Influence of Autonomic Nervous System Activity on Cerebral Autoregulation in Traumatic Brain Injury

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Abstract

Cerebral autoregulation (CAR) describes the ability of the cerebral vascular bed to maintain stable blood flow in the brain autonomously. This independently functioning process can be disturbed by irregular autonomic nervous system (ANS) activity. ANS activity can be measured by heart rate variability (HRV). As HRV and disturbed CAR were independently shown to be mortality predictors in traumatic brain injury (TBI), we assume there is a link between ANS activity measured by HRV and CAR functionality. For this purpose, we analyzed CAR in invasive intracranial (ICP) and arterial blood pressure recordings from 19 TBI patients. CAR parameters were calculated as correlation coefficients of diastolic blood pressure with ICP diastolic value, beat amplitude and beat area. The correlation of heart rate (HR) and RMSSD with CAR parameters was calculated to assess ANS influence on CAR. Our results show a moderate correlation of HR with CAR parameters based on ICP beat area ($r = 0.59$, $p < 0.01$) and ICP beat amplitude ($r = 0.53$, $p < 0.05$). No significant correlation was found between RMSSD and CAR parameters. These results support that ANS activity affects CAR. In particular, it suggests that the sympathetic nervous system is more important than the parasympathetic nervous system in this process.

1. Introduction

Blood volume flow through an uncurved cylindrical vessel is dependent on the pressure gradient along the vessel and vessel diameter as described by the Hagen–Poiseuille equation. Since blood pressure can vary greatly due to endogenous and exogenous challenges to the cardiovascular system, blood volume flow can vary to the same extent. This potential variability is contrary to the need for a state dependant constant blood and thus energy supply to various organs. In particular, the brain needs such a stable supply, as it has no energy stores of its own. For the purpose of reliable blood supply, the cerebral vascular bed possesses the abilities to detect changes in blood pressure and flow and to adjust the vessel diameter and thus flow accordingly by vasoconstriction or vasodilation. The main mechanism of flow regulation is named cerebral autoregulation (CAR). It describes the autonomic contraction and dilation of vascular smooth muscles induced by the opening and closing of mechanosensitive ion channels. But it is not the only effect contributing to vascular smooth muscle tonus. Activity of the autonomic nervous system (ANS), metabolic state and sheer stress induced release of endothelial molecules influence the vascular tone and thereby the working point of CAR. [1]

All these mechanisms can be significantly disturbed if the vascular bed is injured, e.g. by traumatic brain injury (TBI) [2]. To protect the vascular bed and minimize the effects of TBI, one path of current research is the identification of therapeutically adjustable parameters in patients, that allow the utilization of remaining autoregulation capacity. One such parameter is the cerebral perfusion pressure (CPP), which describes the blood pressure at the base of the brain. It has been shown, that there exists an individual optimal CPP (CPP_{opt}), at which CAR performs best and therefore the chance of hypo- or hyperperfusion is minimized [3]. The significance of this parameter is evident by the fact, that the time of deviation from CPP_{opt} is linked to heightened mortality [3].

Another predictor of mortality in TBI is heart rate variability (HRV) [4]. Among others, one conceivable explanation is the alteration of the vascular tone and thus the CAR working point by the ANS, which can be measured by HRV parameters. In septic patients, low correlation between non-invasive CAR parameters and HRV parameters have been found [5]. To date, however, there is no study that focused on the relationship between HRV and CAR in

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TBI patients.

We assume that there is a significant link between HRV and CAR in TBI patients, that shows the influence of the ANS on CAR. To test this assumption, we calculated correlations of heart rate (HR) and HRV parameter RMSSD with CAR parameters for TBI patients from invasive arterial blood pressure (ABP) and intracranial pressure (ICP) measurements.

2. Methods

2.1. Data

We used data of 19 TBI patients recorded at the *Klinikum rechts der Isar*, Technical University of Munich. ABP and ICP were monitored continously with a sampling frequency of 100 Hz. ICP was recorded using an external ventricular drain (Spiegelberg Silverline®, Hamburg, Germany and GE Healthcare, Chicago, IL, USA). Patients age was 62.36 ± 17.07 years (range: 28-81 years) where sixteen patients were male and three female. Different amounts of recordings of different length were available per patient (32.65 ± 20.8 min, range: 7-73 min).

2.2. Data Processing

In order to allow a sufficiently high resolution of the HR analysis and to guarantee the presence of slow regulatory processes (< 0.05 Hz), all recordings were divided into 60 s windows. Multi-scale peak and trough detection implemented in the PPG-beats toolbox [6] was used for beat onset and peak detection in ABP and ICP signals. Premature heart beats were detected via HRVTool [7] function "RRfilter" and removed from the signals. Recording windows with more than 10 % of removal were discarded. No further signal filters were applied.

