Autonomic impairment in severe traumatic brain injury: a multimodal neuromonitoring study

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Reprints will be not ordered

Key words: traumatic brain injury, autonomic, baroreflex, heart rate variability, intracranial pressure, outcome
Abstract

Background: Autonomic impairment after acute traumatic brain injury (TBI) has been associated independently with both increased morbidity and mortality. Links between autonomic impairment and increased intracranial pressure (ICP) or impaired cerebral autoregulation (PRx) have been described as well. However, relationships between autonomic impairment, ICP, PRx and outcome remain poorly explored. Using continuous measurements of heart rate variability (HRV) and baroreflex sensitivity (BRS) we aimed to test whether autonomic markers are associated with functional outcome and mortality independently of intracranial variables. Further, we aimed to evaluate the relationships between autonomic functions, ICP and cerebral autoregulation.

Methods: Waveforms of ICP and arterial blood pressure (ABP) were collected in TBI patients admitted to a single neurocritical care unit. Baseline Glasgow Coma Scale (GCS) and 6 months Glasgow Outcome Scale (GOS) were recorded. BRS was assessed every 10s using a modified cross-correlational method. Frequency domain analyses of HRV were performed automatically every 10 seconds from a moving 300s of the monitoring time window. Mean values of BRS, HRV, ICP, ABP, cerebral perfusion pressure (CPP) and PRx over the entire monitoring period were calculated for each patient.

Results: 262 patients with median age 36 years entered the analysis. The median admission GCS was 6, the median GOS was 3, mortality at 6 months was 23%. BRS (adjusted OR 0.9, p=0.02) and relative power of HF band of HRV (adjusted OR 1.05, p<0.001), were individually associated with mortality independently of age, admission GCS, ICP, PRx or CPP. BRS showed no correlation with ICP, or CPP, the correlation with PRx was strong in older patients (age>60). Relative power of HF correlated significantly with ICP and CPP, but not with PRx. Relative powers of LF correlated significantly with PRx.

Conclusion: Autonomic impairment as measured by HRV and BRS is significantly associated with increased mortality after TBI. These effects, though partially interlinked, seem to be independent of age, trauma severity, ICP or autoregulatory status, and thus represent a discrete phenomenon in the pathophysiology of TBI. Continuous measurements of HRV and BRS in the neuromonitoring setting of severe TBI may carry novel pathophysiological and predictive information.
Introduction

In acute brain injury, decreased heart rate variability (HRV) and decreased baroreflex sensitivity (BRS) are thought to mirror central impairment in coupling between the autonomic and cardiovascular systems. The baroreflex is the main neural mechanism that compensates spontaneous fluctuations in blood pressure and is under full influence of the central autonomic regulation. Suppression of this regulatory system may be caused by impairment of the central processing, and in traumatic brain injury may be a consequence of primary damage or due to the induced stress reaction.(1, 2)

Several studies have observed autonomic changes in patients suffering traumatic brain injury (TBI) by assessing HRV and BRS. These changes are thought to be related to the severity of injury and, more importantly, seem to correlate with increased morbidity and mortality. (3-6) Associations of autonomic system changes with increased intracranial pressure (ICP) have been suggested as well.(3, 4, 7) However, relationships between autonomic impairment, intracranial physiology and outcome remain unclear. None of the previous studies adjusted their outcome analyses for intracranial factors like ICP or the state of cerebral autoregulation, which are both important predictors of outcome in TBI.(8-10)

The autonomic nervous system in acute brain injured patients is also influenced by numerous factors of clinical management. These include sedation, analgesia, vasopressors, inotropes, mechanical ventilation and nursing procedures and create an “ICU noise” that represents an incalculable combination of confounding variables. Most of the previous studies have thus tried to minimise these confounding factors by excluding patients on cardiovascular drugs or on sedatives and using intermittently sampled HRV or BRS. However, when exploring the potential of real-time monitoring autonomic function in TBI patients, one has to consider not only the highly dynamic nature of the disease but also the inherent complex clinical interventions.

