Validation of ICP Derived Cerebrovascular Reactivity Indices Against the Lower Limit of Autoregulation, Part II: Experimental Model of Arterial Hypotension

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Abstract:

To explore the relationship between intra-cranial pressure (ICP) derived indices of cerebrovascular reactivity and the lower limit of autoregulation (LLA) during arterial hypotension. We retrospectively reviewed recorded physiologic data from piglets that underwent controlled hypotension. Hypotension was induced by inflation of a balloon catheter in the inferior vena cava. ICP, cortical laser Doppler flowmetry (LDF), and arterial blood pressure (ABP) monitoring was conducted. ICP derived indices were calculated: pressure reactivity index (PRx – correlation between ICP and mean arterial pressure (MAP)), pulse amplitude index (PAx – correlation between pulse amplitude of ICP (AMP) and MAP), and RAC (correlation between AMP and CPP). LLA was estimated via piecewise linear regression of CPP vs. LDF. We produced error bar plots for PRx, PAx, and RAC against 5 mm Hg bins of CPP, displaying the relationship with the LLA. We compared CPP values at clinically relevant thresholds of PRx, PAx and RAC, to CPP measured at the LLA. Receiver operating curve (ROC) analysis was performed for each index across the LLA using 5 mm Hg bins for CPP. Mean LLA was 36.2 +/- 10.5 mm Hg. Error bar plots demonstrated PRx, PAx and RAC increased with CPP decreasing below the LLA. CPP at clinically relevant thresholds for PRx, PAx, and RAC displayed weak associations with the LLA, indicating thresholds defined in TBI may not be apply a model of arterial hypotension. ROC analysis indicated that PRx, PAx and RAC predicted the LLA, with AUC’s of: 0.806 (95% CI: 0.750 – 0.863, p<0.0001), 0.726 (95% CI: 0.664 – 0.789, p<0.0001), and 0.710 (95% CI: 0.646 – 0.775, p<0.0001), respectively. Three ICP derived continuous indices of cerebrovascular reactivity, PRx, PAx and RAC were validated against the LLA within this experimental model of arterial hypotension, with PRx superior. Keywords: autoregulation, ICP indices, validation, arterial hypotension.
Introduction:

Continuous monitoring of cerebrovascular reactivity is becoming increasingly common within the management of the critically ill neurological patient.\(^1\) The largest volume of literature for continuous monitoring of this aspect of cerebral physiology exists in adult traumatic brain injury (TBI).\(^1, 2\) Various signals derived from multi-modal monitoring can be used as surrogate markers of cerebral blood volume (CBV) of slow or pulsatile (heart) frequency or cerebral blood flow, such as intracranial pressure (ICP) or transcranial Doppler based cerebral blood flow velocity (CBFV).\(^2\) These signals are low-pass filtered and correlated with a driving pressure, such as mean arterial pressure (MAP) or cerebral perfusion pressure (CPP), using moving Pearson correlation coefficients between slow waves of these signals. The concept behind these indices is that slow wave ICP fluctuations are a surrogate for CBV/CBF and they are
changing in response to slow wave changes (slower than 0.05Hz; ie. 0.05 cycle per second or a period of 20 seconds) in a driving pressure, MAP or CPP. They are therefore capable to provide information regarding the cerebrovascular reactivity and thus autoregulatory capacity.

To date, numerous indices of cerebrovascular reactivity have been derived. Given ICP monitoring is common within critically ill neurological patients, ICP-derived indices have received the most attention. Pressure reactivity index (PRx) is the most widely cited index, and is the correlation between slow waves recorded in ICP and MAP. Numerous studies link PRx to patient outcome in TBI, with critical thresholds associated with morbidity and mortality defined within the literature. Furthermore, PRx has been validated in a piglet model against the lower limit of autoregulation (LLA) during arterial hypotension, one of only two indices to be validated in this type of model (the other being near infrared spectroscopy derived COx and HVx).

