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What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury

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Editor's key points

- Brain tissue oxygenation (Pbto2) and near-infrared spectroscopy (NIRS) parameters respond to changes in arterial pressure (AP) and intracranial pressure (ICP).
- NIRS and transcranial Doppler (TCD) signals react first to AP and ICP changes. The reaction of Pbt_{O_2} is delayed, revealing that the analysed modalities monitor different stages of cerebral oxygenation.
- In 77% of events tissue oxygenation index (TOI) and Pbt_{O_2} reacted in the same direction.

Background. Brain tissue partial oxygen pressure (Pbt_{O_2}) and near-infrared spectroscopy (NIRS) are novel methods to evaluate cerebral oxygenation. We studied the response patterns of Pbt_{O_2}, NIRS, and cerebral blood flow velocity (CBFV) to changes in arterial pressure (AP) and intracranial pressure (ICP).

Methods. Digital recordings of multimodal brain monitoring from 42 head-injured patients were retrospectively analysed. Response latencies and patterns of Pbt_{O_2}, NIRS-derived parameters [tissue oxygenation index (TOI) and total haemoglobin index (THI)], and CBFV reactions to fluctuations of AP and ICP were studied.

Results. One hundred and twenty-one events were identified. In reaction to alterations of AP, ICP reacted first [4.3 s; inter-quartile range (IQR) −4.9 to 22.0 s, followed by NIRS-derived parameters and CBFV (10.9 s; IQR: −5.9 to 39.6 s, 12.1 s; IQR: −3.0 to 49.1 s, 14.7 s; IQR: −8.8 to 52.3 s for THI, CBFV, and TOI, respectively), with Pbt_{O_2} reacting last (39.6 s; IQR: 16.4 to 66.0 s). The differences in reaction time between NIRS parameters and Pbt_{O_2} were significant ($P<0.001$). Similarly when reactions to ICP changes were analysed, NIRS parameters preceded Pbt_{O_2} (7.1 s; IQR: −8.8 to 195.0 s, 18.1 s; IQR: −20.6 to 80.7 s, 22.9 s; IQR: 11.0 to 53.0 s for THI, TOI, and Pbt_{O_2}, respectively). Two main patterns of responses to AP changes were identified. With preserved cerebrovascular reactivity, TOI and Pbt_{O_2} followed the direction of AP. With impaired cerebrovascular reactivity, TOI and Pbt_{O_2} decreased while AP and ICP increased. In 77% of events, the direction of TOI changes was concordant with Pbt_{O_2}.

Conclusions. NIRS and transcranial Doppler signals reacted first to AP and ICP changes. The reaction of Pbt_{O_2} is delayed. The results imply that the analysed modalities monitor different stages of cerebral oxygenation.

Keywords: brain tissue partial oxygen pressure; cerebral haemodynamics; cerebral oxygenation; cerebrovascular reactivity; near-infrared spectroscopy; tissue haemoglobin index; tissue oxygenation index

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Adequate cerebral oxygen supply is fundamental to the management of patients after traumatic brain injury (TBI).[1–4] Two currently available methods of evaluating cerebral oxygenation are direct brain tissue partial oxygen pressure (Pbt_{O_2}) and near-infrared spectroscopy (NIRS). Monitoring of Pbt_{O_2} is an invasive technique which has been used in a clinical setting and has been shown to be related to outcome after head injury.[4–8] NIRS is a non-invasive method previously used in fetal medicine and cardiac surgery,[9–11] which has not yet been widely accepted for routine clinical monitoring in the adult neuro-intensive care setting.[12] Traditionally, NIRS uses the modified Beer–Lambert law to quantify the concentration changes of oxygenated and deoxygenated haemoglobin from an unknown baseline. The NIRS-derived

parameters, which are currently being evaluated for monitoring of the adult brain, are tissue oxygenation index (TOI) and total haemoglobin index (THI).[13–15] TOI and THI are calculated using spatially resolved spectroscopy, where a mathematical model based on the photon diffusion theory is used to calculate the differential equation of light attenuation with respect to distance from the source.[16] The advantage of spatially resolved spectroscopy is that the obtained parameters are specific to the intracranial compartment[17] and that the obtained values are normalized and do not represent changes from an unknown baseline. TOI is calculated as the ratio of oxygenated haemoglobin and total tissue haemoglobin, and it has been shown to be an index of cerebral blood flow.[10 16 18–20] THI, on the other hand, describes changes in the total tissue haemoglobin level and has been shown to represent blood volume.[21 22] While in a recent study, the response of Pbt_{O_2} to changes in arterial pressure (AP) and intracranial pressure (ICP) have been described,[23] little is known about the dynamic response patterns of NIRS to different types of stimuli. Despite the similarities, Pbt_{O_2} and NIRS are based on different physical processes and monitor anatomically and physiologically different areas of the brain. We hypothesize that these modalities monitor different stages of cerebral oxygen supply and therefore will demonstrate differences in the reaction times and the patterns of changes in response to fluctuations of AP and ICP. The study aims to observe and categorize the effect of haemodynamically relevant events on cerebral perfusion and oxygenation as seen by transcranial Doppler (TCD), NIRS, and invasive Pbt_{O_2} measurements. The knowledge of these response patterns may aid in determining the level of oxygen supply insufficiency.

Methods

Multimodality brain monitoring was part of the standard clinical protocol used to care for patients after TBI. Written consent was obtained from patients or their next-of-kin to gather and analyse data from all monitoring periods. The study was approved by the institutional Research Ethics Committee.

Patients

Data obtained from 42 patients after closed head injury, admitted to Neurosciences Critical Care Unit (NCCU) in Addenbrooke's Hospital, Cambridge, UK, from October 2008 to June 2009 were analysed.

Patients were managed according to an updated version of a previously published ICP/cerebral perfusion pressure (CPP)-oriented protocol where ICP was maintained below 20 mm Hg and CPP above 60–70 mm Hg.[24] Reduction in ICP was achieved with a stepwise escalation approach by means of head positioning, analgesia, sedation, muscle relaxation, moderate hyperventilation, ventriculostomy, use of osmotic agents, and induced hypothermia. CPP was maintained with fluid expansion, vasopressors, and inotropes. Intracranial hypertension refractory to medical management was treated with either decompressive craniectomy or barbiturate coma. In patients with microdialysis and invasive brain oxygenation monitoring, the target values were: $Pbt_{O_2} > 25$ mm Hg and lactate–pyruvate ratio < 25. Ventilator settings were titrated to maintain a Pa_{CO_2} level of 4.5–5.0 kPa and a Pa_{O_2} of 13–15 kPa.

