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Is age or cardiovascular comorbidity the main predictor of reduced cerebrovascular pressure reactivity in older patients with traumatic brain injury?

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ABSTRACT

Introduction: The Pressure Reactivity index (PRx) has been proposed as a surrogate measure for cerebrovascular autoregulation (CA) and it has been described that older age is associated with worse PRx. The etiology for this reduced capacity remains unknown.
Research question: To investigate the relation between age and PRx in a cohort of patients with traumatic brain injury (TBI) while correcting for cardiovascular comorbidities.
Material and methods: This is a retrospective analysis on prospectively collected data in 151 consecutive TBI patients between 2013 and 2023. PRx was averaged over 5 monitoring days and correlated with demographic, patient and injury data. A multiple regression analysis was performed with PRx as dependent variable and cardiovascular comorbidities, age, Glasgow motor score and pupillary reaction as independent variables. A similar model was constructed without age and compared.
Results: Age, sex, thromboembolic history, arterial hypertension, Glasgow motor score and pupillary reaction significantly correlated with PRx in univariate analysis. In multivariate analysis, age had a significant worsening effect on PRx ($p = 0.01$), while the cardiovascular risk factors and injury severity had no impact. The comparison of the models with and without age yielded a significant difference ($p = 0.01$), underpinning the independent effect of age.
Discussion and conclusion: In the present cohort study in TBI patients it was found that older age independently impaired cerebrovascular pressure reactivity regardless of cardiovascular comorbidity. Pathophysiology of TBI and physiology of ageing seem to line up to synergistically produce a negative effect on brain perfusion.

1. Introduction

Cerebrovascular autoregulation (CA) is the mechanism that maintains adequate brain perfusion in terms of relatively constant cerebral blood flow (CBF) over a range of arterial blood pressures (ABP). CA is mainly brought about by adjustments in arteriolar basal tone in response to alterations in intraluminal pressure and flow (Xiong et al., 2009; Allen et al., 2014). It has been suggested that CA mainly protects against too low CBF in situations of low ABP by a substantial capacity for vasodilation below baseline ABP, and that vasoconstrictive capacity above baseline is less pronounced (Klein et al., 2022).

When the brain is injured, CA function can be impaired, leading to an inability to adequately safeguard brain perfusion. This impairment in turn can result in ischemic or hyperemic damage adding up to the original brain disease state. CA and its dynamic dysfunction has been identified as a crucial factor in the pathophysiology of traumatic brain injury (TBI) (Robertson et al., 1999; Svedung et al., 2022).

To date, it is not possible to obtain real-time adequate monitoring of CA function in patients, since also a reliable real-time continuous monitor of CBF is lacking. However, the Pressure Reactivity index (PRx) has been proposed as a proxy of vasoreactivity and which is calculated as a moving correlation coefficient of intracranial pressure (ICP) and mean arterial blood pressure (Czosnyka et al., 1997). Negative values of PRx then indicate active vasoreactivity and positive values impaired vasoreactivity. Even when being a surrogate for CA, PRx has been extensively investigated in clinical series, and it was demonstrated that PRx averages inversely correlate with outcome following TBI (Sorrentino et al., 2012).

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In addition to brain injury, other factors in patients and healthy humans may affect CA function, and this variability of function is not well documented. Czosnyka et al. and Batson et al. have suggested that higher age compromises pressure reactivity following TBI (Czosnyka et al., 2005; Batson et al., 2022). The impact of ageing on the functional capacity to alter arteriolar basal tone was also demonstrated in a mouse model by Toth et al. (2013). However, the underlying nature of reduced capacity for CA with age remains unknown. A plausible explanation is that endothelial function is altered with increasing age, as was for instance demonstrated in Alzheimer's disease (Jagust et al., 1997). In conjunction with this, but potentially as a trigger mechanism, increased stiffness of large elastic arteries has been proposed (Reeve et al., 2024). Such increased large artery stiffness is also associated with cardiovascular comorbidities associated with ageing. The aim of the present study was to investigate the relation between age and pressure reactivity in a cohort of patients that underwent invasive monitoring following TBI, while correcting for cardiovascular comorbidities.

