Development of an active cerebrovascular autoregulation model using representation learning: a proof of concept study with experimental data

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ABSTRACT

Background and Objectives: It remains a challenge to monitor cerebrovascular autoregulation (CA) reliably and dynamically in an intensive care unit. The objective is to build a proof-of-concept active CA model exploiting advances in representation learning and the full complexity of the arterial blood pressure (ABP) and intracranial pressure (ICP) signal and outperform the pressure-reactivity index (PRx).

Methods: A porcine cranial window CA data set (n = 20) was used. ABP and ICP signals were preprocessed and downsampled to 20 Hz. Quadriphasic CA state labels were assigned to each piglet's CA curve and projected on their preprocessed ABP and ICP time series. Windowed ABP and ICP segments of 300 seconds, reflecting active CA, were used to optimize a neural network to reconstruct its own input. Reconstruction error of ABP and ICP were compared between active CA and inactive CA, and assessed together with PRx over quadriphasic CA states.

Results: The study confirmed that the optimized model achieved stellar reconstruction quality of ABP and ICP segments that derived from active CA while reconstruction quality deteriorated for segments that came from inactive CA. ABP and ICP reconstruction errors steadily increased concurrently with cerebral blood flow deviation from baseline. A significant interaction between variable and CA state showed that the model captured the differential behavior of CA with increasing versus decreasing CPP and offered improved discriminative ability with respect to PRx.

Conclusion: The present work showed that an active CA model can be built using advanced representation learning and the full complexity of 300 second ABP and ICP segments. Upon assessment in an experimental dataset, relevant CA state information was present in both lower and higher frequencies of ABP and ICP. Improved discriminative ability between CA states was attained with respect to PRx, which focuses only on slow-wave ABP and ICP information.

Running Title: Representation learning based CA modelling

Keywords: arterial blood pressure, cerebrovascular autoregulation, intracranial pressure, machine learning, pressure – reactivity index, representation learning

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Authorship contribution statement

Bavo Kempen: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Funding acquisition **Samuel Klein:** Resources **Veerle De Sloovere:** Resources **Maarten De Vos:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision **Bart Depreitere:** Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Introduction

Cerebrovascular autoregulation (CA) is a homeostatic physiological mechanism that ensures an adequate cerebral blood flow (CBF) over a varying range of cerebral perfusion pressures (CPP).[1–4] CPP reflects the pressure gradient between arterial blood pressure (ABP) and intracranial pressure (ICP) (CPP = ABP - ICP). The crucial mechanism driving CA is myogenic: changes in intraluminal pressure and flow are reflected in changes to arteriolar vessel tone, and hence, in cerebrovascular resistance (CVR).[5–7] However, the capacity of CA to adjust arteriolar vessel diameters in response to CPP decreases or increases is limited.[6,8]

Lassen introduced the seminal triphasic CA curve by plotting CBF (y-axis) against CPP (x-axis).[1] A plateau of stable CBF emerged over a wide range of CPP values, edged by a lower -and upper limit of autoregulation (LLA and ULA) which indicate the transition points from active to inactive CA. Recent experimental work showed that the CA curve was quadriphasic, with two ULAs.[6,8] The transition from ULA1 to ULA2 represents a gradual exhaustion of CA. While the static representation of CA remains useful to study the mechanism, its clinical utility is severely limited due to: 1) intra -and inter-individual LLA and ULA(s) variation reflecting the dynamic and gradual nature of CA impairment, and 2) a lack of reliable CBF monitors.[4,6,8–11]

In traumatic brain injury (TBI), CA can be dynamically impaired.[12–16] Knowledge of CA capacity could aide to steer blood pressure out of hypo -and hyperperfusion ranges. Indirect correlation-based CA indices exist that use a CBF surrogate and ABP to capture CA capacity dynamically.[17] Positive or negative correlations are interpreted as inactive or active CA, respectively. Pressure -reactivity index (PRx) is computed as the moving correlation coefficient between 30 consecutive 10 second averages of ICP and ABP, to model the slow-wave (≤ 0.05 Hz) arterial transmission to the brain, i.e. myogenic CVR changes.[17-20] Numerous drawbacks exist to utilizing a simple correlation coefficient to model a complex, multifaceted biological mechanism.[4] Relevant CA higher-frequency components, e.g. Mayer waves (0.1 Hz), cardiac cycle (1-1.3 Hz) and ICP pulse morphology information, among others, are ignored.[21–28] Modelling the full complexity of ABP and ICP could aid in delineating active from inactive CA dynamically.

