Continuous Autoregulatory Indices Derived from Multi-modal Monitoring: Each One is Not Like the Other

Zeiler FA,1-3 Donnelly J4, Menon DK,1 Smielewski P,4 Zweifel C 5, Brady K,6 Czosnyka M4

1. Division of Anaesthesia, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK
2. Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada
3. Clinician Investigator Program, Rady Faculty of Health Science, University of Manitoba, Winnipeg, Canada
4. Section of Brain Physics, Division of Neurosurgery, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK
5. Neurosurgery, Cantonal Hospital Chur, Switzerland
6. Baylor College of medicine, TX

**Corresponding Author:**

Frederick A. Zeiler BSc MD FRCSC (Neurosurgery)

Assistant Professor

Department of Surgery

Rady Faculty of Health Sciences

University of Manitoba

Winnipeg, MB, Canada

Email: [umzeiler@myumanitoba.ca](mailto:umzeiler@myumanitoba.ca)

*Contributing Authors:*

Joseph Donnelly MBChB

Section of Brain Physics

Division of Neurosurgery

University of Cambridge

Email: donnellyj87@gmail.com

David K. Menon MD PhD FRCP FRCA FFICM FMedSci

Head, Division of Anaesthesia, University of Cambridge

Honorary Consultant, Neurosciences Critical Care Unit, Addenbrooke’s Hospital

Professorial Fellow, Queens’ College, Cambridge

Senior Investigator, National Institute for Health Research, UK

Email: dkm13@cam.ac.uk

Pieter Smielewski PhD

Section of Brain Physics

Division of Neurosurgery

University of Cambridge

Email: ps10011@cam.ac.uk

Christian Zweifel MD

Head of Neurosurgery

Kantonsspital Graubunden

Chur, Switzerland

Email: zweifelch@gmx.ch

Ken Brady MD

Associate Professor

Department of Anesthesiology

Baylor College of Medicine

Houston, TX, USA

Email: ken.brady@me.com

Marek Czosnyka PhD

Professor of Brain Physics

Section of Brain Physics

Division of Neurosurgery

University of Cambridge

Cambridge, UK

CB2 0QQ

Email: [mc141@medschl.cam.ac.uk](mailto:mc141@medschl.cam.ac.uk)

**Abstract:**

We assess the relationships between various continuous measures of autoregulatory capacity in an adult TBI cohort. We assessed relationships between autoregulatory indices derived from intracranial pressure (ICP: PRx, PAx, RAC), Transcranial Doppler (TCD: Mx, Sx, Dx), brain tissue-oxygenation (ORx), and spatially resolved near infrared spectroscopy (NIRS resolved: TOx, THx). Relationships between indices were assessed using Pearson correlation coefficient, Friedman (KW) test, Principle component analysis (PCA), Agglomerative Hierarchal Clustering (AHC) and K-Means Cluster Analysis (KMCA). All analytic techniques were repeated for a range of temporal resolutions of data, including minute-by-minute averages, moving means of 30 samples, and grand mean for each patient. Thirty-seven patients were studied. PRx displayed strong association with PAx/RAC across all the analytical techniques: Pearson correlation (r=0.682/ r=0.677, p<0.0001), PCA, AHC and KMCA in the grand mean data sheet. Most TCD based indices (Mx, Dx) were correlated and co-clustered on PCA, AHC and KMCA. Sx was found to be more closely associated with ICP derived indices on Pearson correlation, PCA, AHC and KMCA. NIRS indices displayed variable correlation with each other and with indices derived from ICP and TCD signals. Of interest, TOx and THx co-cluster with ICP based indices on PCA and AHC. ORx failed to display any meaningful correlations with other indices in neither of the analytical method used. Thirty minute moving average and minute-by-minute data set displayed similar results across all the methods. RAC, Mx and Sx were the strongest predictors of outcome at 6 months. Continuously updating autoregulatory indices are not all correlated with one another. Caution must be advised when utilizing less commonly described autoregulation indices (ie. ORx) for the clinical assessment of autoregulatory capacity, as they appear to not be related to commonly measured/establish indices, such as PRx. Further prospective validation is required. Keywords: autoregulation index, autoregulation, multimodal monitoring, co-variance

**Introduction:**

The implementation of multi-modal monitoring (MMM) in adult traumatic brain injury (TBI) has generated a substantial literature on various indices derived from raw or processed physiological signals. Much interest has focused on derived indices of autoregulatory function, which are based on the response of a monitored intracranial variable, such as intracranial pressure (ICP) or cerebral blood flow velocity (CBFV), to slow changes in a hemodynamic parameter, such as mean arterial pressure (MAP) or cerebral perfusion pressure (CPP).1

Pressure reactivity index (PRx; which measures the strength of correlation between ICP and MAP) and transcranial Doppler (TCD) – derived mean velocity index (Mx) (which measures the strength of correlation between mean CBFV and CPP), are two of the more commonly quoted indices of continuous autoregulatory assessment in critically ill TBI patients managed on intensive care units (ICU).2-4 These two indices are moderately correlated with each other,5,6 and in several publications, have shown replicable associations with patient morbidity and mortality.5-14 Further, the identification of critical thresholds for these variables which are associated with worse outcome15,16 provide potential targets for ICU therapies that could improve autoregulatory capacity, or (more practically) target patient-specific CPP ranges based on optimal values of these variables in individuals.17

However, numerous other indices have been described, including those derived from near infrared spectroscopy (NIRS)18-20 and brain tissue oxygen monitors (PbtO2).21-23 . The literature on these “other” continuous indices is limited, and their association with patient outcome is unclear. Further, their correlation with better established autoregulatory indices, such as PRx, is poorly understood outside of animal models. Studies which assess such correlations between autoregulatory indices are difficult: they are labor intensive, and require concurrent placement of several invasive and non-invasive monitors to capture signals for data processing. Consequently, such studies are rare – most published examples compare a single index to outcome, or examine the correlation between two indices. This limited literature does not allow the treating ICU clinician to choose indices for monitoring, cross calibrate indices against each other, and/or have an integrated view of the strength of their association with clinical outcome.

The goal of our study was to utilize an existing patient dataset, where multiple monitoring devices (ICP, ABP, TCD, NIRS and PbtiO2) had been applied, in order to assess the relationship between a range of indices of autoregulatory function. We also wished to examine which of these indices were best correlated with clinical outcome.

**Methods:**

***Patient Population***

The patients included in this study represent a sub-population of a cohort that provide the substrate for previous studies,24-26  which assessed specific NIRS based autoregulatory indices and their association with PRx. A review of this dataset revealed that it contained raw monitoring signals which permitted the measurement of additional indices of autoregulatory capacity. The majority of patients in this cohort had the following monitoring: ICP, CPP, MAP, NIRS, bilateral TCD of the middle cerebral artery (MCA), and PbtO2. Thus, this population provided us the largest number of monitoring devices, and hence allowed assessment of relationships between the largest range of autoregulatory indices.

This study was conducted as a retrospective analysis of a prospectively maintained database cohort, in which two separate sets of recordings were analysed. Long recordings spanned several hours in each case but did not include TCD monitoring, and short recordings (~1-2 hours in duration) in which TCD was available.

All patients suffered mild to severe TBI and were admitted to the Neurosciences Critical Care Unit (NCCU) at Addenbrooke’s Hospital, Cambridge. Those with mild and moderate TBI, displayed progressive deterioration in clinical status, necessitating multi-modal monitoring via a combination of invasive and non-invasive techniques. Treatment received during the recording periods included standard ICP-directed therapy, with an ICP goal of less than 20 mm Hg and CPP goal of greater than 60 mm Hg.

The study was approved by the research ethics committee (29 REC 97/291). Monitoring of above brain modalities was conducted as a part of standard NCCU patient care using an anonymized database of physiological monitoring variables in neurocritical care. Data on age, injury severity, and clinical status at hospital discharge were recorded at the time of monitoring on this database, and no attempt was made to re-access clinical records for additional information. Since all data was extracted from the hospital records and fully anonymized, no data on patient identifiers were available, and formal patient or proxy consent was not sought.

***Signal Acquisition***

Various signals were obtained through a combination of invasive and non-invasive methods. Arterial blood pressure (ABP) was obtained through either radial or femoral arterial lines connected to pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA). ICP was acquired via an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA). NIRS signals were recorded bilaterally over the frontal lobes utilizing the NIRO 200 monitoring. The following NIRS signals were recorded: oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HHb), total oxygenation index (TOI), total hemoglobin index (THI) and total hemoglobin concentration (Hb).