Aside from PRx, two other ICP-derived indices of cerebrovascular reactivity exist. Pulse amplitude index (PAx), the correlation between pulse amplitude of ICP (AMP) and MAP, has been demonstrated to be comparable to PRx in outcome prediction for TBI patients. In cases with low ICP (like for example after decompressive craniectomy) PAx is probably more useful than PRx. However, limited literature exists in the application of PAx clinically. Similarly, RAC, the correlation (R) between AMP (A) and CPP (C), has been recently described within the TBI population, with limited literature to date. It remains currently unknown whether PAx or RAC respect the LLA, similarly to PRx.

Part I of this manuscript series provided support for the validation of PRx and PAx against the LLA in a rabbit model of sustained intra-cranial hypertension. Given PAx and RAC have not been assessed against the LLA in a model of pure arterial hypotension, we elected to explore this within archived experimental piglet data. Thus, producing Part II of the manuscript series on validating ICP derived indices of
cerebrovascular reactivity in experimental models. The goal of this manuscript, Part II of the 2-part series, was to determine if PAX and RAC respect the LLA during arterial hypotension.

**Methods:**

**Animal Model**

The neonatal piglet data described within were retrospectively amalgamated from 3 separate experiments. Inclusion criteria for the current study were normothermic, sham control piglets that had complete and time synchronized data for arterial blood pressure, laser Doppler flowmetry, and ICP from our previously published studies.\(^6,11,12\) Twenty-two piglets met the inclusion criteria: A. control animals from a study on LLA\(^6\) (n=8; age 5 to 10 days; weight 2.2 – 3.9 kg). B. sham controls for a model of cardiac arrest\(^11\) (n=7; age 3 to 5 days; weight 1 – 2.5 kg), and C. sham normothermic controls for a model of cardiac arrest with hypothermic therapy\(^12\) (n=7; age 3 to 5 days; weight 1 – 2.5 kg). All procedures were approved by the Animal Care and Use Committee at Johns Hopkins University and complied with the United States Public Health Service Policy on Human Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals. Furthermore, animal care was in accord with National Institutes of Health Guidelines and ensured the animals’ comfort.
Anesthesia and Surgical Preparation

We previously published detailed methodology of these experiments. Briefly, male piglets were intubated and mechanically ventilated to maintain normocapnea. General anesthesia was provided with isoflurane in a 50%/50% nitrous oxide/oxygen mixture, fentanyl infusion and as needed boluses, and pancuronium or vecuronium infusions. Fentanyl and neuromuscular blockade were given through a femoral venous catheter. The isoflurane dose was held constant for the duration of the experiment. Arterial blood pressure was continuously monitored by an indwelling femoral artery catheter. A 5F esophageal balloon catheter (Cooper Surgical, Trundall Conn) was placed into the contralateral femoral vein and advanced into the inferior vena cava for later induction of hypotension. A ventricular ICP monitor and a cortical LDF probe (Moor Instruments, Devon, UK; model DRT4; 60Hz) to measure cerebral blood flow (CBF) were placed through small cranial burr holes. ICP and LDF were monitored in the same cerebral hemisphere. For all animals pCO₂ was targeted to maintain eucarbia and a pH of 7.35 to 7.45, or a pCO₂ of 40 +/- 5 mm Hg or 40 +/- 7 mm Hg.

Controlled hypotension

The balloon catheter was slowly inflated in the inferior vena cava using a saline syringe pump. Hypotension was induced from baseline to near-zero blood pressure over 2 to 3 hours. This slow induction of hypotension permitted capture of slow wave intracranial pressure fluctuations for analysis of cerebrovascular reactivity.

Signal Acquisition and Processing
All signals from the combined above monitoring modalities were recorded and archived for future retrospective use. All recorded signals were digitized via an A/D converter (DT9804, Data Translation, Marlboro, MA), sampled at frequency of 50 Hertz (Hz) or higher, using ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk). Signal artifacts, such as transducer adjustments, were removed prior to further processing or analysis using tools available in ICM+.