Adoption of advanced machine learning methods to directly model CA from multivariate physiological time series is lacking. A data-driven machine learning approach seems appropriate to model CA directly from the full complexity of ABP and ICP. Sequentially connected encoder -

and decoder neural network architectures excel at modelling multivariate nonlinear interactions by optimizing the encoder -and decoder network concurrently. The encoder network learns to project the input data to an optimal latent representation while the decoder network learns to reconstruct the original input data from the latter latent representation. This method has been widely adopted in the field of anomaly detection. Unsupervised encoder-decoder anomaly detection methods were successful in modelling arrhythmia detection from electrocardiography, among others.[29–35] Anomaly detection involves identifying observations in the data that deviate from the learned concept of normal behavior, often generated by distinct underlying mechanisms.[36] Similarly, active and inactive CA can be considered as normal and abnormal behavior, respectively.

The present work aims to build a proof-of-concept dynamic CA monitor using representation learning and the full complexity of the ABP and ICP signal. An encoder-decoder neural network architecture is optimized to reconstruct its own multivariate ABP and ICP input which reflected an active CA state. Consequently, the model will have learnt a generalized active CA representation, i.e. normal behavior. It is hypothesized that distinct individual signal components and interactions present within and between the ABP and ICP signal characterize the active and inactive CA states. The reconstruction performance of the encoder–decoder model should be worse when the input is governed by inactive CA, i.e. abnormal behavior. An increase in reconstruction error of the ABP and ICP input has the potential to signal when a patient experiences failing CA. In sum, the encoder-decoder model is expected to: 1) adequately reconstruct ABP and ICP segments governed by active CA, with deteriorating performance on ABP and ICP input segments governed by inactive CA, and 2) improve the ability to dynamically discriminate between active -and inactive CA with respect to PRx.

Material and Methods

Data set

The unique data set used for the present study derives from a porcine closed cranial window model previously developed for the study of CA.[6,8] Briefly, twenty 6-week-old male piglets (domestic swine) were non-pharmacologically induced with hypotension or hypertension by gradually inflating a balloon catheter (LeMaitre embolectomy catheter® 1601-54, LeMaitre

Vascular) in the inferior vena cava or abdominal aorta, respectively (Supplementary Figure 1). ABP was monitored through an arterial line placed in the left femoral artery. An intraparenchymal ICP probe (Neurovent®-PTO, Raumedic AG Muenchenberg, Germany) and laser Doppler flowmetry (LDF) probe (Moor VMS-LDF1 with VP14-CBF probe, Moor Instruments, Devon, UK) were placed in two 3-4 mm burr holes behind the coronal suture over the right hemisphere.[6,8] The ICP probe perforated the dura, while the LDF probe did not. Meanwhile, ICM+ software (Cambridge University, Cambridge, UK) was used to store ABP (100 Hz), ICP (100 Hz), and LDF (500 Hz). LDF served as a direct measurement of CBF, validated in previous work utilizing CBF Flux computed from pial arterioles' diameter and red blood cell velocity.[6,8] Animal experimentation in the preceding data gathering study complied with the European Directive 2010/63/EU on the protection of animals used for scientific purposes, and was performed under veterinary supervision adhering to the guidelines imposed by the Ethical Committee.[6,8]

First, the quadriphasic CA definition was used to assign the CA state labels per piglet.[6] A segmented regression was computed per piglet to derive the LLA and ULAs reflecting a change in CA state (Figure 1A). No reliable breakpoints could be computed for 4 out of 20 piglets, which led to their immediate exclusion from the study, resulting in a final data set of 16 piglets ($n_{hypotensive} = 7$). Henceforth, the quadriphasic CA state labels will be defined as: *Active CA*, Low ABP inactive CA = *LiCA*, High ABP Partially active CA = *HPaCA*, High ABP inactive CA = *HiCA*.

