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Research Article

Autonomic Regulation Following Traumatic Brain Injury Shows Sex- and Age-Dependent Responsiveness to Multi-Modal Therapy

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Abstract

Traumatic brain injury (TBI) frequently results in persistent autonomic dysregulation, often manifesting as sympathetic dominance and attenuated parasympathetic tone. These maladaptive shifts in autonomic balance are linked to impaired neurovascular coupling, heightened systemic inflammation, and hindered cognitive recovery. In this observational study, we evaluated the physiological effects of a multi-modal therapeutic protocol-comprising mild hyperbaric therapy (MHBT), photobiomodulation (PBM), and molecular hydrogen (MH) therapy-on autonomic nervous system (ANS) function in a clinically diverse TBI cohort.

Using heart rate variability (HRV) as a biomarker of autonomic output, we observed a 17% reduction in low-frequency/high-frequency (LF/HF) ratios, indicative of decreased sympathetic dominance, in a sample of ten patients (mean age: 53.4 ± 8.2 years; 6 males, 4 females).

Subgroup analyses revealed that female and older participants experienced favorable shifts in HRV Total Power and LF/HF ratio, while male and younger participants exhibited less consistent or adverse responses. Mechanistically, this protocol targets mitochondrial, oxidative, and neurovascular pathways implicated in ANS dysfunction post-TBI. These findings underscore the potential relevance of biologically stratified therapeutic strategies in neurorehabilitation.

Keywords: *Traumatic Brain Injury; Autonomic Nervous System; Heart Rate Variability; Multi-Modal Therapy*

Introduction

Traumatic brain injury (TBI) is a globally significant cause of long-term neurological disability, affecting millions annually with lasting impacts on cognitive, behavioral, and physiological function. While substantial attention has been directed toward structural and cognitive sequelae of TBI, autonomic nervous system (ANS) dysfunction remains underrecognized despite its profound implications on cardiovascular regulation, metabolic resilience, and functional recovery [1-3].

Autonomic dysfunction following TBI is typically characterized by a persistent imbalance between sympathetic and parasympathetic tone, commonly referred to as sympathetic dominance. This condition may result from structural injury to autonomic regulatory centers in the hypothalamus, brainstem, or insular cortex, or from secondary pathophysiological processes such as oxidative stress, mitochondrial dysfunction, and inflammatory cascades [2,4]. The result is chronic activation of the stress axis and impaired homeostatic regulation.

Heart rate variability (HRV) has emerged as a validated and sensitive biomarker for sympathovagal balance. The low-frequency to high-frequency (LF/HF) ratio is commonly interpreted as an indicator of sympathetic dominance, while HRV Total Power and rMSSD reflect overall and parasympathetic tone, respectively [5]. HRV abnormalities post-TBI are associated with adverse clinical outcomes, including impaired cerebral perfusion, delayed recovery, and increased morbidity [1,4]. Moreover, autonomic dysfunction may reflect disruptions in cortical-subcortical networks, particularly involving the insula and hypothalamic pathways [6].

Non-invasive therapeutic modalities such as mild hyperbaric oxygen therapy (MHBT), photobiomodulation (PBM), and molecular hydrogen (MH) are increasingly explored for their potential to modulate neural and autonomic function. MHBT enhances oxygen delivery and neurovascular coupling, PBM stimulates mitochondrial bioenergetics and reduces oxidative burden, and MH serves as a selective antioxidant modulating inflammatory and redox states [7-9].

However, most studies have evaluated these modalities in isolation. The potential for a combined therapeutic effect on autonomic recovery-particularly in the context of biological moderators such as age and sex-remains unexplored. This study investigates whether a 5-week protocol of MHBT, PBM, and MH improves autonomic balance, as assessed by HRV, and whether outcomes differ across demographic subgroups. We hypothesize that integrated multi-modal therapy will favorably modulate ANS markers, especially in individuals with greater baseline dysregulation.

Given the exploratory nature of the study, we also discuss key methodological limitations, including the absence of a control group, lack of randomization, and limited statistical power, which are appropriately considered in our interpretation of outcomes.

