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ORIGINAL ARTICLE

Changes in Cerebral Partial Oxygen Pressure and Cerebrovascular Reactivity During Intracranial Pressure Plateau Waves

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Abstract
Background Plateau waves in intracranial pressure (ICP) are frequently recorded in neuro intensive care and are not yet fully understood. To further investigate this phenomenon, we analyzed partial pressure of cerebral oxygen ($pbtO_2$) and a moving correlation coefficient between ICP and mean arterial blood pressure (ABP), called PRx, along with the cerebral oxygen reactivity index (ORx), which is a moving correlation coefficient between cerebral perfusion pressure (CPP) and $pbtO_2$ in an observational study.
Methods We analyzed 55 plateau waves in 20 patients after severe traumatic brain injury. We calculated ABP, ABP pulse amplitude (ampABP), ICP, CPP, $pbtO_2$, heart rate (HR), ICP pulse amplitude (ampICP), PRx, and ORx, before, during, and after each plateau wave. The analysis of variance with Bonferroni post hoc test was used to compare the differences in the variables before, during, and after the plateau wave. We considered all plateau waves, even in the same patient, independent because they are separated by long intervals.
Results We found increases for ICP and ampICP according to our operational definitions for plateau waves. PRx increased significantly ($p = 0.00026$), CPP ($p < 0.00001$) and $pbtO_2$ ($p = 0.00007$) decreased significantly during the plateau waves. ABP, ampABP, and HR remained unchanged. PRx during the plateau was higher than before the onset of wave in 40 cases (73 %) with no differences in baseline parameters for those with negative and positive ΔPRx (difference during and after). ORx showed an increase during and a decrease after the plateau waves, however, not statistically significant. $PbtO_2$ overshoot after the wave occurred in 35 times (64 %), the mean difference was 4.9 ± 4.6 Hg (mean ± SD), and we found no difference in baseline parameters between those who overshoot and those who did not overshoot.
Conclusions Arterial blood pressure remains stable in ICP plateau waves, while cerebral autoregulatory indices show distinct changes, which indicate cerebrovascular reactivity impairment at the top of the wave. $PbtO_2$ decreases during the waves and may show a slight overshoot after normalization. We assume that this might be due to different latencies of the cerebral blood flow and oxygen level control mechanisms. Other factors may include baseline conditions, such as pre-plateau wave cerebrovascular reactivity or $pbtO_2$ levels, which differ between studies.

Keywords Traumatic brain injury · Cerebral hemodynamics · Cerebral autoregulation · Intracranial pressure plateau waves · Cerebral oxygenation · Cerebral partial pressure of oxygen

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Introduction

Plateau waves or so called "Lundberg A-Waves" in intracranial pressure (ICP) were first described in 1960

[1, 2]. Although known to researchers and frequently observed by clinicians in the field of ICP neuromonitoring, a pubmed literature search (http://www.ncbi.nlm.nih.gov/pubmed) using the search terms "plateau waves" and "intracranial pressure" yields only 17 peer reviewed publications over the past 10 years [3–19].

A review of the literature which was available to us, published between 1960 and 2013, shows that plateau waves occur in several neurological and neurosurgical conditions: head injury [20], ischemic stroke [21], aneurysmal hemorrhage [22], idiopathic intracranial hypertension [13, 16, 23], secondary hydrocephalus [24]; craniosynostosis [15], spinal tumors, leptomeningeal carcinomatosis and encephalitis [25], brain tumors [26], pontine hemorrhage [27], and hypertensive ICH [14, 28]. ICP plateau waves can be recorded in awake patients who have little or no neurological deficits [29, 30]. It has been suggested that they may occur in normal babies [31]. They are thought to originate, at least partially in the midbrain, pons, and brainstem [32–35], with local endothelial or perivascular mechanisms possibly acting as well [36]. Last but not least a global cerebral origin has been suggested [37]. In animal models, plateau waves are generated by thecal sac ligation [38], or obstruction with experimentally induced hydrocephalus [39]. Acetazolamide, dexamethasone, and indomethacin have been used as pharmalogical treatments [14, 40, 41], otherwise hyperventilation as a treatment option has been reported [42, 43].

