

Derangement of Cerebral Blood Flow Autoregulation During Intracranial Pressure Plateau Waves as Detected by Time and Frequency-Based Methods

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Abstract Plateau waves are sudden elevations of intracranial pressure (ICP) above 40 mmHg, lasting at least 5 min, and are associated with cerebral vasodilatation. We studied the performance of several parameters for cerebral autoregulation assessment during 30 plateau waves of 24 patients with traumatic brain injury. Continuous signals were collected for ICP, arterial blood pressure (ABP) and transcranial Doppler flow velocity (FV). Parameters both in the time domain (autoregulation index, ARI and mean flow index, Mx) and the frequency domain (transfer function gain, phase and coherence) were analysed. The role of different inputs, using either ABP or cerebral perfusion pressure (CPP) as input, was also tested.

Autoregulation deteriorated from baseline to plateau, which could be demonstrated by a significant decrease in both ARI between ABP and FV ($p=0.013$) and ARI between CPP and FV ($p=0.014$). There was also a significant increase in Mx between CPP and FV ($p=0.004$), but not in Mx between ABP and FV ($p=0.472$). From the baseline to plateau, there was a significant increase in coherence between the ABP and FV at the very low frequency ($p=0.004$). The transfer function phase and gain, on the other hand, revealed inconsistent performance.

Keywords Plateau waves • Intracranial pressure • Blood pressure • Autoregulation index • Mean flow index • Transfer function

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Introduction

A sudden transient decrease in arterial blood pressure (ABP), with intact cerebral autoregulation, leads to a rapid compensatory dilation of cerebral blood vessels. Accordingly, the blood volume increases, which, in turn, under conditions of “tight” brain, causes an increase in intracranial pressure (ICP). Based on the concept of cerebral perfusion pressure (CPP), the difference between ABP and ICP, this brings a further decrease in CPP and further vasodilation until maximum vasodilation is reached [1–4]. ICP plateau waves refer to ICP increasing up to 50–100 mmHg for 5–20 min, returning to normal values either spontaneously or in response to treatment [3, 5, 6]. The rapid termination of the wave has been described by a vasoconstriction cascade model in which active vasoconstrictive events lead to decreases in CBV and ICP and an increase in CPP [1, 7]. Theoretically, plateau waves are always associated with degradation of the cerebral blood flow autoregulation ability as the vessels reach the state of maximum dilation [8].

Many methodologies have been introduced to assess cerebral autoregulation (CA), both in the frequency domain and in the time domain. These include the autoregulation index (ARI), mean flow index (Mx), transfer function (TF) phase, gain and coherence [9–16]. However, there is still no consensus on which of those approaches is the most suitable for use in traumatic brain injury (TBI). In this study we used plateau wave recordings from patients with TBI as a “test bench” to compare the performance of those parameters in their ability to distinguish between the ICP baseline and plateau phases. Furthermore, we calculated ARI, Mx and TF parameters using either arterial blood pressure (ABP) or cerebral perfusion pressure (CPP) as inputs and using flow velocity (FV) as output.

Materials and Methods

Data Collection

One hundred nineteen patients with TBI admitted to Cambridge University Hospital (Addenbrooke's) between 1992 and 2013 were studied retrospectively (a total number of 495 daily recordings). Daily transcranial Doppler (TCD) recording to assess CA is a part of standard clinical practice in our neurocritical care unit. Data were recorded and analysed anonymously as a part of a standard clinical audit approved by the Neurocritical Care Users Group Committee.

Continuous ICP signals were collected via micro-transducers (Codman & Shurtleff, Raynham, MA, USA or Camino Laboratories, San Diego, CA, USA) inserted intraparenchymally into the frontal region. Flow velocity of the middle cerebral artery (MCA) was monitored via a transcranial medical Doppler-Box (DWL Compumedics, Singen, Germany) with 2-MHz probes. The depth of insonation ranged from 4 to 6 cm and the probes were fixed using a rigid headframe (Lamrack; DWL). The patients remained lying in the bed supine during the whole process. Data from the bedside monitors were digitized using A/D converters (DT 2814, DT9801 and DT9803; Data Translation, Marlboro, MA, USA) and synchronized using data acquisition software ICM+ (Cambridge Enterprise, Cambridge, UK, <http://www.neurosurg.cam.ac.uk/icmplus>), or, in the early years, with a waveform recorder WREC for DOS (W. Zablotny, Warsaw University of Technology). The complete data set was screened for plateau waves and this resulted in a reduced data set of 30 plateau wave recordings in 24 patients.