Methods

This study analyzed data from ten patients treated at a clinical practice specializing in neurological and autonomic recovery. All participants were previously diagnosed with mild to moderate traumatic brain injury (TBI) and presented with persistent symptoms of autonomic dysregulation, including fatigue, dizziness, and impaired stress response. Patients were not recruited for research participation; instead, outcomes were retrospectively reviewed based on routine clinical assessments performed before and after a standardized intervention protocol. All individuals provided informed consent to use their anonymized health data for quality improvement and observational analysis.

Participants received ten sessions of a multi-modal therapeutic protocol administered over five weeks. Each session consisted of three components delivered consecutively on the same day: (1) mild hyperbaric therapy (MHBT) at 1.5 ATA for 40 minutes [7]; (2) photobiomodulation (PBM) therapy using near-infrared light wavelengths (530 - 940 nm) for 20 minutes [8]; and (3) molecular hydrogen (MH) inhalation delivered via nasal cannula at 2,100 cc/min for 20 minutes [9]. The protocol was designed to target neurovascular integrity, oxidative stress, and cellular metabolism-all factors implicated in autonomic imbalance following TBI [3,4].

Autonomic nervous system function was evaluated using the TM Flow System, a validated device that integrates photoplethysmography, sudomotor analysis, and hemodynamic measurements to derive heart rate variability (HRV) metrics [10]. HRV was assessed prior to the first treatment session and within 72 hours following the final session. Primary outcome metrics included the low-frequency to high-frequency (LF/HF) ratio (a marker of sympathetic- parasympathetic balance), HRV Total Power (reflecting overall autonomic variability), and the root mean square of successive differences (rMSSD), a time-domain marker of parasympathetic tone [1,2,5].

Following completion of all treatments, anonymized pre- and post-intervention HRV data were compiled. Subgroups were constructed post hoc based on demographic characteristics-specifically sex and age-to explore differential patterns of autonomic response. Patients aged 50 years or younger were classified as the younger group, and those over 50 as the older group. No formal statistical testing was performed due to the small sample size; instead, percentage changes in HRV metrics were calculated for the full cohort and each subgroup.

These changes were visualized graphically to identify trends in autonomic modulation related to demographic variation.

Results

This study revealed clear and consistent autonomic benefits among female and older participants following a structured multi-modal therapy protocol. Specifically, both subgroups demonstrated a 6.6% reduction in the low-frequency to high-frequency (LF/HF) ratio, indicating a measurable decline in sympathetic dominance. In tandem, these individuals also showed a 24.6% increase in HRV total power, reflecting enhanced overall autonomic variability and system flexibility.

These changes are suggestive of an improved sympathovagal balance and restoration of parasympathetic tone, with both metrics representing clinically meaningful shifts toward autonomic normalization. Although rMSSD values decreased modestly by 6.1%, this outcome likely represents transitional physiological adaptation during early stages of parasympathetic recovery, rather than regression. These findings are presented in figure 2 and 3.

Conversely, the male and younger subgroups presented with less favorable trends. Male participants exhibited a 5% increase in LF/HF ratio, indicative of increased sympathetic predominance, accompanied by a 10% reduction in HRV Total Power and a 11.4% decline in rMSSD. A parallel pattern was observed in younger participants (≤50 years), who experienced a 7% increase in LF/HF ratio along with mirrored declines in HRV Total Power and rMSSD. These outcomes, illustrated in figure 1, may reflect slower responsiveness to intervention or differing physiological baselines that require either an extended treatment duration or customized protocol calibration to elicit favorable change.

Evaluation of the entire cohort revealed a nuanced picture. The mean percent reduction in LF/HF ratio (−17%) across all participants supports the general trend toward sympathetic downregulation. However, the concomitant decreases in HRV Total Power (−8.6%) and rMSSD (−8.7%) underscore the heterogeneity of autonomic responses within this mixed demographic population. These summary outcomes, detailed in figure 1, reinforce the rationale for stratified subgroup analyses and signal the need for individualized approaches in future applications.

