

# Brain Tissue Oxygenation in Children Diagnosed With Brain Death

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## Abstract

**Background** Diagnosing brain death in children is challenging. Guidelines recommend using confirmatory testing to provide ancillary information to support the diagnosis. Brain tissue oxygenation (PbtO<sub>2</sub>) is being increasingly used in the adult neurocritical care for continuous monitoring of the adequacy of brain oxygenation; however, data in pediatrics is limited. Evidence from adult studies suggests that persistent PbtO<sub>2</sub> of 0 mmHg is associated with brain death, but this relationship has not yet been demonstrated in children; therefore, we examined our experience with PbtO<sub>2</sub> monitoring and brain death in children with acute neurological pathology.

**Methods** We retrospectively reviewed patient records from a prospectively maintained database of 85 children who were ventilated for coma due to acute neurological injury and who received intracerebral monitoring.

**Results** We identified five children who had suffered brain death while being monitored. PbtO<sub>2</sub> had decreased to 0 mmHg in all five children at the time of brain death diagnosis. In contrast, PbtO<sub>2</sub> in patients, who did not develop brain death, never decreased to 0 mmHg. We review the benefits and drawbacks of using brain tissue oxygenation as ancillary information in diagnosing brain death in children.

**Conclusions** Preliminary data from this study suggest that PbtO<sub>2</sub> decreases to 0 mmHg when brain death occurs in children. Further study is needed to determine the

limitations, and the sensitivity and specificity of this finding in a larger group of children.

**Keywords** MeSH-brain tissue oxygenation · Children · Brain death · Traumatic brain injury

## Introduction

Published guidelines urge caution when diagnosing brain death in children [1–5]. In theory, immature brains have an increased ability to recover from profound insults when compared to adults, and there are reports of children who appeared to regain function after a diagnosis of brain death was made [6–10]. Yet there are also severe shortages of heart-beating cadaveric child organ donors. Therefore, it is important that diagnosis of brain death in children is sensitive, specific, and not unnecessarily delayed. Published guidelines on diagnosing brain death in children vary in their recommendations, reflecting some of the diagnostic uncertainty. Therefore, confirmatory investigations such as electroencephalogram (EEG), or cerebral blood flow (CBF) have been recommended, or indeed are compulsory in many countries [2–5, 11, 12].

However, these ancillary tests are not without their own challenges. There are technical difficulties associated with performing an EEG on small skulls, and the use of EEG in diagnosing brain death is now regarded as less vital than previously. There are case reports of children in whom EEG activity has returned after periods of electrocerebral silence (ECS). Moreover, brain death can occur without ECS [6, 7, 10, 13]. CBF, as measured by single photon emission computed tomography (SPECT) or four vessel cerebral angiography, is currently the confirmatory test of choice in diagnosing brain death in children [3, 13].

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When brain death occurs, CBF is expected to be absent, causing cerebral ischemia and irreversible cessation of brain function. Yet rarely, CBF to the cortex may continue after brain death has occurred [14, 15]. However, we are unaware of any cases of return of brain stem function after a clinical diagnosis of brain death with continued CBF. In practice though, SPECT scanning is expensive and requires technical expertise. The scanner is typically located outside of the ICU and patients may not be sufficiently stable for transport. Moreover, when brain death occurs after hours, the definitive diagnosis may be delayed if SPECT is not immediately available. Similarly, formal angiography is not readily available.

Therefore, supporting information from bedside tools used routinely for monitoring brain injured patients would be helpful. Transcranial Doppler (TCDS) is a bedside technique that may be helpful in the diagnosis of brainstem death, but insonation of the intracranial vessels is not always possible due to inadequate transtemporal acoustic windows. Therefore, the sensitivity of this test is only around 80%, with a specificity of around 97% [16]. Also, it requires technical expertise that may not always be available, and there is some inter-observer variation.

Brain tissue oxygen (PbtO<sub>2</sub>) monitoring has been used for monitoring brain oxygenation in various centers for more than 15 years [17] and use is increasing in general neurocritical care units. Apart from insertion of the catheter, it requires no further technical expertise to manage, so it has become attractive for continuous monitoring. PbtO<sub>2</sub> monitoring has now been formally introduced at the level of an option in the current guidelines for the management of severe traumatic brain injury (TBI) in adults [18]. To date, PbtO<sub>2</sub> has mostly been reported in the management of adult patients with acute brain injury, for example, secondary to TBI or subarachnoid hemorrhage. However, data are also emerging on the use of PbtO<sub>2</sub> in children. Episodes of low brain tissue oxygen tension (PbtO<sub>2</sub>) are associated with poor outcome [19–22] and PbtO<sub>2</sub> appears to decrease in parallel with CBF [22, 23]. We recently published evidence that low PbtO<sub>2</sub> is independently associated with poor outcome in children [20]. Little data are available on the relationship between PbtO<sub>2</sub> and brain death at present. There are currently only two reports in adult patients, both of which suggest that a PbtO<sub>2</sub> of 0 mmHg has a strong correlation with brain death [24, 25]. PbtO<sub>2</sub> changes in brain death have not been reported in children. Yet this is important given some of the difficulties described in diagnosing brain death in children. Given that use of PbtO<sub>2</sub> appears to be becoming more widespread, data on the association between PbtO<sub>2</sub> and brain death in children would be useful. Therefore, we examined the changes in PbtO<sub>2</sub> in a series of children with acute neurological insults who developed brain death while being monitored.