CPP was determined as: MAP – ICP. Pulse amplitude of ICP (AMP) was determined by calculating the fundamental Fourier amplitude of the ICP signal over a 10 second window, updated every 10 seconds. This was done over the range consistent with the normal range for piglet heart rate (ie. 100 – 350 bpm). Finally, 10 second moving averages (without data overlap) were calculated for all recorded signals: ICP, AMP, ABP (ie. producing MAP), CPP, and LDF measurement of CBF (LDF-CBF). The piglets’ archived signals were retrospectively interrogated and analyzed.

The following continuous indices of cerebrovascular reactivity were derived: PRx (correlation between ICP and MAP), PAx (correlation between AMP and MAP), RAC (correlation between AMP and CPP) and LDF derived Lx (correlation between LDF-CBF and CPP). All indices were derived via moving Pearson correlation coefficients between 30 consecutive 10 second average values of relevant signals and their parameters (ie. 5 minute of data), updated every minute.

**Statistics**

All statistical analysis was conducted utilizing 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/). The following packages were employed: ggplot2, dplyr, tidyverse,
lubridate, segmented, and pROC. Where significance is reported, alpha was set at 0.05. The following analysis described is similar to that performed within previous studies on the LLA. This was done so as to allow comparison between the results, and potentially provide validation of the results seen within that study.

Finding the LLA

In order to determine the LLA of autoregulation in the 22 animals, we employed piecewise linear regression of the CPP versus LDF-CBF plots. The LDF-CBF signal was standardized against the individual animal’s baseline LDF-CBF signal, producing “% change of LDF-CBF from baseline”. This is similar to other studies evaluating LDF-CBF.11,12

The piecewise regression process employed a starting point for estimation of the break-point in either LDF-CBF. This starting point was visually estimated from the ICM+ plots of CPP versus LDF-CBF. The piecewise regression process employed a starting point for estimation of the break-point in either LDF-CBF. This starting point was visually estimated from the ICM+ plots of CPP versus LDF-CBF versus CPP, described above. Despite this initial visual inspection, the automated piece-wise linear regression was conducted via the “segmented” computational package within R statistical software. The “start point” is only a starting reference for the automated algorithm to perform the piecewise regression, with the full range of available CPP values tested during the process. This process functions on the assumption of continuity in data, splitting the data into two distinct linear segments. The intersection point of these two linear segments is considered the breakpoint in the piecewise function. The breakpoint identified by the piece wise regression process is one in which minimized the sum residual square error (SSE) of the two linear segments, above and below this point. This breakpoint represents the LLA, with this method being described previously for the determination of the LLA in experimental models. This was conducted
for each animal, with piecewise regression plots produced denoting the 95% confidence interval (CI) for each fitted linear segment. Finally, the mean LLA for the cohort of 22 piglets was determined by averaging all 22 LLA values obtained.

**Binned Cohort Data and Plot**

After delineating the mean LLA for the cohort, we then produced cohort wide plots to inspect the population trend of various physiologic measures against the LLA. We first binned all data across 5 mm Hg bins of CPP, using R statistical software. The following error bar plots were then produced: CPP vs. % change in LDF-CBF From Baseline, CPP vs. PRx, CPP vs. PAx, CPP vs. RAC, and CPP vs. Lx.