The literature on neurophysiological monitoring parameters other than ABP and ICP itself during plateau waves is very sparse. A hyperemia phase along with large CBF increases has been described in primates [44], while latencies of auditory brainstem evoked potentials remained unchanged [45]. Four papers have reported on the features of cerebral blood flow velocity (CBFV) changes measured with Transcranial Doppler ultrasound (TCD) [3, 7, 10, 43].

It has been stressed that intact cerebral autoregulatory mechanisms are required to generate ICP plateau waves [14, 43, 46]. This coincides with a poor compensatory reserve for a Rosner's vasodilatatory cascade [46], to work as a positive feedback loop.

Cerebral autoregulation can be assessed with the Pressure Reactivity Index (PRx), which is an index calculated from a moving correlation coefficient between mean ABP and ICP, which has gained large acceptance in ICU settings and it has generated a large number of publications [47]. It is clinically most attractive because it does not require an external stimulus. Correlation coefficients range from 1 (entirely lost reactivity) to −1 (completely intact reactivity), and this interpretation applies to all indices used or referred to in this paper.

In addition, partial pressure of cerebral oxygen ($pbtO_2$) recording has been established as a widespread neuromonitoring tool [48]. Similar to PRx, the ORx index has been established [49]. ORx is calculated as a moving correlation coefficient between CPP and $pbtO_2$, which serves to quantify the cerebral oxygen regulation capability. Further research has suggested that the mechanisms of cerebral vascular regulation and cerebral oxygenation regulation are linked [50–53], although this remains a matter of debate [54, 55].

So far only three studies report on $pbtO_2$ during ICP plateau waves [6, 14, 42], and three papers report on the PRx during ICP plateau waves in TBI patients [5, 12, 43], unfortunately only the abstract is available in English in the Oshorov et al. paper [5]. So far one paper has reported on the interaction among $pbtO_2$, PRx, and ORx in ICP plateau waves [6].

Materials and Methods

To further characterize hemodynamic features and study tissue oxygenation during ICP plateau waves in a different dataset, we analyzed 55 plateau waves in 20 patients after severe traumatic brain injury (TBI). These 20 patients were extracted from a set of 50 computer recordings of consecutive TBI patients between November 2009 and April 2011 managed at the Neurocritical Care Unit, Addenbrooke's Hospital, University of Cambridge, United Kingdom.

All patients were sedated and mechanically ventilated receiving standard neurocritical care at Addenbrooke's neurosurgical intensive care unit with details provided elsewhere [3, 12, 43]. Note that this dataset differs from other datasets published from this unit.

Plateau waves were visually identified during post-recording offline analysis and inspection. The identification criterion was a sudden ICP elevation by at least 20 mm Hg matched by a CPP decrease, associated with an increase in ICP pulse waveform with a dominant percussion peak [6].

We calculated ABP, ABP pulse amplitude (ampABP), ICP, CPP, $pbtO_2$, heart rate (HR), ICP pulse amplitude (ampICP), PRx, and ORx, *before (baseline)*, *during*, and *after* each ICP plateau wave. The turning points of the ICP tracing, which are exemplarily shown in Figs. 1 and 2 represent the two clear cutoffs for the three time sections.

First, artefacts detection and removal were applied to raw data of ICP, ABP, and $pbtO_2$. Then PRx and ORx were evaluated as moving linear (Pearson) correlation coefficients between averaged (10 s periods) ICP and ABP (PRx) and CPP and $pbtO_2$ (ORx) calculated over the moving window of 5 min length and updated every 10 s.

The analysis of variance (ANOVA) with Bonferroni post hoc test was used to compare the differences in the variables before, during, and after the plateau wave. We considered all plateau waves, even in the same patient, independent because they are separated by long intervals, which lasted at least 30 min.