## Methods

Data were retrospectively examined from a prospectively maintained database of patients who received intracranial monitoring in the Red Cross War Memorial Children's Hospital between June 2006 and December 2008. Ethics approval was granted by the Human Ethics Board of the University of Cape Town. Intracranial monitoring was indicated in patients with TBI if their post-resuscitation Glasgow Coma Scale (GCS) was  $\leq 8$  or deteriorated to this level after admission. For patients with other pathologies causing coma with the need for intubation and ventilation, the decision to use intracranial monitoring was made based on the anticipated risk of cerebral ischemia and raised intracranial pressure (ICP).

Intracranial monitoring comprised an intracranial pressure monitor (Codman ICP Express [Codman, Raynham, MA] or Camino [Integra Neurosciences, Plainsboro, NJ]) and PbtO<sub>2</sub> monitor (Licox<sup>®</sup> [Integra Neurosciences, Plainsboro, NJ]). Patients with TBI were managed as previously described [19], based on the current recommendations for the management of severe brain injury in children [26]. PbtO<sub>2</sub> monitoring has been used at our hospital since June 2006 for patients who undergo ICP monitoring. PbtO<sub>2</sub> catheters were inserted into normal-appearing right frontal white matter if there were no localized lesions, or into the hemisphere with the greater swelling or that contained a focal lesion. Data from patients were collected after a 2-h run-in period to avoid potential artifacts from a stabilizing catheter, and thereafter on an hourly basis. Hourly PbtO<sub>2</sub> measurements and the maximum and minimum values in the previous hour were recorded.

Brain death was diagnosed according to standard clinical examination and a local protocol. This required that (1) a definitive diagnosis for cause of coma had been made, (2) that the patient had a head CT scan, which was in keeping with the diagnosis of brain death (for example, showing signs of massive edema, herniation, and extensive hypodensity, or 'black brain'), and either (3a) two negative brain stem examinations (including apnea testing) with an observation period of twelve hours between, or (3b) one negative brain stem examination and a SPECT scan demonstrating that there was no CBF. The diagnosis of brain death was based on these factors, with results of PbtO<sub>2</sub> monitoring playing no role. Brain stem testing was carried out as per the UK guidelines for diagnosing brain death [2, 3] by two senior registrar or consultant level doctors.

SPECT scanning was performed using Tc-99m HMPAO as a radiopharmaceutical and a Philips Axis camera.

Patients who died from cardiovascular instability after only one set of tests confirming brain death and a CT scan consistent with the diagnosis were also included in the analysis. This is because death occurred after a period of

cessation of brain stem function in the presence of ongoing cardiac output, as indicated by consistent clinical examination and head CT.

## Results

Eighty-five patients received intracranial monitoring at the Red Cross Children's Hospital between June 2006 and December 2008. Mean age was 6 years (range 5 months to 14 years old) and 75% were male. Eight-one percent were TBI-related, mainly secondary to road traffic accidents. Other causes included meningitis (including tuberculous meningitis), subarachnoid hemorrhage, and Reyes syndrome.

Brain death occurred in five patients while PbtO<sub>2</sub> monitoring was in progress. In all cases, PbtO<sub>2</sub> deteriorated to 0 mmHg before the clinical diagnosis of brain death was made. The deterioration of PbtO<sub>2</sub> to 0 mmHg in patients who developed brain death was characterized also by a failure of response to an increased inspired fraction of oxygen. Therefore, all patients who developed brain death had PbtO<sub>2</sub> of 0 mmHg at the time of brain stem testing, and when PbtO<sub>2</sub> decreased to 0 mmHg it did not recover in any of the cases. Attempts to increase PbtO<sub>2</sub> by increasing the FiO<sub>2</sub> are reflected in the high arterial partial pressure of oxygen values at the time of first negative brainstem examination in some of these patients (Table 1). While PbtO<sub>2</sub> may be affected by several systemic factors, we did not believe that the decrease in PbtO<sub>2</sub> we observed in brain dead patients was related to severe anemia, systemic hypoxia or hypotension (Table 1). Of note, the initial PbtO<sub>2</sub> in all of these patients was also low (Table 1), which may reflect the severity of their disease on admission to the ICU.