**Comparing CPP for Various Clinical Thresholds of PRx, PAx and RAC to LLA**

We wished to conduct a rough comparison of the CPP for clinically defined thresholds of PRx, PAx and RAC to the CPP at the LLA, defined via piecewise regression in each animal. To do so, we employed a simplified piecewise linear regression of CPP vs. PRx and CPP vs. PAx, using these models to determine the CPP in each animal for the following thresholds of PRx and PAx defined in TBI patients. For PRx, the thresholds of 0, +0.25 and +0.35 were tested, based on previous work in TBI\(^4\) and currently unpublished data from our lab.\(^{13}\) For PAx, the thresholds of 0 and +0.25 were tested, based on unpublished work from our lab. Finally, for RAC, the thresholds of -0.10 and -0.05 were tested, again based on unpublished work from our lab. We then compared the CPP values at each threshold for PRx, PAx and RAC, with the CPP values at the LLA using a Pearson correlation coefficient and Bland-Altman analysis. The Bland-Altman analysis was only conducted for those thresholds reaching statistically significant correlations with the LLA (ie. PRx 0, PRx +0.25, and PRx +0.35).
Prediction of Continuous Indices for Impaired Autoregulation

As done in previous studies, we performed receiver operating curve (ROC) analysis of PRx, PAx, RAC and Lx across the cohort defined LLA. This was conducted in order to determine the ability of these indices to predict being either above or below the LLA. For each piglet, 1 mean value for each variable was obtained at each 5 mm Hg bin of CPP (ie. CPP = 40 mm Hg, 45 mm Hg, etc.). We utilized 5 mm Hg bins of CPP for the ROC analysis, given this was what was conducted within the previous study by Brady et al.

This data was then given the binary designation of being above the LLA, or below the LLA, based on the LLA defined previously. The data from all 22 piglets was then used for the ROC analysis. Area under the curve (AUC) for the ROC’s was reported and 95% CI reported via Delong method. Significance values (ie. p-values) for the AUC’s were derived from univariate logistic regression analysis. Comparison between AUC’s was conducted using Delong’s test.

We elected to use the ROC analysis based on population LLA, given this is how the original studies were conducted to validate PRx and NIRS based indices in experimental models. In order to allow comparison across all studies (ie. the previous work, and both Part I and II of this manuscript series), we maintained the analysis as such. Individual animal specific LLA ROC analysis would lead to the inability to compare results to prior and further limit the ability to extrapolate results to other animal models or human TBI data.

Results:

Defining the LLA
Through piecewise linear regression analysis of each piglet, we obtained the LLA for each animal. Figure 1 displays an example of the recorded MAP, ICP, CPP and LDF-CBF signal during the hypotension experiment. While Figure 2 displays two examples of piecewise linear regression analysis of the LLA. The mean LLA was 36.2 +/- 10.5 mm Hg. Appendix A displays all of the piecewise linear regression plots and scatter plots for each of the 22 piglets.

*Figure 1 and 2 here

*Population-Wide Trends*

In order to provide a population-wide assessment of % change in LDF-CBF and the ICP derived indices during changes in CPP, we produce various error bar plots. Figure 3 displays the plot of CPP versus % change in LDF-CBF from baseline, with the vertical dashed line indicating the approximate mean LLA, derived above. This demonstrates that there is a precipitous drop in LDF-CBF below the LLA.

*Figure 3 here

Similarly, we plotted the ICP indices across 5 mm Hg bins of CPP, producing error bar plots. Figure 4 displays these plots. It can be seen that PRx, PAx and RAC all correlated with the LLA, denoted by the vertical dashed line. Appendix B displays the error bar plot for CPP vs. Lx.
Comparing CPP for Various Clinical Thresholds of PRx and PAx to LLA

For each animal, the CPP at each threshold for PRx, PAx and RAC was roughly derived through a simplified piecewise linear model of CPP vs. PRx, CPP vs. PAx, and CPP vs. RAC in each individual animal. These CPP values were compared to the CPP for the LLA derived in each animal, as described above. Table 1 displays the results for Pearson correlation between the CPP at TBI defined critical thresholds and the LLA within the cohort of piglets. Only the PRx thresholds appeared to produce statistically significant correlations, though there are weak in strength. Bland-Altman analysis comparing the CPP values at these PRx thresholds, and the CPP at the LLA, can be found in Appendix C of the supplementary materials. This analysis displays poor agreement between the threshold CPP values and the CPP at the LLA.