PbtO2 monitoring occurred via invasive parenchymal monitoring (Licox probe; Integra, Licox Brain Oxygen Monitoring System, Plainboro, NJ), typically placed in the right frontal lobe a triple lumen bolt (Technicam Ltd).

Finally, TCD assessment of MCA CBFV was conducted via Doppler Box (DWL Compumedics, Singen, Germany) or Neuroguard (Medasonic, Fremont, CA, USA). Two separate recording sessions were obtained for each patient with TCD, lasting ~60 minutes each. Bilateral MCA recordings were obtained in every patient during these sessions. As mentioned above, TCD recordings were only present in the short recording data set.

***Signal Processing***

All recorded signals were recorded using digital data transfer or digitized via an A/D converters (DT9801; Data Translation, Marlboro, MA), where appropriate, sampled at frequency of 50 Hertz (Hz) or higher, using ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, <http://www.neurosurg.cam.ac.uk/icmplus>). Signal artifact were removed manually prior to further processing or analysis.

Post-acquisition processing of the above signals was conducted using ICM+ software. CPP was determined using the formula: CPP = MAP – ICP. Of note, the data recorded from the left TCD had a large amount of artifact, impeding our ability to include it in the majority of patients. Consequently, we excluded the left TCD signals for the short recordings analysis. Given that left sided TCD recordings were discarded, we therefore only report the right sided NIRS based indices as well.

Systolic ABP (ABPs) was determined by calculating the maximum ABP over a 1.5 second window, updated every second. Similarly, diastolic ABP (ABPd) was determined by calculating the minimum ABP over a 1.5 second window, updated every second. Systolic flow velocity (FVs) was determined by calculating the maximum flow velocity (FV) over a 1.5 second window, updated every second. Diastolic flow velocity (FVd) was calculated using the minimum FV over a 1.5 second window, updated every second. Mean flow velocity (FVm) was calculated using average FV over a 10 second window, updated every 10 seconds (ie. without data overlap). Pulse amplitude of ICP (AMP) was determined by calculating the fundamental Fourier amplitude of the ICP pulse waveforms over a 10 second window, updated every 10 seconds.

Ten second moving averages (updated every 10 seconds to avoid data overlap) were calculated for all recorded signals: ICP, ABP (which produced MAP), ABPs, ABPd, CPP, FVm, FVs, FVd, TOI, and THI. For the PbtO2 signal, 30 second means were calculated, as previously described by Jaeger et al.21

Autoregulation indices were derived in a similar fashion across modalities; an example is provided for PRx: A moving Pearson correlation coefficient was calculated between ICP and MAP using 30 consecutive 10 second windows (ie. five minutes of data), updated every minute. Details on each index calculation can be found in Table 1.

***\*Table 1 here***

Data for this analysis were provided in the form of a minute by minute time trends of the parameters of interest for each patient. This was extracted from ICM+ in to comma separated values (CSV) datasets, which were collated into one continuous data sheet (compiled from all patients). We then determined 30 minute moving averages (non-overlapping) for every index, and individual patient grand means for each index. The statistical analysis was performed on all 3 data sheets for each data sheet: minute-by-minute, 30 minute moving averaged, and grand means.

Three separate data sheets were employed given the currently unknown autocorrelative structure within each of these physiologic indices. Furthermore, given PbtO2 based indices are typically calculated over varying window lengths (such as 30 minutes or longer), which are longer than all other ICP/TCD/NIRS based indices, we wanted to make sure that there was no difference in the results of our analysis based on the calculation windows and averaging process of the data.

***Statistics***

*General Statistics*Statistics were performed utilizing XLSTAT (Addinsoft, New York, United States; https://www.xlstat.com/en/) add-on package to Microsoft Excel (Microsoft Office 15, Version 16.0.7369.1323) and R statistical software (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

Tests for normality were performed using the Shapiro-Wilks test for all indices and measured variables. All indices and variables were determined to be non-parametric in nature. Alpha was set at 0.05 for all results describing a p-value.

All statistical tests were performed on each of these data sheets, resulting in three sets of results.

We employed a Pearson correlation coefficient matrix to assess correlation between the various indices, which was conducted after performing a Fisher transformation to the data set (which normalizes the correlation coefficient distribution). This was the only test in which transformed data was utilized within the analysis.

Grouped variance between different combinations of indices was assessed using the Friedman test with and without multiple comparisons, to account for within subject variation. The main assumption for the use of this test was that all indices were measuring the same physiologic variable (ie. autoregulation). The Friedman test was performed on the following combinations of data: all indices, ICP derived indices (PRx, PAx, RAC), PbtO2 derived indices (ORx-5, ORx-30, ORx-60), NIRS derived indices (THx, TOx, THx\_a, TOx\_a), and TCD (in the short recordings) derived indices (Mx, Sx, Dx, Mx\_a, Sx\_a, Dx\_a). The results for both the with and without multiple comparisons were identical, hence only the Friedman test with multiple comparisons is mentioned within the results section.

*Multivariate Clustering and Assessment of Co-variance*

Finally, multivariate statistics were performed to delineate further the associations between the various indices. Currently, it is unclear as to which multivariate clustering technique is superior within the exploration of time series based physiologic variables, thus we chose to employ an array of testing techniques. Three different multi-variate methods were employed in order to assess the co-variance within various combinations of indices. This was done, so as to be comprehensive and to provide confirmation of the potential clustering seen in any individual given test.

First, principle component analysis (PCA) was performed using a Spearman type PCA, chosen to account for the non-parametric data distribution in the dataset (with significance set at p<0.05). PCA has been described in detail in other publications, and is ideally suited as an “exploratory” statistic for small patient cohorts with large numbers of variables.27-29 The purpose of PCA is to highlight which combinations of variables explain the overall variance within the entire dataset, and thus which variables may be related and of further interest to study via other methods. We refer the readers to cited publications on PCA for more information.27-29

Second and third, agglomerative hierarchal clustering (AHC) and k-means based cluster analysis (KMCA) (using Euclidean distance) were also performed. These tests provide an overall assessment of the similarity between variables, grouping them into clusters (or stems on a dendrogram, as seen within AHC) based on the mean distance away from one another, as assessed by Euclidean distance.

For the AHC, the statistical strength of the correlation between the clusters produced in the dendrograms was quantified using cophenetic correlation coefficients. Cophenetic correlations coefficients were produced by the Spearman correlation between the original Euclidean distance matrix calculated for the ACH, and the cophenetic distance matrix. The cophenetic distance is defined as the distance between two clusters that contain two indices individually and the point where both clusters are merged (ie. it represents the height on the dendrogram at which the branch points occur). The cophenetic correlation coefficient is believe to be an estimate of how well the AHC dendrogram maintains pairwise distances when compared with the original data set (ie. the baseline distance matrix between variables).

With the KMCA, the number of clusters can be set by the investigator. We utilized the “Elbow method” of KMCA in order to determine the appropriate number of clusters for the final analysis. The Elbow method consists of computing all possible k-means clusters. Subsequently, a plot of the within-group sum of squares versus cluster number, allowed selection of an inflection point (or “elbow”) at which the plot showed the most dramatic slope change. This is deemed the “most appropriate” cluster number for the final analysis.

*Outcome Analysis – Logistic Regression*

Finally, a binary univariate logistic regression analysis was performed, comparing each index to dichotomized outcome. Outcome was assessed by the Glasgow Outcome Scale (GOS) at 6 months post-injury. The patient outcomes were dichotomized into: “Good Outcome” (GOS of 4 or 5) and “Poor Outcome” (GOS of 3 or less). We also assessed the association of each index to mortality.

**Results:**

***Patient Demographics***

The median age of the patients within this previously described retrospective TBI cohort was 33 years (range: 16 to 76 years), with a median admission GCS of 7 (range: 3 to 14). Three patients underwent surgical evacuation of mass lesions upon admission to hospital. For further details on the patient population, we refer the readers to previous publications focused on the clinical characteristics of this cohort.24-26  After removal of those patients without PbtO2 monitoring, there were a total of 37 patients included in the final analysis. An example of the various signal and autoregulatory index changes during a plateau wave from one of the patient datasets can be seen in Figure 1, while the co-variation of these signals and indices during systemic hypertension can be seen in Figure 2.

\****Figure 1 and 2 here***

***Inter-Index Correlation***

The Pearson correlation coefficient matrix for the grand mean data set can be seen in Table 2. The Pearson matrices for the 30 minute average and minute-by-minute data sheets (and all Pearson p-value matrices) provided very similar results and are hence not shown here, but are available in Appendix A of the supplementary materials. In the grand mean data set, PRx was noted to display strong correlations with PAx RAC and Sx/Sx\_a. PRx displayed weak correlations with the remaining indices, with r-values less than 0.3 (p<0.0001 for all). PAx and RAC displayed similar correlation patterns to PRx.