In one patient, an initial brain stem examination elicited only a corneal reflex with no gag or pupillary reflexes and no response to central pain. PbtO<sub>2</sub> remained at 0.8 mmHg during this examination. This patient was retested 1 h later, after PbtO<sub>2</sub> had decreased to 0 mmHg, and the complete brain stem examination was negative. Of note, brain temperature in this patient progressively decreased during this period; at the time of the second clinical examination, it was 2 °C lower than core body temperature. Four hours later, the patient died of cardiovascular instability.

### Other patients (non-brain dead)

By contrast, PbtO<sub>2</sub> was never 0 mmHg in any patient who did not develop brain death. PbtO<sub>2</sub> did not deteriorate to 0 mmHg in any of our other patients who were monitored during this period ( $n = 80$ ), even when infarction occurred and the PbtO<sub>2</sub> catheter was located within the infarcted area. For these other 80 patients, initial PbtO<sub>2</sub> was 17.3

(range 1.8–64.5) mmHg and the lowest PbtO<sub>2</sub> was 11.5 (range 0.2–29.1) mmHg. Of these patients, five experienced an episode where PbtO<sub>2</sub> was less than 2 mmHg, and three experienced PbtO<sub>2</sub> less than 1 mmHg, but in all patients these episodes were transient and responded promptly to intervention. None of these patients experienced a PbtO<sub>2</sub> of 0 mmHg. The lowest PbtO<sub>2</sub> recorded in a patient who survived was 0.2 mmHg. This episode, occurred for less than 10 min, was not associated with absent brainstem reflexes, and like episodes of very low PbtO<sub>2</sub> in other patients, responded promptly to intervention. Episodes of low PbtO<sub>2</sub> in general though, were associated with poor outcome as is described in our other reports [20].

## Discussion

In this retrospective case series, PbtO<sub>2</sub> decreased to 0 mmHg in all children who developed brain death. By contrast, although episodes of low PbtO<sub>2</sub> occurred in other patients, it did not deteriorate to 0 mmHg in any of our other patients who did not develop brain death. These preliminary results suggest that PbtO<sub>2</sub> of 0 mmHg is associated with brain death in children, similar to that in adults, and may be useful corroborative information in the diagnosis of brain death in children.

These findings are limited by the sample size; therefore, these results should be regarded as preliminary. Brain death is not a common occurrence in most single centers; and PbtO<sub>2</sub> monitoring is not yet widely used. In fact, in the two adult case series, which also studied the association between PbtO<sub>2</sub> and brain death, refer to only 6 and 11 patients [24, 25].

The actual area of brain tissue monitored by the PbtO<sub>2</sub> monitor is small, and conceivably it may not reflect global brain tissue oxygen tension. However, when PbtO<sub>2</sub> is measured in normal-appearing white matter the value appears to reflect global brain oxygenation [23]. Therefore, probe placement is critical, and confirmation of probe position using repeat CT head is an important part of the procedure.

Another potential source of error is in the diagnosis of brain death. A limitation of any retrospective study is that local criteria for a diagnosis may differ from that used at other centers. In the case of diagnosing brain death, there are no internationally recognized criteria, but instead a number of partially conflicting local guidelines [2, 4, 12]. The Red Cross Children's Hospital uses a pragmatic approach, which is flexible and satisfies the criteria that irreversible cessation of brain stem function has occurred (see "Methods" section). This approach could be criticized because it is not the same as other standards, but it would

**Table 1** Clinical characteristics of patients diagnosed with brain death

Demographics		Injury		Brain stem examination									
Age	Sex	Insult type	Mechanism	Initial GCS	Initial PbtO <sub>2</sub> (mmHg)	First brain stem examination	MAP at time of first examination (mmHg)	Hb at time of first examination (g/dl)	PaO <sub>2</sub> at time of first examination (mmHg)	Time to second examination	Second brain stem examination	Confirmatory testing	PbtO <sub>2</sub> at time of death (mmHg)
8years, 11 months	Male	TBI	Crush injury	2t/15	0	Negative	102	9	296.4	12 h	Negative	None	0
1 year 3 months	Female	TBI	Crush injury	2t/15	0	Negative	88	11.6	160.36	Spontaneous death at 6 h	n/a	TCDS, SPECT	0
5 months	Male	Meningitis	Pneumococcal meningitis	5/15	5	Negative	68	10	76	n/a	SPECT used	SPECT	0
4 years 9 months	Female	TBI	MVA, passenger	2t/15	4.1	Negative	79	10	288.8	Spontaneous death at 4 h	n/a	None	0
5 years 6 months	Female	TBI	MVA, passenger	6/15	2.8	Negative	81	12	398.24	n/a	SPECT used	SPECT	0