LLA ROC Analysis

Through ROC analysis across the LLA, using the data from the 22 piglets, we were able to identify the AUC’s for each continuous index. The AUC for PRx, PAx and RAC was: 0.806 (95% CI: 0.750 – 0.863, p<0.0001), 0.726 (95% CI: 0.664 – 0.789, p<0.0001), and 0.710 (95% CI: 0.646 – 0.775, p<0.0001), respectively. Finally, the AUC for Lx was 0.809 (95% CI: 0.754 – 0.863, p<0.0001). Comparing AUC’s via Delong’s test, there was a statistically significant difference between the AUC’s generated, when comparing PRx to PAx (p=0.0004), and PRx to RAC (p<0.0001). However, the AUC’s for PAx and RAC were
not statistically different (p=0.214). ROC curves can be seen within Appendix D of the supplementary materials.

**Discussion:**

Through retrospective analysis of archived experimental piglet data, we have been able to find a cohort of animals subjected to pure arterial hypotension, allowing for the assessment of ICP derived continuous indices against the LLA. A few important points deserve highlighting.

First, we have been able to provide confirmatory evidence that PRx correlates with the LLA within a model of hypotension. This was conducted using both the animal data from the initial publication documenting this relationship, plus another 14 sham control animals from other experiments. We have also been able to demonstrate a similar AUC (0.806, p<0.0001) in the prediction of the LLA using PRx.

Finally, evaluating clinically relevant thresholds for PRx, we have been able to show that all PRx thresholds fail to produce strong correlations with the LLA within a model of arterial hypotension. This was confirmed via poor agreement with the LLA on Bland-Altman analysis for all PRx clinical thresholds tested. This is likely because these thresholds have been defined within adult TBI populations, and thus the underlying disease and influence of ICP elevation post-injury may produce these thresholds that are disease specific. It is therefore not surprising that these thresholds do not necessarily respect the LLA in a model of pure hypotension. As with PAx and RAC, it must be stated that given the small numbers of animals within the current study, strong conclusions regarding these clinical thresholds cannot be made at this time. This work remains preliminary.
Second, for the first time, we have provided some evidence validating PAx and RAC against the LLA within a model of hypotension. This suggests that both indices provide information regarding cerebral autoregulatory capacity with a moderate accuracy. However, we were unable to provide conclusive evidence that the index threshold values, as defined in a TBI population, respect the LLA within this current model. The Pearson correlations between the LLA and the CPP at these thresholds were poor and not statistically significant. It remains uncertain as to whether the TBI defined critical thresholds for PAx and RAC can be applied outside of the TBI population, given the poor performance of these thresholds within this model of arterial hypotension. Further, it remains unclear as to whether these thresholds represent relevant aspects of cerebral autoregulation, aside from associations with patient outcome in TBI. It is also likely that threshold values for reactivity indices may vary by individual. It must be acknowledged these results are preliminary.