2.3. Cerebral Blood Volume Flow

Following the Monroe-Kellie doctrine, changes in volume of one cranial compartment (blood, cerebrospinal fluid or brain parenchym) inflict compensating volume changes in other compartments of the closed skull system and are accompanied by changes in ICP [8]. In stationary conditions without ongoing pathological swelling processes, changes in blood volume are hypothesized to be the main contributor to changes in ICP. For this reason, ICP characteristics are used as a proxy for cerebral blood flow measurement. In the literature, ICP mean value and ICP pulse amplitude have been used, where the mean value changes are thought to be a direct proxy of slow vasogenic changes and pulse amplitude to be a feature of vascular tone [9]. It has also been shown, that the intracranial volume waveform (e.g. movement of blood and cerebrospinal fluid) correlates strongly with intracranial pressure waveform [10]. This allowed us to hypothesize that features that represent changes in the overall ICP waveform, such as ICP beat area, reflect changes in cerebral blood volume flow. We therefore used the diastolic ICP values (ICP_{dia}) per beat and the morphological features of beat amplitude (ICP_{amp}) and beat area (ICP_{area}) from onset-to-onset as a measure of cerebral blood volume flow (see Figure 1).

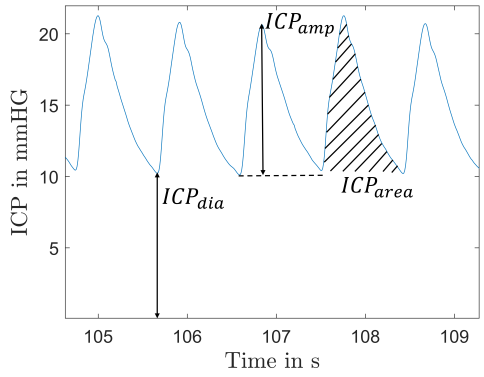


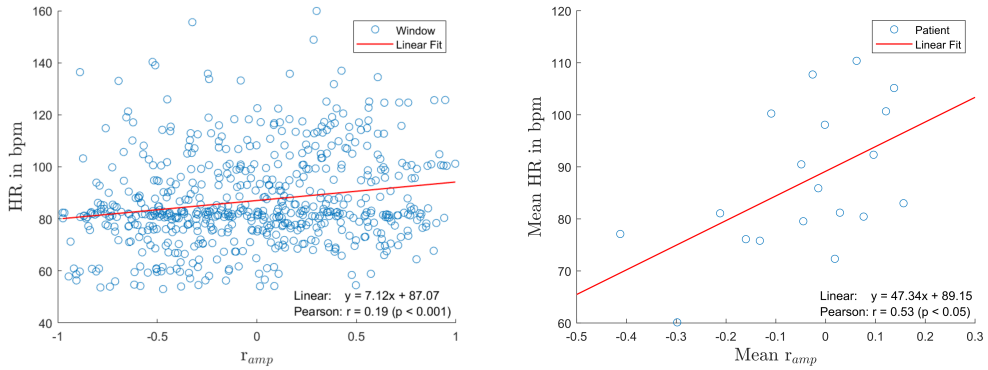
Figure 1: Representation of considered features calculated from cerebral blood flow for every intracranial pressure (ICP) beat. ICP_{dia}, value of ICP in diastole; ICP_{amp}, difference of beat peak ICP and beat onset ICP ; ICP_{area}, integral of pulsatile part of ICP signal from beat onset to onset.

2.4. Cerebral Autoregulation

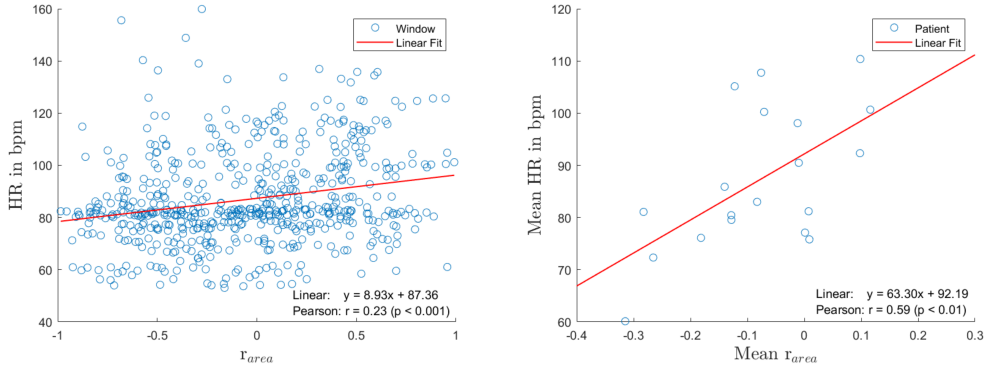
CAR can be assessed by transfer function or correlation analysis between signals of arterial and cerebral blood flow. Classic correlation analysis by the means of the established parameter pressure reactivity index (PRx) is done by calculating the Pearson correlation of 30 consecutive mean values of non-overlapping 10 s windows (5 min) between ICP and arterial blood pressure [2]. Hereby a low-pass filter is established, allowing for the examination of the very low frequency band up to $\frac{f_s}{2} = 0.05$ Hz. Because of the shorter recording windows (1 min instead of 5 min), we used a 10-second moving average filter with maximum overlap for filtering ICP and diastolic ABP signals, instead of non-overlapping windows. We then calculated the Pearson correlation between ICP beat amplitude and diastolic ABP (r_{amp}), ICP beat area and diastolic ABP (r_{area}) and diastolic ICP and diastolic ABP (r_{dia}) between the filtered signals for every window.

