Brain Tissue Oxygen Monitoring in Children—A Review

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Abstract

Brain tissue oxygen monitoring is a relatively new technique for continuous measurement of focal brain tissue oxygen tension ($PbtO_2$). There are several studies of $PbtO_2$ monitoring in adult patients but few in children. The goal is the prevention, or early detection and treatment, of secondary insults. Episodes of low $PbtO_2$ are associated with worse outcome, and treatment directed by $PbtO_2$ may benefit patients, but there is no Class I evidence as yet. What determines $PbtO_2$ is multifactorial and the underlying pathophysiological events affecting $PbtO_2$ may be complex. The clinician using this technology must understand the technical and physiological aspects, as well as the limitations, of $PbtO_2$ monitoring if there is to be any clinical benefit. However, whether $PbtO_2$ monitoring delivers overall benefit across centers of different expertise requires a randomised controlled trial. This review examines the current literature on $PbtO_2$ monitoring with a focus on children, the important technical and physiological factors, and an approach to using a $PbtO_2$ monitor.

Keywords

Brain tissue oxygen, children, traumatic brain injury, head trauma, subarachnoid hemorrhage, brain perfusion, technical

The introduction of brain tissue oxygen ($PbtO_2$) monitoring into the neuro-intensive care unit (NICU) has created exciting opportunities for intervention but requires many questions to be answered before it can achieve widespread adoption. This article will cover the technical aspects of $PbtO_2$ monitoring, the physiological correlates of $PbtO_2$, the published literature on $PbtO_2$ monitoring in children, and practical approaches to monitoring and managing $PbtO_2$ in the clinical situation.

$PbtO_2$ is measured and monitored continuously using a thin catheter inserted into brain parenchyma. It is increasingly being used in the management of patients with acute neurological pathology, most commonly severe traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH), to complement other forms of monitoring. The ease of use and the potential for continuously monitoring the adequacy of brain oxygenation and measuring its response to intervention in realtime have contributed to its growing popularity in the NICU, as clinicians try to avoid or ameliorate secondary injury to maximize the chance of a favorable outcome.

Post mortem[1] and clinical studies[2–4] suggest that secondary brain hypoxia–ischemia contributes significantly to poor outcome after TBI; therefore, the rationale for monitoring appears to be strong. The purposes of monitoring oxygenation of the brain are four-fold: to detect episodes of threatened brain ischemia/hypoxia early and respond immediately; to detect the adverse effects of therapy directed at other physiological parameters (e.g. hyperventilation for increased intracranial pressure [ICP]); to titrate therapy (e.g. optimizing cerebral perfusion pressure); and to assist interpretation of perturbations of other modalities, such as ICP. However, it is only recently that methods that enable monitoring of some aspects of brain oxygenation have begun to be used regularly in the NICU, of which $PbtO_2$ arguably appears to be the most promising.

Alternatives for continuous oxygenation monitoring such as jugular venous saturation ($SJVO_2$) and near-infrared spectroscopy (NIRS) appear to have more limitations, which has restricted wider use. $SJVO_2$ monitoring has a reduced time-of-good-quality-data[5] (related to artifacts and repeated calibrations required) and may miss focal ischemia.[6,7] NIRS is popular for somatic monitoring and for cerebral monitoring when the brain is normal (for example in cardiac anesthesia), but it may be more limited in neurocritical care, where a wet chamber between the optode and skin, subdural air after craniotomy, extracranial contamination, scalp swelling, subdural blood, SAH, and brain swelling may reduce the reliability of the signal and therefore its clinical application.[8–11] Normal NIRS signals have been found with complete brain ischemia.[12]

However, there are also limitations of $PbtO_2$ monitoring that need to be considered. The catheter monitors a restricted area of brain tissue and the determinants of $PbtO_2$ are still debated and require further examination. Although the association between low $PbtO_2$ and poor outcome appears to be strong, it is much less certain whether $PbtO_2$-directed therapy improves outcome. Lastly, while several studies of $PbtO_2$ monitoring in adult patients have been conducted, much less is known about $PbtO_2$ monitoring in children.

