Citation	Klein S.P., Fieuws, S. (2020), Effects of Norepinephrine, Propofol, and Hemoglobin Concentration on Dynamic Measurements of Cerebrovascular Reactivity in Acute Brain Injury Journal of Neurotrauma, Aug 10.
Archived version	Author manuscript: the content is identical to the content of the published paper, but without the final typesetting by the publisher
Published version	http://dx.doi.org/10.1089/neu.2020.7160
Journal homepage	Journal of Neurotrauma
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IR	https://lirias2.kuleuven.be/viewobject.html?cid=1&id=3078039

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Effects of Norepinephrine, Propofol, and Hemoglobin Concentration on Dynamic Measurements of Cerebrovascular Reactivity in Acute Brain Injury

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Abstract

Effects of treatment-associated variables on cerebrovascular autoregulation (CA) in acute brain injury patients remain unclear. As deficient CA is associated with worse outcomes and ideas about CA-steered management are emerging, this question is relevant. We investigated effects of norepinephrine and propofol infusion rates and hemoglobin concentration on dynamic measurements of cerebrovascular reactivity as surrogate for CA. A retrospective analysis of 91 traumatic brain injury (TBI) and 13 stroke patients admitted to the intensive care unit (ICU) of the Leuven University Hospitals was performed. Low-resolution autoregulation index (LAX) and high-frequency pressure reactivity index (PRx) were calculated as measurements of cerebrovascular reactivity. Data was binned into 5-, 15-, and 60-min intervals. Bivariate time-series analysis using lagged cross-correlations were calculated after pre-whitening and differencing. Linear mixed models evaluated effects of age, gender, cardiovascular risk, brain comorbidity, Glasgow Coma Scale (GCS), pupil reactivity, and type of injury. Median dose of norepinephrine, propofol and hemoglobin concentration was 7.8 µg/kg/h (Q1 3.6-Q3 13.8), 3 mg/kg/h (Q1 1.9-Q3 4.3), and 9.2 g·dL⁻¹ (Q1 8.2-Q3 10.5), respectively. Mean cross-correlations for 24 lags were close to zero and not significant for all variables. No significant differences as function of age, gender, cardiovascular risk, brain comorbidity, GCS, pupil reactivity, and type of injury were found. Dynamic intracranial pressure-based measurements of cerebrovascular reactivity in acute brain injured patients are not affected by gradually adjusted norepinephrine or propofol infusion rates or slow changes in hemoglobin concentration within the typical ranges during ICU admission. Future trials on cerebrovascular reactivity-steered management and treatment of CA impairment may not have to take these variables into account.

Introduction

Propofol and norepinephrine (NE) are widely used in the management of patients suffering severe brain injury admitted to the intensive care unit. Sedation of traumatic brain injury (TBI) and severe stroke patients leads to amnesia and anxiolysis, and is used to treat hypoxia, hypercapnia, systemic hypertension, and intracranial hypertension.¹ A potential side effect of sedation is systemic hypotension, leading to a decrease in cerebral perfusion pressure (CPP), cerebral hypoxia, and poor patient outcome. Vasoactive agents are used to maintain CPP within adequate levels. Cerebrovascular pressure reactivity as a surrogate measure of cerebral autoregulation (CA), has been demonstrated as a prognostic factor after severe TBI, with a strong association between disturbed cerebrovascular reactivity and poor outcome.²⁻⁵

Propofol has been shown to preserve cerebrovascular autoregulation in healthy individuals.⁶ Data on the effects of propofol on CA in patients with acute brain injury are scarce. A small patient study documented a deterioration of cerebrovascular pressure autoregulation after an increase in propofol infusion rates in TBI patients.⁷

Vasoactive agents such as dopamine, epinephrine, and NE have not sufficiently been studied regarding their effects on CA. Experimental animal research has demonstrated that NE preferentially protected CA in female

but not in male newborn piglets after fluid percussion injury. However, NE protected CA in male and female juvenile piglets after TBI, indicating that the same vasoactive drug elicits both age- and sex-dependent differences in CA.^{8,9} Data on the effects of NE on CA in adult animals are lacking, and human data are not available.

