended confirmatory testing. Every state in the United States has a definition of brain death; 31 states have adopted the Uniform Determination of Death Act (1981) (15,16). The act codified the equivalence of the loss of all cardiovascular function and the loss of all brain function as being dead.

It is vitally important to clearly understand the criteria for establishing brain death. Modern resuscitative and intensive care medicine allows support of cardiac function after all opportunity for meaningful survival has passed. Brain death is not a quality of life issue; rather, it is a state in which survival is no longer anticipated, even in a vegetative state. Multiple disciplines take an interest in these established criteria, including physicians, clergy, law enforcement, the legal community, and the government. The Uniform Determination of Death Act is the most widely accepted document in the United States; however, it is very vague.

The American Academy of Neurology (AAN) Practice Parameters for Determining Brain Death in Adults (summary statement [8]) established clinical criteria for a brain death declaration. From 1976 to 1994, the AAN performed a Medline search of all pertinent literature because there was a need "for standardization of the neurologic examination criteria for the diagnosis of brain death."

In 1995, the Report of the Quality Standards Subcommittee of the American Academy of Neurology attempted to clarify the concept of brain death with specific clinical guidelines. According to the AAN, the prerequisite for establishing brain death is "the absence of clinical brain function when the proximate cause is known and demonstrably irreversible." There need to be no confounding factors such as drug intoxication or hypothermia. Core temperature needs to be greater than 32°C.

The clinical examination criteria are divided into three principle areas: (a) coma or unresponsiveness, (b) the absence of brain stem reflexes, and (c) apnea testing, which had been the most variably applied criteria (17). Specific methodology for establishing apnea has been described (8,18). A re-evaluation 6 hours after the first evaluation is recommended but not required. The use of more than one physician has also been variably recommended (18,19).

The clinical diagnosis of brain death can be confounded by other clinical circumstances. The co-existence of shock, hypothermia, drug intoxication, poisoning, metabolic abnormalities, facial trauma, sleep apnea, and pulmonary diseases all can confuse the assessment of brain death (18,20). Specific neurological syndromes such as Guillain-Barré Syndrome or Locked-In Syndrome can mimic the nonresponsiveness of true brain death (20).

On the other hand, sometimes certain activities or functions seen in the patient experiencing brain death are confusing to the physician or family (16). Reflex motion of the extremities and complex motions can be observed during brain death. Patients may be able to maintain blood pressure, sweating, and blushing and have a tachycardia response to appropriate stimuli (20). The absence of diabetes insipidus (which implies function of a portion of the hypothalamus) is still consistent with brain death (20).

The AAN recommends confirmatory neurophysiological or radiological testing, but such testing is not mandatory. Confirmatory tests include cerebral angiography, electroencephalography, TCD ultrasonography, <sup>99m</sup>Tc hexamethylpropyleneamineoxime brain scan, and somatosensory or brain stem-evoked potentials. Unfortunately, some of these tests require transport of the patient to the radiology suite or call for specialized equipment and/or personnel. This can delay the brain death determination as a result of scheduling or other technical difficulties.

It would be advantageous to have a bedside adjunctive or confirmatory test that could signal the clinical deterioration to brain death. Ideally, this would not require transport of the patient and could be easily assessed by the health care team at the patient's bedside. For this purpose, Diaz-Reganon et al. (3) suggested the use of venous oxygen saturation at the jugular bulb (CvjO<sub>2</sub>). They used a ratio of SvO<sub>2</sub>/SjO<sub>2</sub> (CvjO<sub>2</sub> = SvO<sub>2</sub>/SjO<sub>2</sub>). A ratio of less than 1 was observed in 114 patients with brain death. Only four patients who went on to experience brain death had a CvjO<sub>2</sub> greater than 1, demonstrating a sensitivity of 96.6%. The specificity was 99.3%, with one patient who had a CvjO<sub>2</sub> of less than 1 surviving in a vegetative state. This ratio can be easily calculated by the nursing staff at the bedside using SjO<sub>2</sub> monitors. Unfortunately, SjO<sub>2</sub> monitors are rarely used because of problems with reliability and accuracy.

Similarly to SjO<sub>2</sub>, PbtO<sub>2</sub> can be used as an adjunctive test for brain death. van Santbrink et al. (4) reported that the moment of death can be accurately determined by PbtO<sub>2</sub>. Patients with significant neurological compromise may already have PbtO<sub>2</sub> monitors established. The PbtO<sub>2</sub> information is very robust and more easily monitored than SjO<sub>2</sub>; PbtO<sub>2</sub> is subject to less false-positive or -negative values because of technical malfunction than SjO<sub>2</sub>.

PbtO<sub>2</sub> monitoring does suffer from problems with misplaced monitors, monitors placed in hematoma cavities, or broken monitors; these problems can be uncovered with appropriate testing. Failure of the monitor can be assessed by treating the patient with FIO<sub>2</sub> equal to 100% and assessing for an appropriate response from the monitor. Additionally, a computed tomography scan can verify the correct placement of the probe to ensure it is in tissue and

not imbedded in a blood clot or outside of the brain parenchyma. These problems would result in abnormally low values of PbtO<sub>2</sub>. The trend toward brain death can be followed in real time because PbtO<sub>2</sub> tracing allows for accurate assessment of the progressive failure to oxygenate of the brain. As PbtO<sub>2</sub> approaches 0, a clinical examination for brain death can be performed, and traditional confirmatory tests may be obtained where appropriate or desired. Use of PbtO<sub>2</sub> as a sole confirmatory test is subject to limitations in interpretation because of its inherently focal nature. Further clinical research is necessary to establish the appropriateness of using PbtO<sub>2</sub> alone as a confirmatory test.