Second, raw ABP and ICP time series were extracted from the ICM+ .hdf5 data format.[37] Extreme values were filtered out using absolute values (ABP > 300 mmHg; ABP < 10 mmHg; ICP < -5 mmHg) and a z-score filter ($\mu_{Signal} \pm 3 * \sigma_{Signal}$) per piglet. No data imputation was performed. The CA transition points determined per piglet (Figure 1A) were utilized to project the CA state onto the corresponding extracted ABP and ICP time series data (Fig 1B), followed by downsampling from 100 Hz to 20 Hz with a 10 Hz low-pass Butterworth filter of the 5th order.[38,39]

Model Architecture

Model architecture consisted of an encoder and decoder model. The encoder model employed TimesBlocks[35] (Figure 2), a temporal 2D - variation modelling technique which achieved stellar performance on unsupervised multivariate time series anomaly detection benchmarks, among other tasks. The complete explanation and rationale of TimesBlocks can be found in Wu et al. (2023) with accompanying illustrations and code.[35] A fully connected layer, a series of linear transformations, served as decoder network.

Model Optimization

The model is optimized to reconstruct its own input (i.e. active CA ABP and ICP time series) and as such is forced to learn a generalizable representation of said input. Sixteen piglets were subdivided in a train (n=12), validation (n=2) and test (n=2) data sets following a so called cross-validation procedure. The complete optimization and evaluation procedure can be found in Supplementary Algorithm 1. In essence, eight unique permutations of the data set were created where the available 16 piglets were randomly assigned to the train, validation and test data set, stratified on ABP manipulation (hypotension vs. hypertension). Eight models were optimized and tested with the corresponding unique data subsets to ensure robustness of the results. The train data set was used to optimize the model and the validation data set served as intermediate check to ensure generalizability. The test data set was used to independently assess the final performance of each model after convergence. Each training and validation data set consisted of concurrent ABP and ICP segments of 300 seconds (20 Hz) extracted from data that belonged to the active CA state with a 99 % overlap. For the test data set, 300 second (20 Hz) segments were extracted from all CA states without overlap. Model training, validation and testing was performed with Python 3.9.16 (Python Software Foundation, Delaware, US).[40,41]

Model Performance Assessment

Model performance was assessed both qualitatively and quantitatively for all CA states. The qualitative check was performed by randomly sampling and visualizing ABP and ICP test data set segment reconstructions with its respective original input. Quantitative assessment consisted of evaluating ABP and ICP reconstruction error trends over time, and over CPP in comparison with the average reconstruction error under active CA and with respect to baseline LDF. Linear

mixed effect models were used to assess whether: (1) CA state affected PRx, or (2) CA state affected ABP and ICP reconstruction errors. [42] In linear mixed effect model (1) PRx served as the dependent variable (DV) and CA state as the independent variable (IV), with a by-piglet random intercept and slope for CA state. In linear mixed effect model (2), log transformed reconstruction error (LogMSE) served as the DV with a main effect of CA state, variable (i.e. ABP, ICP) and their interaction as IV, with by-piglet, cross-validation fold random intercepts and slopes for variable and CA state. Detailed linear mixed effect model model specifications can be found in the supplementary material (Equation 1-2). If CA state was a significant predictor for (1) PRx (i.e. main effect) or (2) reconstruction error (i.e. interaction with variable), the effect of CA state (e.g. Active CA vs LiCA) was further investigated using pairwise comparisons (asymptotic z-test), corrected with Holm-Bonferroni for multiple comparisons.[43]

Secondary analyses and visualizations were performed in R (R Foundation, Vienna, Austria).[44–46]

Results

The trained model was evaluated on an independent test data set that consisted of unseen hypo -and hypertension experimental data. To evaluate PRx performance, the same unique hypo -and hypertension data were utilized. The distribution of test segments evaluated per CA class was as follows: (1) PRx: Active CA = 86.57%; LiCA = 2.43%; HPaCA = 6.09%; HiCA = 4.91%, (2) Our model: Active CA = 87.74%; LiCA = 1.92%; HPaCA = 4.09%; HiCA = 6.25%.

Model Performance

To initially assess reconstruction performance of the optimized models, a qualitative ABP and ICP signal reconstruction inspection was warranted. A zoomed 10 seconds from a total of 300 seconds view is provided here (Figure 3). The full respective traces can be found in the supplementary material (Supplementary Figure 2-5).