PbtO2 based indices (ORx-5/ORx-30/ORx-60) failed to display strong correlations with any of the other indices of autoregulatory assessment within the grand mean data set. However, strong correlations were seen between ORx-30 and ORx-60. All r-values were 0.250 or less, with most failing to reach statistical significance. The only exception to this was with the correlation between ORx-60 and THx (r= -0.341, p=0.039). This raises the question as to whether ORx-30 or ORx-60 can safely be utilized as a surrogate for autoregulatory assessment.

The TCD based indices (Mx, Sx and Dx) displayed interesting correlation patterns within the grand mean data set. Robust correlations were observed for Mx *vs*. Dx (r=0.911, p<0.0001), and Mx *vs* Sx (r=0.726, p<0.0001) were seen. Furthermore, the TCD indices derived against CPP (Mx, Sx, and Dx) were strongly correlated with those derived from MAP (Mx\_a, Sx\_a, and Dx\_a). Mx displayed a moderate correlation with the ICP derived indices (PRx, PAx, and RAC) with r-values ranging from 0.3 to 0.4. Mx was strongly correlated with the spatially resolved NIRS indices (TOx and THx): TOx (r=0.618, p<0.0001) and THx (r=0.487, p=0.002). Sx and Sx\_a were correlated with the ICP derived indices, Mx and Dx (as previously mentioned), with the remaining correlations being weak. Finally, Dx and Dxa only displayed strong correlations between Mx and Sx, with the remaining index correlations being weak.

The NIRS based spatially resolved indices displayed strong intra-technique correlations. Only the statistically significant strong correlations are reported, with the remaining displaying weak correlations (r-values <0.3) (the exact r-values can be seen in Table 1). TOx displayed moderate-to-strong correlations with THx, PRx, Mx, Sx and Dx. THx displayed moderate-to-strong correlations with TOx, RAC, Mx, Sx and Dx. Of note, most NIRS based autoregulatory indices displayed weak, or absent, correlation to ICP derived indices (such as PRx, PAx or RAC). Importantly, NIRS based indices displayed moderate-to-weak correlation with PRx, with most r-values around 0.3 or less.

***\*Table 2 here***

***Friedman Test (with multiple comparisons) for Grouped Similarity Between Indices***

A Friedman test, with multiple comparisons, was conducted on different groups of indices, in order to assess if similar variance existed between the means in each group. The main assumption made for this statistical test was that each index measured the same physiologic parameter (ie. autoregulation) with the same range of measurement.

In the grand mean sheet, the Friedman test on the whole group of indices (ie. 16 variables in total), indicated that these indices were dissimilar (p<0.0001, Q = 249.797). Testing of clusters of indices based on the modality they were derived from showed that, even within clusters, there was clear lack of similarity between the ICP based indices (ie. PRx, PAx and RAC; p<0.0001, Q = 48.054), the TCD based indices (ie. Mx, Mxa, Sx, Sxa, Dx and Dxa; p<0.0001, Q = 141.046), and the NIRS-based indices (p<0.0001Q = 38.849). However the PbtO2 based indices (ORx-5, ORx-30 and ORx-60) were found to share substantial commonality based on the Friedman test (p=0.155, Q = 3.722). Similar results were found for the 30-minute mean and minute-by-minute data sheets, described in Appendix B of the supplementary materials.

***Inter-Index Relationships - Multivariate Tests (PCA, AHC and KMCA)***

*PCA*

A range of multivariate tests were performed (ie. PCA, AHC and KMCA) to further assess inter-index relationships. For the grand mean data, the PCA test was performed utilizing a Spearman type PCA (given the non-parametric nature of the dataset). Twenty principal components (PC) (also referred to as factors (F)) were identified, with the first 8 PC’s composing ~90% of the overall variance in the dataset. PC eigenvalue data, Scree plots, and variable specific loadings can be seen in Appendix C of the supplementary materials.

A loading biplot for PC1 (denoted F1) and PC2 (denoted F2) can be seen in Figure 3. As can be seen in Figure 3, the ICP derived indices (PRx, PAx and RAC) are clustered in the same quadrant of the biplot, contributing to the overall variance of mainly PC1. Furthermore, PRx/PAx/RAC appeared to be associated with TCD based Sx and Sx\_a, in terms of their contributions to the variance of the whole data set. Similarly, the TCD based indices (Mx, Mx\_a, Dx and Dx\_a) were co-located within the area of the biplot most associated with both PC1 and PC2. NIRS based spatially resolved THx, THx\_a, TOx and TOx\_a were co-located with the Sx/Sx\_a TCD indices. Of note, ORx-/ORx-30/ORx-60 were all co-located, but separated from the other variables, indicating they are essentially unrelated to all the other indices. Furthermore, ORx-5/ORx-30/ORx-60 were located close to the origin of the biplot, indicating that they contribute little variance to the two main principal components of the data sheet. The 30-minute mean and minute-by-minute data sets displayed similar results, and can be seen in Appendix C of the supplementary materials.

**\*Figure 3 here**

*AHC*

We wished to further assess the inter-index relationships, and thus applied AHC analysis to see if different associations appeared. Figure 4 displays the hierarchal dendrogram generated from this analysis on the minute-by-minute data. As can be seen within the dendrogram, the TCD based indices, ICP based indices, PbtO2 based indices and NIRS based indices seem to co-cluster under similar branches. Another relation of interest is that of Sx/Sxa with PRx/PAx/RAC, where these indices arise from the same limb of the dendrogram. This is concordant with the results of the Pearson correlation matrix and the PCA. In addition, the spatially resolved NIRS indices (THx, THx\_a, TOx and TOx\_a) appear to co-localize with the Sx/Sx\_a TCD indices on the dendrogram (similar to the Pearson and PCA).

An interesting association was observed between the NIRS indices and PRx and PAx. This was seen in the PCA (and KMCA; see subsequently), but was not robustly demonstrated by the Pearson correlation coefficients. Finally, ORx-5/ORx-30/ORx-60 clustered on a separate limb of the dendrogram, having little association with the other indices. The cophenetic correlation coefficient derived for the AHC dendrogram displayed in Figure 4 was 0.822, indicating a statistically robust clustering. Applying AHC to the 30 minute and grand mean data sets resulted in similar hierarchical dendrograms with similar clustering of indices (cophenetic correlation coefficients of r=0.812 and r=0.746 respectively), confirming the relations/clustering seen in the minute-by-minute data set.

***\*Figure 4 here***

*KMCA*

To complete our cluster analysis, we employed the KMCA, using seven centers of cluster (based on Euclidean distance and the Elbow method of cluster number determination). Appendix D of the supplementary materials displays a table of the KMCA cluster groupings based on autoregulatory index, with the clusters displaying similar patterns to the AHC described above.

***Binary Univariate Outcome Analysis***

A Univariate logistic regression analysis compared each autoregulatory index with binary outcomes at six months, assessed using the GOS, dichotomized in two ways: “Good” (4 or 5) vs. “Poor” (3 or less) outcome, and “Alive” vs. “Dead”. Table 3 outlines the area under the receiver operating curve (AUC) for each index as a predictor of the two outcome categories, along with P-values for the logistic regression models. We split the indices into two groups: A. “Invasive” indices – composed of those requiring CPP for calculation, and B. “Non-invasive indices” – composed of those derived from MAP, which could be derived via non-invasive continuous MAP measurement.

All models produced by univariate logistic regression failed to reach statistical significance, given the small patient numbers (n=37). However, some interesting trends merit comment. Within the “invasive” index group, the ICP derived indices (PRx, PAx and RAC) displayed the highest AUC’s in both the prediction of “good” vs. “poor” outcome and mortality, with positive values of these indices associated with “poor” outcome and mortality. RAC was the strongest predictor of both outcomes (AUC = 0.730).

In comparison, within the “non-invasive” index group, the TCD based indices (Mx\_a Sx\_a and Dx\_a) displayed better prediction of both dichotomized outcome, compared to the NIRS indices. Mx\_a and Sx\_a displayed the strongest predictive capabilities out of the “non-invasive” indices.

It must be re-emphasized that given the small patient cohort studied, none of the aspects of the logistic regression reached statistical significance. Therefore, the above described relationships are trends that require further validation.