Technical Aspects of Brain Tissue Oxygen Monitoring

Three $PbtO_2$ devices have been produced commercially: Licox (Integra Neurosciences, Plainsboro, NJ), Neurotrend (Codman, Raynham, MA), and Neurovent-PTO (Raumedic, Münchberg, Germany). Of these, the Licox system is most widely used, and also measures brain temperature in the same catheter (IT2). The Neurotrend is no longer commercially available. The Neurovent-PTO is novel in that it also measures ICP, but is new on the market and few data on its clinical reliability are currently available. The Licox system is based on a Clarke-type polargraphic cell containing two electrodes covered by a membrane. The amount of O_2 diffusing across this membrane depends on local tissue pO_2 and determines the electrical current between the two electrodes.[12] Several studies have confirmed the reliability of the $PbtO_2$ signal, *in vitro* accuracy, and low sensitivity and zero drift over time.[5,14–18] The sampling area is approximately 14–17mm3.[5,19] Local tissue damage is minimal[15] and complications are rare.[14] The time-of-good-quality-data is in the region of 99%;[14] repeat calibration is not required and artifacts are unusual. Although the $PbtO_2$ readings are usually stable within one hour of insertion, sometimes the adaptation period may take up to two hours.[14,20,21]

Normal and Abnormal Brain Tissue Oxygen Values

Normal values in humans are not precisely known. Because the $PbtO_2$ value is influenced strongly by local cerebral blood flow (CBF), the value varies widely depending on the metabolic activity and diffusion characteristics of the region being monitored.[22] However, variability is reduced during periods of ischemia.[21] Extrapolation from studies that have measured $PbtO_2$ in animals and human studies monitoring relatively normal brain suggest that normal values for $PbtO_2$ are around 25–30mmHg.[5,17,19,23] Studies of $PbtO_2$ in aneurysm surgery demonstrate the decline in $PbtO_2$ associated with ischemia due to temporary clipping.[24–26] Poor outcome in TBI patients is more likely when $PbtO_2$ falls progressively below 20mmHg.[27–29] Scheufler et al.[21] demonstrated in an animal model that CBF levels below 20ml/100g/minute correlated with $PbtO_2$ levels below 10mmHg. This also appears to correlate with critical ischemic thresholds in human studies.[5,30] Low $PbtO_2$ values (<10mmHg) are associated with perturbations in microdialysis parameters, decreased mitochondrial function and impaired neuronal activity.[21,30–32]

Choosing the Site of Monitoring

Because the device measures focal, not global, oxygenation, the choice of the site of monitoring is important for the interpretation of the results and optimal management of the patient. When the brain is diffusely injured or when there is a global insult, monitoring $PbtO_2$ in frontal white matter appears to provide a useful approximation of global changes in brain oxygenation.[5,19,21,33–35] If there is focal injury, many clinicians aim to monitor tissue in the penumbra of the lesion, as $PbtO_2$ is usually lower in these tissues.[36] Similar focal/global principles are relevant also to monitoring with microdialysis. $PbtO_2$ values require interpretation based on tissue being monitored, for both generalization of the results to the rest of the brain and interpretation of the $PbtO_2$ response to intervention. Peri-contusional (or peri-lesional) brain may demonstrate altered pathophysiological responses to interventions that require a different interpretation compared with 'non-lesioned' brain.[6,34,37]

Factors that Influence Brain Tissue Oxygen

The best descriptor of what $PbtO_2$ monitoring in the brain reflects is debated. Often considered a measure of the balance between supply and demand of oxygen in the tissues, it has variably been associated with CBF,[38–41] product of blood flow and oxygen content,[15] mean transit time of blood through the brain,[42] arteriovenous difference of oxygen,[43] and end-capillary venous PO_2.[21,44] In general terms, it is probably best considered a measure of factors that affect both the perfusion and diffusion characteristics of brain tissue. Some of the important practical factors that influence $PbtO_2$ are discussed below.

