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LETTER TO THE EDITOR

Changes in cardiac autonomic activity during intracranial pressure plateau waves in patients with traumatic brain injury

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Dear Editors,

Recent reports show that autonomic activity is altered during changes in intracranial pressure (ICP) in both animal [1], and human models [2] assessed via microneurography. In line with these studies, patients suffering from severe traumatic brain injury (TBI) often experience acute intracranial hypertensive insults called "plateau waves" [3]. These plateau waves are a physiological phenomenon during which ICP rapidly increases to 40–100 mmHg, resulting in a reduction in cerebral perfusion pressure and, consequently, cerebral blood flow (see Fig. 1; [4]). The duration of these cerebral insults can be variable, lasting from several minutes to over 30 min [4]. However, the physiological mechanisms underlying plateau waves and the consequences of these insults remain unclear. The current dogma for the mechanism(s) governing plateau waves can be described as a "vasodilatory cascade," which purports a positive feedback loop potentially commenced by a brief initial vasodilatatory stimuli (e.g. transient decrease in mean blood pressure [MAP]) [5]. Nevertheless, it has been demonstrated that long-lasting (i.e. > 30-min) plateau waves are related to poorer patient outcome (i.e. increased mortality [4]) and may cause irreversible brain ischemia injury [4]. Advancing our current understanding of the mechanism(s) that govern plateau waves in TBI patients is imperative to improve treatment strategies during these secondary cerebral insults. Cerebral vasodilation can be signaled via several tightly regulated pathways, such as changes in arterial blood gases, metabolism, MAP (i.e. cerebral autoregulation) and autonomic activity (reviewed in [6]). With reference to the latter mechanistic pathway, it was recently demonstrated that elevated relative power of the high-frequency band of heart rate (HR) and reduced baroreflex sensitivity (BRS) were related to poor patient outcome after TBI [7], which illustrates the importance of further exploring the utility of HR variability (HRV) and BRS in the clinical setting.

Both HRV and BRS have been used extensively to assess changes in cardiac autonomic nervous activity in

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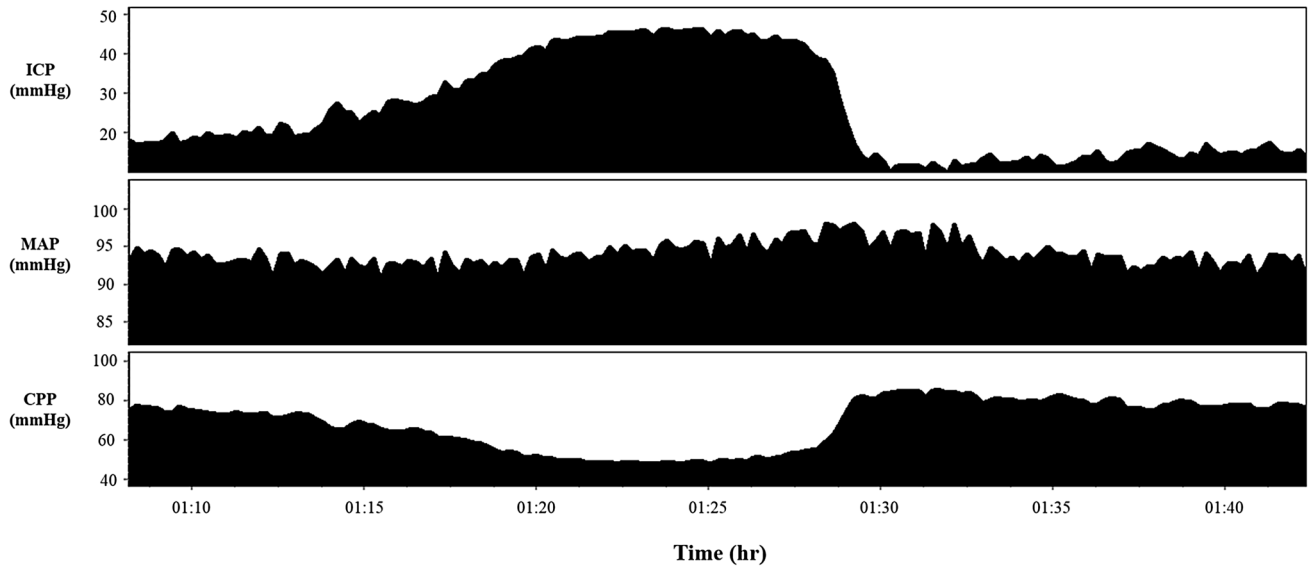