2. Material and method

2.1. Patient population and variables

The study includes 151 patients who underwent invasive monitoring of ICP and ABP following TBI at the University Hospitals Leuven between 2013 and 2023 and in whom monitoring data was captured at frequencies of 50 Hz or greater in ICM+ (Cambridge Enterprise, Cambridge, UK). Each patient received a radial arterial line for the continuous measurement of ABP with the ABP pressure transducer always kept at ear level. ICP was monitored using a parenchymal Codman Microsensor probe (Codman, Raynham, MA, USA). All patients also received an external ventricular drain in the right or left frontal horn to enable drainage of cerebrospinal fluid in case of elevated ICP.

PRx was computed as a dynamic Pearson correlation coefficient between ICP and ABP over 30 consecutive 10-s averages, equivalent to 5 min of data, after ICP and ABP signal artefact removal in ICM+ (Czosnyka et al., 1997). Relevant demographic, injury, comorbidity and outcome data is prospectively collected for TBI patients for the purpose of ongoing quality monitoring and benchmarking and this database was used for the current study. Collected data used for the present analysis included age, sex, presence of preexisting arterial hypertension, hypercholesterolemia, diabetes mellitus, thromboembolic events and the smoking history. Thrombo-embolic events included arterial events such as cerebrovascular accidents and myocardial ischemia as well as venous events such as deep venous thrombosis (DVT) and pulmonary embolus (PE). The core IMPACT score for each patient was calculated based on age, admission Glasgow Coma Score (GCS) and pupillary reflexes (Steyerberg et al., 2008). Data were pseudonomyzed before analysis. The study was approved by the local Ethics Board (Commissie Medische Ethiek UZ KU Leuven/Onderzoek; study number S57981).

2.2. Statistical analysis

ICP, ABP and PRx were averaged over the first 5 days of monitoring. Analysis was done in R studio version R-4.3.1 for Windows, CRAN. We investigated the correlation of PRx with age, sex, thromboembolic history, arterial hypertension, hypercholesterolemia, diabetes mellitus, smoking, GCS motor score, pupillary reflexes, and investigated whether age is an independent predictor of PRx in a backward stepwise multiple regression model including the mentioned variables. This exercise was repeated without including age as a variable in the model set up. F-test was used to compare the two models of linear regression.

In addition, a the above multiple regression analysis with age was repeated but only including patients of 55 years and older as a sensitivity analysis. This would be expected to reduce the effect of age due to a more narrow age span, but increase the effect of cardiovascular risk factors due to a higher incidence. All variables passed the Shapiro-Wilk test for testing normal distribution at a probability level of less than 0.05.

3. Results

The mean age in the cohort of 151 patients was 44.8 years (SD 21.9, range 0–87). Thirty-nine patients (25.8%) were female and 112 male (74.2%). Ninety-nine patients (65.6%) had an admission GCS $\leq$8. Nineteen (12.6%) were under the age of 18 and 12 (7.9%) succumbed to their injuries in the hospital. 56 patients had at least one cardiovascular risk factor. The most common vascular risk factors were arterial hypertension (n = 30, 19.9 %) and smoking (n = 25, 16.6%), followed by hypercholesterolemia (n = 15, 9.9%), diabetes mellitus (n = 14, 9.3 %) and the presence of a thromboembolic history (n = 14, 9.3%). The IMPACT core calculator predicted a mean probability of unfavorable outcome at 6 months of 0.55 (SD 0.24) and a mean probability of 6 month mortality of 0.43 (SD 0.25). Age was not correlated with the combined effect of Glasgow motor score and pupillary reaction (injury severity): p = 0.30.

PRx and age positively correlated with a Pearson correlation coefficient of 0.31 (p<0.001)(Fig. 1). Beside age, also sex, thromboembolic history, arterial hypertension, core IMPACT score, Glasgow motor score and pupillary reaction score had a significant univariate correlation with PRx, and were (except IMPACT score) included in a multiple regression analysis with PRx as dependent variable. The final model is shown in Table 1. The model reveals a significant independent but limited positive relation of age with PRx (p = 0.01). The cardiovascular risk factors lost significance as independent predictors in the model, In order to investigate the independent relation of age with respect to PRx further, a model without age and a model with age was constructed. Upon comparing both models with the F-test using ANOVA, a significant p-value was observed (F-score = 6.80, p = 0.01)(Table 2). The latter underscores a distinctive correlation of age with PRx beyond the influence of injury severity indicators such as the Glasgow motor score and pupillary reaction, but also beyond cardiovascular risk factors associated with increasing age.