\****Table 3 here***

**Discussion:**

The use of continuously updating measures of autoregulatory capacity has gained acceptance within the ICU and neuro-critical care communities, receiving support through recently published international multi-modal monitoring consensus statements.2,3 Most of the literature on these indices addresses PRx or Mx, with PRx emerging as the most commonly utilized method of continuous autoregulatory assessment in TBI.1,2 PRx is based on the concept that the 10-second by 10-second variation in a surrogate measure of pulsatile cerebral arterial blood volume (ie. ICP) in association with a driving force for cerebral blood flow (ie. MAP), yields valuable information about cerebral pressure autoregulatory capacity. To date, the literature supports a strong association between PRx and patient outcome,15,16 with PRx utilized for the determination of patient specific optimum CPP.17 Furthermore, PRx and TOx (equivalent of COx) are the only two indices which have been validated experimentally, using the gold standard measure of autoregulation (the lower limit of autoregulation on the Lassen curve). 30,31 Within Brady et al,30 it was demonstrated within piglet models that PRx and TOx nicely respect the lower limit of autoregulation when CPP is manipulated, with increasingly positive values found below this limit. Thus, PRx and TOx currently serve as the only two clinically applicable indices which have been shown to represent autoregulation in controlled animal studies, and there for serve as the only “validated” indices to date.

Numerous other indices of “autoregulation” can be derived by applying the concept of a moving Pearson correlation coefficient between a haemodynamic input function (CPP or MAP) and a measure of cerebrovascular physiology. However robust support for the clinical use of these “other” indices, such as those derived via non-PRx based correlations (ie. between ICP, TCD, NIRS and PbtO2 derived signals), is lacking. Thus, it is currently unknown to what extent these “other” indices actually measure autoregulation, and if they are correlated to a commonly utilized assessment of autoregulatory capacity, such as PRx.

Our retrospective analysis of this small cohort of patients with ICP, MAP, TCD, NIRS and PbtO2 monitoring provides interesting insights into these inter-index associations, with concordant results across three distinct data sheets: minute-by-minute, 30-minute non-overlapping mean, and grand mean data. A few important relationships are highlighted below.

First, and most importantly, these indices are not all related. This is clear based on all forms of analysis that we undertook: Pearson correlation, Friedman test (with and without multiple comparisons), PCA, AHC and KMCA. Thus, for the treating clinician, it is critical to understand that these indices are derived from different invasive/non-invasive cranial monitoring, and may measure different aspects of physiology. One cannot simply substitute a less commonly described index for one that has been well defined, such as PRx. With that said, our analysis produced some interesting relationships which could drive further study.

Second, PRx displayed strong correlations with PAx and RAC across Pearson correlation, PCA, AHC and KMCA. It is not surprising that these indices are related, since they are all derived from ICP or AMP. Of note, PRx was not found to be strongly correlated to Mx (r=0.356, p<0.0001), a finding confirmed in all three data sheets across the short recordings. This is in contradiction to a previously defined strong correlation between PRx and Mx5,6 The reason for this is likely related to the small patient numbers, short monitoring duration and impact of injury/treatment heterogeneity.

Third, TCD based indices (regardless if calculated via CPP or MAP) are associated and co-cluster during formal cluster analysis. This is unsurprising, and has been previously described in larger cohorts. What was interesting was the strong association of Sx/Sx\_a with the ICP derived indices across all of the analyses. This strong relationship with PRx/PAx/RAC may stems from the contribution of systolic peaks in CBF to ICP and its derivatives (ie. AMP), suggesting Sx/Sx\_a may be closely associated with PRx/PAx/RAC. This is in contrast to Mx/Dx (and their MAP derivatives), which may more closely relate to cerebral blood volume (CBV), and therefore do not strongly associate with PRx/PAx/RAC on Pearson, PCA, AHC and KMCA. These relationships require further investigation and physiologic validation. However, the strong association between Sx/Sx\_a with PRx/PAx/RAC may imply that Sx/Sx\_a might be the best surrogate for PRx/PAx/RAC, compared to the other invasive/non-invasive indices.

Fourth, PbtO2 based indices (ORx-5/ORx-30/ORx-60) all failed to display strong correlations with any of the other indices, as assessed through Pearson correlation, KW, PCA, AHC and KMCA. This was confirmed across the minute-by-minute, 30 minute, and grand mean data. Notably, but not surprisingly, ORx-5, ORx-30, and ORx-60 were found to be co-related on Pearson correlation, PCA, ACH and KMCA across all data sheets and recording lengths. The divergence of ORx from the other indices measured likely stems from the fact the PbtO2 is a slowly changing parameter, at a frequency that is lower than most slow waves. Taking all of this into consideration, ORx may be a questionable assessment of autoregulatory capacity and should be utilized with caution in the clinical setting. Derivation of patient specific CPP optimal values based on ORx, as described in some studies,31,32 should be interpreted with caution, as PbtO2 can be greatly influenced by many systemic factors, and since these indices do not appear to be associated strongly with any of the other indices, including the thoroughly studied PRx/Mx. Moreover, using thresholds defined by other indices (ie. PRx or Mx)15,16 with ORx should be avoided entirely, since it appears that this index is not the same as PRx or Mx.

Fifth, NIRS based indices displayed variable correlation with indices derived from ICP, PbtO2 and TCD signals, especially PRx and Mx. The NIRS indices display intra-modality correlation of varying degrees (increasing in the 30 minute and grand mean data sets). Further, these NIRS indices seem to co-cluster on PCA, AHC and KMCA. Of interest, with both PCA and AHC, TOx/THx (and their MAP based equivalents) appear to cluster with the ICP derived indices. Based on the animal studies validating PRx and TOx against the lower limit of the Lassen curve,30,31 the association between ICP derived indices and TOx/TOx\_a is not that surprising. The cluster of THx and THx\_a with the ICP derived indices has not been well documented. It is possible that the spatially resolved NIRS indices, with parent signals designed to exclude the contamination of extracranial blood flow, may represent frontal lobe pulsatile cortical blood flow through the small arteries/arterioles. This may explain the clustering and association with PRx/PAx/RAC/Sx/Sx\_a, and not Mx/Dx which are potentially more representative of CBV. In addition, the 'classic' clustering of these indices has been to group TOx/Mx group together (CBF effects) and THx/PRx together (CBV effects). Our multi-technique analysis provides inference that are not concordant with these classical views, and suggest that the NIRS based spatially resolved indices are more closely related to ICP (for both THx and TOx). These NIRS indices may therefore both be metrics of CBV (perhaps oxygenated and deoxygenated versions). This relation was confirmed on every test (PCA, ACH and KMCA) across all data sheets. Further to this, the relationships described within the manuscript are statistically robust. The ACH dendrogram, for example, is a statistically significant and robust outcome based on a strong cophenetic correlation coefficient (r=0.822). This indicates a quite strong AHC intra-cluster association, and essentially means the clusters on this test are not by chance. This was of course confirmed with the grouped variances within PCA and grouped clustering on KMCA testing. However, despite our results, further exploration of these relationships is required in order to better understand the physiology and associations between indices of autoregulation.

Finally, univariate logistic regression analysis comparing each index (invasive and non-invasive) with dichotomized patient outcomes provided some interesting trends, though our small sample size means that these analyses fail to reach statistical significance, even for indices that have previously been shown to correlate with outcome. Within the invasive index category, the ICP derived indices provided the strongest prediction of both mortality and “good” versus “poor” outcome. RAC produced the highest AUC for both categories of outcome prediction. The worst outcome prediction was provided by the PbtO2 derived indices (ORx-5/ORx-30/ORx-30). Within the non-invasive index category, Mx\_a and Sx\_a were superior to all other indices (both TCD and NIRS derived), and thus may be the best surrogate measures of autoregulatory capacity in the absence of invasive ICP monitoring. Despite the interesting trends, it must be re-emphasized that given the small patient cohort, none of the results from univariate analysis were statistically significant.

*Limitations*

Despite these interesting results, some critical limitations within our study must be addressed. First, this is a retrospective cohort study. The patient population is composed of those with heterogenous injury patterns, ICU/hospital courses and potentially varied ICU therapies during the recorded signals. This impacts the inter-patient signal variability and potentially the results of our analysis. This may be exemplified by our lack of strong correlation between PRx and Mx, which has been previously defined in larger cohorts of TBI patients with TCD recordings.5,6 Therefore, our results are only hypothesis generating and by no means definitive in terms of the relationships between the various autoregulatory indices.

Second, the population was small, consisting of only 37 patients. Third, the duration of signal recording was quite limited for each patient within the short recording cohort, with typically only two sessions lasting one hour each in duration. Thus, depending on the individual patient events (ie. suctioning, ICP therapies, etc.) during these period, various segments of data were either too artefactual to include in the final analysis (such as during suctioning or turning), or significantly impacted by administered therapies (such as hypertonic saline boluses). Furthermore, we demonstrated weaker correlation between THx\_a and PRx, than in a previously published study, based on similar recordings.24 We believe the reason for the weaker correlation coefficient stems from the fact that the population of this current study is only a sub-population the original group (i.e. those with all the monitoring modalities available). Also, we only used the short (1-2 hour) recordings, given these were the only recordings available with TCD.