Third, the “old” way of viewing these continuous indices is likely too simplistic (ie. positive is “bad” and negative is “good”). As was seen with the results of this study, even below the LLA, PAx and RAC remained in the negative range until extremely low values for CPP. We do believe they still respect and measure the LLA, as the analysis demonstrates that they both become progressively more positive as CPP decreases. However, each index is clearly different and requires detailed evaluation on its own, in specific pathologies, in order to identify what index value may indicate “impaired” vs. “intact” cerebrovascular reactivity. This can be seen in our recent publication on thresholds for ICP indices and for TCD derived Sx/Sx-a.\textsuperscript{13,14} The thresholds associated with clinical outcome for some indices can be negative, indicating that the cutoff point for “impaired” reactivity may in fact be a negative value for some indices. This is also likely true for the threshold associated with the LLA in humans for some indices, though has yet to be proven. Thus, using a blanket rule for all indices (ie. positive is “bad” and negative is “good”) should probably be avoided.
Finally, the clinically defined thresholds for PRx, PAx, and RAC tested are defined within a TBI population. Thus, exploring how they relate to the LLA in an animal model of arterial hypotension may explain why many of the thresholds for PRx, PAx and RAC don’t appear to be related to the LLA. As mentioned above, the results of this analysis are preliminary and thus strong conclusions about the relationship between the clinical thresholds and the LLA cannot be made. Further validation of our results is required. Further to this, as mentioned within the limitations of Part I of this manuscript series, even though the CPP at some of the clinically defined index thresholds appeared to be related to the LLA within this piglet model, one must interpret this with caution. As the LLA represents the point at which cerebral autoregulation becomes impaired (ie. not the point at which vascular reactivity is completely lost), the lack of strong associations with CPP at thresholds defined by clinical outcome is not surprising. These thresholds for the ICP defined indices were derived from TBI patient outcome at 6 months post injury. As a result, these index thresholds may represent the severe end of the autoregulation spectrum, the point of complete failure of vascular reactivity. Hence, the relationship between the CPP at thresholds and the LLA may not be robust, as they could be representing different aspects of impaired cerebrovascular reactivity. As well, one must assume that there are individual animal-based differences in vascular reactivity, introducing the influence of potential random effects.

Much further interrogation of these clinically defined index thresholds is required, with the current analysis providing some preliminary insight. One may question why compare animal to human data for these indices (ie. using human derived outcome thresholds)? The reason for doing this was to highlight the difficulties in extrapolating results of such animal studies directly to human TBI monitoring and care, emphasizing the need for future work on defining PRx, PAx and RAC thresholds for the LLA (ie. not clinical global outcome) in humans. We address potential future research directions within the “Future Directions” subsection in this discussion.
**Limitations**

Despite the interesting and promising results, a few limitations deserve emphasis. First, this is a retrospective analysis of an amalgamated cohort of piglets from 3 separate experiments. Though the anesthetic, procedures and experimental hypotension techniques were similar for all animals, the cohorts were not exactly identical. For example, 8 of the animals were a little older (ie. 5 to 10 days, versus 3 to 5 days), with slightly higher weights. This could influence the cerebrovascular response slightly. Second, despite have a sizable cohort of piglets for this retrospective analysis, it is still a relatively small number of animals, thus the conclusions drawn must be taken with caution. Further to this, it must be acknowledged that given fluctuations in both ICP and MAP commonly seen in clinical care of human TBI, the results found in this study mainly apply to animal models of normal ICP more directly. Thus, limiting the ability to extrapolate these results to human TBI care.

**Future Directions**

Based on the results from Part I and II of this manuscript series, exploring the ability of ICP derived indices to measure the LLA in experimental models, some confidence exists in the ability of these indices to measure autoregulation. Directly extrapolating the results from these two animal studies to human TBI is difficult, given species related differences and the relatively controlled settings of these models. Specific thresholds for the LLA in these two animal cohorts cannot be translated to humans, however the ability of the ICP derived indices to measure the LLA provides confidence for their ability to do so in humans. However, there are further analysis which is required to confirm these results and validate these indices in other circumstances.
First, rarely are ICP or MAP altered in isolation within the clinical TBI setting. Thus, further models evaluating fluctuations in MAP, towards the LLA, during episodes of sustained ICP elevation are required. These models could evaluate ICP sustained at various levels (ie. 20 to 30 mm Hg, 30 to 40 mm Hg, etc.) while driving MAP towards and below the LLA. Similar analysis of the ICP derived indices could then occur. The ability of these indices to measure the LLA during these circumstances would provide further confidence in their use in clinical TBI monitoring.

Second, the upper limit of autoregulation (ULA) also needs investigation. No studies to date have confirmed the ability of any continuous measure of cerebrovascular reactivity to accurately measure the ULA. This could be done again both with and without various ICP elevations, mimicking the physiologic variation seen in clinical TBI practice. MAP would then be driven towards and above the ULA using potentially a combination of vasopressors and/or intra-aortic balloon. Through these experiments, if the ability to measure the ULA is confirmed, this would assuredly solidify these ICP indices as true measures of autoregulation.