Monitoring and clinical data

Invasive monitoring included ICP (Codman ICP, MA, USA) and Pbt_{O_2} (Licox, Integra Neurosciences Ltd, Hampshire, UK). Monitoring probes were inserted into computed tomography (CT)-normal parenchyma in the frontal area at a depth of ~2.5 cm, via a triple access device (Technicam, Newton Abbot, UK). Non-invasive monitoring included TOI and THI measured with NIRO-200 (Hamamatsu Photonics UK Ltd, UK) and cerebral blood flow velocity (CBFV) using a TCD ultrasonograph (DWL Compumedics Ltd, Germany).

TOI and THI are measured using spatially resolved spectroscopy. The method relies on the photon diffusion theory.[16] A photodiode emitting three wavelengths of light within the near-infrared spectrum (775, 810, and 850 nm) is coupled with a set of three photodiode detectors (with 1 mm separation). Equation (1) demonstrates the principal of spatially resolved spectroscopy.[16]

$$\frac{\partial A}{\partial \rho} = \frac{1}{\ln 10} \times \left(\sqrt{\mu a \times \mu s'} + \frac{2}{\rho} \right) \quad (1)$$

Where A is attenuation, ρ the distance from light impulse source, μa means absorption coefficient, and; $\mu s'$ the reduced scatter coefficient.

The NIRO-200 measures $\partial A/\partial \rho$ at three wavelengths, therefore allowing the calculation of the coefficients of absorption and scatter. Because the first-order approximation of the scatter coefficient can be treated as a constant (k), the relative concentrations of oxygenated and deoxygenated haemoglobin can be obtained (k*O_2Hb and k*HHb, respectively).[16] TOI is calculated as $O_2Hb/O_2Hb+HHb$ and it is expressed as a percentage (%), while THI is calculated as $O_2Hb+HHb$ and it is expressed as a relative value, representing a change form the baseline, expressed in arbitrary units (a.u.).

All parameters were sampled at a frequency of 50 Hz. AP, ICP, and Pbt_{O_2} were monitored continuously, and NIRS and TCD monitoring were performed daily for periods of ~15 and 1 h per day, respectively. All data were recorded synchronously using ICM+ software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/). For analysis, only the periods with all monitoring modalities were used. Consequently, data available for analysis consisted of ~1 h of monitoring per patient, per day. Gas exchange was assessed with arterial blood gas (ABG) analysis during each of the monitoring sessions. Furthermore, screening of patients' medical notes was performed to identify any obvious respiratory pathology.

Recordings were stored digitally as a part of prospective project managed by C.Z. oriented on the use of NIRS for the assessment of autoregulation of blood flow in TBI patients.[15] Data were re-analysed retrospectively for the purpose of this study.