When the multiple regression analysis including age was repeated for patients of 55 years and older only, the effect of age on PRx lost significance. Although the cardiovascular risk factors have a higher incidence in this group, they were not associated with a statistically significant effect on PRx (Table 3).

4. Discussion

In our analysis on 151 patients with TBI, we observed a weak but

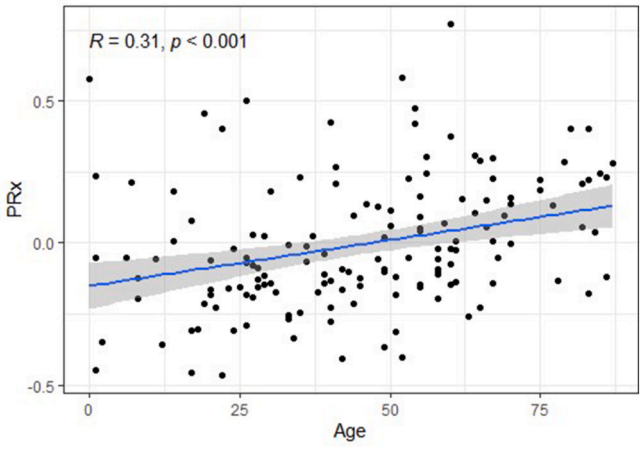

Fig. 1. Correlation between the Pressure Reactivity index (PRx) and age (Pearson R = 0.31; p < 0.001, n = 151).

Table 1
Multiple regression model for PRx as dependent variable (n = 151).

	Estimate	St. Error	t value	p
(Intercept)	−0.236	0.078	−3.012	0.004
Age	0.004	0.002	2.607	0.011
Thromboembolic history	0.117	0.111	1.050	0.297
Arterial hypertension	−0.071	0.092	−0.767	0.445
Hypercholesterolemia	−0.050	0.150	−0.337	0.737
Glasgow motor score	0.005	0.015	0.357	0.722
Pupillary reaction	0,007	0,024	0.303	0,763

significant correlation between increasing age and reduced cerebrovascular pressure reactivity, that remained significant after accounting for concurrent cardiovascular morbidity. This substantiates the assertion that the adverse impact of age on pressure reactivity is not solely attributable to coexisting cardiovascular comorbidities.

It has been found in previous studies that PRx worsens with older age (Czosnyka et al., 2005; Batson et al., 2022). However, this reporting was in the context of TBI and not in healthy individuals, that do not undergo invasive brain monitoring. Therefore, the question is raised whether this deterioration of PRx is unique to brain injury, as dynamic CA assessed by transcranial Doppler in healthy individuals was demonstrated to be independent of age (Carey et al., 2000). Importantly, PRx is a surrogate marker for autoregulatory function and falls short to completely encompass CA, as does probably any other current method used in humans.

One of the explanations traditionally provided for the phenomenon of PRx worsening in older age is that vascular function deteriorates with age due to wearing. Endothelial injuries tend to increase due to diseases such as arterial hypertension, hypercholesterolemia, and diabetes. This phenomenon is for instance observed in cases of vascular cognitive impairment (Jagust et al., 1997). However, our study establishes a relationship between age and PRx independent of these vascular comorbidities. This indicates the presence of an unknown factor that underlies this relation. An age-related impairment of autoregulatory function itself has been demonstrated in mice, in which it was found that dysregulation of the 20-HETE/TRPC pathway with age was associated with impairment of both the myogenic response as well as flow-induced construction in cerebral arteries (Toth et al., 2013). This functional maladaptation to high blood pressure in older cerebral arteries was also associated with microglia activation and neuroinflammation. Other factors, such as low insulin-like growth factor levels in ageing, have been associated with cerebrovascular changes (Sonntag et al., 2013). In similar mice experiments, it was demonstrated that IGF-1 deficiency reduced the adaptive vasoconstriction in response to arterial hypertension (Toth et al., 2014),