Third, the impact of decompressive craniectomy (DC) is also important to evaluate. We know that DC impacts ICP and PRx values in clinical practice. Only through experimental models will we truly understand the impact on autoregulation that DC has. Furthermore, producing experimental models in which ICP and MAP are altered post-DC would allow us to evaluate the ability of these ICP indices to measure both the LLA and ULA post craniectomy. It is currently unknown as to whether index values post craniectomy are reliable measures of cerebrovascular reactivity.
Fourth, our current understanding of “thresholds” of ICP based indices in adult TBI are based on global clinical outcomes, not actual thresholds of the LLA or ULA. This is the current main limitation to this type of monitoring in clinical practice. Derivation of ICP index thresholds for the LLA and ULA in humans is difficult, given clinical care is directed at avoiding these extremes of MAP, and the design of a clinical study to assess this is fraught with potential dangers to the subjects. We believe these threshold studies will require two types of data. First, multi-center widespread data collection for all critically ill patients with cranial monitoring, so that cerebrovascular reactivity indices during physiologic extremes may be captured in a large number of patients. This would allow stratification by age, sex and pathology, creating a potential normative value range for index thresholds. Second, larger mammal/primate models, evaluating the LLA and ULA may provide the closest controlled evaluation of index thresholds. This may allow extrapolation of these experimental derived thresholds to human clinical practice. It is acknowledged, that such animal models are costly and would require multi-center coordination to be conducted successfully.

Finally, aside from ICP derived indices of cerebrovascular reactivity, other invasive and non-invasive multi-modal monitoring devices can provide indices of vascular reactivity. These too require investigation within the types of future animal models described above, prior to widespread implementation and confidence in their ability to measure cerebral autoregulation.

**Conclusions:**

The three ICP derived continuous indices of cerebrovascular reactivity, PRx, PAX and RAC were evaluated against the LLA within this experimental model of arterial hypotension. All three indices appear to respect the LLA within this model of pure arterial hypotension, with PRx being superior.
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References:


Figure 1: Example of Physiologic Signal Changes During Hypotension

a.u. = arbitrary units, CPP = cerebral perfusion pressure, ICP = intracranial pressure, LDF-CBF = laser Doppler flowmetry cerebral blood flow, MAP = mean arterial pressure, mm Hg = millimeters of Mercury.
Figure 2: Examples of Piecewise Linear Regression Analysis of LLA

CPP = cerebral perfusion pressure, LDF-CBF = laser Doppler flowmetry cerebral blood flow, mm Hg = millimeters of Mercury.
Panel A + B = Piecewise linear regression and scatter plot for one patient. Panel C + D = piecewise linear regression and scatter plot for one patient. NOTE: dashed line on piecewise linear regression plots represents the 95% confidence intervals for the fitted lines.
Figure 3: Population-Wide – CPP versus % Change in LDF From Baseline.

$\text{CPP} = \text{cerebral perfusion pressure}, \text{LDF} = \text{laser Doppler flowmetry}, \text{mm Hg} = \text{millimeters of Mercury}$. NOTE: vertical dashed line represents the approximate mean LLA for the population defined through piecewise linear regression in each animal.
Figure 4: Population-Wide Error Bar Plots – CPP vs. PRx, CPP vs. PAx and CPP vs. RAC

AMP = pulse amplitude of ICP, a.u. = arbitrary unite, CPP = cerebral perfusion pressure, ICP = intra-cranial pressure, PAx = pulse amplitude index (correlation between AMP and MAP), PRx = pressure reactivity index (correlation between ICP and MAP), RAC = correlation between AMP and CPP. NOTE: vertical dashed line represents the approximate mean LLA for the population, derived through piecewise linear regression in each animal.