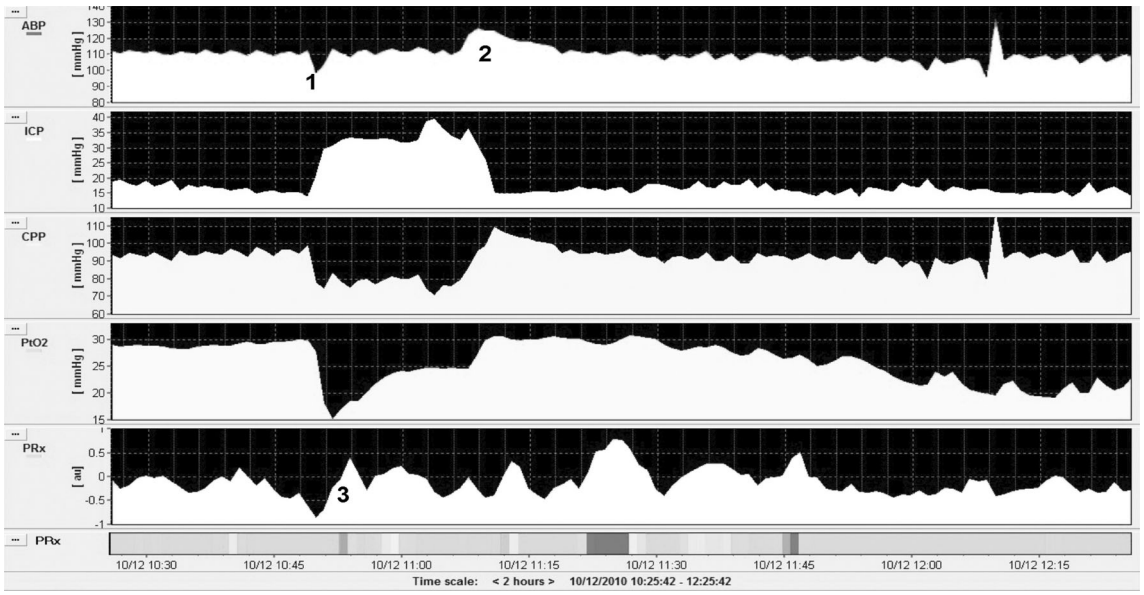

Fig. 1 This figure shows an ICP plataeu wave. Note the slight ABP drop at the beginning of the wave (*1*) and the stable ABP during the plateau phase with a slight ABP overshoot at the end (*2*). Cerebral partial pressure of oxygen (PtO_2) decreases initially from 30 to 15 mmHg, and then recovers without an overshoot. Also note the large PRx increase at the beginning of the plateau wave (*3*) although it is apparent that there are a number of other episodes of PRx increases without a corresponding plateau wave

