Clinical Neurophysiology 129 (2018) 1161–1169

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Eyeball pressure stimulation induces subtle sympathetic activation in patients with a history of moderate or severe traumatic brain injury

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ARTICLE INFO

Article history:
Accepted 7 March 2018
Available online 30 March 2018

Keywords:
Eyeball pressure stimulation
Oculocardiac reflex
Traumatic brain injury
Central autonomic dysfunction

HIGHLIGHTS

- Patients with a history of traumatic brain injury (TBI) had impaired blood pressure control at rest.
- In these patients, eyeball pressure fails to increase cardiovagal outflow but raises blood pressure.
- These results suggest baroreflex-independent central autonomic dysfunction in patients after TBI.

ABSTRACT

Objective: After traumatic brain injury (TBI), there may be persistent central-autonomic-network (CAN) dysfunction causing cardiovascular-autonomic dysregulation. Eyeball-pressure-stimulation (EPS) normally induces cardiovagal activation. In patients with a history of moderate or severe TBI (post-moderate-severe-TBI), we determined whether EPS unveils cardiovascular-autonomic dysregulation.
Methods: In 51 post-moderate-severe-TBI patients (32.7 ± 10.5 years old, 43.1 ± 33.4 months post-injury), and 30 controls (29.1 ± 9.8 years), we recorded respiration, RR-intervals (RRI), systolic and diastolic blood-pressure (BPsys, BPdia), before and during EPS (120 sec; 30 mmHg), using an ocular-pressure-device (Okulopressor®). We calculated spectral-powers of mainly sympathetic low (LF: 0.04–0.15 Hz) and parasympathetic high (HF: 0.15–0.5 Hz) frequency RRI-fluctuations, sympathetically mediated LF-powers of BPsys, and calculated normalized (nu) LF- and HF-powers of RRI. We compared parameters between groups before and during EPS by repeated-measurement-analysis-of-variance with post-hoc analysis (significance: $p < 0.05$).
Results: At rest, sympathetically mediated LF-BPsys-powers were significantly lower in the patients than the controls. During EPS, only controls significantly increased RRIs and parasympathetically mediated HFnu-RRI-powers, but decreased LF-RRI-powers, LFnu-RRI-powers, and LF-BPsys-powers; in contrast, the patients slightly though significantly increased BPsys upon EPS, without changing any other parameter.
Conclusions: In post-moderate-severe-TBI patients, autonomic BP-modulation was already compromised at rest. During EPS, our patients failed to activate cardiovagal modulation but slightly increased BPsys, indicating persistent CAN dysregulation.
Significance: Our findings unveil persistence of subtle cardiovascular-autonomic dysregulation even years after TBI.

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https://doi.org/10.1016/j.clinph.2018.03.011
1388-2457/

1. Introduction

Traumatic brain injury (TBI) is a leading cause of disability and mortality (Ghajar, 2000; Maas et al., 2008). In the USA, TBI annually accounts for more than 50,000 fatalities (CDC grand rounds, 2013). Mild TBI is most common (CDC grand rounds, 2013) while approximately 25% of injuries are moderate or severe TBIs (moderate-severe TBIs) (CDC grand rounds, 2013). At least 5.3 million US citizens suffer from cognitive, behavioral and emotional disabilities due to a history of TBI (Ghajar, 2000; Fleminger and Ponsford, 2005; Maas et al., 2008; Masel and DeWitt, 2010). Moreover, there is evidence of increased long-term mortality rates and significantly reduced long-term survival among TBI survivors (Walker et al., 1971; Lewin et al., 1979; Rish et al., 1983; Conroy and Kraus, 1988; Kilaru et al., 1996; Strauss et al., 1998; Baguley et al., 2000; Shavelle et al., 2001; Brown et al., 2004; Pentland et al., 2005; McMillan and Teasdale, 2007; Baguley et al., 2008a,b; McMillan et al., 2011; Baguley et al., 2012; McMillan et al., 2014). So far, mechanisms of increased long-term fatalities are unclear.

In patients who had a history of TBI and died unexpectedly, Black and Graham found unremarkable cerebral autopsies and concluded that central autonomic dysfunction might contribute to sudden fatalities even years after TBI (Black and Graham, 2002).

In patients with a history of mild TBI but without clinically overt signs or symptoms of neurological or autonomic dysfunction, we showed impaired autonomic modulation at rest and upon orthostatic challenge (Hilz et al., 2011a,b). In these patients, we recently also studied cardiovascular autonomic responses to parasympathetic challenge by means of eyeball pressure stimulation (EPS) (Hilz et al., 2015). EPS induces heart rate slowing by activating the oculocardiac reflex (OCR) which involves the long and short ciliary nerves to the ophthalmic division of the trigeminal nerve, the Gasserian ganglion, the main sensory nucleus of the trigeminal nerve at the floor of the fourth ventricle, short internuclear fibers in the reticular formation, and efferent pathways originating from the motor nucleus of the vagus nerve and reaching the myocardium via depressor vagal nerve fibers (Lang et al., 1991; Schaller, 2004; Hemmer et al., 2010).