Fourth, the erratic nature of spontaneous slow waves may be the main driving factor as to why some indices failed to produce reproducible relationships. It may be that in the continuous measure of these indices within the ICU, we should apply filters related to slow wave power, focusing only on those periods in which power and signal coherence meet a certain threshold. This could potentially improve some of the relationships seen. Longer recording sessions would be required for this.

Fifth, even the metric of autoregulation provided by individual indices are dissimilar, it is important to highlight that this does not indicate that CPP-optimum derived from these indices is divergent as well. This would need to be explored in patients with all of the above monitoring modalities, across much longer recording intervals.

Sixth, the application of the Friedman test in this circumstance (ie. to compare across indices) is controversial, given one can argue that these indices are not the same and in fact don’t measure the same physiology. Thus, the results of the KW analysis should be interpreted with caution. However, we were able to confirm the results of the KW analysis by displaying the inter-index dissimilarities using Spearman ranked correlation, PCA, ACH and KMCA.

Seventh, the use of multivariate statistical tests, such as PCA, are meant as “exploratory” methods of analyzing small patient cohorts with many recorded variables. PCA, AHA and KMCA are not definitive tests, in that they do not indicate statistically significant associations or correlations between various combinations of variables. These tests are merely designed to provide some idea on groupings of variables across the entire data set, and serve only to drive further directed studies of specific relationships identified. Thus, the associations of Sx/Sx\_a and the NIRS indices with PRx/PAx/RAC require further investigation in order to better understand the physiologic link between these indices.

It must be re-emphasized that this study in no way indicates that the various indices described either measure, or do not measure, autoregulatory capacity. In addition, the relationships (or lack thereof) described within this manuscript are based on a small population with some significant limitations, and thus should be taken as a preliminary exploratory analysis. This study was only meant to further explore, the inter-index relationships in a cohort of patients with many monitoring devices. The result of our analysis require validation. Based on this study, we plan on prospectively validating these results on a new cohort of adult TBI patients by obtaining long recording sessions, including TCD. Further to this, given the potential for autocorrelative structure within the data as we move from observation to observation within a given patient, and the potential for inter-patient differences, our future analysis will include advanced analysis of the autocorrelative structure within and between various indices, plus the application of non-linear mixed effects modelling in order to account for both within and between patient differences.

**Conclusions:**

Continuously updated autoregulatory indices, based on correlations between haemodynamic inputs (CPP and MAP) and indices of cerebrovascular physiology derived from a range of invasive and non-invasive monitors, are different, and can be poorly correlated with one another. However, these indices cluster in several groupings , which provide insights regarding the pathophysiology that underlies their production. Caution must be advised when utilizing less commonly described autoregulation indices (such as ORx) for the clinical assessment of autoregulatory capacity, as they appear to not be related to commonly measured/establish indices, such as PRx. Further prospective validation of these results is required.

**Disclosures:** FAZ has received salary support for dedicated research time, during which this project was partially completed. Such salary support came from: the Cambridge Commonwealth Trust Scholarship, the Royal College of Surgeons of Canada – Harry S. Morton Travelling Fellowship in Surgery, the University of Manitoba Clinician Investigator Program, R. Samuel McLaughlin Research and Education Award, the Manitoba Medical Service Foundation, and the University of Manitoba - Faculty of Medicine Dean’s Fellowship Fund.

DKM has consultancy agreements and/or research collaborations with GlaxoSmithKline Ltd; Ornim Medical; Shire Medical Ltd; Calico Inc.; Pfizer Ltd; Pressura Ltd; Glide Pharma Ltd; and NeuroTraumaSciences LLC.

MC and PS have financial interest in a part of licensing fee for ICM+ software (Cambridge Enterprise Ltd, UK).

MC is an honorary co-Director of Technicam Ltd- producer of Cranial Access Device used for CMD insertion.

**Acknowledgments:** This work was made possible through salary support through the Cambridge Commonwealth Trust Scholarship, the Royal College of Surgeons of Canada – Harry S. Morton Travelling Fellowship in Surgery, the University of Manitoba Clinician Investigator Program, R. Samuel McLaughlin Research and Education Award, the Manitoba Medical Service Foundation, and the University of Manitoba Faculty of Medicine Dean’s Fellowship Fund.

These studies were supported by National Institute for Healthcare Research (NIHR, UK) through the Acute Brain Injury and Repair theme of the Cambridge NIHR Biomedical Research Centre, an NIHR Senior Investigator Award to DKM, and an NIHR Research Professorship to PJAH. Authors were also supported by a European Union Framework Program 7 grant (CENTER-TBI; Grant Agreement No. 602150)