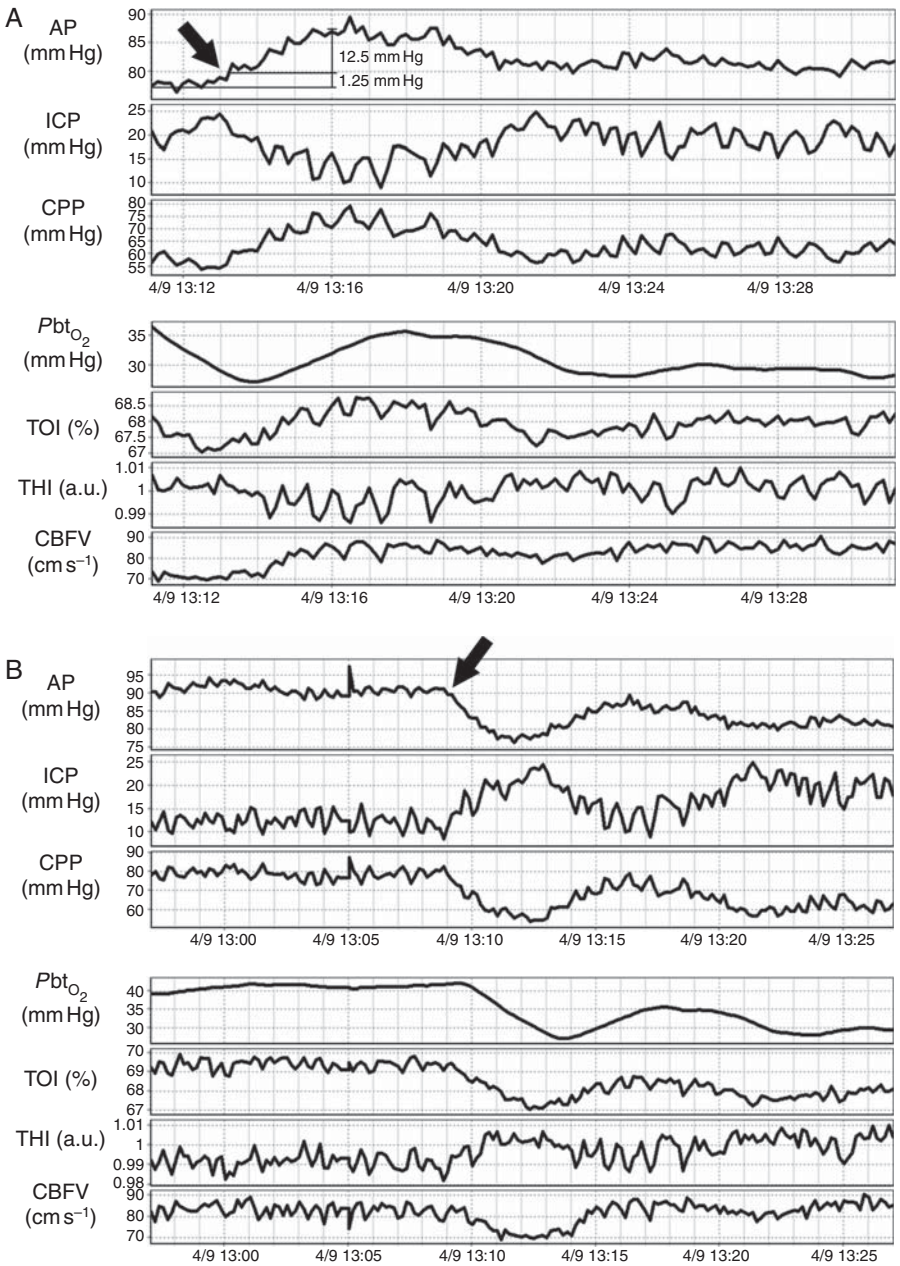

Fig 1 Two AP-led events: (A) hypertensive and (B) hypotensive (black arrows demarcate onset of event). In both events, the direction of changes of ICP is opposite to the direction of changes in AP, the initiating factor, demonstrating good cerebrovascular reactivity. A unidirectional change of Pbt_{O_2} and TOI consistent with the variation of AP and CPP is visible: increase in (A) and decrease in (B). Changes of Pbt_{O_2} and TOI are also consistent with the changes of CBFV. THI remains relatively stable during hypertensive events (A) while increases in hypotensive events (B), reflecting presumably a vasodilatory effect leading to the observed, compensatory increase in ICP. AP trace in (A) depicts the method used to determine the onset of an event. AP, arterial pressure; CBFV, cerebral blood flow velocity; CPP, cerebral perfusion pressure; ICP, intracranial pressure; THI, tissue haemoglobin index; TOI, tissue oxygen index; Pbt_{O_2}, brain tissue partial oxygen pressure.

Data analysis

Data analysis was performed using ICM+ software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus/). Sampled signals of AP, ICP, CBFV, Pbt_{O_2}, TOI, and THI were subject to manual artifact removal. Artifacts which were excluded consisted of periods without a detectable pulse waveform in the AP, ICP, or CBFV signals and rapid, bimodal variations due to physiological stimulation of the patient. All signals were treated with a moving-average filter over 10 s.

Transient changes were defined as a 'significant event' when they constituted a sustained change lasting from 20 s to 45 min, which was >5 mm Hg for ICP and 15 mm Hg for AP. The Pbt_{O_2}, TOI, and THI responses were considered for

analysis if Pbt_{O_2} >4 mm Hg, TOI >1.5%, and THI >0.075 (a.u.), and if they were clearly distinguishable from the surrounding baseline variation.[23] The time-point when a sustained change in AP or ICP passed 10% of its maximum amplitude was used as the onset of an event (Fig. 1A). In this way, the analysis was oriented at observation of time delays between changes of signals interpreted as an input (AP and ICP) and the responses to these variations.

In the first instance, data were analysed for the presence of significant events in AP and ICP. Secondly, we sought to examine the alterations in Pbt_{O_2}, TOI, and THI that were associated with these events. Thirdly, changes in CBFV were examined. All identified events were subsequently classified into groups depending on the triggering change into either AP- or ICP-led. The latencies between the onset of changes seen in AP or ICP and the subsequent reactions of Pbt_{O_2}, TOI, THI, CBFV, and ICP (for AP-led events) were calculated. Finally, the state of cerebrovascular reactivity was examined. Cerebrovascular reactivity is one of the mechanisms of cerebral autoregulation and it describes the capacity of cerebral microcirculation to react to spontaneous changes in transmural pressure.[25] It has been shown that cerebrovascular reactivity can be assessed using the pressure reactivity index (PRx).[26] PRx was calculated as a Pearson's correlation coefficient between thirty consecutive 10 second averaged values of AP and ICP using a 300 s moving window, as described previously.[26] PRx ≥0.2 was chosen to be indicative of disturbed cerebrovascular reactivity.[27] For events which lasted <300 s (direct calculation of PRx from that period was impossible), PRx was calculated from a window beginning both immediately prior and immediately after the event, so that the overall duration was 300 s.

Statistical analysis

Data were not parametric. Friedman's ANOVA was used to determine the differences between multiple variables within a group of events. Significance was set at $P<0.05$. The Wilcoxon signed-rank test was used for comparing the specific latencies between the triggering change (AP and ICP) and reactions of Pbt_{O_2}, TOI, THI, and CBFV. The Bonferroni correction for multiple comparisons was used with a significance level set at $P<0.007$. The Mann–Whitney *U*-test was used to compare the latencies between patients with intact and impaired cerebrovascular reactivity. Correlations between latencies and PRx were determined using Spearman's rank correlation coefficient.

Results

Forty-two patients fit the inclusion criteria. The mean age of patients was 37 yr. On admission, there were 32 patients with severe head injury [Glasgow Coma Scale (GCS) 3–8], seven with moderate injury (GCS 9–12), and three with mild injury (GCS 13–15). However, subsequently, all patients required intensive care and mechanical ventilation. Thirty-one patients (74%) had a diffuse type of injury (Marshall grade 1–4), five (12%) had a mass lesion which was evacuated (Marshall grade 5) while six (14%) had a non-evacuated mass lesion (Marshall grade 6) (Table 1).

Table 1 Baseline characteristics of monitored patients. AP, arterial pressure; ASDH, acute subdural haemorrhage; CBFV, cerebral blood flow velocity; CPP, cerebral perfusion pressure; DAI, diffuse axonal injury; DC, decompressive craniectomy; EDH, epidural haemorrhage; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IVH, intraventricular haemorrhage; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; Pbt_{O_2}, brain tissue partial oxygen pressure; P_{CO_2}, partial pressure of arterial CO_2; P_{O_2}, partial pressure of arterial O_2; Sp_{O_2}, arterial oxygen saturation; TCD, transcranial Doppler; THI, tissue haemoglobin index; TOI, tissue oxygenation index; tSAH, traumatic subarachnoid haemorrhage