Materials and Methods

The autoregulation index value was calculated by comparing impulse responses estimated from real data with impulse responses (IR) derived from Tiecks' model [17]. The IR of real data was estimated via the fast Fourier transform (FFT) algorithm [18, 19] using mean adjusted, normalized signals (scaled by the inverse of the standard deviation). FV and ABP were divided into four segments with 120 s recording each and transformed with the FFT algorithm using a 50 % overlap of segments (Welch method). The cross-spectra and auto-spectra of ABP and FV, the transfer function and coherence were estimated using the average value of the four segments [13, 19]. The time domain IR was computed from the inverse FFT of the transfer function, with a cutoff frequency of 0.5 Hz. After comparing the IR from real data with the ten IR curves of Tiecks' model, the best-fit curve selected using the minimum squared error criterion was chosen as the ARI value for the segment, labelled here as

ARIa. The same calculation has also been conducted using CPP instead of ABP, giving a parameter labelled ARIC.

Transfer function analysis is used to describe the transmission characteristic from input to output. It can reveal the behaviour of a linear system at different frequencies. The TF phase shows the time shift between input and output at a given frequency and the TF gain illustrates how much of the variance of output was caused by the fluctuations of input at that frequency [20, 21]. In this study, TF gain, phase and coherence in the frequency range of 0.01–0.05 Hz (very low frequency, VLF) and 0.05–0.15 Hz (low frequency, LF) were calculated using the FFT algorithm, as above [13, 19]. Both ABP and CPP were used as input respectively and here we use "a" or "c" for abbreviation, for example, "gain_a_VLF" referred to the gain between ABP and FV in the very low frequency range (Table 1). All the calculations were updated every 10 s.

Mean flow index (Mx) was calculated as a moving Pearson's correlation coefficient using 5-min windows of 10-s averages of CPP and FV [22, 23]. The results were averaged for each recording, labelled "Mxc". In addition, the calculations were repeated using ABP as input, instead of CPP, labelled "Mxa".

Statistical analysis of variables was performed using IBM SPSS Statistics (version 19) software. Results are presented in a mean value \pm standard deviation. *t* tests were used to analyse differences in autoregulatory indices between baseline and plateau. The Pearson's correlation coefficient between these parameters was calculated, recorded as *r*. Results were considered significant at $p < 0.05$.

Results

The average values of ABP, ICP and FV for all 24 patients can be found in Table 2. During plateau, mean ICP increased from 21.7 ± 8.3 mmHg to 43.8 ± 12.7 (mean \pm SD, $p < 0.05$) accompanied by a decrease in FV ($p < 0.05$) and CPP ($p < 0.05$). However, mean ABP did not show a very significant difference between baseline and plateau; an example of the behaviour of ABP, ICP, CPP and FV is presented in Fig. 1. Following the rise in ICP, the ARI decreased significantly in both ARIa ($p = 0.013$) and ARIC ($p = 0.014$), indicating deterioration of cerebral autoregulation during the plateau phase (Fig. 2a, b). Index Mxc increased significantly from 0.12 ± 0.40 at baseline to 0.47 ± 0.47 at plateau ($p = 0.004$), again showing deterioration of autoregulation. However, we could not find a significant difference between baseline and plateau when using Mxa (Fig. 2d, $p = 0.472$).

Only "phase_c" at the very low frequency range (0–0.05 Hz) showed a significant difference between baseline and plateau ($p = 0.02$). Neither "phase_a" nor "gain_a" was associated with an increased ICP at plateau (Fig. 3, $p > 0.05$).

Table 1 Abbreviations used in this paper

Abbreviation	Full name	Abbreviation	Full name
ABP	Arterial blood pressure	Phase_a_VLF	Phase between ABP and FV at very low frequency
ICP	Intracranial pressure	Phase_a_LF	Phase between ABP and FV at low frequency
FV	Flow velocity	Phase_c_VLF	Phase between CPP and FV at very low frequency
CA	Cerebral autoregulation	Phase_c_LF	Phase between CPP and FV at low frequency
CPP	Cerebral perfusion pressure	Gain_a_VLF	Gain between ABP and FV at very low frequency
ARI	Autoregulation index	Gain_a_LF	Gain between ABP and FV at low frequency
Mx	Mean flow index	Gain_c_VLF	Gain between CPP and FV at very low frequency
TF	Transfer function	Gain_c_LF	Gain between CPP and FV at low frequency
VLF	Very low frequency, 0–0.05 Hz	Coh_a_VLF	Coherence between ABP and FV at very low frequency
LF	Low frequency range, 0.05–0.15 Hz	Coh_a_LF	Coherence between ABP and FV at low frequency
TBI	Traumatic brain injury	Coh_c_VLF	Coherence between CPP and FV at very low frequency
		Coh_c_LF	Coherence between CPP and FV at low frequency