Brain Tissue Oxygen and Arterial Partial Pressure of Oxygen

Being a measure of the partial pressure of oxygen, $PbtO_2$ is significantly affected by the arterial partial pressure of oxygen (PaO_2). Therefore, even in conditions where arterial blood is near full saturation and increased PaO_2 does not change oxygen content significantly, increased PaO_2 is followed by increased $PbtO_2$.[45,46] Accordingly, the arteriovenous difference of oxygen strongly influences $PbtO_2$.[43] Similarly, progressive systemic hypoxia leads to a decline in $PbtO_2$ and increased anerobic metabolism.[15,47,48] A potential limitation is that the ventilator fraction of inspired oxygen (FiO_2) setting may significantly influence the $PbtO_2$ reading in the absence of substantial changes in oxygen delivery. On the other hand, dissolved oxygen may be preferentially used for tissue oxygenation,[49,50] and increased tissue oxygen pressure may overcome tissue barriers to diffusion[51] and may improve metabolism.[52] The relative benefits of hyperoxia on $PbtO_2$ and metabolism in TBI, however, are currently debated.[52–55]

Brain Tissue Oxygen and Arterial Partial Pressure of Carbon Dioxide

$PbtO_2$ varies with changes in arterial partial pressure of carbon dioxide ($PaCO_2$) if CO_2 reactivity is preserved,[6,56–59] largely secondary to the vasoactive effects of $PaCO_2$. Therefore, hypocarbia may induce or worsen cerebral ischemia, and relative hypercarbia may improve local CBF and therefore local oxygenation in areas at risk for ischemia.[57] However, if hypercarbia significantly increases cerebral blood volume, and therefore ICP, the reduced cerebral perfusion pressure (CPP) may have the opposite effect on $PbtO_2$. This, and variations in the strength of CO_2 reactivity in the cerebral vessels, as well as different responses in abnormal tissue, may account for occasional 'paradox' reactions of $PbtO_2$ in response to CO_2 changes.[6,23] Moderate hyperventilation without monitoring brain oxygenation is no longer recommended.[60,61]

Brain Tissue Oxygen and Intracranial Pressure

Increased ICP may reduce $PbtO_2$, either by the local tissue pressure effect or by reduction of cerebral perfusion pressure (CPP). Reports of

decompressive craniectomy and barbiturate therapy in adult TBI have demonstrated improved $PbtO_2$ after relief of high ICP.[62–64] However, when results are pooled the overall relationship between ICP is poor[20,65] because $PbtO_2$ does not depend on ICP alone.

Brain Tissue Oxygen and Cerebral Perfusion Pressure

Several studies have examined the relationship between $PbtO_2$ and CPP but have produced conflicting results.[23,66–73] Most studies examining the effects of induced hypertension on $PbtO_2$ have demonstrated an increase in $PbtO_2$ in response to augmented CPP. In part, variations of response may reflect differences in the status of pressure autoregulation. In experimental models, $PbtO_2$ shows a close relationship with changes in CBF.[15,59] Therefore, $PbtO_2$ may have a close relationship with progressive oligemia and warn of impending ischemia.[21]

Brain Tissue Oxygen and Hemoglobin

Isovolemic hemodilution reduces brain oxygenation and increases lesion size in TBI under experimental conditions,[74] and $PbtO_2$ decreases after hemorrhagic shock but responds to resuscitation.[75–77] Therefore, the avoidance of significant anemia in TBI is warranted. However, the thresholds for transfusion are unclear because transfusion has potential systemic adverse effects, transfused stored blood does not have the same oxygen-carrying capacity as the patient's blood, and the impact of the change in rheology in the microvasculature is uncertain. Blood transfusion has a variable influence on $PbtO_2$, but prediction of the response based on pre-transfusion variables is elusive.[78–80]

Diffusion Barriers to Brain Tissue Oxygen

Oxygen transport in the tissues occurs by diffusion, which is affected by PaO_2.[81] The diffusion distance between O_2 in the capillary and the cell is an important factor determining intracellular oxygen tension, so tissue oxygen decreases non-linearly in the extracellular space with increasing distance from the vessel.[82] Diffusion-limited tissue oxygenation in TBI may be as important as perfusion-limited ischemia, but is more difficult to diagnose. In TBI, microvascular factors that may increase the diffusion distance for oxygen include cytotoxic cell swelling, perivascular edema, collapsed capillaries, and arteriovenous shunting.[51] If these factors play a significant role in impairing oxygen diffusion to the cell, the partial pressure of oxygen in the capillary may be of greater significance than in normal physiology.