TBI traumatic brain injury; MVA motor vehicle accident; CT computer tomography, TCDS trans-cranial Doppler sonography; SPECT single photon emission computer tomography

be highly unlikely that any of the patients in this series were not brain dead. Therefore, it is likely that the deterioration of PbtO<sub>2</sub> to 0 mmHg in these patients reflects a pattern that is seen after brain death ensues, particularly when one also considers the data from the adult studies. However, whether the decrease of PbtO<sub>2</sub> to 0 mmHg reliably occurs with brain death, with a sufficiently high sensitivity and specificity for it to be used as an ancillary investigation for brain death, requires further study.

The use of PbtO<sub>2</sub> monitoring in supporting the diagnosis of brain death has several advantages. First, PbtO<sub>2</sub> is being increasingly used in the management of TBI and subarachnoid hemorrhage in adults in many centers, and experience in children is increasing [20, 28, 29]. The monitoring is continuous and is sensitive to changes in CBF and tissue oxygenation [30–32]. When cerebral perfusion pressure and CBF decrease, PbtO<sub>2</sub> consistently decreases. Current methods used to support or confirm the diagnosis of brain death require technical expertise or transfer of the patient out of the neurocritical care unit. Second, the time period needed to confirm brain death may be shorter. This may help to partially decrease parent's anxiety and suffering as well as minimizing ischemic damage to transplantable organs.

However, many questions remain regarding the use of PbtO<sub>2</sub> monitoring in the confirmation of brain death in children. First, as discussed above, in the few cases where CBF does not fall to 0 ml/min despite brain death [22, 23], it is possible that PbtO<sub>2</sub> may also fail to decrease to 0 mmHg. A larger sample of patients with results of both CBF and PbtO<sub>2</sub> is needed to confirm or refute this hypothesis, as brain death with continued CBF is thought to occur in less than 10% of clinically brain dead patients 24 h after loss of brainstem reflexes [15]. In this circumstance, PbtO<sub>2</sub> may be a surrogate marker of CBF, with a similar sensitivity for the diagnosis of brain death. Another possibility is that PbtO<sub>2</sub> may not fall to 0 mmHg due to residual cellular oxygen after cellular death. This is unlikely, particularly in view of the fast aerobic metabolism of neurones and glial cells, and because brain death is usually associated with progressive ischemia and anaerobic glycolysis. However, more data are needed to clarify this. Second, there is a possibility that poor probe placement could lead to an erroneous measurement of PbtO<sub>2</sub> of 0 mmHg, for example, if the probe tip is within an isolated infarct. Such results have been observed by Smith et al. [24], but have never been observed in this institution. This problem would be excluded by routine head CT scan following probe placement, as is performed when PbtO<sub>2</sub> is monitored and so should not present any diagnostic uncertainty. Third, the effects of a transient decrease of PbtO<sub>2</sub> to 0 mmHg for less than 30 min as described by

Smith et al. [24] is not known in children. In our sample, all patients with a PbtO<sub>2</sub> of 0 mmHg for any length of time remained at 0 mmHg and did not respond to intervention. However, it may be possible that some patients might experience a transient PbtO<sub>2</sub> of 0 mmHg without developing brain death. Given that brain infarction is a function both of the depth of ischemia and the duration thereof, it would be reasonable to presume that this situation would not persist for long without irreversible brain injury occurring. Indeed, in our cohort only three patients who did not develop brain death had a PbtO<sub>2</sub> of less than 1 mmHg, and in each case this was for less than 15 min. All of our patients who had a PbtO<sub>2</sub> of 0 mmHg also experienced brain death. It is possible that a brief episode of 0 mmHg may not be associated with brain death; however, further study is needed to determine the minimum length of time of PbtO<sub>2</sub> = 0 mmHg that is associated with brain death.

## Conclusions

In this small case series, PbtO<sub>2</sub> of 0 mmHg shows a strong association with brain death in children, consistent with evidence in adult studies [24, 25]. In addition to its clinical utility in managing patients at risk of hypoxic/ischemic injury, PbtO<sub>2</sub> monitoring has the potential to support the diagnosis of brain death in severely brain injured children. However, further study is required to answer several remaining questions regarding such practice, and in particular to provide information on the sensitivity and specificity of PbtO<sub>2</sub> data in the diagnosis of brain death in children. Use of PbtO<sub>2</sub> monitoring may help to add clarity to the challenge of diagnosing brain death in children and help elucidate some of the mechanisms of irreversible injury to the brain.

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