N	42
Age [mean (SD), yr]	37 (19)
Sex (*n*)	
Male	32
Female	10
Injury severity	
Admission GCS (median, range)	8 (3–14)
GCS 3–8 (%)	32 (76)
GCS 9–12 (%)	7 (17)
GCS 13–15 (%)	3 (7)
Injury type (*n*)	
DAI	7
Diffuse haemorrhagic contusions	18
Brain oedema w/o contusions	6
Focal mass lesion—non-evacuated	6
Evacuated mass lesion (ASDH, EDH)	5
IVH	3
tSAH	1
Treatment	
Primary craniotomy	5
DC	2
EVD	3
Conservative	35
Monitoring time per session [mean (SD), min]	74.8 (21)
Number of cases with monitoring of modality (*n*)	
AP	42
ICP	42
Pbt_{O_2}	42
NIRS	42
TCD	30
Physiological parameters	
P_{CO_2} [mean (SD), kPa]	4.84 (0.65)
P_{O_2} [mean (SD), kPa]	15.09 (2.86)
Sp_{O_2} (%)	98
MAP [mean (SD), mm Hg]	88 (9)
ICP [mean (SD), mm Hg]	17 (6)
CPP [mean (SD), mm Hg]	71 (9)
CBFV [mean (SD), cm s^{-1}]	67 (24)
Pbt_{O_2} [mean (SD), mm Hg]	24 (7)
TOI [mean (SD), %]	68 (5)
THI [mean (SD), a.u.]	0.99 (0.08)

Table 2 Classification of events and characterization of responses in relation to the triggering parameter. AP, arterial pressure; CBFV, cerebral blood flow velocity; ICP, intracranial pressure; Pbt_{O_2}, brain tissue partial oxygen pressure; PRx, pressure reactivity index; THI, tissue haemoglobin index; TOI, tissue oxygen index; +, a change in the same direction as the direction of changes of the triggering parameter; −, a change in the opposite direction to the direction of changes of the triggering parameter

Event type	Triggering parameter	Cerebrovascular reactivity	Direction of changes in relation to triggering parameter				
			ICP	Pbt_{O_2}	TOI	THI	CBFV
AP-led (n=96)	AP change	Intact (PRx <0.2) (n=37)	−	+	+	No change	+
		Impaired (PRx ≥0.2) (n=59)	+	−	−	+	+
				+	−		
				−	+		
ICP-led (n=25)	ICP change	Impaired (PRx ≥0.2)	N/A	−	−	+	−

There were 105 monitoring sessions performed with a median of 2 sessions per patient (range 1–8) on days 1–9 [median 2; inter-quartile range (IQR): 1–3] post-injury. The mean duration of monitoring per session was 74.8 (21) min. The mean ICP was 17 mm Hg, with a CPP of 71 mm Hg and an MAP of 88 mm Hg. There were two patients with CBFV >120 cm s^{-1}, suggesting traumatic vasospasm. However, the Lindegaard ratio was <3.0 and there was no subarachnoid blood on the CT. There were no significant differences in the monitored parameters (ICP, CPP, Pbt_{O_2}, TOI, THI, and FV) depending on the type of pathology [diffuse axonal injury, diffuse haemorrhagic contusions/brain oedema, focal mass lesion]. Although, there were no significant differences in the absolute values of the monitored variables between patients with hyper- and normocapnia, a moderate inverse correlation was found between TOI and P_{CO_2} (R=−0.44; P<0.05). When compared between patients with impaired and intact cerebrovascular reactivity (PRx <0.2 indicated intact cerebrovascular reactivity), no significant differences were found for the absolute values of the monitored parameters.

One hundred and twenty-one transient events were identified. The observed patterns of changes are summarized in Table 2, while the averaged time delays between the onset of changes in the analysed parameters and the onset of changes in AP are summarized in Table 3.

AP-led events (n=96)

Two types of AP-led events were observed: hypotensive and hypertensive (Fig. 1). Overall, the onset of ICP, Pbt_{O_2}, TOI, CBFV, and THI changes was always delayed with respect to AP. The shortest delay was seen for ICP—median 4.3 s (IQR: −4.9 to 22.0 s), while the longest for Pbt_{O_2}—median 39.6 s (IQR: 16.4 to 66.0 s) (Table 3). The duration of latencies was significantly different between signals (ANOVA P<0.001). When compared between specific signals, the differences in latencies of NIRS-derived indices and Pbt_{O_2} revealed statistical significance (P<0.001). Furthermore, the difference in latencies of ICP and Pbt_{O_2} was significant (P<0.001), while that of ICP and NIRS-derived parameters was not. When latencies were analysed separately for groups of events occurring during intact and impaired cerebrovascular reactivity, no significant differences were observed (Table 3).

ICP-led events (n=25)

There were 25 events triggered by an alteration in ICP. The differences in the observed latencies showed statistical significance (ANOVA P=0.04; Table 3). When analysed separately, the differences between latencies of NIRS-derived indices and Pbt_{O_2} did reveal significant differences (P>0.05).

During ICP-led events, Pbt_{O_2}, TOI, and CBFV consistently decreased while THI increased (Fig. 2).

Influence of cerebrovascular reactivity on the response of oxygenation parameters to changes in AP

Although no significant correlation between the latencies of all analysed parameters and the state of cerebrovascular reactivity was observed, differences in the reaction patterns were noted. In events occurring while the state of cerebrovascular reactivity was intact (PRx <0.2; n=37), the changes in Pbt_{O_2} and TOI were concordant and followed the direction of AP (Fig. 3A). In response to an increase in AP, THI remained unchanged or changed only minimally (Fig. 3A), while in response to a decrease in AP, THI increased (Fig. 1B).

In events occurring while cerebrovascular reactivity was impaired (PRx ≥0.2; n=59) three distinct patterns of Pbt_{O_2} and TOI responses have been identified. In the majority of cases, changes in Pbt_{O_2} and TOI were concordant (n=31); however, in contrast to events with intact cerebrovascular reactivity, Pbt_{O_2} and TOI decreased despite an increase in AP and CBFV (Fig. 3B). There were 21 events where Pbt_{O_2} decreased while TOI increased and seven where Pbt_{O_2} increased while TOI decreased in response to increasing AP and CBFV (Fig. 3C and D). Overall, in 71% of AP-led events and in 77% of all events, the direction of changes of TOI was concordant with the direction of changes of Pbt_{O_2}.

The *post hoc* power calculation revealed that the study was not sufficiently powered to detect significant differences between latencies; therefore, the presented results may be prone to type II error.