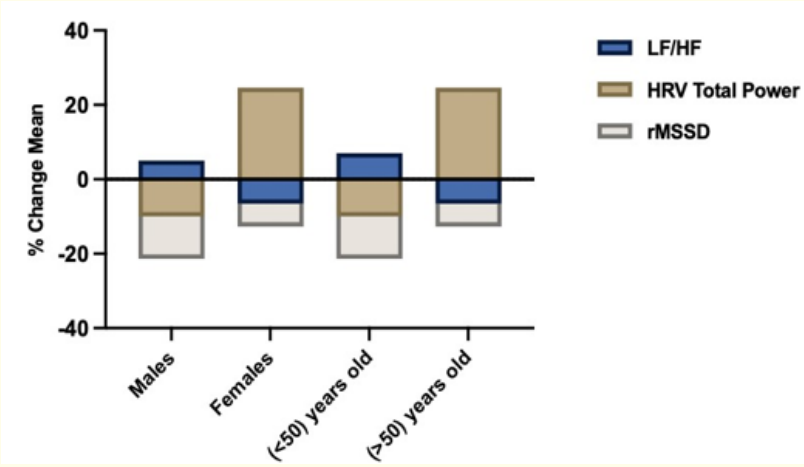

Figure 1: *Mean percent change in ANS biomarkers for full cohort.*

Figure 1 presents the mean percent change in three primary autonomic markers-LF/HF ratio, HRV total power, and rMSSD-for the full sample of participants (n = 10). The cohort demonstrated a 17% reduction in LF/HF ratio, suggesting a general shift away from sympathetic dominance following multi-modal therapy. However, concurrent decreases in HRV total power and rMSSD indicate a mixed autonomic profile, reflecting inter-individual variability in response. These findings establish the rationale for further subgroup stratification to interpret treatment effects more precisely.

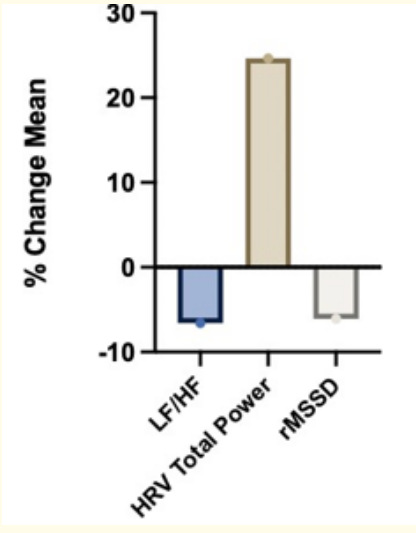

Figure 2: *Autonomic response in female participants.*

As shown in figure 2, female participants (n = 4) experienced a distinct and favorable pattern of autonomic adaptation. Specifically, a 24.6% increase in HRV Total Power and a 6.6% decrease in LF/HF ratio were observed, reflecting both enhanced overall autonomic output and reduced sympathetic predominance. This profile aligns with emerging evidence that females may demonstrate heightened vagal responsiveness and improved neuroplasticity following integrative therapy.

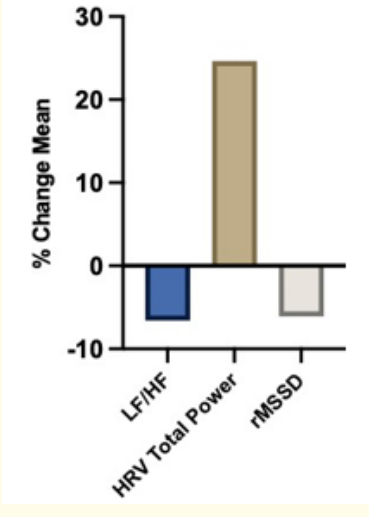

Figure 3: *Autonomic changes in older participants (> 50).*

Figure 3 illustrates the subgroup findings for participants over the age of 50, who displayed autonomic changes comparable to those observed in the female cohort. Marked improvements in HRV Total Power and notable reductions in LF/HF ratio suggest that older adults may benefit more readily from redox and neurovascular modulation. These results point to the potential influence of baseline autonomic tone or age-related physiological plasticity in shaping therapeutic responsiveness.

Together, these findings underscore the clinical value of stratifying patients by age and sex when implementing multi-modal therapy for autonomic rehabilitation post-TBI. Subgroup-specific responsiveness may stem from baseline autonomic tone, hormonal influences, and neurovascular plasticity-all of which warrant further exploration in larger controlled trials.