The primary aim of our study was to test the hypothesis that changes in continuously monitored autonomic function are associated with functional outcome after TBI independent of intracranial physiology (ICP and cerebral autoregulation) and despite the inherent and unpredictable “ICU noise”. The secondary aim was to elucidate the relationships between continuously measured autonomic functions, ICP and cerebral autoregulation.
Methods

Subjects

Data from 327 TBI patients admitted to the neurocritical care unit of the Addenbrooke’s Hospital, Cambridge University between 2003-2009 and undergoing multimodal monitoring including arterial blood pressure (ABP) and intracranial pressure (ICP) were analyzed retrospectively. All patients were sedated, intubated, and received mechanical ventilation during the whole recording period. A cerebral perfusion pressure (CPP)- and ICP-oriented protocol for management of head injury was followed, with CPP maintained at > 60 mm Hg and ICP < 20–25 mm Hg. Baseline neurological status of each patient was determined using the Glasgow Coma Scale (GCS) score on admission. In patients who were deemed too unstable to undergo formal neurological assessment on admission, the GCS score collected on scene was used. The clinical outcome was assessed at 6 months by using the Glasgow Outcome Scale (GOS). Primary outcome measure was mortality at 6 months (GOS 1). Secondary outcome measures were poor outcome, defined as GOS dead and persistent vegetative state (GOS 1 and 2) and unfavorable outcome defined as GOS dead, persistent vegetative state and severe disability (GOS 1, 2 and 3). All monitoring modalities recorded in the study were part of the standard clinical care.

Data Acquisition and Processing

ABP was monitored invasively through the radial or femoral artery with the aid of a standard pressure monitoring kit (Baxter Healthcare, CardioVascular Group) and was zeroed at the level of the right atrium. ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor, Codman & Shurtleff) inserted into the frontal cortex. All signals were digitized using an analog-to-digital converter (DT9801, Data Translation), sampled at a frequency of 100 Hz, and recorded using a laptop computer with ICM+® software (Cambridge Enterprise, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). The same software was later used for the retrospective analysis of all stored signals. Time-averaged values of ICP, ABP, and CPP (CPP = ABP – ICP) were calculated using waveform time integration over 60-second intervals. Cerebral autoregulation was monitored using the pressure reactivity index (PRx), calculated as a moving Pearson correlation coefficient between changes in 30 consecutive 10-second averages of ABP and corresponding ICP signals (with 80% overlap of data). Averaging over 10 seconds was used to suppress the influence of pulse and respiratory waves.
Heart rate variability

According to the international guidelines on HRV analysis(13), we used parameters from time and frequency domain analysis. For all HRV parameters we used 300s time series of RR intervals updated every 10s. In the time domain we calculated standard deviation (SD), standard deviation of the difference between sequential beats (SDSD), and square root of the mean squared difference between sequential beats (RMSSD). In the frequency domain we used Lomb-Scargle periodogram to calculate spectral power of RR time series in the low frequency range (LF: 0.04-0.15Hz), the high frequency range (HF: 0.15-0.4Hz), the total power (TP: 0.04-0.4Hz) and the LF/HF ratio. Further, for HF and LF, relative (ratio of the components power divided by the sum of HF, LF and VLF components total power) powers were calculated.

Baroreflex sensitivity

Baroreflex sensitivity (BRS) was calculated using a modification of the sequential cross-correlation method. (14) The modified function uses arterial blood pressure systolic peaks to create RR intervals time series, using an automated detection algorithm. The slope of the linear regression between 10s series of RR intervals and the corresponding 10s series of systolic blood pressure is then calculated. In order to remove the influence of an unknown time delay of the baroreceptor response, a cross-correlation function is used to maximize the correlation coefficient. The RR window is shifted against the systolic pressure window in a stepwise manner and the highest correlation is reported, if it fulfils the criteria outlined below. In order to ensure that the correlation calculations are always performed on the same number of data points irrespective of the lag applied to RR series, the actual data buffer is extended with each window shift. Valid BRS value is returned only if the correlation coefficient is significant at p<0.01, and if no irregular beats (ectopics) are detected by the software. To compensate for the influence of uncorrelated noise the slope returned is adjusted (divided by) the correlation coefficient. The BRS is updated every 10s and expressed in ms/mmHg.