Table 3 Latencies between the triggering event (AP or ICP) and the reactions of Pbt_{O_2}, TOI, THI, CBFV, and ICP. AP, arterial pressure; CBFV, cerebral blood flow velocity; ICP, intracranial pressure; IQR, inter-quartile range; Pbt_{O_2}, brain tissue partial oxygen pressure; PRx, pressure reactivity index; THI, tissue haemoglobin index; TOI, tissue oxygen index. *Statistical significance ($P<0.007$) between the difference in the reaction time ICP and other parameters. §Statistical significance ($P<0.007$) between the difference in the reaction time of Pbt_{O_2} and other parameters. All data presented as median plus IQR

	Trigger—Pbt_{O_2} (s)	Trigger—TOI (s)	Trigger—THI (s)	Trigger—CBFV (s)	Trigger—ICP (s)	Friedman ANOVA
AP-led ($n=96$)	39.6 (IQR: 16.4 to 66.0)*,§	14.7 (IQR: −8.8 to 52.3)§	11.0 (IQR: −5.9 to 39.6)§	12.1 (IQR −3.0 to 49.1)	4.3 (IQR −4.9 to −22.0)*	$\chi^2=37$, $P<0.001$
PRx <0.2 ($n=37$)	42.3 (IQR: 22.6 to 57.0)*,§	12.2 (IQR: −32.3 to 32.2)§	11.7 (IQR: −18.3 to −32.2)§	26.8 (IQR: −3.0 to 49.1)	11.7 (IQR: −4.4 to 33.7)*,§	NS
PRx ≥0.2 ($n=59$)	37.1 (IQR: 16.4 to 94.9)*,§	17.6 (IQR: 2.2 to 60.0)*,§	10.6 (IQR: −1.9 to 53.3)*,§	3.5 (IQR: −0.8 to 30.8)	1.4 (IQR: −8.1 to 21.8)*	NS
ICP-led ($n=25$)	22.9 (IQR: 11.0 to 53.0)	18.1 (IQR: −20.6 to 80.7)	7.1 (IQR: −8.8 to 195.0)	34.0 (IQR: −7.9 to 45.2)	N/A	$\chi^2=8$, $P=0.04$

Discussion

Our results show that Pbt_{O_2}, TOI, and THI (monitored with NIRS) respond to changes in AP and ICP and that the direction of changes of TOI is concordant to that of Pbt_{O_2} in 77% of the analysed events. However, the differences in latencies between the modalities suggest that Pbt_{O_2} and NIRS monitor different stages of cerebral oxygen supply.

Time delays between modalities

A stereotyped temporal sequence of responses was observed in all events, regardless of the initiating factor. Overall, changes in ICP were the earliest consequences of AP increases, occurring with a median delay of <5 s. The reaction time of THI and TOI, just over 10 and 14 s, respectively, was comparable with that of CBFV. However, the sequence of events is suggestive of THI being more susceptible to blood volume changes, with an early reaction visible before changes in CBFV. TOI, on the other hand, demonstrates a delayed reaction (visible after changes in CBFV) indicating an influence of oxygenation changes secondary to modification of cerebral blood flow. This assumption is further supported by the observed differences in patterns of THI changes during events with intact and impaired cerebrovascular reactivity. In the first case, only small changes are seen in THI, typically opposite to changes in AP, while during impaired cerebrovascular reactivity, THI changes follow those of AP (similarly to changes in ICP, which are representative of vascular dilation and blood volume changes).

In contrast, changes in Pbt_{O_2} were visible last and typically delayed by almost 40 s (Table 3), suggesting that local tissue stores of oxygen buffered the changes in oxygen delivery.

The observed sequence of events supports the assumption that AP and ICP fluctuations exert changes which spread from the proximal, large arteries, through the microvascular compartment to the parenchyma.

Effects of AP changes on Pbt_{O_2}, TOI, and THI

We have demonstrated that both TOI and Pbt_{O_2} follow AP changes, while THI changes in the opposite direction. These results differ from previous work describing the relationship of Pbt_{O_2} and spontaneous fluctuations in AP.[28] It has been shown that Pbt_{O_2} passively follows changes in AP only during impaired cerebrovascular reactivity, which formed the basis behind the autoregulatory index ORx.[28] However, the averaging period used when calculating ORx was 1 h, while in our study, the median duration of the analysed events was 431 s. We hypothesize that the events studied here may have been too short to reflect the autoregulatory mechanisms involved in oxygen delivery.

When analysing events which occurred during impaired cerebrovascular reactivity, we have observed opposite reactions of Pbt_{O_2} and TOI (Fig. 3). Equation (2), which was proposed by Tachtsidis and colleagues,[29] provides a possible explanation for the relationship between TOI and blood oxygen saturation, CBF, cerebral oxygen metabolism, and cerebral blood volume (CBV). It is, therefore, possible that