Table 2 Mean values of ABP, ICP, CPP, FV at baseline and plateau

	ABP (mmHg)	ICP (mmHg)	CPP (mmHg)	FV (cm/s)	Mxa	Mxc	AR1a	AR1c
Baseline	94.2±12.8	21.7±8.3	72.5±4.5	56.5±31.4	0.21±0.34	0.12±0.40	3.39±1.58	4.02±2.46
Plateau	93.8±11.5	49.9±15.3	43.8±12.7	48.6±27.7	0.28±0.42	0.47±0.47	2.18±1.99	2.45±2.21

Mean value ± standard deviation

Mxa mean flow index (Mx) between ABP and FV, Mxc Mx between CPP and FV, AR1a ARI between ABP and FV, AR1c ARI between CPP and FV

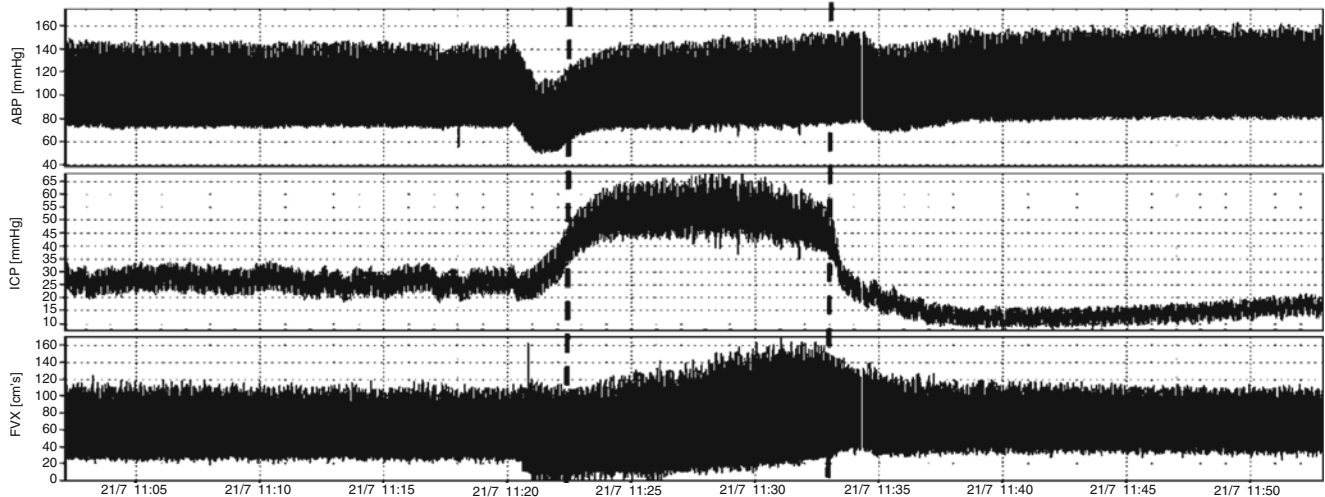


Fig. 1 An example of a plateau wave. ABP arterial blood pressure, ICP intracranial blood pressure, FVX flow velocity