Statistics

The data are presented as median values, range and interquartile range. The nonparametric Wilcoxon rank-sum test was used to compare medians across the outcome categories (mortality, poor outcome or unfavorable outcome). Nonparametric Spearman correlations and associated p-values were used to correlate patient average values of HRV parameters, BRS, ICP, CPP, and PRx. For
outcome analysis, one mean value of the variables HRV, BRS, PRx, CPP, and ICP was calculated for each patient (mean over the entire monitoring period). The effect of “classical” predictors (age, admission GCS, ICP, CPP, PRx) and/or autonomic variables on outcome was investigated by logistic regression models. For each independent variable, intuition for the degree of its adjusted effect on the outcome was obtained from crude restricted cubic splines (with the number of knots varying from 3 to 5) and a formal hypothesis test for linearity. The best subset selection algorithm was applied. This is an exhaustive method that searches the best model, based on the lowest Akaike Information Criterion (AIC), among those obtained from all possible subsets of independent variables. Comparison between nested models was also performed with the log-likelihood ratio test. The area under the ROC curve was used as a measure of the discrimination ability of a model. Statistical analyses were performed using the SPSS version 19 software and the R language and software environment for statistical computation, version 2.12.1. The significance level was set at 0.05.

Ethics

Data collection and analysis has been approved by the Neurocritical Care Users’ Committee and the Research Ethics Committee (29 REC 97/291).

Results

Population

327 consecutive severe TBI patients were screened for the entry into the study. 53 patients were excluded because of incomplete outcome data. Further 10 patients were excluded because of artifacts in the HRV and BRS analysis mainly due to atrial fibrillation or other arrhythmias, leaving thus 262 patients in the final dataset. Excluded patients did not differ significantly in age, median GCS, median GOS, median ICP, median CPP or median PRx from those included in the final dataset (data not shown). The median age of the patients was 36 years (range 16-76.4, IQR 25), 141 (53.8%) were male, median GCS was 6 (range 3-15, IQR 5), median GOS at 6 months was 3 (range 1-5, IQR 2). Six (2.3%) patients underwent primary decompressive craniectomy, 19 (7.2%) underwent secondary decompressive craniectomy. Median ICP was 16.1 mm Hg (3-51, IQR 6.3), median CPP was 77.2 mm Hg (56-102, IQR 7.6) and median PRx was 0.07 (-0.3 – 0.7, IQR 0.2). Mean ± SD monitoring duration was 154.34 hours +/- 126.3 hours (Q1 = 49.5 hours, Q3 = 218.5 hours, IQR = 169 hours). The respective percentage of data availability as a function of the total monitoring duration were: arterial
blood pressure 92.4% (SD 12), heart rate 90.4% (SD 14), ICP 91.9% (SD 15), CPP 86.8% (SD 18), PRx 86.3% (SD 18), BRS 48.7% (SD 20.1), relative power of HF 90.8% (SD 13.8), relative power of LF 89.1% (SD 19) and LF/HF ratio 90.72% (SD 14). Example of time trends from one patient is shown in Figure 1.

**Outcome and mortality**

Mortality at 6 months in the group of patients included in the analysis was 23.3%. Poor outcome was reached in 67 patients (25.6%) and unfavorable outcome in 149 patients (56.9%). For the univariate comparison of clinical and autonomic variables between survivors and non-survivors see Table 1. Among the “classical” predictors, statistically significant differences between the survivors and non-survivors were identified for all variables but GCS (p=0.072). As for the autonomic variables, the LF total power (p=0.833), the LF relative power (p=0.137) and the HRV total power (p=0.701) failed to have statistically significant different medians across survivors and non-survivors (Table 1).

Firstly, the model considering only the “classical” predictors was calculated. For mortality and poor outcome, the whole predictor was found to be linear in age, admission GCS and PRx and to be quadratic in ICP (Table 2). Compared to a linear effect, the quadratic effect of ICP produced greater probabilities for mortality within the high range of ICP values. The variable CPP was not found to have a statistically significant (adjusted) effect (p=0.616 for mortality; p=0.197 for poor outcome). The model for the unfavorable outcome was linear in age, GCS and ICP and has failed to identify significant effects for CPP (p=0.800) and PRx (p=0.124), see Table 2.

Subsequently, the model considering simultaneously all predictors, “classical” and autonomic, was explored. The number of independent variables constrained all effects to be linear. Among all possible subsets of predictors, the model with the lowest AIC identified age, GCS, PRx, ICP, BRS and relative power of HF as the variables with a statistically significant effect on mortality (Table 3). For the poor outcome, the best-AIC logistic regression model identified the same statistically significant predictors as the model for mortality (Table 3). The chosen model for the unfavorable outcome extended the classical model from before, adding relative and total HF power (Table 3).