Brain Tissue Oxygen and Outcome in Adult Patients

Several studies have examined the relationship between $PbtO_2$ and outcome after TBI in adult patients.[17,18,20,27,29,83–86] Low $PbtO_2$ occurs most commonly in the first 24 hours after TBI,[20,85] which is consistent with the lower CBF, increased lactate, and cellular acidosis seen during this period.[4,87] The risk for poor outcome has been linked with the depth and duration of cerebral hypoxia.[20,27] Valadka et al.[27] demonstrated that the longer $PbtO_2$ values were below 20mmHg, the greater the likelihood of dying, with the difference between patients alive and dead becoming significant at $PbtO_2$ values less than 6mmHg (the difference gradually widening the lower the threshold became). Two studies have examined $PbtO_2$-monitored patients with historical controls and have suggested that a $PbtO_2$-targeted approach may be of benefit to patients.[29,88] $PbtO_2$ appears to decrease to zero when brain death occurs.[89,90]

Brain Tissue Oxygen Monitoring in Children

The rationale for using additional monitors to help determine the choice of therapy in children with acute brain injury is arguably stronger than for adults. For example, in adult severe TBI there is considerable debate about what CPP target should be aimed for.[91–93] Management of CPP in children is further complicated by the changing physiological profiles and normative values with age, in particular those that relate to ICP and blood pressure (BP). Therefore, a marker of the adequacy of BP and ICP control to deliver oxygen to the brain would appear to be of great value. However, there are few papers that have specifically examined $PbtO_2$ monitoring in children.[28,94,95] The evidence from these agrees with the adult studies that low $PbtO_2$ is associated with poor outcome. In particular, the longer patients had $PbtO_2$ below 20mmHg, the more likely they were to have a poor outcome,[28] with the key threshold of 10mmHg having the strongest association with outcome.[96] Markers of primary injury severity do not appear to predict which patients are at risk for secondary brain tissue hypoxic insults.[97] Importantly, significantly low $PbtO_2$ (<10mmHg) may occur in up to 30% of patients despite conventional treatment according to internationally accepted recommendations for the management of pediatric severe TBI.[28]

In the largest of these pediatric studies (52 children with severe TBI), low $PbtO_2$ (<10mmHg) was independently associated with poor outcome (mortality and dichotomized outcome parameters using the Glasgow Outcome Score and Pediatric Cerebral Performance Category Score).[96] Furthermore, $PbtO_2$ was the strongest predictor of outcome in multivariate analysis, which included injury severity, Glasgow Coma Scale, and ICP and CPP secondary insults. Mortality in the series was low (9.6%). $PbtO_2$ has a weak correlation with ICP and CPP in pediatric TBI when measured as secondary insults and as time-linked observations in all patients,[28,65] probably because several factors influence $PbtO_2$. $PbtO_2$ may be low despite normal ICP, and high ICP may occur with normal or even elevated $PbtO_2$ (as may occur with hyperemia). However, in individual children, high ICP may compromise $PbtO_2$, and therapy such as decompressive craniectomy may reduce ICP and improve $PbtO_2$.[98,99] Little has been published about $PbtO_2$ monitoring for other pathologies in children. One such study reported the occurrence of a precipitous decline of $PbtO_2$ in patients with tuberculous meningitis despite full treatment with anti-tuberculous medication and steroids, and normalized ICP and BP.[100] At our institution, low $PbtO_2$ was associated with the development of delayed cerebral infarction on head computed tomography (CT) scan in patients with trauma, SAH, cerebral infection, and metabolic encephalopathy (unpublished data).

In summary, studies in children suggest that episodes of low $PbtO_2$ are common in TBI, are not predicted by other conventional monitoring, and are associated with poor outcome. Although mortality in the largest series was low, and historical cohort studies in adults suggest benefit to patients, $PbtO_2$-directed treatment has not been subjected to a randomized trial as yet.