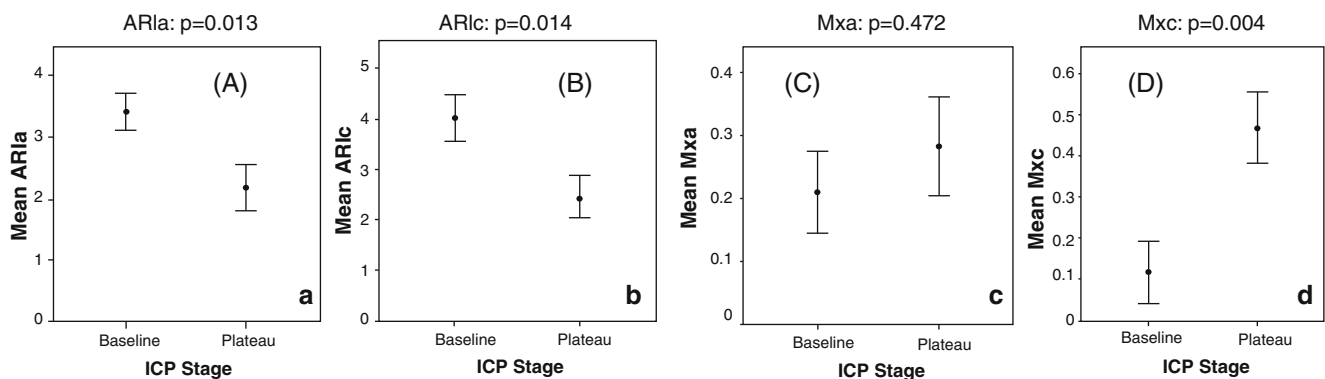


Fig. 2 Autoregulation index (AR1a and AR1c) and mean flow index (Mxa and Mxc) during baseline and plateau. Error bar standard error

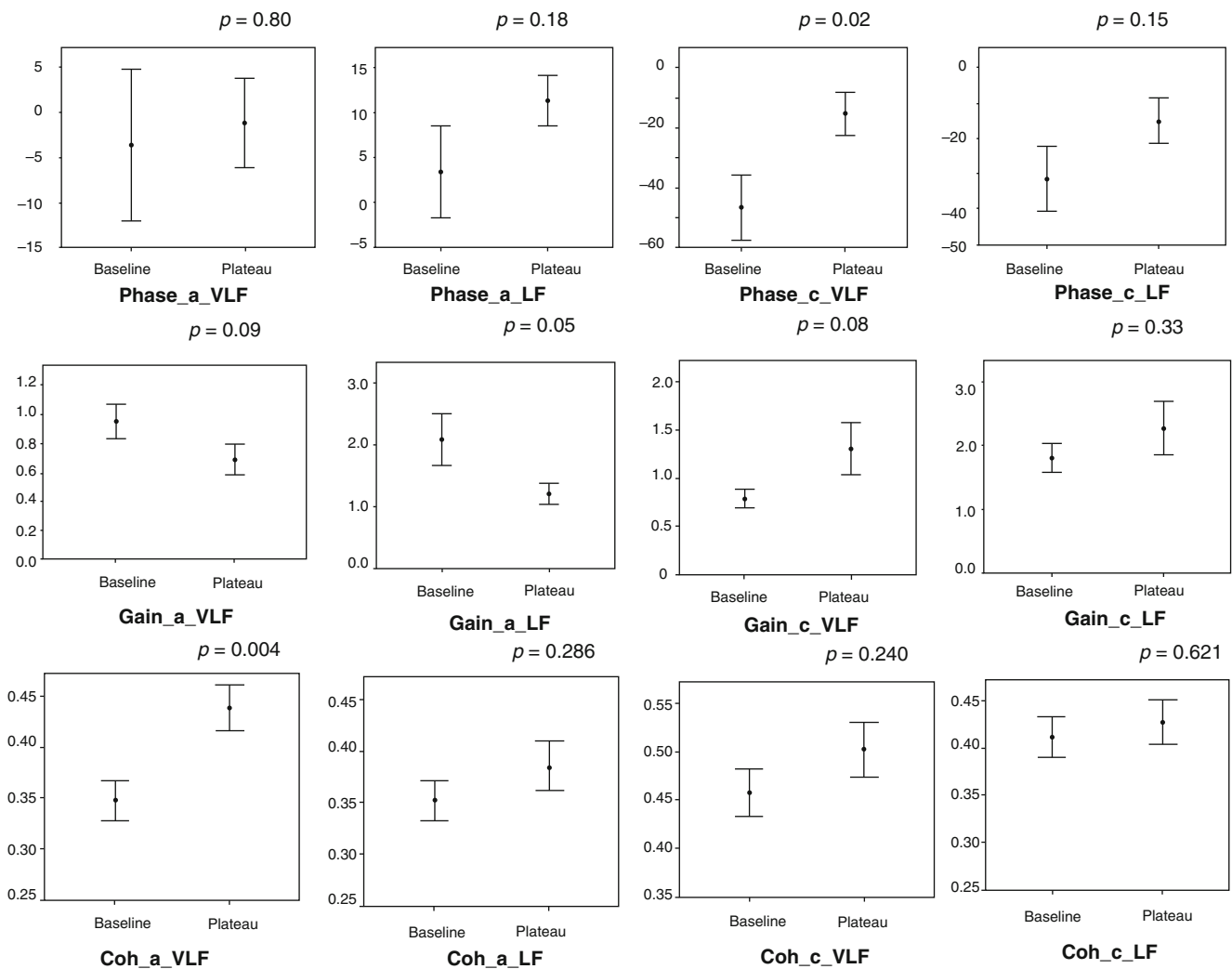


Fig. 3 Mean value of phase and gain and coherence of transfer function at baseline and plateau. *Gain_a_VLF* transfer function (TF) gain between arterial blood pressure (ABP) and flow velocity (FV) at 0–0.05 Hz, *Gain_a_LF* TF gain between ABP and FV at 0.05–0.15 Hz,