**References:**

1. Zweifel, C., Lavinio, A., Steiner, L.A., Radolovich, D., Smielewski, P., Timofeev, I., Hiler, M., Balestreri, M., Kirkpatrick, P.J., Pickard, J.D., Hutchinson, P., and Czosnyka, M. (2008). Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. Neurosurg Focus 25, E2.
2. Czosnyka, M., Miller, C.; Participants in the International Multidisciplinary Consensus Conference on Multimodality Monitoring. (2014). Monitoring of cerebral autoregulation. Neurocrit Care 21 Suppl 2, S95-102.
3. Le Roux, P., Menon, D.K., Citerio, G., Vespa, P., Bader, M.K., Brophy, G., Diringer, M.N., Stocchetti, N., Videtta, W., Armonda, R., Badjatia, N., Bösel, J., Chesnut, R., Chou, S., Claassen, J., Czosnyka, M., De Georgia, M., Figaji, A., Fugate, J., Helbok, R., Horowitz, D., Hutchinson, P., Kumar, M., McNett, M., Miller, C., Naidech, A., Oddo, M., Olson, D., O'Phelan, K., Provencio, J.J., Puppo, C., Riker, R., Roberson, C., Schmidt, M., and Taccone, F. (2014). Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care 21 Suppl 2, S1-26.
4. Zweifel, C., Dias, C., Smielewski, P., and Czosnyka, M. (2014). Continuous time-domain monitoring of cerebral autoregulation in neurocritical care. Med Eng Phys 36, 638-645.
5. Budohoski, K.P., Czosnyka, M., de Riva, N., Smielewski, P., Pickard, J.D., Menon, D.K., Kirkpatrick, P.J., and Lavinio, A. (2012). The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. Neurosurgery 71, 652-660.
6. Czosnyka, M., Smielewski, P., Kirkpatrick, P., Laing, R.J., Menon, D., and Pickard, J.D. (1997). Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 41, 11-17.
7. Czosnyka, M., Smielewski, P., Piechnik, S., and Pickard, J.D. (2002). Clinical significance of cerebral autoregulation. Acta Neurochir Suppl 81, 117-119.
8. Czosnyka, M., Balestreri, M., Steiner, L., Smielewski, P., Hutchinson, P.J., Matta, B., and Pickard, J.D. (2005). Age, intracranial pressure, autoregulation, and outcome after brain trauma. J. Neurosurg 102, 450-454.
9. Czosnyka, M., Smielewski, P., Czosnyka, Z., Piechnik, S., Steiner, L.A., Schmidt, E., Gooskens, I., Soehle, M., Lang, E.W., Matta, B.F., and Pickard, J.D. (2003). Continuous assessment of cerebral autoregulation: clinical and laboratory experience. Acta Neurochir Suppl 86, 581-585.
10. Czosnyka, M., Smielewski, P., Piechnik, S., Al-Rawi, P.G., Kirkpatrick, P.J., Matta, B.F., and Pickard, J.D. (1999). Critical closing pressure in cerebrovascular circulation. J. Neurol Neurosurg Psychiatry 66, 606-611.
11. Czosnyka, M., Smielewski, P., Piechnik, S., Schmidt, E.A., Seeley, H., al-Rawi, P., Matta, B.F., Kirkpatrick, P.J., and Pickard, J.D. (2000). Continuous assessment of cerebral autoregulation--clinical verification of the method in head injured patients. Acta Neurochir Suppl 76, 483-484.
12. Eide, P.K., Czosnyka, M., Sorteberg, W., Pickard, J.D., and Smielewski, P. (2007). Association between intracranial, arterial pulse pressure amplitudes and cerebral autoregulation in head injury patients. Neurol Res 29, 578-582.
13. Gao, L., Smielewski, P., Czosnyka, M., and Ercole, A. (2016) Cerebrovascular signal complexity six hours after intensive care unit admission correlates with outcome after severe traumatic brain injury. J. Neurotrauma 33, 2011-2018.
14. Hiler, M., Czosnyka, M., Hutchinson, P., Balestreri, M., Smielewski, P., Matta, B., and Pickard, J.D. (2006). Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. J. Neurosurg 104, 731-737.
15. Sorrentino, E., Diedler, J., Kasprowicz, M., Budohoski, K.P., Haubrich, C., Smielewski, P., Outtrim, J.G., Manktelow, A., Hutchinson, P.J., Pickard, J.D., Menon, D.K., and Czosnyka, M. (2012). Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care 16, 258-266.
16. Sorrentino, E., Budohoski, K.P., Kasprowicz, M., Smielewski, P., Matta, B., Pickard, J.D., and Czosnyka, M. (2011). Critical thresholds for transcranial Doppler indices of cerebral autoregulation in traumatic brain injury. Neurocrit Care 14, 188-193.
17. Needham, E., McFadyen, C., Newcombe, V., Synnot, A.J., Czosnyka, M., and Menon, D. (2016). Cerebral perfusion pressure targets individualized to pressure-reactivity index in moderate to severe traumatic brain injury: a systematic review. J. Neurotrauma Jun 27. [Epub ahead of print]
18. Diedler, J., Zweifel, C., Budohoski, K.P., Kasprowicz, M., Sorrentino, E., Haubrich, C., Brady, K.M., Czosnyka, M., Pickard, J.D., and Smielewski, P. (2011). The limitations of near-infrared spectroscopy to assess cerebrovascular reactivity: the role of slow frequency oscillations. Anesth Analg 113, 849-857.
19. Highton, D., Ghosh, A., Tachtsidis, I., Kolyva, C., Panovska, J., Elwell, D., and Smith, M. (2012). Deoxyhaemoglobin as a biomarker of cerebral autoregulation. Crit Care 16, S106-S107.
20. Highton, D., Ghosh, A., Tachtsidis, I., Panovska-Griffiths, J., Elwell, C.E., and Smith, M. (2015) Monitoring cerebral autoregulation after brain injury: multimodal assessment of cerebral slow-wave oscillations using near-infrared spectroscopy. Anesth Analg 121, 198-205.
21. Jaeger, M., Schuhmann, M.U., Soehle, M., and Meixensberger, J. (2006). Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. Crit Care Med 34, 1783-1788.
22. Lang, E.W., Kasprowicz, M., Smielewski, P., Pickard, J., and Czosnyka, M. (2015). Changes in cerebral partial oxygen pressure and cerebrovascular reactivity during intracranial pressure plateau waves. Neurocrit Care 23, 85-91.
23. Menzel, M., Soukup, J., Henze, D., Clausen, T., Marx, T., Hillman, A., Miko, I., Grond, S., and Rieger, A. (2003). Brain tissue oxygen monitoring for assessment of autoregulation: preliminary results suggest a new hypothesis. J. Neurosurg Anesthesiol 15, 33-41.
24. Zweifel, C., Castellani, G., Czosnyka, M., Helmy, A., Manktelow, A., Carrera, E., Brady, K.M., Hutchinson, P.J., Menon, D.K., Pickard, J.D., and Smielewski, P. (2010). Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. J. Neurotrauma 27, 1951-1958.
25. Diedler, J., Zweifel, C., Budohoski, K.P., Kasprowicz, M., Sorrentino, E., Haubrich, C., Brady, K.M., Czosnyka, M., Pickard, J.D., and Smielewski, P. (2011). The limitations of near-infrared spectroscopy to assess cerebrovascular reactivity: the role of slow frequency oscillations. Anesth Analg 113, 849-857.
26. Smielewski, P., Czosnyka, M., Zweifel, C., Castellani, G., Brady, K., Hogue, C., Steiner, L.A., Hutchinson, P., Kirkpatrick, P., Menon, D., and Pickard, D. (2009). Multicentre experience of using ICM+ for investigations of cerebrovascular dynamics with near infrared spectroscopy. J. Neurotrauma 26, A47.
27. Helmy, A., Antoniades, C.A., Guilfoyle, M.R., Carpenter, K.L., and Hutchinson, P.J. (2012) Principal component analysis of the cytokine and chemokine response to human traumatic brain injury. PLoS One 7, e39677.
28. Pandey, M. (2015). Multivariate Analysis II: Principle component analysis (PCA). In: *Biostatistics: Basic and Advanced*, 1st Ed. MV Learning: India, pps. 454-456.
29. Crawley, M.J. (2013). Multivariate Analysis. In: *The R Book*, 2nd ed. Wiley-Blackwell, pps. 809-813.
30. Brady, K.M., Lee, J.K., Kibler, K.K., Easley, R.B., Koehler, R.C., and Shaffner, D.H. (2008). Continuous measurement of autoregulation by spontaneous fluctuations in cerebral perfusion pressure: comparison of 3 methods. Stroke 39, 2531–2537.
31. Blaine Easley, R., Kibler, K.K., Brady, K.M., Joshi, B., Ono, M., Brown, C., and Hogue, C.W. (2013). Continuous cerebrovascular reactivity monitoring and autoregulation monitoring identify similar lower limits of autoregulation in patients undergoing cardiopulmonary bypass. Neurol Res 35, 344-354.
32. Dias, C., Silva, M.J., Pereira, E., Monteiro, E., Maia, I., Barbosa, S., Silva, S., Honrado, T., Cerejo, A., Aries, M.J., Smielewski, P., Paiva, J.A., and Czosnyka, M. (2015). Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. Neurocrit Care 23, 92-102.
33. Dengler, J., Frenzel, C., Vajkoczy, P., Horn, P., and Wolf, S. (2013). The oxygen reactivity index and its relation to sensor technology in patients with severe brain lesions. Neurocrit Care 19, 74-78.

Figure 1: Patient Example of Index Variation During Plateau Wave



*CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, min = minutes, mm Hg = millimeter of Mercury, PRx (between ICP and MAP), PAx (between AMP and MAP), RAC (between AMP and CPP), ORx (between PbtO2 and CPP; 5 = 5 minutes calculation window, 30 = 30 minute calculation window, 60 = 60 minute calculation window), Mx (between FVm and CPP), Sx (between FVs and CPP), Dx (between FVd and CPP), TOx (between TOI and CPP), and THx (between THI and CPP).*

Figure 2: Patient Example of Index Variation during Increase in MAP



*CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, min = minutes, mm Hg = millimeter of Mercury, PRx (between ICP and MAP), PAx (between AMP and MAP), RAC (between AMP and CPP), ORx (between PbtO2 and CPP; 5 = 5 minutes calculation window, 30 = 30 minute calculation window, 60 = 60 minute calculation window), Mx (between FVm and CPP), Sx (between FVs and CPP), Dx (between FVd and CPP), TOx (between TOI and CPP), and THx (between THI and CPP).*

Figure 3: PCA Loading Biplot of F1 (PC1) vs. F2 (PC2) – Minute-by-Minute Data Set



PCA = principle component analysis, F = factor, PC = principle component, F1 = PC1 = principle component #1, F2 = PC2 = principle component #2. PC1 and PC2 are the two components which contribute the largest amount of variance to the entire data set. The above biplot of PC1 vs. PC2 displays which variables contribute variance to PC1 and PC2. The longer the arm connecting (0,0) to the variable (such as PRx), the larger the contribution of that variable. Similarly, the quadrant on the biplot in which the variable falls correlates to its contribution to a particular PC. The upper left quadrant is primarily PC2; lower left quadrant is neither PC1 or PC2; the upper right quadrant is PC1 and PC2; the lower right quadrant is primarily PC1.

Figure 4: AHC Dendrogram - Minute by Minute Data



AHC = agglomerative hierarchal clustering; The described indices are Pearson correlation coefficients between various variables: PRx (between ICP and MAP), PAx (between AMP and MAP), RAC (between AMP and CPP), ORx (between PbtO2 and CPP; 5 = 5 minutes calculation window, 30 = 30 minute calculation window, 60 = 60 minute calculation window), Mx (between FVm and CPP), Mx\_a (between FVm and MAP), Sx (between FVs and CPP), Sx\_a (between FVs and MAP), Dx (between FVd and CPP), Dx\_a (between FVd and MAP), TOx (between TOI and CPP), TOx\_a (between TOI and MAP), THx (between THI and CPP) and THx\_a (between THI and MAP).