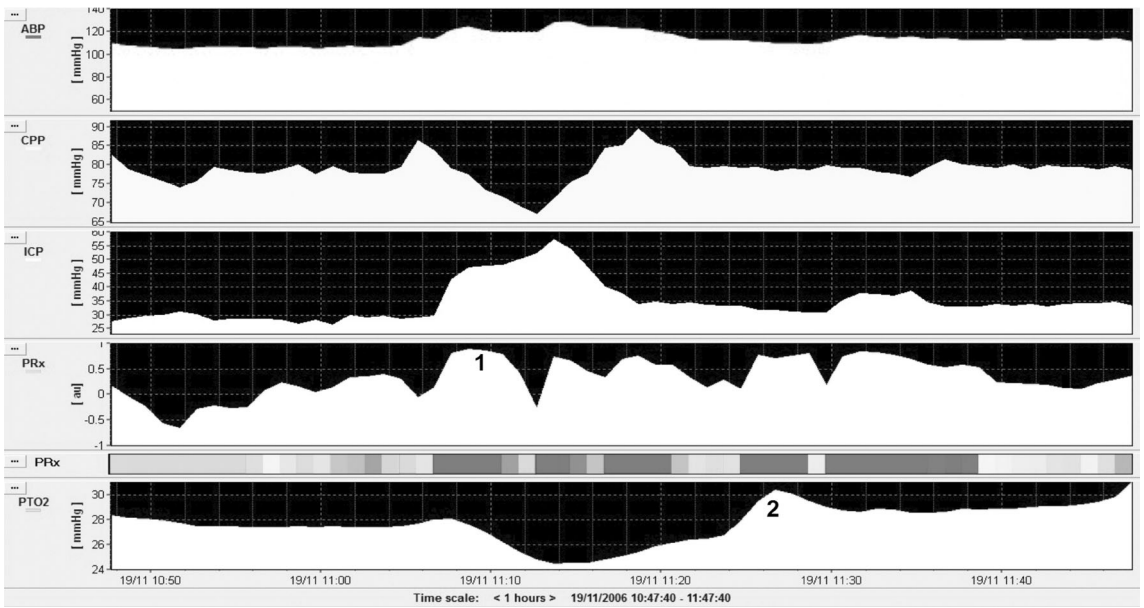

Fig. 2 This figure shows an ICP plateau wave on the third tracing along a monitored patient's course after TBI. PRx increases (*1*); cerebral partial pressure of oxygen (PTO_2) drops, recovers, and then displays a slight overshoot at the PtO2 recovery (*2*). Similar to Fig. 1, it is again apparent that there are a number of other episodes of PRx increases without a corresponding plateau wave

The ICM+ system and software (http://www.neurosurg.cam.ac.uk/ICMplus/) were used for both online data recording and offline analysis. A Licox® $pbtO_2$ probe (GMS-Integra, Kiel-Mielkendorf, Germany) was used for cerebral partial pressure of oxygen measurements. In keeping with the standard protocol at Addenbrooke's hospital ICP and Licox probe positions are checked using standard CT. No untoward effects were observed with the use of ICP or oxygen probes.

Computerized data monitoring which supports critical care management is standard clinical practice on the Neurosurgical ICU at Addenbrooke's Hospital, Cambridge UK. Use of the data for anonymous audit and publications is approved by the Local Ethical Committee.

Table 1 Monitored physiological values

	Before	During	After	*p*
ABP	97.5 ± 10.9	100.2 ± 11.6	98.1 ± 11.5	ns
ampABP	22.7 ± 5.3	23.5 ± 5.6	24.3 ± 6.2	ns
ICP	21.3 ± 6.7	48.0 ± 9.9	18.9 ± 7.1	n/a
ampICP	3.4 ± 2.4	7.9 ± 4.6	3.0 ± 2.1	n/a
CPP	76.2 ± 10.1	52.2 ± 13.4	79.2 ± 12.4	<0.00001
PtO2	22.4 ± 9.3	16.5 ± 8.8	24.4 ± 10.3	0.00007
HR	68 ± 13	70 ± 15	70 ± 14	ns
PRx	0.11 ± 0.29	0.38 ± 0.36	0.17 ± 0.40	0.00026
ORx	0.06 ± 0.27	0.24 ± 0.42	0.17 ± 0.38	ns

All physiological values are expressed in mmHG, mean ± stan.dev

HR in beats/min

PRx and ORx are correlation coefficients

ns not significant, *n/a* not applicable (according to the operational definition of a plateau waves)

Results

We found *increases* for ICP and ampICP according to the operational definition of a plateau wave. We found significant *increases* for PRx ($p = 0.00026$), and significant *decreases* for CPP ($p < 0.00001$), and $pbtO_2$ ($p = 0.00007$), during the ICP plateau waves. ABP, ampABP, and HR remained unchanged.

Pressure reactivity index during the plateau wave was higher than before the onset of the wave in 40 cases (73 %) with no differences in baseline parameters for those with negative and positive PRx (difference during and after).

Oxygen reactivity index showed an increase during and a decrease after the plateau waves, however, not statistically significant.

Mean $pbtO_2$ baseline <mean $pbtO_2$ after (overshoot) occurred 35 times (64 %), the mean difference was 4.9 ± 4.6 (mean ± SD), and we found no difference in baseline parameters between those who overshoot and those who do not overshoot.

Table 1 provides numerical results in detail.

Figs. 1 and 2 show exemplary monitoring cases.

Discussion

This study confirms previous observations on physiological parameters made with ICP plateau waves, e.g., stable ABP and HR, which contrasts them to autoregulatory ICP variations in response to changing ABP [56–58]. The ICP increases with an average of 125 % during the plateau, which compares to other studies with a 172 % ICP increase [6], 101 % [12], or 117 % [43], which supports the comparability of the studies.

Rosner and Becker have described the *four* phases of a plateau wave [46]:

1. The premonitory drift phase with an ICP increases after an ABP decrease. This autoregulatory action may trigger a plateau wave, as shown in Fig. 1.
2. The plateau phase with a rapid ICP increase and CPP decreasing further. The plateau lasts as long as the CPP remains stable and above ischemic levels.
3. The ischemic response, characterized by CPP being returned toward normal by increases in ABP in response to very low CPP's.
4. The resolution phase with a rapid ICP decline to baseline and ABP/CPP stabilization, which can be explained by autoregulatory vasoconstriction [46].