A Practical Guide to Managing Low Brain Tissue Oxygen—An Institutional Approach
Placement of Catheters

At our institution, a $PbtO_2$ monitor is placed whenever we monitor ICP in patients with acute neurological pathology. The catheter is placed into

right frontal white matter if there are no focal lesions, or in an area close to a lesion or contusion if there is focal pathology. The $PbtO_2$ readings are allowed to settle for one hour before any intervention is planned. FiO_2 is increased to test the monitor for an appropriate response to PaO_2. A head CT scan is performed when the patient is stable to confirm the location of the catheter tip.

Treatment of Low Brain Tissue Oxygen

Our approach to low $PbtO_2$ emphasizes individualization of patient care. The type of injury, profiles of ICP and BP, status of pressure auto-regulation, metabolic dysregulation, and systemic injury/disease are but some of the issues that influence decisions in the individual patient. In general terms, we begin with a search for a possible reversible cause for low $PbtO_2$, such as high or borderline ICP, low CPP, low hemoglobin, low PaO_2, low $PaCO_2$, subclinical seizures, or cerebral vasospasm. If there is an apparent cause for low $PbtO_2$ that can be identified, we address this first. In the absence of these, we elevate the CPP by 5–10mmHg and observe its effect on $PbtO_2$ and ICP. If $PbtO_2$ improves and ICP is either unchanged or marginally increased, we continue at the higher CPP. If $PbtO_2$ does not improve, artificial elevation of CPP may not be beneficial and only the adverse effects remain. If ICP increases in tandem with the

BP increase (as occurs when pressure autoregulation is impaired), a decision is made balancing the risks of higher ICP and low $PbtO_2$ based on the absolute values of each. If hemoglobin is less than 10g/dl, we transfuse the patient to examine the effect of higher hemoglobin on $PbtO_2$. If ICP is controlled, we allow the $PaCO_2$ to be maintained at a higher level in the hope that this will promote cerebral vasodilation. If the above methods are not effective, or as a temporary intervention while other therapies are prepared, we increase the FiO_2 to increase the partial pressure of oxygen in the tissues.

Interpretation of Other Variables

In addition to the treatment of low $PbtO_2$, we have found the response of $PbtO_2$ helpful to interpret other monitored variables or interventions. For example, high ICP may be due to several factors. If $PbtO_2$ is also high (especially if transcranial Doppler flow velocities are elevated), this suggests the high ICP may be due to hyperemia. In this case, lowering $PaCO_2$ may be a useful strategy, and monitoring $PbtO_2$ may add a degree of safety while doing this. When transcranial Doppler velocities are elevated, $PbtO_2$ may help distinguish between hyperemia and vasospasm. Low $PbtO_2$ in the face of high ICP may be due to the rise in ICP, or both may be caused by a third factor, such as subclinical seizures. ∎