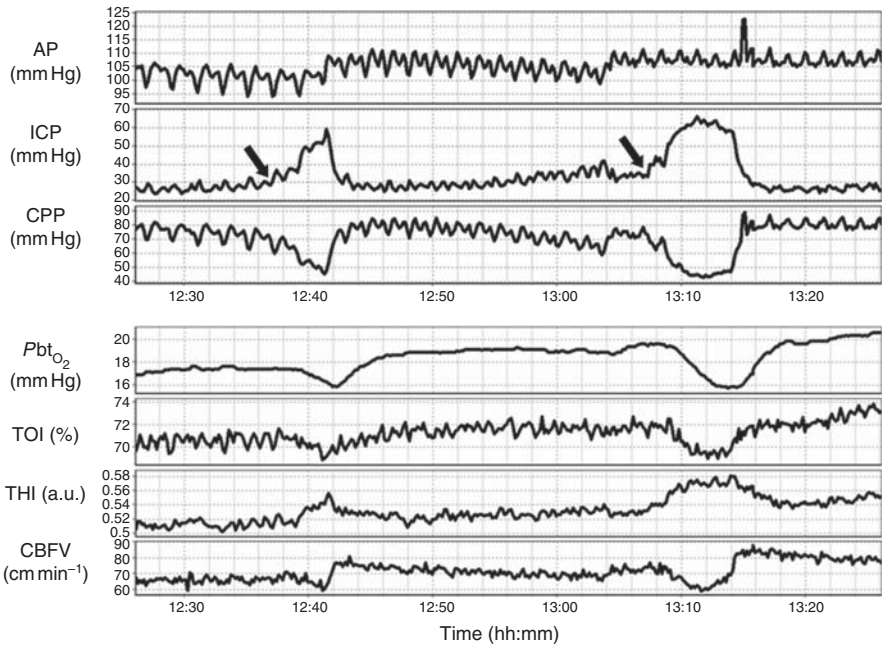

Fig 2 Two ICP-led events during a single recording from one patient (black arrows). An increase in ICP is the initiating factor and results in a decrease in CPP. Pbt_{O_2} and TOI decrease, mirroring the changes of CPP. The decrease in CBFV is a reflection of the dilated microvascular bed and is accompanied by an increase in THI, reflecting an increase in CBV. AP, arterial pressure; CBFV, cerebral blood flow velocity; CPP, cerebral perfusion pressure; ICP, intracranial pressure; THI, tissue haemoglobin index; TOI, tissue oxygen index; Pbt_{O_2}, brain tissue partial oxygen pressure.

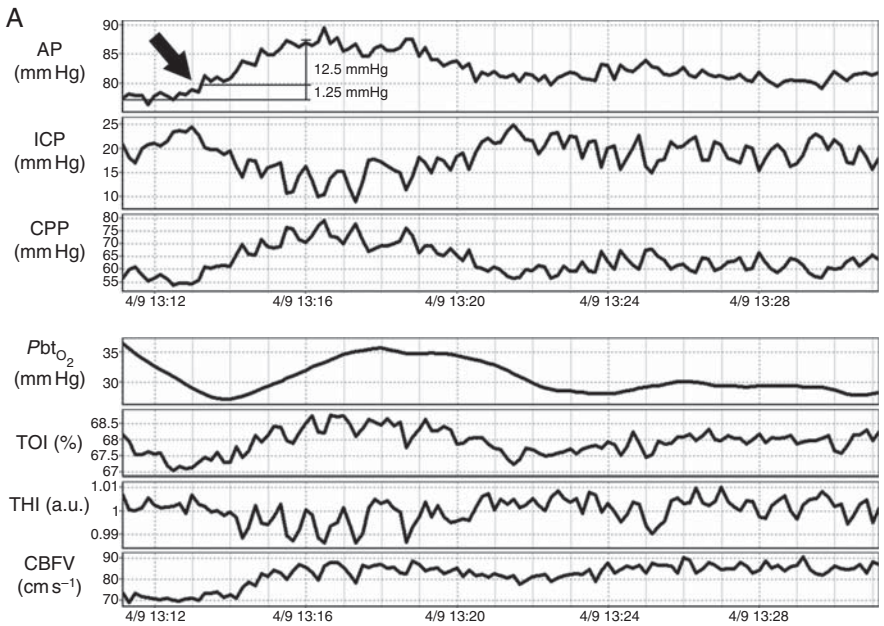

Fig 3 Example of four AP-led events during intact (A) and impaired cerebrovascular reactivity (B–D). All events represent an increase in AP (black arrows demarcate the onset of stimulus); however, in (A), it is accompanied by a decrease in ICP while in (B), (C), and (D) by an increase in ICP, representing passive pressure–volume transmission. Different patterns of responses of Pbt_{O_2} and TOI are seen: (A) both Pbt_{O_2} and TOI increase; (B) both Pbt_{O_2} and TOI decrease; (C) Pbt_{O_2} decreases while TOI increases; and (D) Pbt_{O_2} increases while TOI decreases. In all events, CBFV follows the changes in AP, but the reaction is more pronounced in (B), (C), and (D). No change in THI is seen in (A), while an increase is seen in (B) and (C) representing increased CBV and a decrease in (D) representing decreased CBV. AP, arterial pressure; CBFV, cerebral blood flow velocity; CBV, cerebral blood volume; CPP, cerebral perfusion pressure; ICP, intracranial pressure; THI, tissue haemoglobin index; TOI, tissue oxygen index; Pbt_{O_2}, brain tissue partial oxygen pressure.