The area under the ROC curve (AUC) obtained for the best mortality, poor outcome and unfavorable outcome models was 0.844, 0.824 and 0.771, respectively, showing that the models exhibited a good discrimination ability.
**Autonomic parameters, age and GCS**

Age correlated weakly with the relative HF powers ($r=-0.17$, $p=0.01$) and with relative LF powers ($r=0.13$, $p=0.03$). GCS showed no significant correlations with any of the autonomic parameters.

**Autonomic parameters and ICP, CPP and PRx**

ICP correlated well with relative HF power ($r=0.34$, $p<0.001$), with relative LF power ($r=-0.29$, $p<0.001$) and with LF/HF ratio ($r=-0.38$, $p<0.0001$). CPP correlated with relative HF powers ($r=-0.33$, $p<0.001$), weakly with relative LF powers ($r=0.14$, $p=0.02$) and well with LF/HF ratio ($r=0.34$, $p<0.001$). PRx correlated weakly only with relative power of LF ($r=0.18$, $p=0.01$). On the whole, BRS showed no significant correlations with intracranial variables, see also Figure 2 and Figure 3. However, there was a strong age-dependent trend towards higher correlation coefficients between PRx and BRS (up to 0.76), reaching significance in the elderly (above 60 years), see Figure 4.

**Discussion**

In our group of sedated and ventilated patients with severe brain trauma there was a significant association of both low baroreceptor sensitivity and decreased heart rate variability with higher mortality and poor outcome. We also found evidence of increased parasympathetic activity (increased HF powers) and decreased LF/HF ratio in non-survivor and those with poor outcome. These continuously monitored indicators of autonomic function seem to be linked to TBI outcome independently of age, initial trauma severity, ICP levels or autoregulatory status raising the future prospect of autonomic nervous system targeted therapy.

Our results are consistent with findings from previous studies. In classical studies by Wintchell (5) and Biswas in children(3) a decrease in LF/HF ratio was also reported. A study by Kox with severe brain injury patients requiring intensive care showed concordantly higher HF powers and lower LF/HF ratio as compared to healthy volunteers. (16) Goldstein et al observed decreased RR interval variability, decreased LF powers of HRV and BP in a case mix of brain injury nonsurvivors.(17) Another TBI series found low BRS, low RR variability and a decrease in LF/HF ratios in nonsurvivors from TBI. (2) However what is unique about our findings, is that none of the previous studies adjusted for ICP or CPP effects, despite several former reports underlining associations between increased ICP/decreased CPP and autonomic changes.(3, 5, 7, 18) Thus, based on the presented results it seems that despite being correlated with ICP or CPP, the autonomic changes may have additive,
independent, associations with TBI outcome. Furthermore, the results also suggest that autonomic changes are linked to worse outcome independently of the cerebral autoregulatory status. In terms of clinical interpretation of the model, for every unit increase in baroreflex sensitivity the odds for mortality is expected to decrease by 11.2%. For every unit increase in relative HF power the odds for mortality is expected to increase by 4.6%.

Higher HF powers and lower LF/HF ratios in non-survivors may indicate principally an increased vagal and decreased sympathetic activity in patients with poor outcome. The HF power is believed to reflect cardiac parasympathetic activity while the LF power, although much more complex, is often assumed to have a dominant sympathetic component. Logically, LF/HF ratio is then suggested to mirror sympato-vagal balance. However, mounting evidence indicates that these assumptions are naïve and oversimplified given the complex non-linear interactions between the sympathetic and the parasympathetic systems. (19-22) This holds particularly true for the interpretation of LF power as the main component of cardiac sympathetic regulation. The LF component seems rather to reflect a mix of sympathetic, parasympathetic, and unidentified factors and furthermore parasympathetic factors may account for a significant proportion of the variability. (22) As a consequence, the LF/HF ratio is problematic to interpret as well. Some authors consider the LF powers of HRV to represent baroreflex activity. (23) Consistent with this theory, LF powers correlated with BRS (r=0.41, p<0.001, data not shown). Overall, TBI nonsurvivors and those with poor outcome in our study seem to exhibit relatively increased vagal activity and decreased baroreflex sensitivity. But whether or not the sympathetic activity is significantly affected, reduced relatively or absolutely, remains speculative.