Fig. 1 Representative trace of a plateau wave in a patient with traumatic brain injury. As illustrated on the figure, during a plateau wave, intracranial pressure (*ICP*) rapidly increases, while mean arterial pressure (*MAP*) stays relatively constant, which results in a temporary reduction in cerebral perfusion pressure (*CPP*)

both healthy and clinical populations, and their accessibility in the clinical setting make these parameters an attractive index as they have clear prognostic value in heart failure [8], stroke [9] and, more recently, in TBI patients [7]. The purpose of the current investigation was to retrospectively quantify cardiac autonomic activity in patients with TBI during ICP plateau waves using HRV and BRS as indirect measurements of cardiac autonomic nervous activity. We hypothesized that during plateau waves in TBI patients, HRV assessed in both the time and frequency domain and BRS assessed in the time domain would be altered, reflecting changes in cardiac autonomic activity. To test our hypothesis, we identified a total of 94 plateau waves (Electronic Supplementary Material) in 39 patients admitted to hospital with TBI. Each patient had continuous measurements of ICP (via ICP bolt), MAP (via radial arterial catheter), and HR (via electrocardiogram). The patients (25 males; 14 females) had an average age of 37.7 ± 15.6 years ($\pm$ standard deviation) and an median admission Glasgow Coma Scale score of 5 (interquartile range 3–8).

The average data period analyzed during baseline, during plateau waves and after plateau waves was 27.6 ± 5.4, 9.7 ± 4.6 and 28.4 ± 4.4 min, respectively. The primary findings of our study were: (1) during plateau waves, both HRV and BRS analyzed in the time domain were elevated compared to baseline, and (2) HR low-frequency (HR LF) power and HR high-frequency (HR HF) power decreased relative to baseline, and the HR LF/HF ratio was elevated during plateau waves (see Table 1 for results). Collectively, these data support the notion that cardiac autonomic activity is altered during plateau waves in patients with TBI.

Although the most widely accepted mechanism of plateau waves is a vasogenic feedback loop triggered by a transient decrease in MAP, resulting in an increase in cerebral blood volume, and thus ICP [1], the intrinsic mechanism(s) that govern plateau waves are unclear. Collectively, the changes observed in HRV (time and frequency domain) and BRS (time domain) indicate that cardiac autonomic activity was altered during intracranial plateau waves. These results directly support more recently published data that indicate that ICP alters autonomic nervous activity [1, 2]; however, in these investigations the authors also reported substantial increases in MAP alongside ICP. During plateau waves, we observed only minor changes (~4 mmHg) in MAP, making our data unique. For reasons more thoroughly explained in the following paragraph, the direction that cardiac autonomic activity changes (i.e. increasing or decreasing) and, more specifically, the relative changes in sympathetic and parasympathetic nervous activity (SNA and PNA, respectively) during plateau waves cannot be determined with confidence. Regardless, it is possible that the observed changes in cardiac autonomic activity may reflect changes in cerebral blood vessel diameter and thus in cerebral blood volume.