Table 1: Autoregulation Indices and Calculation Methods

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Index** | **Signals Correlated** | **Signal Averaging (sec)** | **Pearson Correlation Coefficient Calculation Window (min)** | **Index Calculation Update Frequency (sec)** |
| PRx | ICP and MAP | 10 | 5 | 60 |
| PAx | AMP and MAP | 10 | 5 | 60 |
| RAC | AMP and CPP | 10 | 5 | 60 |
| Mx | FVm and CPP | 10 | 5 | 60 |
| Mx\_a | FVm and MAP | 10 | 5 | 60 |
| Sx | FVs and CPP | 10 | 5 | 60 |
| Sx\_a | FVs and MAP | 10 | 5 | 60 |
| Dx | FVd and CPP | 10 | 5 | 60 |
| Dx\_a | FVd and MAP | 10 | 5 | 60 |
| TOx | TOI and CPP | 10 | 5 | 60 |
| TOx\_a | TOI and MAP | 10 | 5 | 60 |
| THx | THI and CPP | 10 | 5 | 60 |
| THx\_a | THI and MAP | 10 | 5 | 60 |
| ORx-5 | PbtO2 and CPP | 30 | 5 | 60 |
| ORx-30 | PbtO2 and CPP | 30 | 30 | 60 |
| ORx-60 | PbtO2 and CPP | 30 | 60 | 60 |

CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, min = minute, PbtO2 = brain tissue oxygenation, sec = seconds, TOI = total oxygenation index, THI = total hemoglobin index.

Table 2: Pearson Correlation Coefficient Matrix – Grand Mean Data Set



The described indices are Pearson correlation coefficients between various variables: PRx (between ICP and MAP), PAx (between AMP and MAP), RAC (between AMP and CPP), ORx (between PbtO2 and CPP; 5 = 5 minutes calculation window, 30 = 30 minute calculation window, 60 = 60 minute calculation window), Mx (between FVm and CPP), Mx\_a (between FVm and MAP), Sx (between FVs and CPP), Sx\_a (between FVs and MAP), Dx (between FVd and CPP), Dx\_a (between FVd and MP), TOx (between TOI and CPP), TOx\_a (between TOI and MAP), THx (between THI and CPP) and THx\_a (between THI and MAP). \*Values in bold typeface are those which reached statistical significance (p<0.05).

Table 3: Binary Univariate Logistic Analysis – Comparing Indices of Autoregulation to Dichotomized Outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **“Good” vs. “Poor” Outcome – AUC** | **“Good” vs. “Poor” Outcome – p value** | **“Alive” vs. “Dead” Outcome – AUC** | **“Alive” vs. “Dead” Outcome – p value** |
| ***“Invasive” Indices*** |  |  |  |  |
| **PRx** | 0.624 | 0.295 | 0.680 | 0.165 |
| **PAx** | 0.656 | 0.176 | 0.752 | 0.083 |
| **RAC** | 0.730 | 0.131 | 0.752 | 0.075 |
| **Mx** | 0.593 | 0.495 | 0.608 | 0.506 |
| **Sx** | 0.556 | 0.503 | 0.656 | 0.365 |
| **Dx** | 0.497 | 0.921 | 0.576 | 0.838 |
| **TOx** | 0.624 | 0.261 | 0.576 | 0.398 |
| **THx** | 0.624 | 0.251 | 0.560 | 0.657 |
| **ORx-5** | 0.519 | 0.848 | 0.648 | 0.634 |
| **ORx-30** | 0.556 | 0.659 | 0.608 | 0.245 |
| **ORx-60** | 0.524 | 0.713 | 0.608 | 0.321 |
| ***“Non-invasive” Indices*** |  |  |  |  |
| **Mx\_a** | 0.704 | 0.213 | 0.616 | 0.403 |
| **Sx\_a** | 0.593 | 0.444 | 0.592 | 0.561 |
| **Dx\_a** | 0.640 | 0.485 | 0.536 | 0.787 |
| **TOx\_a** | 0.624 | 0.207 | 0.472 | 0.699 |
| **THx\_a** | 0.540 | 0.520 | 0.536 | 0.576 |

AUC = area under the receiver operating curve, The described indices are Pearson correlation coefficients between various variables: PRx (between ICP and MAP), PAx (between AMP and MAP), RAC (between AMP and CPP), ORx (between PbtO2 and CPP; 5 = 5 minutes calculation window, 30 = 30 minute calculation window, 60 = 60 minute calculation window), Mx (between FVm and CPP), Mx\_a (between FVm and MAP), Sx (between FVs and CPP), Sx\_a (between FVs and MAP), Dx (between FVd and CPP), Dx\_a (between FVd and MP), TOx (between TOI and CPP), TOx\_a (between TOI and MAP), THx (between THI and CPP) and THx\_a (between THI and MAP).

**Appendix A: Pearson Correlation Coefficient Testing – 30 minute mean and minute-by-minute data sheets**

**Grand Mean Data Set – p value matrix**



**30 Minute and Minute by Minute Data**

**Our analysis of the 30-minute mean and minute-by-minute data sheets revealed weaker correlation coefficients between all of the indices, as seen in Appendix A. However, the p-values for all correlations within the Pearson matrix remained strongly significant. Most patterns of correlation between indices described in the grand mean data were displayed within both the 30 minute average and minute-by-minute data sheets.**

**Strong intra-technique correlations were seen in both of these data sheets (as in the grand mean sheet). Mx failed to reach a strong correlation with PRx across the 30 minute and minute-by-minute data sets. ORx-5/ORx-30/ORx-60 also displayed similar trends with all indices as we evaluated the 30 minute and minute-by-minute data sheets. For further details, please refer to Appendix A of the supplementary materials.**

**30 Minute Mean Data Set – Pearson Matrix**



**30 Minute Mean Data Set – p value matrix**



**Minute-by-Minute Data Set – Pearson Matrix**



**Minute-by-Minute Data Set – p value matrix**



**Appendix B: Friedman Test for 30 minute and Minute-by-minute Data Sets**

Analysis on the 30-minute data sheet revealed: Friedman total (p<0.0001, Q = 692.258), Friedman for ICP indices (p<0.0001, Q = 217.000), Friedman for the TCD indices (p<0.0001, Q = 563.385), Friedman for the PbtO2 indices (p=0.004, Q = 11.023) and Friedman for the NIRS indices (p<0.0001, Q = 92.486) . Again, this indicates that these index groupings are not similar.

Finally, completing the Friedman analysis on the minute-by-minute data sheet displayed the following results: Friedman total (p<0.0001, Q = 11168.218), Friedman for the ICP indices (p<0.0001, Q = 6403.922), Friedman for the TCD indices (p<0.0001, Q = 11884.279), Friedman for the PbtO2 indices (p<0.0001, Q = 227.196), and Friedman for the NIRS indices (p<0.0001, Q = 1214.456).

**Appendix C – Short Recordings: PCA Eigenvalues Table, Scree Plot and Factor Loadings Table**

**\* PCA = principle component analysis, F = factor, PC = principle component, F1 = PC1 = principle component #1, F2 = PC2 = principle component #2. PC1 and PC2 are the two components which contribute the largest amount of variance to the entire data set.**

**\*Biplots of PC1 vs. PC2 display which variables contribute variance to PC1 and PC2. The longer the arm connecting (0,0) to the variable (such as PRx), the larger the contribution of that variable. Similarly, the quadrant on the biplot in which the variable fallscorrelates to its contribution to a particular PC. The upper left quadrant is primarily PC2; lower left quadrant is neither PC1 or PC2; the upper right quadrant is PC1 and PC2; the lower right quadrant is primarily PC1.**

\***Eigenvalue tables display the eigenvalue for each principle component (PC) (also denoted F), with the % variability and cumulative variability for each factor/principle component.**

**\*Scree plot displays the same information form the eigenvalue table in a histogram format, with each F (or PC) along the x-axis, the eigenvalue along the left side y-axis and the % variability along the right y-axis. Furthermore, the red line on the graph displays the cumulative variability with the addition of each F (or PC) moving from F1 to F18.**

**\*Factor loading tables display the loading of each variable (ie. PRx, etc.) for each principle component. Loading varies from -1 to +1, with negative values indicating that particular variable is less likely to contribute to the variance in that particular factor (F). Similarly, positive loadings indicate that particular variable likely contribute to the variance in that corresponding factor (F).**

**\*Contribution % of Variables tables displays the % contribution to the variance of each individual variable for each individual factor (F).**