How autonomic changes contribute to poor TBI outcome remains hypothetical. Increased vagal activity may exert immunosuppressive effects through the cholinergic anti-inflammatory pathway(24) resulting in increased susceptibility to infections and sepsis after TBI. Indeed, increased rates of infections and sepsis have been observed after TBI. (25, 26) The immune response after TBI seem to be severely impaired including decreased T-helper and NK-cell activity and reduced production of TNFa, IL-1b, IL-6,IL-8, IFNg and IL-12. (25, 27) Decreased baroreflex sensitivity mirroring probably more complex autonomic changes involving both the parasympathetic and sympathetic arms has been linked to cardiovascular complications and cardiac death, insulin resistance and hyperglycemia, brain edema formation or immunosuppression.(28, 29) All these factors may potentially contribute to secondary brain injury after TBI and worse outcome. Thus, as has already been proposed in other types of acute brain injury (28, 30), the current data raises the possibility of autonomic impairment as a future therapeutic target in TBI.
Our outcome analysis inevitably focused on single (per patient), averaged, measurements. However, given the significant and consistent results achieved here, one can in the future explore the time evolution of the autonomic system impairment/recovery in the context of development of secondary insults in the acute phase of severe brain trauma treatment. In our cohort we were able to calculate valid BRS and HRV values making them potential candidate for real-time trending alongside vital signs and the cerebral autoregulation index. Perhaps, similarly to cerebral autoregulation, or in relation with it, one can use the continually updated status of the autonomic system to offer individualised thresholds for critical care management.

Limitations

In contrast to previous studies, which used selected short-term HRV measurements, free of interventions and confounding medication, we used long-term indiscriminate averaging of the HRV and BRS indices. Our presumption was that, ultimately, the brain injury induced profound impairment in the autonomic regulation would outweigh the transient changes inherent and inseparable from the critical care environment such as changes in body temperature, body position changes, volume status, respiratory rate and tidal volume, nursing manoeuvres, ambient noise, critical illness/complications and last but not least alterations in the medical therapy. Reassuringly, we were able to reproduce the general findings of the previous studies. Of course, one cannot exclude the possibility that some measurements were skewed by the ‘ICU bias’ in the same direction, therefore mimicking results consistent with the previous literature, however, we consider this probability as low. Nevertheless, this indiscriminate approach has to be considered as a major limitation of our study.

However, given our congruent results, and the potentially added value of trending the autonomic system in real time we feel that the benefits of this approach outweigh its limitations. Our study has strengths including the prospective and standardized collection of physiological, clinical and outcome data, relative high number of subjects and uniform group including exclusively TBI patients. In comparison, previous studies used short, one time-point measurements in low a number of subjects (n usually around 20), were retrospective in its nature and included a case mix of brain injury patients with various etiologies.

Conclusion
Long-term continuous measurement of autonomic parameters as BRS and HRV in the neurocritical care setting is feasible and may provide valuable additive physiological and prognostic information. In severe TBI deterioration in measures of the autonomic functions seems to offer an independent value in its association with poor outcome. The nature of links between autonomic dysfunction and outcome is so far underexplored. However, given the importance of autonomic changes for TBI outcome, optimizing the autonomic function may perhaps be considered a future therapeutic target in brain injury.

**Conflict of interests**

The software for brain monitoring ICM+ is licensed by the University of Cambridge (Cambridge Enterprise Ltd). Peter Smielewski and Marek Czosnyka have a financial interest in a part of the licensing fee.

**Acknowledgement**

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References

23. Goldstein DS, Bento O, Park MY, et al. Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes. Experimental physiology 2011;96(12):1255-1261.