2.5. Heart Rate and Heart Rate Variability

To estimate the activity of the ANS, we calculated two parameters for each 60 s window via HRVTool [7]. The



(a) per-window r_{amp} (b) per-patient r_{area}



(c) per-window r_{area} (d) per-patient r_{area}

Figure 2: Scatter plots of arterial blood pressure (ABP) and intracranial pressure (ICP) derived cerebral autoregulation parameter values a) r_{amp} per window b) r_{amp} per patient, c) r_{area} per window and d) r_{area} per patient and heart rate (HR). Red line represents the linear regression. r_{amp}, correlation coefficient between ABP diastole and ICP beat amplitude); r_{area}, correlation coefficient between ABP diastole and ICP beat area)

RR time series was created from the peak-to-peak interval length of the ABP signals. For the measurement of parasympathetic activity, we calculated RMSSD [11]. Because no HRV parameter is said to truly represent sympathetic tone, we calculated the HR as an indicator of sympathetic activity in TBI [12]. Subsequently we calculated the Pearson correlation between HR and r_{amp}, r_{area} and r_{dia} and RMSSD and r_{amp}, r_{area} and r_{dia}. In addition to the per-window calculation, we also averaged the correlation and HRV parameters to calculate the correlation on a per-patient basis.

3. Results

We found high correlations (r = 0.72, p < 0.001) between r_{area} and r_{amp} over all windows of all patients. Moderate correlation was found between r_{dia} and r_{amp} (r = 0.57, p < 0.001) and r_{dia} and r_{amp} (r = 0.57, p < 0.001).

Table 1 shows the resulting correlation coefficients between CAR parameters and HR and RMSSD. On a per-window level, all parameters showed a significant (p < 0.001) correlation to HR and only r_{area} showed a significant (p < 0.05) correlation to RMSSD. When considering using mean values per patient, HR showed significant correlation with r_{amp} (r = 0.53, p < 0.05) and r_{area} (r = 0.59, p < 0.01). Hereby no significant correlation was found regarding HR and r_{dia} and RMSSD and all CAR parameters. Figure 2 shows the most significant correlations between HR and CAR parameters and the resulting linear fit.

4. Discussion and Outlook

On a per-window basis, very low to low but significant correlations between CAR parameters and HR were revealed. When analyzing the mean values per patient, a moderate correlation between r_{amp} and HR and between r_{area} and HR emerged. These findings suggest, that

Table 1: Results of correlation analysis between heart rate (HR) and RMSSD for the parameters r_{amp} (Correlation: ABP diastole - ICP beat amplitude), r_{area} (Correlation: ABP diastole - ICP beat area) and r_{dia} (Correlation: ABP diastole - ICP diastole).

	HR				RMSSD			
	per-window		per-patient		per-window		per-patient	
Parameter	r	p	r	p	r	p	r	p
r_{amp}	0.19	<0.001	0.53	0.012	-0.06	0.157	-0.30	0.214
r_{area}	0.23	<0.001	0.59	0.008	-0.10	0.017	-0.31	0.191
r_{dia}	0.14	<0.001	0.16	0.522	-0.06	0.128	-0.36	0.136

HR contains information about the functionality of CAR. However, the difference between the per-window and the per-patient approach indicates, that a low or high HR does not automatically reflect the absolute state of CAR, but there is a general trend that patients with a lower HR show a higher incidence of direct regulation and thus a more negative value in r_{amp} and r_{area}. Assuming that increased HR in TBI patients is produced by a high sympathetic activity [12], these findings support that ANS activity, in this case of the sympathetic system, is influencing autoregulatory capabilities. As a secondary result, r_{area} showed high correlation to r_{amp} and moderate correlation to r_{dia}, while at the same time showing the highest correlation to HR. This might indicate, that r_{area} can be used to represent parts of autoregulatory processes, that r_{amp} and r_{dia} can not grasp. In the case of RMSSD, only a very low significant correlation in the case of r_{area} was found across all recording windows. No significant correlation was found for any CAR parameter, when using patient mean values. As this parameter is thought to be a marker of parasympathetic activity, our results showed, that parasympathetic activity seems to have little influence on the autoregulatory processes in this TBI cohort.

Our findings are limited by the small size of patients, general short recording time and the lack of ground truth for the state of CAR and patient outcome. Therefore, further studies are needed to validate our findings. Also the influences of window length, moving average length and overlap need to be investigated.

A potential future analysis for estimating the significance of HR or other outcome-related parameters in TBI could involve calculating mortality based on the deviation from the optimal patient state. This optimal patient state could be determined via an expansion of CPP_{opt} calculation. Further dimensions could be added to the two-dimensional map of PRx vs. CPP. In addition, it could be investigated whether the time of patients deviating from the minima of the measured hyperplane shows a better prediction of mortality than the time deviating only from CPP_{opt}.

Acknowledgments

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