Gain_c_VLF TF gain between cerebral perfusion pressure (CPP) and FV at 0–0.05 Hz, *Gain_c_LF* TF gain between CPP and FV at 0.05–0.15 Hz

For “coh_a” and “coh_c”, there was a significant increase in “coh_a_VLF” from 0.35 ± 0.11 at baseline to 0.44 ± 0.12 at plateau ($p=0.004$). No significant differences were found in other coherence values ($p>0.05$).

Discussion

During plateau waves, ICP increases owing to vasodilation followed by an increase in blood volume. After the vessel has dilated to its maximum size, the vascular resistance and the compliance of large cerebral arteries reach their extreme levels [7, 24–26]. The cerebral blood flow autoregulation ability will be weakened accordingly because the vessel loses its pressure reactivity. This degradation in CA was

depicted in the ARI as being significantly decreased at the top of the ICP plateau and in the Mx as being significantly increased. This finding suggests a possible negative relationship between Mx and ARI. Changes in Mxc are more pronounced from baseline to plateau than changes in Mxa. This finding has also been observed in previous studies [2, 20, 21]. On the other hand, ARI proved to be sensitive to changes in autoregulation induced by the plateau waves, although less significantly than Mxc in our material, irrespective of whether ABP or CPP was used as the input. This is perhaps because the model that ARI is based on explicitly uses ABP as input. If CPP is used as input instead, errors in the estimation of ARI are likely to be introduced. On the other hand, neglecting ICP waves, by using ABP as the input, is likely to introduce errors in assessment of autoregulation, particularly when high amplitude of ICP slow waves

Table 3 Mean value of cerebral autoregulation (CA) parameters during baseline and plateau

ICP Stage		Phase_a (degree)		Phase_c (degree)		Gain_a		Gain_c		Coh_a		Coh_c	
		VLF	LF	VLF	LF	VLF	LF	VLF	LF	VLF	LF	VLF	LF
Baseline	Mean value	-3.64	3.38	-46.6	-31.4	0.95	2.10	0.79	1.81	0.35	0.35	0.46	0.41
	SD	44.7	27.2	57.2	48.2	0.60	2.17	0.47	1.17	0.11	0.11	0.13	0.12
Plateau	Mean value	-1.12	11.33	-15.3	-15.1	0.69	1.20	1.30	2.27	0.44	0.39	0.50	0.43
	SD	26.76	15.35	37.85	34.25	0.54	0.87	1.42	2.22	0.12	0.14	0.16	0.12

Phase_a phase between ABP and FV, *Phase_c* phase between CPP and FV, *Gain_a* gain between ABP and FV, *Gain_c* gain between CPP and FV, *VLF* very low frequency, 0–0.05 Hz, *LF* low frequency, 0.05–0.15 Hz

is expected, as seen during plateau waves. This may explain why both ARIa and ARIc demonstrated similar sensitivity to changes in autoregulation induced by plateau waves, which was lower than Mxc.

The increase in coherence between ABP and FV at ICP plateau implies a more direct transmission from input to output, suggesting loss of autoregulation. However, the transfer function did not behave consistently. Theoretically, if we consider CA as a high-pass filter, the better the autoregulation, the longer the time delay from input to output, and the smaller the gain. In this study, neither gain nor phase demonstrated a significant difference between baseline and plateau. In some cases, the TF phase even increased during plateau. This finding may reflect the non-linear effects of the CA system (Table 3).

Our results confirm that both ARI (ABP- or CPP-based) and Mx (CPP-based) could be used reliably as indicators of deteriorating cerebral autoregulation. On the other hand, the transfer function-derived parameters, phase, gain and coherence, showed rather inconsistent behaviour in our group of patients, and thus their use in TBI patients with plateau waves is perhaps not advisable.

Conflict of Interest ICM+ Software is licensed by Cambridge Enterprise, Cambridge, UK, <http://www.neurosurgery.com.ac.uk/icmplus/>. MC and PS have a financial interest in a fraction of the licensing fee.

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