1. Graham DI, et al., *J Neurol Neurosurg Psychiatry*, 1989;52:346–50.
2. Pigula FA, et al., *J Pediatr Surg*, 1993;28:310–14, discussion 315–16.
3. Chesnut RM, et al., *J Trauma*, 1993;34:216–22.
4. Bouma GJ, et al., *J Neurosurg*, 1992;77:360–68.
5. Kiening KL, et al., *J Neurosurg*, 1996;85:751–7.
6. Gupta AK, et al., *Anesth Analg*, 1999;88:549–53.
7. Coles JP, et al., J *Cereb Blood Flow Metab*, 2004;24:202–11.
8. Vavilala MS, *Pediatr Crit Care Med*, 2007;8:192–3.
9. Wartenberg KE, et al., *Crit Care Clin*, 2007;23:507–38.
10. Nagdyman N, et al., *Intensive Care Med*, 2005;31:846–50.
11. Buchner K, et al., *Zentralbl Neurochir*, 2000;61:69–73.
12. Schwarz G, et al., *J Neurosurg Anesthesiol*, 1996;8:189–93.
13. Siegemund M, et al., *Intensive Care Med*, 1999;25:1044–60.
14. Dings J, et al., *Neurosurgery*, 1998;43:1082–95.
15. Zauner A, et al., *Neurosurgery*, 1995;37:1168–76, discussion 1176–7.
16. Hoelper BM, et al., *Acta Neurochir (Wien)*, 2005;147:767–74, discussion 774.
17. Maas AI, et al., *Acta Neurochir Suppl (Wien)*, 1993;59:50–57.
18. Meixensberger J, et al., *Acta Neurochir Suppl (Wien)*, 1993;59:58–63.
19. Lang EW, et al., *Neurosurg Rev*, 2007;30:99–106, discussion 106–7.
20. van den Brink WA, et al., *Neurosurgery*, 2000;46:868–76, discussion 876–8.
21. Scheufler KM, et al., *J Neurosurg Anesthesiol*, 2004;16:210–19.
22. Lubbers DW, Baumgartl H, *Kidney Int*, 1997;51:372–80.
23. Dings J, et al., *Acta Neurochir (Wien)*, 1996;138:425–34.
24. Kett-White R, et al., *J Neurosurg*, 2002;96:1013–19.
25. Doppenberg EM, et al., *J Neurosurg*, 1997;87:809–16.
26. Hoffman WE, et al., *Surg Neurol*, 1999;51:654–8.
27. Valadka AB, et al., *Crit Care Med*, 1998;26:1576–81.
28. Figaji AA, et al., *Neurosurgery*, 2008;63:83–91, discussion 91–2.
29. Stiefel MF, et al., *J Neurosurg*, 2005;103:805–11.
30. Valadka AB, *J Neurotrauma*, 1998;15:509–19.
31. Hlatky R, et al., *J Neurotrauma*, 2004;21:894–906.
32. Huchzermeyer C, et al., *J Neurosci*, 2008;28:1153–62.
33. Rossi S, et al., *Acta Neurochir Suppl*, 2000;76:199–202.
34. Johnston AJ, et al., *Intensive Care Med*, 2004;30:791–7.
35. van den Brink WA, et al., *J Neurotrauma*, 1998;15:813–24.
36. Sarrafzadeh AS, et al., *Acta Neurochir Suppl*, 1998;71:186–9.
37. van Santbrink H, et al., *Acta Neurochir (Wien)*, 2003;145:429–38, discussion 438.
38. Doppenberg EM, et al., *Surg Neurol*, 1998;49:650–54.
39. Doppenberg EM, et al., *Acta Neurochir Suppl*, 1998;71:166–9.
40. Jaeger M, et al., *Acta Neurochir (Wien)*, 2005;147:51–6, discussion 56.
41. Valadka AB, et al., *Acta Neurochir Suppl*, 2002;81:299–301.
42. Hemphill JC,3rd, et al., *AJNR Am J Neuroradiol*, 2005;26:1095–1100.
43. Rosenthal G, et al., *Crit Care Med*, 2008;36:1917–24.
44. Gupta AK, et al., *J Neurosurg*, 2002;96:263–8.
45. Menzel M, et al., *J Neurosurg Anesthesiol*, 1999;11:240–51.
46. Rosenthal G, et al., *J Neurosurg*, 2008;108:59–65.
47. Cohen PJ, et al., *J Appl Physiol*, 1967;23:183–9.
48. Leniger-Follert E, et al., *Pflugers Arch*, 1975;359:81–95.
49. Habler OP, et al., *Transfusion*, 1998;38:135–44.
50. Suttner S, et al., *Anesth Analg*, 2004;99:2–11.