ABP and ICP reconstruction error increased over time when approaching inactive CA states (LiCA, HPaCA), visualized by centering the onset of inactive CA as time point zero per piglet (Figure 4). ABP and ICP reconstruction error increases occurred concurrently with an in -or decrease in LDF. Similarly, ABP and ICP reconstruction error increased concurrently with LDF when plotted against CPP (Figure 5A), and followed LDF percentage de/increase more closely than PRx on both the low -and high CPP side (Figure 5B).

Statistical analyses were performed for the developed model's ABP and ICP log transformed reconstruction error (LogMSE) (Figure 6A) and PRx (Figure 6B) separately. A significant main effect of CA state (p < 1e-04), variable (p < 1e-04) and their interaction (p = .0001) emerged to predict LogMSE. Further pairwise comparisons (Supplementary Table 1) revealed that: (1) ABP active CA reconstruction error was significantly lower than inactive CA reconstruction error ($Est._{ActiveCA-HPaCA}$ = -.5193 $\pm$ .1975, p = .0343; $Est._{LiCA-ActiveCA}$ = .9968 $\pm$ .2605, p = .0009; $Est._{ActiveCA-HiCA}$ = -1.3614 $\pm$ .1594, p < 1e-04), and (2) ICP active CA reconstruction error was significantly lower than fully inactive CA reconstruction error ($Est._{LiCA-ActiveCA}$ = 2.4006 $\pm$ .2605, p < 1e-04; $Est._{ActiveCA-HiCA}$ = -.9601 $\pm$ .1594, p < 1e-04), but not HPaCA ($Est._{ActiveCA-HPaCA}$ = -.0288 $\pm$ .1975, p = .8839) (Figure 6A). ICP reconstruction error increased more than ABP reconstruction error in LiCA with respect to active CA while the opposite holds true in HPaCA and HiCA. In the second analysis, PRx served as the DV and only CA state as IV. CA state was a significant predictor of PRx value (p = .0122). Pairwise comparisons (Supplementary Table 2) of the fixed CA state effect on PRx revealed that PRx governed by active CA was on average significantly lower than PRx governed by HiCA ($Est._{ActiveCA-HiCA}$ = -.4183 $\pm$ .1382, p = .0148), but not LiCA nor HPaCA (Figure 6B).

Discussion

The present study using experimental CA data from a cranial window piglet model demonstrated that a machine learning approach is suitable to delineate active CA from inactive CA. The state-of-the-art deep representation learning architecture, utilizing TimesBlocks[35], was used to successfully learn an active CA representation from 300 second concurrent ABP and ICP segments sampled at 20 Hz. The model converged to a generalized representation of active CA based on the multivariate ABP and ICP input data which significantly differed from inactive CA as shown by the increased reconstruction errors.

Representation learning models are a powerful tool to extract meaningful information from complex multivariate input data.[30–35,47] The proposed model architecture had the capacity to adequately learn an active CA representation from ABP and ICP which allowed it to qualitatively reconstruct test data governed by active CA, with negligible quantitative reconstruction error. As hypothesized, reconstruction error of ABP and ICP governed by inactive CA was significantly higher than the reconstruction error of ABP and ICP governed by active CA. Interestingly, the

reconstruction performance displayed a significant interaction between quadriphasic CA state and variable, allowing to differentiate between hypo -and hypertensive inactive CA. The model's invariance to absolute signal changes excludes that absolute in -or decreases in ABP or ICP (in mmHg) caused said interaction. Instead, our model may have learnt multivariate active CA frequency, amplitude and phase representation.

PRx seemed to follow the expected trend with a negative median correlation under active CA and a positive median correlation for inactive CA (Figure 6B). However, large overlaps between CA states due to its low signal-to-noise ratio limited its discriminative ability.[4,48–50] The developed model's reconstruction errors achieved a more pronounced significant difference between active and inactive CA states with respect to PRx. It may be that the model exploited additional CA information found in the ICP signal such as Mayer waves which correlate with cerebral hemodynamics, and ICP pulse morphology which contains information on cerebrovascular hemodynamics and cerebrospinal pressure-volume compensation, and their relation to ABP signal components.[21-28]