In patients with a history mild TBI, we found paradoxical cardiovascular responses to EPS (Hilz et al., 2015). From these findings, we concluded that there is a subtle, subclinical dysfunction of the central autonomic network (CAN) which might contribute to cardiovascular irregularities at rest and particularly upon autonomic challenge (Hilz et al., 2011a,b, 2015).

In contrast to mild TBIs, moderate or severe TBIs are associated with more severe, macroscopic brain lesions (Ghajar, 2000; Malec et al., 2007; Maas et al., 2008). Thus, impairment of central autonomic control seems more likely to occur in patients with a history of moderate or severe TBI than in patients who had experienced mild TBI.

We hypothesize that central autonomic modulation is also impaired in patients with a history of moderate or severe TBI and causes prominent impairment of cardiovascular adjustment to cardiovagal autonomic challenge.

In this study, we therefore evaluated cardiovascular autonomic responses to parasympathetic challenge in patients with a history of moderate or severe TBI (Hilz et al., 2015).

2. Patients and methods

2.1. Participants

In 51 patients (12 women and 39 men, mean age 32.7 ± 10.5 years) who had suffered moderate or severe TBI (post-moderate-severe TBI) 6–144 months before this study (mean interval since the TBI 43.1 months; standard deviation 33.4 months), we assessed heart rate (HR), blood pressure (BP), and autonomic parameters at rest and during parasympathetic challenge by eyeball pressure stimulation (EPS). We first retrospectively evaluated the medical records, physical and neurological status and the severity of TBI at the time of the initial injury from a registry of TBI patients; then, we invited patients meeting our inclusion criteria to participate in the study. To classify TBI severity we used the Glasgow Coma Scale (GCS) score at the time of the initial trauma as well as the Mayo TBI Severity Classification System which has a high specificity (98%) to retrospectively determine moderate-severe TBI (Malec et al., 2007). Diagnosis of moderate-severe TBI was established if one or more of the following criteria applied (Malec et al., 2007): *"(1) death due to this TBI, (2) loss of consciousness of 30 minutes or more, (3) post-traumatic anterograde amnesia of 24 hours or more, (4) worst Glasgow Coma Scale score within the first 24 hours <13 (unless invalidated upon review, e.g., attributable to intoxication, sedation, systemic shock), (5) one or more of the following present: intracerebral, subdural or epidural hematoma, cerebral or hemorrhagic contusion, penetrating TBI (dura penetrated), subarachnoid hemorrhage, brain stem injury"* (Malec et al., 2007; Brown et al., 2011).

We used the following exclusion criteria: (1) patients in whom the TBI manifestations were caused by alcohol, drugs, medications, other injuries or therapies for other injuries, (2) patients with a history of diseases or on any medication that might affect autonomic modulation. The results in the TBI patients were compared to the findings in 30 age- and gender-matched healthy participants (10 women and 20 men, mean age 29.1 ± 9.8 years) (Hilz et al., 2015).

The study had been approved by the Institutional Review Board (IRB) of New York University and the Ethics Committee of the University of Erlangen-Nuremberg, Germany. We explained the purpose and nature of the study as well as possible risks of the applied study procedures according to the declaration of Helsinki, and then obtained written informed consent from the study participants.

2.2. Measurements of bio-signals

All study participants refrained from caffeine, nicotine and alcohol for 18 hours prior to the study, as these substances might interfere with the cardiovascular autonomic modulation (Low, 1997) and might possibly alter cardiovascular responses to autonomic challenge tests such as the eyeball pressure stimulation. To minimize possible acute withdrawal effects, we only enrolled participants who were no heavy users of caffeine, nicotine and alcohol but felt comfortable with our request to abstain from caffeine, nicotine or alcohol prior to our study. Participants were tested in a reclining armchair in a quiet room with 24 °C ambient temperature and stable humidity, between 9 a.m. and 2 p.m., after resting for 40 minutes (Hilz et al., 2015).

During a 2-minute resting period and a 2-minute period of eyeball pressure stimulation, we recorded RR-intervals via a standard 3-lead electrocardiogram (ECG). The three superficial skin ECG electrodes were placed on the chest, under the left and right clavicles in the midclavicular line, and over the left costal arch. We used finger pulse photoplethysmography (Portapres; TPD Biomedical Instrumentation, Amsterdam, The Netherlands) to continuously measure beat-to-beat systolic and diastolic BP (BPsys, BPdia) at the left hand (Hilz, 2002). A respiratory belt which is based on piezoelectric principles was used to monitor respiration at the lower thorax, at the point of maximal respiratory excursion (Hilz, 2002).