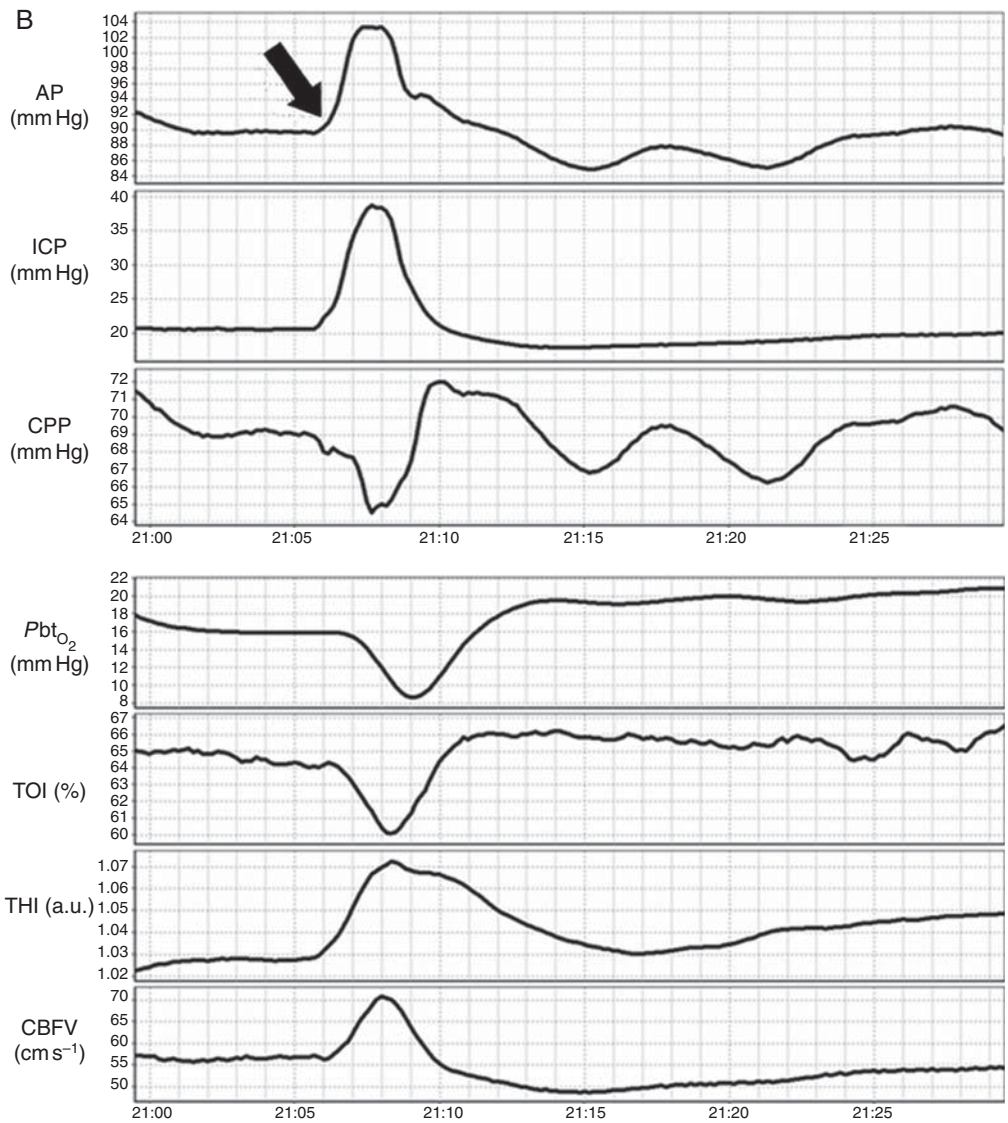

Fig 3 Continued

as a result of increased AP, blood is passively pushed into the dilated cerebral microvasculature increasing CBV, resulting in a relative increase in oxygenated haemoglobin and in consequence an increase in TOI. This is also supported by the observed increase in THI, representing increased CBV. Vasodilatation in such cases would not be reflected by $P\text{bt}_{O_2}$ measurements where free, diffused oxygen is measured.[30]

$$\text{TOI} = Sa_{O_2} - \left(\frac{\text{CBV}_{\text{ven}}}{\text{CBV}_{\text{ven}} + \text{CBV}_{\text{art}}}\right) \times \left(\frac{\text{CMRO}_2}{k \times \text{CBF} \times [\text{Hb} \times 10^{-2}]}\right) \times 100\% \quad (2)$$

Where TOI is the tissue oxygenation index, Sa_{O_2} the arterial blood oxygen saturation, CBV_{ven} the venous CBV, CBV_{art} the arterial CBV, CMRO_2 the cerebral metabolic rate of oxygen, k the oxygen combining power of haemoglobin, CBF the cerebral blood flow, and Hb the haemoglobin Sa_{O_2}.

Effects of ICP changes on $P\text{bt}_{O_2}$, TOI, and THI

During ICP-led events, predominantly plateau waves, both $P\text{bt}_{O_2}$ and TOI decreased and remained decreased for the whole duration of the wave. Plateau waves are thought to be a result of a vascular dilatory cascade, leading to an increase in CBV with a corresponding decrease in CBFV and CPP.[31–33] The observed decreases in $P\text{bt}_{O_2}$ and TOI during these events are presumably a consequence of the decreases in cerebral perfusion, resulting in a decrease in oxygen supply. The observed decreases in cerebral oxygenation for the whole duration of the wave support the need for rapid interventions lowering ICP in such situations.[34]

