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| **Title:** | Changes in cardiac autonomic activity during intracranial pressure plateau |
|  | waves in patients with traumatic brain injury |
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1. Dear Editors,
2. Recently, there have several reports that autonomic activity is altered during changes in
3. intracranial pressure (ICP) in both animal [1], and human models [2] using microneurography. In
4. line with these studies, patients suffering from severe traumatic brain injury (TBI) often experience
5. acute intracranial hypertensive insults called “plateau waves” [3]. These plateau waves are a
6. physiological phenomenon where ICP rapidly increases to 40-100 mmHg – resulting in a reduction
7. in cerebral perfusion pressure (CPP), and thus, cerebral blood flow (*see figure 1*; [4]). The duration
8. of these cerebral insults can be variable, lasting from several minutes to over 30-minutes in length
9. [4], however, the physiological mechanisms and consequences of plateau waves still remains
10. unclear. The current dogma for the mechanism(s) governing plateau waves can be described as a
11. “vasodilatory cascade”, which purports a positive feedback loop potentially commenced by a brief

62 initial vasodilatatory stimuli [e.g. transient decrease in mean blood pressure (MAP)] [5].

1. Nevertheless, it has been demonstrated that long lasting (i.e. >30-minutes) plateau waves are
2. related to reduced patient outcome (i.e. increased mortality [4]), and may cause irreversible brain
3. ischemia injury [4]. Advancing our current understanding of the mechanism(s) that govern plateau
4. waves in TBI patients is imperative to improve treatment strategies during these secondary cerebral
5. insults. Cerebral vasodilation can be signaled via several tightly regulated pathways such as
6. changes in arterial blood gases, metabolism, MAP (i.e. cerebral autoregulation), and autonomic
7. activity (*reviewed in:* [6]). In reference to the latter mechanistic pathway, it was recently
8. demonstrated that elevated relative power of the high frequency band of heart rate (HR), and
9. reduced baroreflex sensitivity (BRS), were related to poor patient outcome after TBI [7], which
10. illustrates the importance of further exploring the utility of heart rate variability (HRV) and BRS
11. in the clinical setting.