Anemia is a common problem in critically ill patients. In most intensive care units, a restrictive strategy of red blood cell transfusion is preferred and moderate anemia ($7\text{--}9\text{ g g}^{-1}\text{ dL}^{-1}$) is tolerated.¹⁰ Low hemoglobin (Hb) concentrations may lead to decreased cerebral oxygen delivery, and one may assume that decreased cerebral oxygenation due to anemia may influence the effectiveness of CA. Contra-intuitively, red blood cell transfusion in severe TBI patients has been associated with a worsening of CA.¹¹ A case report in a 22-month-old girl suggested intact CA with a shift of the lower limit of autoregulation to the right after acute isovolemic anemia during orthopedic surgery.¹² In healthy individuals, hypervolemic hemodilution impaired dynamic CA measurements.¹³ The physiological explanation for the link between Hb levels, red blood cell transfusion, and CA is still lacking, but there is some evidence for a potential association.^{8–11}

The aim of this study was to investigate the effects of propofol, NE infusion rate, and Hb concentration on dynamic cerebrovascular pressure reactivity metrics as a surrogate of CA in acute brain-injured patients.

Methods

Study design and population

This retrospective study includes a total of 104 acute brain injury patients who had continuous monitoring of arterial blood pressure (ABP) and intracranial pressure (ICP) and were admitted to the University Hospitals Leuven, Belgium, between 2010 and 2017. Ninety-one TBI and 13 stroke patients were included.

Data collection and signal processing

Demographics (age, gender), cardiovascular risk factors (arterial hypertension, type 2 diabetes, smoking, dyslipidemia), history of brain comorbidity (TBI, stroke, epilepsy), pupil reactivity, and Glasgow Coma Scale (GCS) on admission were recorded. Atherosclerotic cardiovascular disease risk was calculated using the updated Framingham risk assessment tool, allowing body mass index to be substituted for total cholesterol and high-density lipoprotein cholesterol when laboratory data are not available.¹⁴ Cardiovascular disease risk was stratified based on the risk score: low ($< 10\%$), moderate ($10\text{--}19\%$), or high ($> 20\%$) risk of a cardiovascular disease event. Propofol and norepinephrine infusion rates were available on a minute-by-minute interval in the electronic medical records. Hemoglobin concentration values were sampled multiple times per day per patient according to the clinical need, and stored in the electronic medical records. For further processing, hemoglobin values were linearly interpolated. The dataset based on the norepinephrine measurements was used to define the time frame per patient.

Measurements before first and after last measurements were assumed to be constant (i.e., equal to first and last, respectively). Arterial blood pressure was measured through a radial arterial line connected to a pressure transducer. ICP was acquired by an intraparenchymal strain gauge probe (Codman Microsensor; Codman, Raynham, MA). The low-resolution autoregulation index (LAX) for time interval x at a given time $t(0)$ was calculated as the correlation coefficient between minute-by-minute measurements of ICP and mean arterial blood pressure for the time interval $[t(-x+1), t(0)]$. LAX values were calculated for the time intervals 3, 5, 10, 20, 30, 60, 90, and 120 min. To obtain only one LAX measurement every minute, we took the median of the above listed.¹⁵ In 91 of the 104 patients, high-frequency ABP and ICP waveform data was recorded at 50 Hertz or higher (ICM+ software, Cambridge Enterprises). For patients with high-frequency waveform data, the pressure reactivity index (PRx) was calculated as a moving Pearson correlation coefficient between ICP and ABP using 30 consecutive 10-sec windows (5 min of data), updated every minute.¹⁶ Signal artifacts were removed manually by a clinician before calculation of LAX and PRx.