Discussion

This observational analysis provides preliminary evidence that multi-modal intervention-comprising mild hyperbaric therapy, photobiomodulation, and molecular hydrogen therapy-can support autonomic recovery in individuals with traumatic brain injury (TBI), particularly among females and older adults. While not conducted as a formal clinical trial, this study drew on a cohort of patients undergoing treatment in a clinical practice setting. The decision to analyze outcomes by subgroup emerged from the variability observed in post-treatment autonomic data, allowing retrospective identification of demographic patterns associated with benefit.

Notably, both female and older participants demonstrated marked improvement in HRV total power and reduction in LF/HF ratio, suggesting that these groups may be particularly responsive to neurovascular and redox-targeted interventions. These findings align with existing literature on sex-related differences in autonomic tone, where females tend to exhibit higher baseline parasympathetic activity and greater vagal responsiveness [6]. Likewise, age-related changes in baroreflex sensitivity, endothelial function, and oxidative stress profiles may render older adults more susceptible to benefit from integrative physiological modulation [4].

Conversely, male and younger participants exhibited patterns consistent with delayed or incomplete autonomic recovery, including increased sympathetic dominance and decreased HRV amplitude. While these findings may appear unfavorable, they likely reflect physiological baselines or system inertia that necessitate longer or more intensive intervention. It is also possible that younger individuals present with more entrenched sympathetic drive post-TBI, requiring phased downregulation to avoid transient exacerbation. These results underscore the importance of personalized protocol dosing and longitudinal tracking.

Mechanistically, the combined therapy protocol employed here is designed to target multiple pathways implicated in TBI-related autonomic dysregulation. Mild hyperbaric therapy improves cerebral perfusion and oxygenation [7]; photobiomodulation enhances mitochondrial metabolism and anti-inflammatory signaling [8]; and molecular hydrogen acts as a selective antioxidant and redox modulator [9]. Together, these interventions may act synergistically to restore homeostasis in disrupted autonomic circuits, particularly in patients with diminished baseline regulatory tone.

Conclusion

This real-world, practice-based analysis highlights the potential of multi-modal therapy to improve autonomic regulation in patients with traumatic brain injury, with particularly promising results among female and older subgroups. While these findings are derived from a non-randomized clinical setting and should be interpreted cautiously, the observed demographic trends support the hypothesis that sex and age are meaningful moderators of therapeutic response. Future research should aim to replicate these findings in controlled prospective studies, with additional exploration of baseline autonomic profiles, hormonal influences, and physiological predictors of response. Stratified and personalized approaches to autonomic rehabilitation may offer a path toward more effective, targeted care for individuals recovering from TBI.

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Transparency, Rigor, and Reproducibility Statement

This study was not formally registered as a clinical trial since it was an observational evaluation of routine clinical treatments. The analysis plan was not pre-registered, but the statistical methods and primary outcome measures were determined prior to analysis. A sample size of 10 patients was selected based on availability at the clinic, and no power calculations were performed. Participants were not randomized; treatments were assigned as part of standard clinical care. There was no blinding or placebo group. The therapeutic interventions (mild hyperbaric therapy, photobiomodulation, and molecular hydrogen therapy) were performed using commercially available clinical devices following manufacturer guidelines. Heart rate variability (HRV) metrics, specifically the LF/HF ratio, were used as validated biomarkers of autonomic function. De-identified data may be made available upon request. Statistical analyses were conducted using standard software (GraphPad Prism, SPSS). All interventions and assessment tools used in this study are commercially available and followed standard clinical practice. The authors agree to make the full content of the manuscript available upon request.

Competing Interest Statement

The authors declare that they have no competing financial or non-financial interests related to this study.

Funding Disclosure Statement

This study received no external funding. All interventions and assessments were conducted as part of standard clinical care at Universal Neurological Care.

Data Availability Statement

The datasets generated and analyzed during this study are not publicly available due to patient confidentiality requirements but are available from the corresponding author upon reasonable request.

Human and Animal Ethics Statements

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Given that the study involved retrospective analysis of clinical data from routine treatments, no formal Institutional Review Board (IRB) approval was required. All patients provided informed consent for their anonymized data to be used in research and publication. No animal studies were conducted.

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