ABP and ICP reconstruction error increases followed the corresponding percentage difference from baseline LDF closely when plotted against time and CPP. Strikingly, ABP and ICP reconstruction errors increased concurrently over time and CPP when LDF started to deviate from baseline, which happened prior to the time points indicative of the transition from active CA to (partially) inactive CA.[6] The latter observation reflects an often overlooked drawback by deriving CA labels from the Lassen -or quadriphasic CA curve. The optimal least squares fit derived breakpoint(s) do not necessarily reflect the actual deflection point from stable LDF in time nor CPP (cf. Figure 4). That ICP and ABP reconstruction errors responded immediately to LDF deviation, means that the model was able to overcome this limitation and generalize over ABP and ICP input which reflected a stable LDF. PRx transitioned to positive correlations with a noticeable delay with respect to LDF deviation from baseline over CPP.

Limitations

The presented study did encompass several limitations. The animal model data set utilized to train, validate and test the model was relatively small (n = 16). However, cross-validation showed that the obtained results were robust since they generalized over eight subsets of unique piglet train, validation and test data sets. This is a healthy physiology animal model, and hence,

pathophysiological situations that dynamically impair CA were not part of the generated data and thus were not analyzed. The animal model used concerned piglets that were 6 weeks old, however, their cerebral and cardiovascular physiology is akin to humans.[6,8] Physiology studies confirmed that 6 week old piglets have the capacity to actively vasodilate -or vasoconstrict pial arterioles in response to changes in CPP, and show a robust CA capacity.[6,8,51–53]

Future Perspectives

Some crucial steps need to be taken to further develop the present proof-of-concept into a validated CA monitor. First, more experimental data, akin to the used data set, needs to be gathered, with additional alterations (e.g. CO_2, ICP). Second, an experimental severe TBI data set with dynamic CA impairment needs to be developed to validate the proof-of-concept. Third, retrospective exploration of the outlined method and subsequent prospective validation in human TBI patients. Finally, the equivalent method can be used to model an inactive CA representation which could work in conjunction with the active CA model to further improve discriminative performance.

Conclusion

The presented proof-of-concept study showed that the proposed novel method and model works as intended and can develop into a state-of-the-art dynamic CA monitor. It was sufficient to use 300 second segments of ABP and ICP sampled at 20 Hz to directly derive changes in CBF.

Code and Data Availability Statement

The code and data that support the findings of this study are available from the corresponding author on reasonable request.

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FIGURE LEGENDS

Figure 1. An example of cerebrovascular autoregulation (CA) state projection on arterial blood pressure (ABP) time series. A) The quadriphasic curve constructed from a hypo -and hypertension piglet experiment data set. Cerebral perfusion pressure (CPP) was plotted against the percentage change of laser doppler flowmetry (LDF) from baseline values prior to arterial blood pressure (ABP) manipulation. Lower limit of autoregulation (LLA) and upper limits of autoregulation (ULA1 and ULA2) were computed using segmented regression with 1 and 2 breakpoints, respectively.[6,8] B) Projection of CA states determined in A) on the respective hypo - and hypertension experiment piglets' ABP time series. The time series data used in the present study were annotated per piglet with the respective CA states accordingly.

Figure 2. Model architecture. The architecture consisted of a sequentially connected encoder and decoder neural network which was input with 300 seconds of concurrent arterial blood pressure (ABP) and intracranial pressure (ICP) segments sampled at 20 Hertz (Hz). Model is optimized to reconstruct the original ABP and ICP input segments utilizing mean squared error (MSE) loss. The encoder network comprised of a data embedding layer and two residually connected TimesBlocks[35], each selective for the top eight frequencies. Inception blocks consisted of 6 kernels with 0.1 dropout. Activation functions used were Gaussian Error Linear Units. Latent representation comprised of eight dimensions. A simple linear feed forward layer reconstructs the input data from the latent representation in the decoder network. The model comprised of 73 522 trainable parameters and was optimized on a single NVIDIA V100 GPU for 100 epochs with a batch size of 32 and the adaptive moment estimation (Adam) optimizer with a starting learning rate of 0.0001. Model training was halted when the validation loss did not decrease for 5 consecutive epochs.

Figure 3. Original arterial blood pressure (ABP) and intracranial pressure (ICP) input traces and respective reconstructions from the test data set. Left and right figures per row concern concurrent standardized ABP and ICP traces, respectively. Here, a zoomed 10 seconds from a total of 300 seconds view is provided. Row one to four displays an ABP and ICP trace (blue) and

its reconstruction (red) randomly sampled from the active cerebrovascular autoregulation state (Active CA), hypotensive Low inactive CA (LiCA) state, hypertensive High Partially active CA (HPaCA) state, and High inactive CA (HiCA) state, respectively.