Near-infrared spectroscopy studies have revealed alterations in the hemodynamics of the brain with ageing. In particular a lower connectivity of blood flow oscillations between brain regions was observed in the 0.052–0.145Hz range, indicating reduced low-frequency oscillations in older adults when compared to younger individuals (Andersen et al., 2018; Yeung and Chan, 2021). These low-frequency oscillations have been identified as a potential measure for CA (Andersen et al., 2018; Yeung and Chan, 2021; Meltzer et al., 2000). This may suggest that the structural integrity of cerebral vasculature presents itself as a pivotal factor. Hence, age-related changes in vessel compliance, elasticity, and in the integrity of the blood-brain barrier are candidate sources of alterations in CA capacity. These structural transformations, in turn, may exacerbate the impact of traumatic insults on the ageing brain. An additional consideration is in the biochemical composition of the brain, subject to age-induced alterations (Lee and Kim, 2022).

The present study's primary limitation lies in its single-center nature and sample size. The TBI population is inherently diverse, encompassing a spectrum of injuries and patient profiles. Nevertheless, for the variables included, there were no missing data, and we believe that the sample size is compatible with drawing conclusions on the study's objective, albeit that a larger cohort would enable to further reduce white noise. In this regard, future work will involve combining single center and existing multicenter databases into harmonized larger data repositories that should allow for more granular analyses. The Marshall score was not included due to a lack of available CT scan data. A prior study conducted by Hiler et al. found no significant relationship between mean ICP values, CA status and Marshall CT scan classification (Hiler et al., 2006). Averaging monitoring and PRx data over a span of 5 days offers statistical advantages due to the consolidation of information into a single data point but signal dynamics are not represented. Employing time-varying analysis methods or leveraging machine learning algorithms could offer more nuanced insights and is a plan for the future. Finally, pressure reactivity is considered a proxy for assessing the function of CA, but is not synonymous. Vasoreactivity is a broader term that encompasses the ability of blood vessels to respond to pressure stimuli, whereas CA specifically refers to the brain's ability to maintain adequate CBF.

Notwithstanding limitations, our study does indicate that advanced age independently correlates with a reduction in physiological cerebrovascular defense mechanisms, a phenomenon which is then further compounded by concurrent age-related factors contributing to worse outcomes following TBI, including diminished overall physiological reserve, attenuated recovery capacities, and increased risk for complications. Further work is needed to fully understand the effects of ageing on cerebrovascular (patho)physiology, in which animal models explicating brain hemodynamic physiology should pave the way.

5. Conclusion

The results of the present cohort study in monitored TBI patients demonstrate that older age independently impairs cerebrovascular pressure reactivity regardless of cardiovascular morbidity. In this

Table 3
Multiple regression model for PRx as dependent variable in patients of 55 years or older (n = 57).

	Estimate	Std. Error	t value	p
(Intercept)	−0.113	0.433	−0.261	0.797
Age	0.005	0.007	0.819	0.424
Thromboembolic history	0.047	0.128	0.370	0.716
Arterial hypertension	−0.133	0.140	−0.949	0.355
Hypercholesterolemia	0.003	0.234	0.013	0.990
Glasgow motor score	−0.035	0.029	−1.206	0.243
Pupillary reaction	−0.013	0.053	−0.253	0.803

Table 2
Analysis of variance table for two multiple regression models predicting PRx with and without age (n = 151).

Analysis of Variance

•Model 1: PRx ~ Thromboembolic history + Arterial Hypertension + Hypercholesterolemia + Glasgow motor score + pupillary reaction
•Model 2: PRx ~ Age + Thromboembolic history + Arterial Hypertension + Hypercholesterolemia + Glasgow motor score + pupillary reaction

Res.	Df	RSS	Df	Sum of Sq	F	Pr(>F)
1	74	4.65				
2	73	4.26	1	0.40	6.80	0.011

context, pathophysiology of TBI and physiology of ageing seem to line up to synergistically produce a potential negative effect on adequate brain perfusion. Understanding these interdependencies holds promise for tailoring interventions and therapies to better address the unique challenges faced by older individuals in the aftermath of TBI.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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