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

1. nervous activity in both healthy, and clinical populations, and their accessibility in the clinical
2. setting make them an attractive index as they have clear prognostic value in heart failure [8], stroke
3. [9], and more recently, in TBI patients [7]. The purpose of the current study was to retrospectively
4. quantify cardiac autonomic activity in patients with TBI during ICP plateau waves using HRV and
5. BRS as indirect measurements of cardiac autonomic nervous activity. We hypothesized that during
6. plateau waves in TBI patients, HRV assessed in both the time and frequency domain, and BRS in
7. the time domain, would be altered, reflecting changes in cardiac autonomic activity. To test our
8. hypothesis, we identified a total of 94 plateau waves (*see supplemental material*) in 39 patients
9. admitted with TBI. Each patient had continuous measurements of ICP (via ICP bolt), MAP, and
10. HR. Patients (25 males; 14 females) had an average age of 37.7 ± 15.6 yrs (± SD) with an median
11. admission Glasgow Coma Scale score of 5 (interquartile range: 3-8).
12. The average data period analyzed during baseline, during plateau waves, and after plateau
13. waves was 27.6 ± 5.4 minutes, 9.7 ± 4.6 minutes, and 28.4 ± 4.4 minutes, respectively. The primary
14. findings of the current study were: 1) During plateau waves, both HRV and BRS analyzed in the
15. time domain were elevated compared to baseline, and 2) HR low-frequency (HR LF) power and
16. HR high-frequency (HR HF) power decreased compared to baseline, and the HR LF/HF ratio was
17. elevated during plateau waves (*see table 1 for results*). Collectively, these data support the notion
18. that cardiac autonomic activity is altered during plateau waves in patients with TBI.
19. Although the most widely accepted mechanism of plateau waves is a vasogenic feedback
20. loop triggered by a transient decrease in MAP, resulting in an increase in cerebral blood volume,
21. thus ICP [1], the intrinsic mechanisms that govern plateau waves are unclear. Collectively, the
22. changes observed in HRV (time and frequency domain) and BRS (time domain) indicate that
23. cardiac autonomic activity is altered during plateau waves, despite minimal change in MAP. These
24. results directly support more recently published data, which indicate that ICP alters autonomic
25. nervous activity [1,2], however, in these investigations the authors also reported substantial
26. increases in MAP alongside ICP. During plateau waves, we observed only minor changes (~4-
27. mmHg) in MAP, making these data unique. For reasons more thoroughly explained in the
28. methodological limitations section below, the direction that cardiac autonomic activity is changing
29. (i.e. increasing or decreasing), and more specifically, the relative changes in sympathetic and
30. parasympathetic nervous activity (SNA and PNA, respectively) during plateau waves can not be
31. determined with confidence. Regardless, it is possible that the observed changes in cardiac
32. autonomic activity may reflect changes in cerebral blood vessel diameter, thus cerebral blood
33. volume.
34. The use of HRV and BRS as indexes of cardiac autonomic activity has been under scrutiny
35. as it has become increasingly apparent that these indexes may not accurately represent changes in
36. SNA and PNA – in part due to the non-linear relationship between SNA and PNA, and regional
37. differences in autonomic activity (e.g. cerebral vs peripheral autonomic activity [10]). In fact,
38. previous reports suggest that HRV only reflects SNA in certain conditions [5]. Lastly, although
39. this is the largest data set to describe changes in cardiac autonomic activity during plateau waves,
40. it is likely that patients followed separate treatment avenues, thus, could be subject to clinical
41. “noise”. Nevertheless, both HRV and BRS were altered during plateau waves in TBI patients with
42. minimal changes in mean HR and MAP, therefore, the current investigation provides strong
43. evidence that cardiac autonomic activity is changing during plateau waves. Despite the short-
44. comings of using HRV and BRS, using other techniques to measure autonomic nervous activity
45. would be incredibly difficult to achieve due to the unpredictable occurrences of plateau waves.
46. Future studies could employ an animal model to simulate plateau waves and measure cerebral
47. autonomic activity via norepinephrine spillover.
48. The current novel investigation has demonstrated that during pathological increases in ICP
49. (i.e. plateau waves) in patients with TBI, cardiac autonomic activity was altered measured via
50. changes in HRV and BRS. Elucidating the mechanism(s) responsible for plateau waves in TBI
51. patients is important since severe and long lasting plateau waves have been previously linked to
52. poor patient outcome [7].
53. **Conflict of Interest:** ICM+ software is licensed by the University of Cambridge, Cambridge
54. Enterprise Ltd. M.C. and P.S. have a financial interest in a part of its licensing fee.

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1. **Author contributions:** M.M.T., J.D., and M.C., were responsible for conception and design of
2. the current study. All authors contributed to the analysis, interpretation of the data, along with
3. drafting the article or critically revising it for important intellectual content. All authors approved
4. the final version of the manuscript and all person designated as authors qualify for authorship, and
5. all those who qualify for authorship are listed.

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1. **List of Tables:**
2. **Table 1: Measurements of autonomic activity before, during, and after plateau waves in**
3. **patients with traumatic brain injury**

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| --- | --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **Plateau** | **After** | **Baseline vs** | **Plateau vs** | **Baseline vs** |
|  |  |  |  | **Plateau** | **After** | **After** |
| **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 |
|  |  |  |  |  |  |  |
| **HRsd (ms)** | 18.7 ± 13.0 | 46.3 ± 31.7 | 19.3 ± 13.8 | <0.001 | <0.001 | =1.00 |
|  |  |  |  |  |  |  |
| **HRrmssd (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 |
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1. *Definition of abbreviations:* ICP, intracranial pressure; MAP, mean arterial pressure; CPP, cerebral
2. perfusion pressure; HR, heart rate; HRsd, standard deviation between R-R intervals; HRrmssd,
3. root mean square of successive differences in R-R intervals; HR LF, heart rate variability relative
4. low frequency power; HR HF, heart rate variability relative high frequency power; HR LF/HF,
5. ratio between relative low and high frequency power; BRS, baroreceptor sensitivity. P-values
6. represent statistical significance between baseline and plateau waves. Data is presented as mean ±
7. SD.

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1. **Figures**



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

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