**Summary of 30-minute mean and Minute-by-minute Data - PCA**

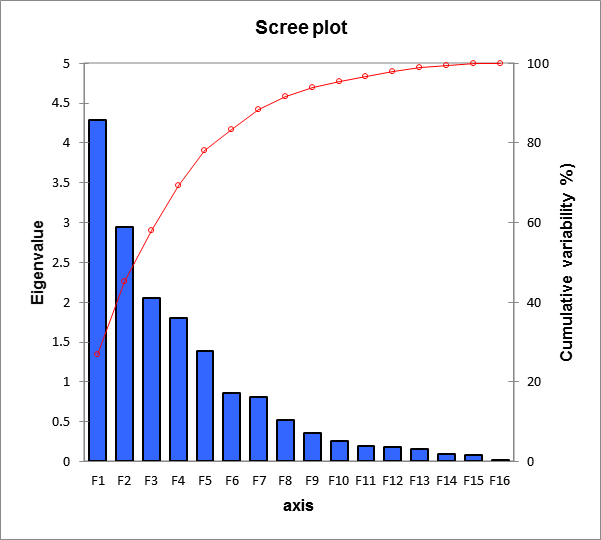
**Using the 30-minute mean data sheet, PCA analysis displayed similar results for the PC’s and biplot, supporting our results described for the minute-by-minute analysis. Finally, using the grand mean data sheet, similar PCA results were displayed with the exception of the PbtO2 based indices (ORx-5, ORx-30 and ORx-60). Within the grand mean PCA, ORx-5/ORx-30/ORx-60 contributed more to the variance of the data set, with positive loadings towards PC1 and PC2. The PbtO2 indices still displayed a lack of association with other indices in the minute-by-minute data sheet. These can be seen in Appendix B of the supplementary materials.**

1. ***Minute-by-Minute Data Set:***

***Eigenvalues Table***



***Scree Plot***

******

***Factor Loading Table***



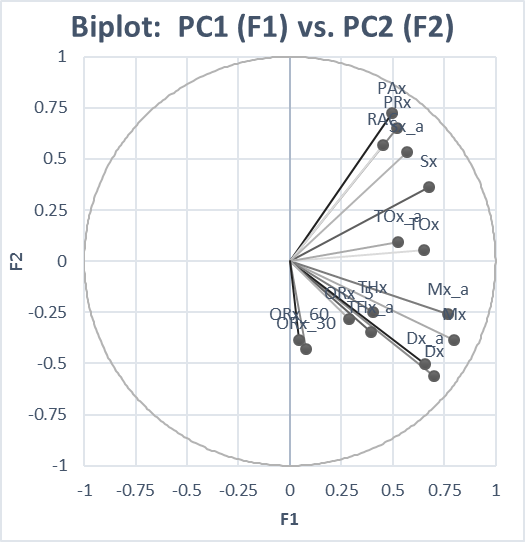


***% Contribution of Variables***





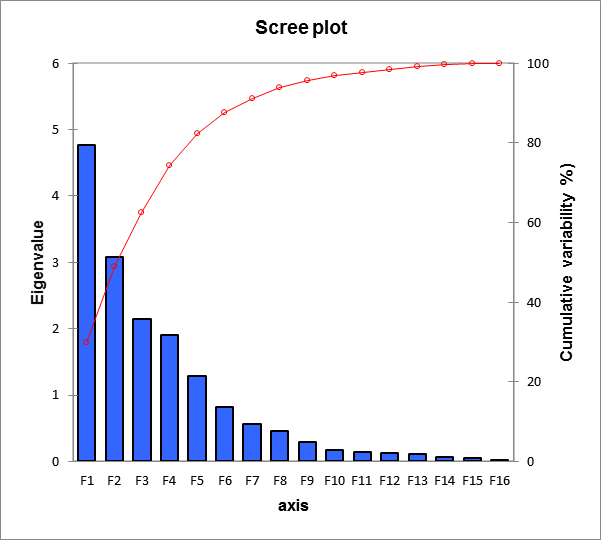
1. ***30 Minute Mean Data Set:***

******

***Eigenvalue Table***



***Scree Plot***

******

***Factor Loading***



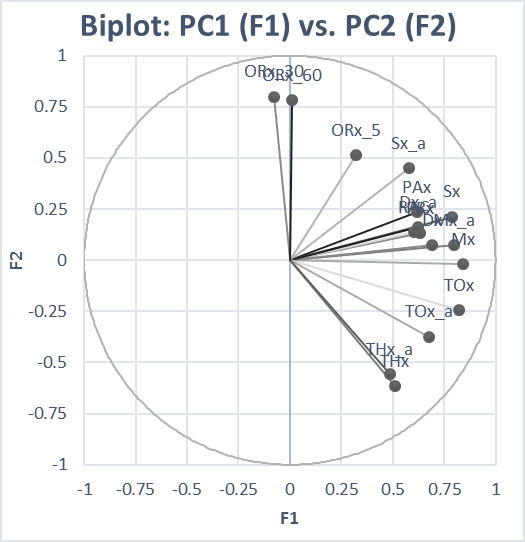


***% Contribution of Variables***





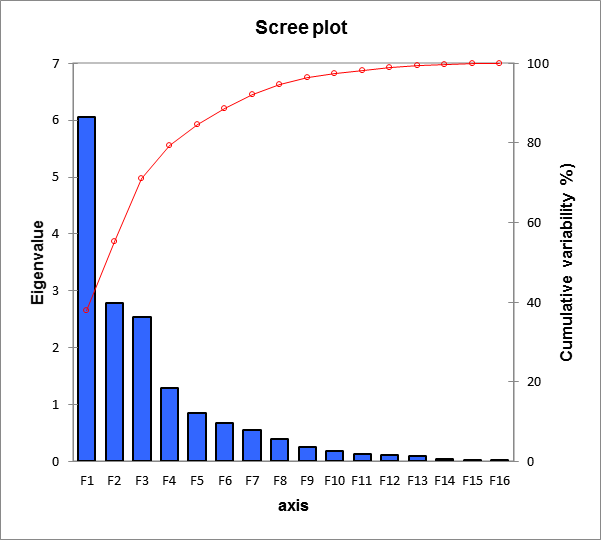
1. ***Grand Mean Data Set:***

******

***Eigenvalue Table***



***Scree Plot***

******

***Factor Loadings***





***% Contribution of Variables***





**Appendix D – K-means Cluster Analysis – Minute by Minute, 30 Minute Mean and Grand Mean Data Sets**

***Overall KMCA Analysis Summary:***

**\*PRx/PAx/RAC appear to co-cluster. Mx/Mxa and Dx/Dxa appear to co-cluster, similar to the AHC dendrogram in Figure 4. The remaining NIRS based indices co-cluster into groups that are similar to the AHC dendrogram in Figure 4. Of note, Sx and Sx\_a co-cluster with the ICP derived indices (PRx and PAx), similar to the Pearson matrix, PCA and AHC. The KMCA was repeated for the 30 minute and minute-by-minute data sets, and displayed similar clustering of the indices as seen in the grand mean analysis.**

***Minute by Minute Data Set – Cluster Table***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cluster 1** | **Cluster 2** | **Cluster 3** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** |
| PRx | RAC | Mx | Mx\_a | THx | TOx | ORx-5 |
| PAx |  | Dx | Dx\_a | THx\_a | TOx\_a | ORx-30 |
| Sx |  |  |  |  |  | ORx-60 |
| Sx\_a |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

KMCA = k-means cluster analysis. \*KMCA conducted with 7 cluster centers

***Within cluster sum of squares (SS) by cluster: 42.47543 46.71725 61.35890 650.63337 0.00000 528.40926 76.96110 (between\_SS / total\_SS = 80.4 %)***

***Minute by Minute Data Set – Elbow Plot***

******

***30 Minute Mean Data Set – Cluster Table***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cluster 1** | **Cluster 2** | **Cluster 3** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** |
| PRx | RAC | Mx | Mx\_a | TOx | THx | ORx-5 |
| PAx |  | Dx | Dx\_a | TOx\_a | THx\_a | ORx-30 |
| Sx  Sx\_a |  |  |  |  |  | ORx-60 |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

***Within cluster sum of squares (SS) by cluster: 1.4012609 1.1493068 10.2822580 33.3944048 0.8222987 0.7421790 (between\_SS / total\_SS = 75.5 %)***

***30 Minute Mean Data Set – Elbow Plot***

******

***Grand Mean Data Set***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cluster 1** | **Cluster 2** | **Cluster 3** | **Cluster 4** | **Cluster 5** | **Cluster 6** | **Cluster 7** |
| PRx | RAC | Mx | Mx\_a | TOx | THx | ORx-5 |
| PAx |  | Dx | Dx\_a | TOx\_a | THx\_a | ORx-30 |
| Sx |  |  |  |  |  | ORx-60 |
| Sx\_a |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Within cluster sum of squares (SS) by cluster: 2.7381970 0.1408618 0.1399097 0.0000000 1.1011242 0.2575963 0.2193379 (between\_SS / total\_SS = 86.1 %)

***Grand Mean Data Set – Elbow Plot***

******