For our analysis, we have chosen *three* phases, which occur along an ICP plateau wave: *before (baseline)*, *during*, and *after* the plateau waves, in keeping with similar series [12, 43]. We choose to combine the Rosner phases 2 and 3 into one phase because it was not possible to pick up short variations as the $pbtO_2$ signal is a slow reacting, non pulsatile parameter [59].

Our series confirms a previous report, recorded at a different institution, which shows significant $pbtO_2$ decrease during the plateau of the wave compared to baseline [6]. They report a decrease from 21.4 to 16.7 (22 %) compared to a decrease from 22.4 to 16.5 (26 %) in our series. This decrease does not come unexpectedly along with the concomitant CPP decrease. It has been reported that relative $pbtO_2$ changes are predominately determined by regional CBF because 90 % of $pbtO_2$ changes were correlated to simultaneous CBF changes [60]. This concept is shared by others [61]. Radolovich et al. have reported that $pbtO_2$ generally tracks the CPP direction [54], which can be appreciated in our series.

As much as we expected a significant oxygen reactivity impairment, our data did not show this although we note its impairment during the ICP plateau wave. The ORx increases from 0.06 to 0.24, compared to an increase from 0.15 to 0.26 in a comparable series [6]. We speculate that the plateau wave terminates before cerebral oxygen reactivity is significantly disturbed because of the latency of the oxygen regulation system.

Pressure reactivity index impairment has been reported in another series from our institution with a PRx increase from 0.055 to 0.2 [12], compared to an increase from 0.11 to 0.38 in this study. In an earlier series, the reactivity impairment was more pronounced during the plateau phase with a PRx increase from 0.0053 to 0.7 [43]. This impairment has also been reported using a different autoregulatory index, called Mx [43]. The Mx reflects cerebral autoregulatory capacity and it is based on a correlation coefficient between ABP and CBFV measured with TCD

[62]. We confirm autoregulatory impairment indicated by a PRx increase during the plateau phase.

Our results also show a rather rapid $pbtO_2$ restoration and ORx improvement once the downward slope of the ICP plateau wave commences, and in the phase following the plateau. This is also seen for the PRx. In 64 % of plateau waves, we note a slight $pbtO_2$ overshoot at the end of the ICP plateau wave. This number matches exactly the 64 % reported by Dias et al. [6]. In an attempt to identify those who overshoot, we assumed that their baseline parameters were different but found no difference between the groups. Dias et al. report that those who overshoot had a lower baseline PRx, indicating better reactivity [6]. It is noted that baseline reactivity in their series was better than in ours; −0.05 vs 0.11.

Our figures also show that there are a number of other episodes of PRx increases without a corresponding plateau wave. This indicates that we cannot define any autoregulatory threshold, indicated by a certain Mx or ORx value, which promotes or triggers a plateau wave. Post-hoc identification of plateau waves may deprive the possibility to differentiate between spontaneous plateau waves and those induced by e.g., hypercapnia, nursing, positioning, bowl movement, and fewer and other frequent causes/confounders. That is one of the longstanding issues in recording and interpreting physiological data from any "live" Neuro ICU setting. This issue has been discussed ever since such data have been examined and published, and it is usually called "study limitations", which applies here as well [6, 12]. We have no way of controlling for such confounding factors because these data do not come from an animal lab with the possibility to control for many confounding factors. On the other hand none of the above has even been systematically examined to show that they can reliably produce ICP plateau waves. This is in keeping with the observation can they occur spontaneously and may or may not be triggered by any of the above. The origin of plateau waves cannot be answered with this study.

Conclusions

Arterial blood pressure remains stable in ICP plateau waves, while cerebral autoregulatory indices show distinct changes, which indicate cerebrovascular reactivity impairment at the top of the wave. $pbtO_2$ decreases during the waves and may a slight overshoot after normalization. This might be due to different latencies of the cerebral blood flow and oxygen level control mechanisms, in addition to baseline conditions.

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