51. Menon DK, et al., *Crit Care Med*, 2004;32:1384–90.
52. Tolias CM, et al., *J Neurosurg*, 2004;101:435–44.
53. Magnoni S, et al., *J Neurosurg*, 2003;98:952–8.
54. Nortje J, et al., *Crit Care Med*, 2007;36:273–81.
55. Diringer MN, et al., *J Neurosurg*, 2007;106:526–9.
56. Imberti R, et al., *J Neurosurg*, 2002;96:97–102.
57. Manley GT, et al., *J Trauma*, 2000;48:1025–32, discussion 1032–3.
58. Schneider GH, et al., *Acta Neurochir Suppl*, 1998;71:62–5.
59. Hemphill JC,3rd, *Neurosurgery*, 2001;48:377–83, discussion 383–4.
60. Muizelaar JP, et al., *J Neurosurg*, 1991;75:731–9.
61. Adelson PD, et al., *Pediatr Crit Care Med*, 2003;4:S45–8.
62. Stiefel MF, et al., *J Neurosurg*, 2004;101:241–7.
63. Jaeger M, et al., *J Neurol Neurosurg Psychiatry*, 2003;74:513–15.
64. Thorat JD, et al., *J Clin Neurosci*, 2008;15:143–8.
65. Figaji AA, et al., *Childs Nerv Syst*, 2009;25(10):1335–43.
66. Bruzzone P, et al., A*cta Neurochir Suppl*, 1998;71:111–13.
67. Johnston AJ, et al., *Crit Care Med*, 2005;33:189–95, discussion 255–7.
68. Coles JP, et al., *Brain*, 2004;127:2479–90.
69. Reinert M, et al., *Acta Neurochir (Wien)*, 2003;145:341–9, discussion 349–50.
70. Stocchetti N, et al., *Acta Neurochir Suppl*, 1998;71:162–5.
71. Unterberg AW, et al., *J Trauma*, 1997;42:S32–7.
72. Marin-Caballos AJ, et al., *Crit Care*, 2005;9:R670–76.
73. al-Rawi PG, et al., *Zentralbl Neurochir*, 2000;61:74–9.
74. Hare GM, et al., *J Appl Physiol*, 2007;103:1021–9.
75. Knudson MM, et al., *J Trauma*, 2003;54:242–52.
76. Manley GT, et al., *Adv Exp Med Biol*, 2003;530:311–17.
77. Manley GT, et al., *J Trauma*, 1999;46:261–7.
78. Leal-Noval SR, et al., *Intensive Care Med*, 2006;32:1733–40.
79. Leal-Noval SR, et al., *Curr Opin Crit Care*, 2008;14:156–62.
80. Smith MJ, et al., *Crit Care Med*, 2005;33:1104–8.
81. Baumgartl H, et al., *Comp Biochem Physiol A Mol Integr Physiol*, 2002;132:75–85.
82. Scheufler KM, et al., *Anesth Analg*, 2002;95:1042–8.
83. Stiefel MF, et al., *J Neurosurg*, 2006;105:568–75.
84. Zauner A, et al., *Neurosurgery*, 1997;41:1082–91, discussion 1091–3.
85. van Santbrink H, et al., *Neurosurgery*, 1996;38:21–31.
86. Bardt TF, et al., *Acta Neurochir Suppl*, 1998;71:153–6.
87. Clausen T, et al., *J Neurosurg*, 2005;103:597–607.
88. Meixensberger J, et al., *J Neurol Neurosurg Psychiatry*, 2003;74:760–64.
89. Palmer S, Bader MK, *Neurocrit Care*, 2005;2:17–22.
90. Smith ML, et al., *Neurol Res*, 2007;29:755–9.
91. Rosner MJ, et al., *J Neurosurg*, 1995;83:949–62.
92. Nordstrom CH, *Neurosurgery*, 2006;58:E590, author reply E590.
93. Robertson CS, et al., *Crit Care Med*, 1999;27:2086–95.
94. Stiefel MF, et al., *J Neurosurg*, 2006;105:281–6.
95. Narotam PK, et al., *J Pediatr Surg*, 2006;41:505–13.
96. Figaji AA, et al., *Childs Nerv Syst*, 2009;25(10):1325–33
97. Figaji AA, et al., *Neurosurg Focus*, 2008;25:E4.
98. Figaji AA, et al. In: Manley G, Hemphill C, Stiver S (eds), *Intracranial Pressure and Brain Monitoring XIII (Acta Neurochirurgica Supplementum 102)*, 2008.
99. Figaji AA, et al., *Childs Nerv Syst*, 2007;23:1331–5.
100. Figaji AA, et al., *Pediatr Crit Care Med*, 2008;9:e25–30.