Statistical analysis

A two-stage approach was used to evaluate the relation between either propofol or NE infusion rate and either LAX or PRx. The same approach was used for the relation between hemoglobin concentration and either LAX or PRx.

In a first step, a bivariate time-series analysis was performed within each subject for each time period separately (referred to as a “block”), where each time period had consecutive measurements (i.e., no missing information), and was long enough to capture the relevant dependencies between and within both time series. Splitting the time series in different periods per subject was required since for most subjects there were interruptions in the time series. This implies that per-subject multiple cross-correlation functions were available. Note that minute-per-minute measurements were available, being binned into longer intervals of 5, 15, and 60 min. Twenty-four fixed time intervals (lags) of either 5-, 15- and 60-min bins were analyzed to assess the relationship between changes in propofol/NE infusion rates or hemoglobin concentration and delayed changes in LAX or PRx.

To obtain meaningful cross-correlations, the time-series were pre-whitened by fitting autoregressive integrated moving average (ARIMA) models to the medication time-series and applying the same model to the autoregulation time-series (after differencing both time series in each of the multiple blocks to facilitate obtaining stationarity).¹⁷ For each block, the optimal ARIMA model was determined based on the combination of autoregressive and moving average parameters minimizing the Bayesian information criterion.

In a second step, the mean cross-correlation function over all blocks of all subjects (up to 24 lags) and the confidence interval (CI) at a specific lag was calculated using a linear mixed model with a random subject effect to handle the potential correlation between the multiple results (multiple lags, possible multiple blocks) of the same patient. Since the number of observations differed between the blocks, the natural logarithm of number of observations was used as a weight in the model. To take into account multiple testing (due to considering multiple lags), an approach proposed by Sankoh and colleagues was used to adjust the alpha-level in the construction of the confidence intervals for the mean cross-correlation.¹⁸ This correction is less conservative than a Bonferroni correction and is based on the mean pairwise correlation between the lags. If the mean correlation between the cross-correlations obtained at the different lags would equal zero, the correction equals the Bonferroni adjustment.

Further, linear mixed models were used to evaluate at each lag the mean cross-correlation as a function of gender, brain comorbidity, GCS, pupils, age, cardiovascular risk, and type of injury (separately for each of these variables). Note that for age and GCS, the values were standardized such that the slope from the mixed model equaled a correlation coefficient. Corrections for multiple testing (over all lags) were again based on the approach of Sankoh and colleagues.¹⁸ Further, to obtain one global test for any difference in mean-cross-correlation as function of a specific variable, a linear mixed model was used simultaneously on all lags using restricted cubic splines (with four knots) to model the relation between the lag and the cross-correlation.¹⁹ The global test referred to the main effect of the variable (e.g., gender) and the interaction with the effect of lag. The model contained a random intercept for subject and a random intercept for the lag-subject combination (lag nested within subject).

All analyses have been performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC).

Results

Data from 104 patients were available. The mean age was 48 years (range, 1–85), and 64% were males. The median GCS was 10 (interquartile range, 6–14). Both pupils were reactive to light in 72% of patients, in 11% only one pupil was reactive, in 12% both pupils were not reactive to light, and in 5% there was no pupillary data available. Cardiovascular risk profile was low in 65%, moderate in 17%, and high in 17% of patients. Twelve percent of patients had a history of brain comorbidity. Eighty-eight percent were TBI patients and 12% stroke patients ([Table 1](#)).

For norepinephrine and propofol infusion rates and hemoglobin concentrations, the pairwise correlation for each lag with PRx and LAX resulted in nonsignificant adjusted alpha levels for each of the 5-, 15- and 60-min bins. Results for norepinephrine 5-min bins, propofol 5-min bins, and hemoglobin 60-min bins are shown in Table 3, Table 4, and Table 5, respectively.

The influence of different patient-specific variables on the crosscorrelation of norepinephrine infusion rate, propofol infusion rate, and hemoglobin concentration with PRx and LAx was further explored using a linear mixed model. The mixed model resulted in non-significant alpha levels for each of the 5-, 15- and 60-min bins (Table 6).