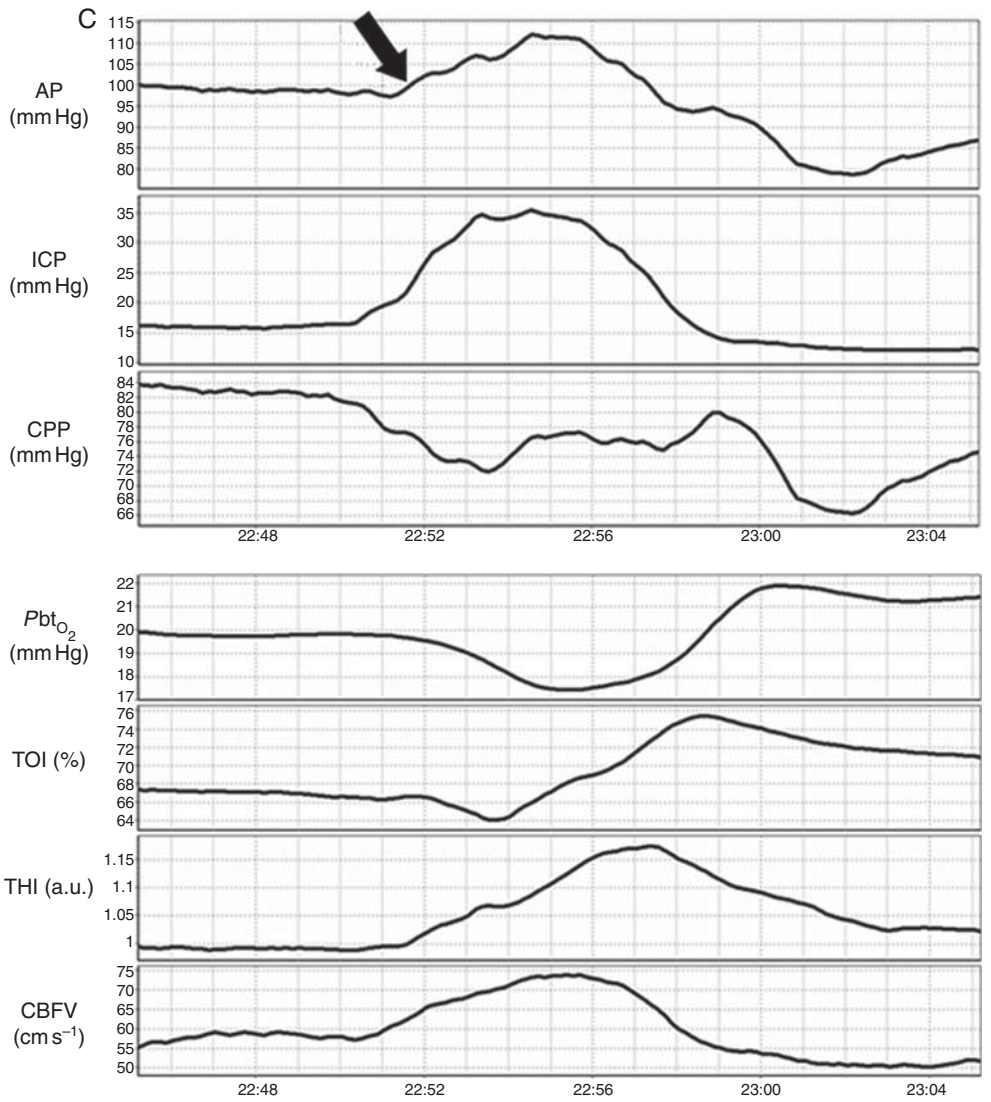

Fig 3 Continued

Limitations

There are several limitations to our study. First, the retrospective nature of the analysis does not allow concluding causality between the trigger events (AP and ICP changes) and the reactions of the oxygenation parameters. Although, it is likely that changes in AP and ICP influenced cerebral oxygenation, it is also plausible that a third factor was responsible for both the haemodynamic, ICP, and oxygenation changes. Furthermore, the relationship of the location of $P\text{bt}_{O_2}$ and NIRS probes with regard to the site of injury was not considered. However, we believe that assessment of the temporal profile of the observed changes, which was the aim of the study, should not have been altered by the location of the probes. We were also unable to retrieve exact information regarding the ventilator setting of the monitored patients. We acknowledge that it is potentially erroneous to draw definitive conclusions from cerebral oxygenation monitoring without precise knowledge of oxygenation and gas exchange. However, the obtained ABG analyses, although not continuous, demonstrate the absence of respiratory failure/insufficiency during the monitoring period. We have used the PRx for assessment of cerebrovascular reactivity. Although, the methodology of calculating PRx[26] includes AP, we do not think this precludes its use in analysing response patterns to AP changes. PRx relies on spontaneous fluctuations of AP (frequency of 0.3–3 beats min^{-1}) and it does not take into account the large-scale changes that are the subject of this study.

In all cases, the earliest reaction to changes in AP and ICP was seen in THI and CBFV followed by TOI, with changes in $P\text{bt}_{O_2}$ visible last, implying that all modalities monitor different stages of supplying oxygen to the brain. Therefore, we conclude

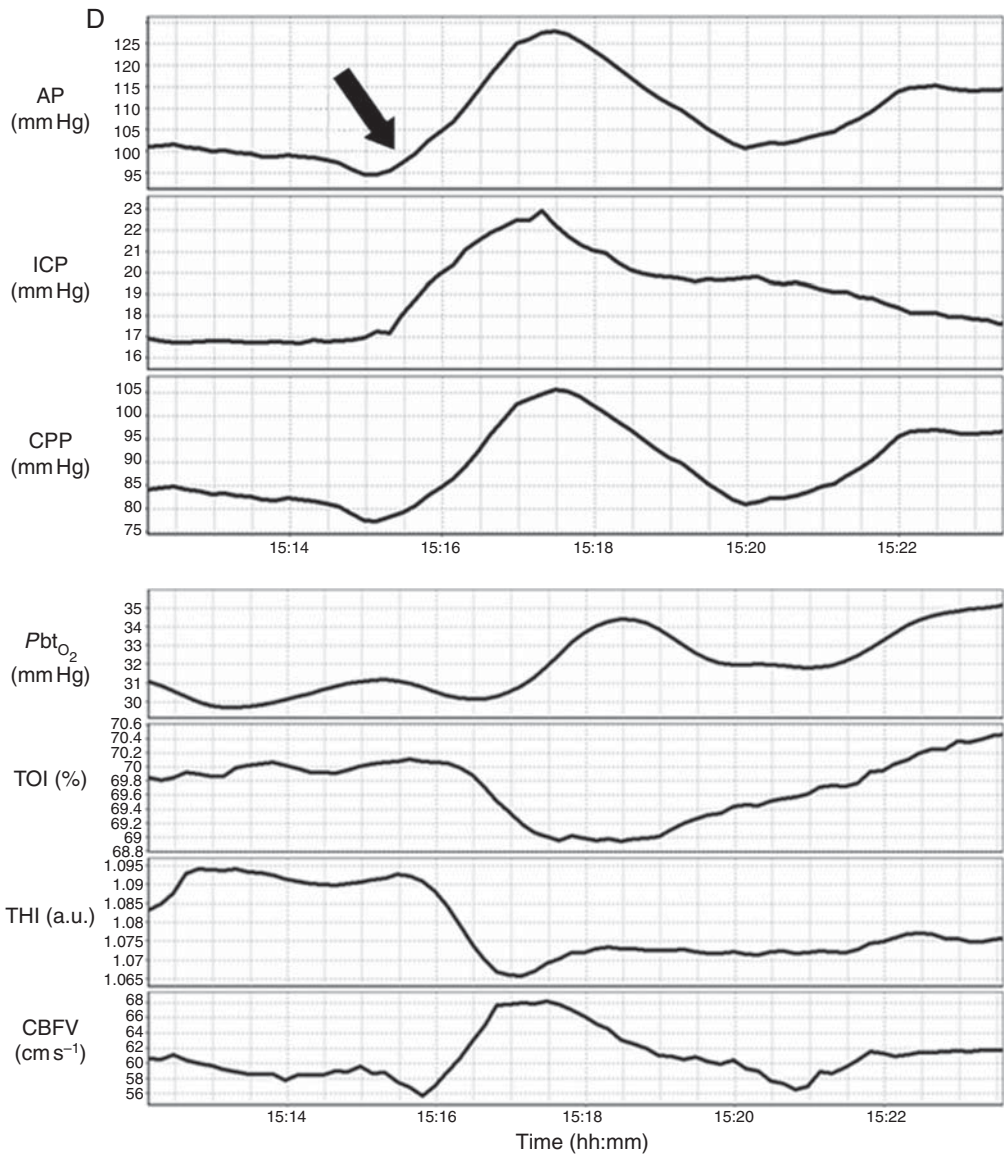

Fig 3 Continued

that Pbt_{O_2} and NIRS are complementary methods which should be analysed with respect to other intracranial parameters. Both methods show complex interrelationships with other haemodynamic determinants. The observed results suggest that multimodal brain monitoring can be used to evaluate the different stages of cerebral oxygen supply.

Declaration of interest

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