Evaluation of the 11 patients who experienced brain death using PbtO<sub>2</sub> monitoring revealed two patterns of deterioration to no cerebral oxygenation. The most common pattern, observed in eight patients, was the elevation of ICP (approaching mean arterial pressure), which resulted in critical fall in CPP. This represents a primary failure of perfusion of the brain. The lack of perfusion results in ischemia of the brain and resultant brain death. The second pattern, observed in three patients, was the lack of a primary failure of CPP. In these three patients, apparently adequate perfusion was maintained, at least as far as can be determined by an adequate CPP. Two of the patients did have marginally elevated ICP, but adequate mean arterial pressure allowed for CPP greater than 60 mmHg. The third patient had low ICP throughout his hospital stay. Two of the patients required CPR during their early posttraumatic clinical course. These patients may have suffered cerebral anoxia with injury to the brain parenchyma and microvasculature. The mechanism for fall in PbtO<sub>2</sub> to 0 in these three cases may have been primary metabolic failure of the brain. The maintenance of appropriate CPP is not adequate in this circumstance to overcome the primary cerebral injury. The patient then deteriorates to clinical brain death.

This second pattern of progression to brain death is particularly concerning. Our current treatment of severe dysfunction of the brain (based in large part on the American Association of Neurological Surgeons/Brain Trauma Foundation Guidelines for Managing Severe Head Injury, 1995, revised 2000 [5]) may inadequately address the treatment needs of this group of patients. The basic principles espoused in these guidelines is maintenance of perfusion and oxygenation. The guidelines do not specifically address issues of metabolic or ischemic injury. Methodology needs to be developed to fully understand the metabolic failures that lead to brain death. Thereby, treatment strategies can be developed to address the needs of this group of patients. Much of this work is ongoing, as various research groups examine the metabolic function of the injured brain as well as treatments that may modify these events.

PbtO<sub>2</sub> accurately predicts brain death when it falls to a 0 value that is consistent with no cerebral oxygenation. The use of PbtO<sub>2</sub> as a sole confirmatory test for brain death in the setting of an appropriate clinical examination will require the evaluation of a larger number of patients to assess its sensitivity and specificity before it can be recommended for use in this circumstance.

## References

1. Swash M, Beresford R. Brain death, still-unresolved issues worldwide. *Neurology* 2002;58:9,10.
2. Wijdicks E. Determining brain death in adults. *Neurology* 1995;44:1003–1011.
3. Diaz-Raganon G, Minambres D, Holanda M, Gonzalez-Herrera S, Lopez-Espadas F, Garrido-Diaz C. Usefulness of venous oxygen saturation in the jugular bulb for the diagnosis of brain death: report of 118 patients. *Intensive Care Med* 2002;28:1724–1728.
4. van Santbrink H, Maas A, Avezaat C. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *Neurosurgery* 1996;38:21–31.
5. Bullock R, Chestnut R, Clifton G, et al. Guidelines for the Management of Severe Brain Injury. Brain Trauma Foundation/American Association of Neurological Surgeons, 1995.
6. Palmer S, Bader MK, Azhar Q, et al. The impact of using the traumatic brain injury guidelines on outcomes in a community hospital setting. *J Trauma* 2001;50(4):657–664.
7. Palmer S, Bader M, Palmer S, et al. Early Cerebral Oxygen Desaturation in Traumatic Brain Injury With Normal Intracranial Pressure. CNS Oral Presentation, San Diego, 2001.
8. The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults (summary statement). *Neurology* 1995;45:1012–1014.
9. Black PM. Brain death. *N Engl J Med* 1978;299(pt 1):338–344.
10. Lovask D. Brain death and organ donation. *Crit Care Nurs Clin North Am* 2000;12:531–538.
11. Mollaret P, Boulou M. Le coma depasse (memoire preliminaire). *Rev Neurol (Paris)* 1959;101:3–5.
12. Fisher CM. Brain death—a review of the concept. *J Neurosci Nurs* 1991;23:330.
13. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *JAMA* 1968;205:337.
14. Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Royal Medical Colleges and their Faculties in the Royal Kingdom on 11 October 1976. *Br Med J* 1976;2:1187,1188.
15. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the president's commission for the study of ethical problems in medicine and biomedical and behavioral research. *JAMA* 1981;246:2184.
16. Capron A. Brain death—well settled but still unresolved. *N Engl J Med* 2001;344(16):1244–1246.
17. Lang C. Apnea testing by artificial CO<sub>2</sub> augmentation. *Neurology* 1995;45:966–969.
18. Wijdicks E. Brain death worldwide, Accepted facts but no global consensus in diagnostic criteria. *Neurology* 2002;58:20–25.
19. Wijdicks E. The diagnosis of brain death. *N Engl J Med* 2001;344:1215–1221.
20. Karakatsanis K, Tsanakas J. A critique on the concept of “brain death.” *Issues Law Med* 2002;18:127–141.