Figure 1: Example of time trends of intracranial and autonomic variables for one patient as sampled by one minute.
Figure 2: Association between selected HRV parameters, BRS and ICP. With increasing ICP, relative HF power increases and relative LF power decreases. Analogous, LF/HF ratio decreases. BRS shows no significant changes.
Figure 3: Association between selected HRV parameters, BRS and CPP. With decreasing CPP, relative HF power increases and relative LF power decreases. Analogous, LF/HF ratio decreases. There is a trend toward lower BRS with decreased CPP.
Figure 4. Relation between age and Spearman r for the BRS- PRx correlation.
Table 1. Comparison of clinical and autonomic variables between TBI survivors and non-survivors at 6 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors, n=201</th>
<th>Non-survivors, n=61</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range, IQR)</td>
<td>33 (16-76, 23)</td>
<td>44 (18-76, 32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GCS, median (range, IQR)</td>
<td>7 (3-15, 6)</td>
<td>5 (3-14, 5)</td>
<td>0.072</td>
</tr>
<tr>
<td>ICP, mmHg, median (range, IQR)</td>
<td>15.8 (4.5-29.0, 5.6)</td>
<td>17.6 (3.0-50.9, 9.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>CPP, mmHg, median (range, IQR)</td>
<td>77.7 (57.7-100.1, 6.6)</td>
<td>74.2 (56.2-102.1, 11.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>PRx, median (range, IQR)</td>
<td>0.05 (-0.29-0.70, 0.20)</td>
<td>0.14 (-0.30-0.70, 0.23)</td>
<td>0.002</td>
</tr>
<tr>
<td>BRS, ms/mmHg, median (range, IQR)</td>
<td>6.6 (1.6-18.8, 4.2)</td>
<td>5.1 (1.3-18.7, 4.0)</td>
<td>0.026</td>
</tr>
<tr>
<td>HF power, ms², median (range, IQR)</td>
<td>160.0 (9.9-1853.9, 285.4)</td>
<td>115.0 (6.2-1840.3, 212.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>HF relative power, median (range, IQR)</td>
<td>25.8 (5.0-65.4, 17.5)</td>
<td>33.4 (6.6-81.8, 22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF/HF ratio, median (range, IQR)</td>
<td>1.6 (0.2-8.3, 1.3)</td>
<td>1.0 (0.0-8.8, 1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LF power, ms², median (range, IQR)</td>
<td>598 (9-133927, 1883)</td>
<td>748 (1-41628, 2291)</td>
<td>0.833</td>
</tr>
<tr>
<td>LF relative power, median (range, IQR)</td>
<td>22.1 (7.7-39.5, 7.5)</td>
<td>19.9 (2.6-45.7, 12.1)</td>
<td>0.137</td>
</tr>
<tr>
<td>HRV total power, ms², median (range, IQR)</td>
<td>2551 (90-250617, 3802)</td>
<td>2169 (56-66197, 4228)</td>
<td>0.701</td>
</tr>
</tbody>
</table>
Table 2. Multiple logistic regression models to predict outcome at 6 months including “classical” predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Mortality at 6 months</th>
<th>Poor outcome at 6 month (GOS 1,2)</th>
<th>Unfavorable outcome at 6 months (GOS 1-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj OR</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.061</td>
<td>1.036-1.087</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.821</td>
<td>0.733-0.919</td>
<td>0.001</td>
</tr>
<tr>
<td>ICP, mmHg</td>
<td>0.699</td>
<td>0.507-0.965</td>
<td>0.030</td>
</tr>
<tr>
<td>ICP², mmHg²</td>
<td>1.015</td>
<td>1.005-1.024</td>
<td>0.002</td>
</tr>
<tr>
<td>PRx</td>
<td>12.879</td>
<td>1.668-99.423</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Table 3. Multiple logistic regression models to predict mortality at 6 months including “classical” and autonomic variables.

<table>
<thead>
<tr>
<th>Model for mortality</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRS, ms/mmHg</td>
<td>0.888</td>
<td>0.801-0.984</td>
<td>0.024</td>
</tr>
<tr>
<td>HF relative power, ms²</td>
<td>1.046</td>
<td>1.019-1.074</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.073</td>
<td>1.046-1.101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.800</td>
<td>0.713-0.899</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP, mmHg</td>
<td>1.140</td>
<td>1.062-1.225</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRx</td>
<td>11.927</td>
<td>1.559-91.254</td>
<td>0.017</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model for poor outcome</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRS</td>
<td>0.887</td>
<td>0.804-0.978</td>
<td>0.016</td>
</tr>
<tr>
<td>HF relative power, ms²</td>
<td>1.041</td>
<td>1.015-1.068</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>1.068</td>
<td>1.043-1.095</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.802</td>
<td>0.718-0.897</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICP, mmHg</td>
<td>1.132</td>
<td>1.058-1.211</td>
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<td>PRx</td>
<td>7.317</td>
<td>1.041-51.420</td>
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<thead>
<tr>
<th>Model for unfavorable outcome</th>
<th>Adj OR</th>
<th>95% CI</th>
<th>p-value</th>
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<tr>
<td>HF relative power, ms²</td>
<td>1.027</td>
<td>1.003-1.051</td>
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<tr>
<td>HF power, ms²</td>
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<td>0.998-1.000</td>
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<td>Age</td>
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<td>1.037-1.080</td>
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<td>Admission GCS</td>
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<td>0.741-0.888</td>
<td>&lt;0.001</td>
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<tr>
<td>ICP, mmHg</td>
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<td>1.017-1.144</td>
<td>0.012</td>
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