Figure 4. Percentage change of arterial blood pressure (ABP) and intracranial pressure (ICP) mean squared reconstruction error (MSE) and of percentage change of laser Doppler flow (LDF) from baseline over time visualized per piglet experimental condition. LiCA, HPaCA and HiCA reflect the Low inactive CA, hypertensive High Partially active CA, and High inactive CA, respectively. The onset of LiCA and HPaCA was centred as time point 0 to combine the data of all piglets within the experimental condition. Data points were smoothed using a locally weighted non parametric regression with an α of 0.75 and visualized with their 95% confidence intervals.

Figure 5. Percentage change of ABP and ICP mean squared reconstruction error (MSE) and pressure-reactivity index (PRx) over cerebral perfusion pressure (CPP). A) ABP and ICP MSE percentage difference from active CA. B) PRx plotted against corresponding CPP values. Both graphics were visualized with laser Doppler flow (LDF) percentage difference from baseline depicted on the right y-axis. Data points were smoothed using a locally weighted non parametric regression with an α of 0.75 and visualized with their 95% confidence intervals.

Figure 6. Model test prediction error and pressure-reactivity index (PRx) distribution along quadriphasic cerebrovascular autoregulation (CA) states. LiCA, Active CA, HPaCA, and HiCA correspond to the hypotensive inactive CA, active CA, hypertensive partially active CA, and hypertensive inactive CA states, respectively. A) Model test log mean squared reconstruction error (LogMSE) per quadriphasic CA state. LogMSE was computed per reconstructed concurrent ABP and ICP segment of 300 seconds. A lower LogMSE reflects better reconstruction performance. B) PRx distribution along CA state. ABP and ICP data was modelled with a linear mixed effects model (LMM) with a main effect of variable, CA state and their interaction as fixed effect. PRx data was modelled with a LMM with CA state as fixed effect. The fixed effect CA

states were subsequently contrasted and corrected for multiple comparisons with Holm–Bonferroni correction. Note, that for the ABP - ICP model, the CA states contrasts were conditioned on Variable. **** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$; ns = not significant.

SUPPLEMENTARY DIGITAL CONTENT LEGENDS

Supplementary Figure 1. Hypotension and hypertension was non-pharmacologically induced in twenty 6-week-old male piglets (domestic swine) by gradually inflating a balloon catheter in the inferior vena cava or abdominal aorta, respectively. This illustration was kindly provided by Dr. Gabriel Montaldo and Dr. Alan Urban.

Supplementary Algorithm 1: Procedure model training and evaluation. The unique piglets present in the complete data set were randomly assigned to a training (n=12), validation (n=2) and test (n=2) data set, stratified on arterial blood pressure (ABP) manipulation using fourfold nested cross-validation (cv_training_dataset, cv_validation_dataset, cv_test_dataset). Training and validation data sets comprised of active cerebrovascular autoregulation (CA) data, while test data set consisted of Low ABP inactive CA (LiCA), Active CA, High ABP Partially active CA (HPaCA), and High ABP inactive CA (HiCA). The training data set was used to globally standardize the training, validation and test data sets to ensure that loss values between ABP and ICP were on the same scale (cf. step 2 and 7). To ensure that each individual time series (ABP and ICP) was standard normal distributed and thus invariant to absolute or relative differences in ABP and ICP values, a second standardization step took place they were standardized on their own mean and standard deviation (cf. step 3.2.1 and 3.2.3). He initialization was used to initialize model parameters θ, an Adaptive Moment Estimation optimizer was used with learning rate 0.0001, number of epochs "T" = 100, Batch size "B" = 32, early stopping manifested if validation loss did not decrease for 5 consecutive epochs.

Supplementary Equation 1: Linear mixed effects model (LMM) to assess effect of cerebrovascular autoregulation (CA) state on the Pressure-reactivity index (PRx). The equation describes the maximal random effects structure justified by the experimental design. Afterwards, the LMM was simplified to a fixed main effect for CA state, and a by-piglet random intercept and slope for CA state with an uncorrelated random effects structure. Pairwise contrasts were computed on the main effect of CA state, using Holm – Bonferroni correction for multiple

comparisons. Low ABP inactive CA (LiCA) state, High ABP Partially active CA (HPaCA) state, and High ABP inactive CA (HiCA) state.