The use of HRV and BRS as indexes of cardiac autonomic activity has been under scrutiny as it has become increasingly apparent that these indexes may not accurately represent changes in SNA and PNA—in part due to the nonlinear relationship between SNA and PNA and regional differences in autonomic activity (e.g. cerebral vs. peripheral

Table 1 Measurements of cardiac autonomic activity before, during and after plateau waves in patients with traumatic brain injury

Measures	Timing of measurement			Significance[a]		
	Baseline	During plateau waves	After plateau waves	Baseline vs. during plateau waves	During plateau waves vs. after plateau waves	Baseline vs. after plateau waves
ICP (mmHg)	20.6 ± 5.9	49.6 ± 6.5	18.6 ± 6.3	< 0.001	< 0.001	= 0.021
MAP (mmHg)	97.2 ± 11.3	101.9 ± 14.3	96.4 ± 10.6	< 0.001	< 0.001	= 1.00
CPP (mmHg)	76.6 ± 11.4	52.2 ± 14.3	77.8 ± 10.8	< 0.001	< 0.001	= 0.590
HR (bpm)	72.4 ± 19.6	75.7 ± 19.1	74.4 ± 17.5	= 0.002	= 0.120	= 0.501
HR_{sd} (ms)	18.7 ± 13.0	46.3 ± 31.7	19.3 ± 13.8	< 0.001	< 0.001	= 1.00
HR_{rmssd} (ms)	16.1 ± 15.3	18.7 ± 15.0	15.4 ± 14.8	= 0.068	< 0.021	= 1.00
HR LF (nu)	20.1 ± 9.9	11.3 ± 8.8	18.7 ± 9.3	< 0.001	< 0.001	= 0.566
HR HF (nu)	26.4 ± 18.9	11.5 ± 14.5	23.6 ± 17.1	< 0.001	< 0.001	= 0.535
HR LF/HF	1.75 ± 1.71	2.42 ± 1.99	1.52 ± 1.24	= 0.004	< 0.001	= 0.346
BRS (ms/mmHg)	7.13 ± 6.7	8.57 ± 6.96	6.91 ± 7.58	= 0.005	= 0.014	= 0.100

Data are presented as the mean ± standard deviation

ICP Intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *HR* heart rate, HR_{sd} standard deviation between R–R intervals, HR_{rmssd} root mean square of successive differences in R–R intervals, *HR LF* heart rate variability relative low-frequency power, *HR HF* heart rate variability relative high-frequency power, *HR LF*/*HF* ratio between relative low- and high-frequency power, *BRS* baroreceptor sensitivity

[a]*P* values represent statistical significance between baseline and plateau waves

autonomic activity [10]). In fact, previous reports indicate that HRV only reflects SNA in certain conditions [5]. Lastly, although this is the largest data set to describe changes in cardiac autonomic activity during plateau waves, it is likely that patients followed separate treatment avenues; thus, the data could be subject to clinical "noise." Nevertheless, both HRV and BRS were altered during plateau waves in TBI patients with minimal changes in mean HR and MAP; therefore, the current investigation provides strong evidence that cardiac autonomic activity changes during plateau waves. Despite the short-comings of using HRV and BRS, measuring autonomic nervous activity using other techniques would be incredibly difficult due to the unpredictable occurrences of plateau waves. Future studies could employ an animal model to simulate plateau waves and measure cerebral autonomic activity via norepinephrine spillover.

The current novel investigation has demonstrated that during pathological increases in ICP (i.e. plateau waves) in patients with TBI, cardiac autonomic activity was altered, as measured using changes in HRV and BRS. Elucidating the mechanism(s) responsible for plateau waves in TBI patients is important since severe and long-lasting plateau waves have been previously linked to poor patient outcome [7].

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Author contribution MMT, JD and MC were responsible for conception and design of the current study. All authors contributed to the analysis and interpretation of the data and drafted the article or critically revised it for important intellectual content. All authors approved the final version of the manuscript, and all person designated as authors qualify for authorship. All those who qualify for authorship are listed.

Compliance with ethical standards

Conflict of Interest ICM+ software is licensed by the University of Cambridge, Cambridge Enterprise Ltd. MC and PS have a financial interest in a part of its licensing fee.

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