Supplementary Equation 2: Linear mixed effects model (LMM) to assess effect of cerebrovascular autoregulation (CA) state and reconstructed variable on the reconstruction error. The log mean squared error (LogMSE) reflects the arterial blood pressure (ABP) and intracranial pressure (ICP) reconstruction errors. A main effect of CA state, variable (ABP, ICP) and their interaction was considered and denoted in the equation with the maximal random effects structure justified by the experimental design. The final LMM was simplified to a main effect of CA state, variable (ABP, ICP) and their interaction, and a by-piglet, cross-validation fold random intercepts and slopes for variable with an uncorrelated random effects structure. Pairwise contrasts were computed on the interaction effect of CA state and variable by conditioning on the variable to derive the (non)significant differences between CA states per variable, using Holm – Bonferroni correction for multiple comparisons. Low ABP inactive CA (LiCA) state, High ABP Partially active CA (HPaCA) state, and High ABP inactive CA (HiCA) state.

Supplementary Figure 2. Original arterial blood pressure (ABP) and intracranial pressure (ICP) input traces (blue) and respective reconstructions (red) from the test data set active CA. The left and right figures per row concern concurrent standardized ABP and ICP traces, respectively. Each ABP and ICP trace is provided with a 10 second zoom window derived from the 300 seconds input - reconstruction segments.

Supplementary Figure 3. Original arterial blood pressure (ABP) and intracranial pressure (ICP) input traces (blue) and respective reconstructions (red) from the test data set Low ABP inactive Cerebrovascular Autoregulation (LiCA). The left and right figures per row concern concurrent standardized ABP and ICP traces, respectively. Each ABP and ICP trace is provided with a 10 second zoom window derived from the 300 seconds input - reconstruction segments.

Supplementary Figure 4. Original arterial blood pressure (ABP) and intracranial pressure (ICP) input traces (blue) and respective reconstructions (red) from the test data set High ABP Partially active Cerebrovascular Autoregulation (HPaCA). The left and right figures per row concern concurrent standardized ABP and ICP traces, respectively. Each ABP and ICP trace is provided with a 10 second zoom window derived from the 300 seconds input - reconstruction segments.

Supplementary Figure 5. Original arterial blood pressure (ABP) and intracranial pressure (ICP) input traces (blue) and respective reconstructions (red) from the test data set High ABP inactive Cerebrovascular Autoregulation (HiCA). The left and right figures per row concern concurrent standardized ABP and ICP traces, respectively. Each ABP and ICP trace is provided with a 10 second zoom window derived from the 300 seconds input - reconstruction segments.

Supplementary Table 1. Log mean squared error (LogMSE) contrasts over cerebrovascular autoregulation (CA) states, conditioned on variable. First, a linear mixed effect model was fit with main effect of CA state, variable (ABP, ICP) and their interaction (cf. Supplementary equation 2) and LogMSE as dependent variable. To determine whether reconstruction error (LogMSE) significantly increased under inactive CA states with respect to the active CA state for each variable (ABP, ICP) separately, pairwise contrasts of the CA state and variable interaction, conditioned on variable, were evaluated and adjusted with the Holm-Bonferroni correction. The asymptotic z-test was used to assess pairwise contrasts due to the large number of data points available (infinite degrees of freedom). Here, the authors were mainly interested in the contrasts of active CA with the inactive CA states (cf. Figure 6).

Supplementary Table 2. Pressure-reactive index (PRx) contrasts over cerebrovascular autoregulation (CA) states. First, a linear mixed effect model was fit with main effect of CA state (cf. Supplementary equation 1) and PRx as dependent variable. To determine whether PRx significantly increased under inactive CA states with respect to the active CA state, pairwise contrasts of the CA state were performed and adjusted with the Holm-Bonferroni correction. The

asymptotic z-test was used to assess pairwise contrasts due to the large number of data points available (infinite degrees of freedom). Here, the authors were mainly interested in the contrasts of active CA with the inactive CA states (cf. Figure 6).