Discussion

Our study did not reveal alterations in dynamic ICP-based cerebrovascular reactivity measurements (PRx and LAx) following changes in propofol and norepinephrine infusion rates or hemoglobin concentration in acute brain-injured patients. The novelty of our study is the use of a time-series approach to study the effects of patient-specific and treatment variables following acute brain injury on dynamic cerebrovascular reactivity metrics as a surrogate for CA. Time series modeling and analysis have been proven to be very useful for continuous datasets assessing cerebrovascular reactivity.^{20–23} The dependence of (patho-) physiological variables to each other is not always instantaneous, and often the response occurs after a certain lapse of time (lag). A time-series lagged correlation analysis is therefore well suited to study large datasets from patients in the intensive care unit and identify delayed correlations between two physiological variables. Our retrospective dataset represents the clinical reality of acute brain-injured patients admitted to the intensive care unit.

Our results are in contrast to the findings published by Steiner and colleagues.⁷ In a small group of patients with traumatic brain injury, a deterioration of the static rate of autoregulation (SROR) and mean velocity index (Mx) as a measure of CA was found after an important increase in propofol infusion rates (3–4 mg/kg/h increased to 6–8 mg/kg/h) over a relative short time period. The majority of patients in our series had low to normal infusion rates of propofol (median 3.1 mg/kg/h, 25th–75th percentiles 1.9–4.3), that were gradually adjusted to clinical need. A possible explanation for these contrasting findings may be the difference in absolute infusion rates and the time period of rate adjustments. A rapid increase in propofol infusion rate may be associated with a deterioration of cerebrovascular reactivity. On the contrary, a gradual increase in propofol infusion rate did not seem to influence dynamic cerebrovascular reactivity in our analysis.

Another important difference lies in the method of cerebrovascular reactivity measurement that was used. Steiner et al. demonstrated that differences between SROR, Mx, and PRx exist, and PRx was shown to be a more robust estimator of CA than Mx.²⁴ Zeiler and colleagues demonstrated a poor performance of Mx to predict the lower limit of CA in an experimental animal model.²⁵ In this animal model using laser Doppler flow as a measure of cerebral blood flow, PRx performed better than Mx to predict the lower limit of CA. To the best of our knowledge, ours is the first study reporting the influence of norepinephrine infusion rate on dynamic ICP-based CA measurements in acute brain-injured patients.

Acute changes in hemoglobin concentration have been shown to impair CA, either by hemodilution or by RBC transfusion.^{11,13} In our retrospective series, we did not find a correlation between relative slow changes in hemoglobin concentrations and dynamic measures of cerebrovascular reactivity in a 24-h time window. We speculate that rapid changes in hemoglobin concentration could have a detrimental effect on cerebrovascular reactivity, while dynamic cerebrovascular reactivity is not influenced by gradual non-acute changes in hemoglobin concentration.

These results contribute to the safety profile of the intravenous combination of propofol-norepinephrine in acute brain-injured patients. Similarly, our data suggest that the current hemoglobin policy appears to be safe in terms of CA. Apart from safety, it also seems that future trials on CA-based blood pressure management may not have to be stratified for the above variables, nor could we estimate from the current analysis that adjustment of these variables may become a treatment of impaired CA.

Our analysis inevitably is associated with limitations. First, the present analysis is based on a retrospective single-center cohort of patients. Our study reflects the very specific, albeit standard, clinical management strategy of a single center. This theoretically limits the generalization of our results to different management strategies. Second, cerebrovascular reactivity indices PRx and LAx are only surrogate measures of CA and currently there is no “gold standard” for measurement of arteriolar autoregulatory capacity. Even though PRx is currently the best-accepted method to continuously monitor CA status in patients, it has not yet been validated directly against the actual smooth muscle cell phenomenon of CA in an *in vivo* animal experiment.^{26,27} LAx is based on longer time windows than PRx and theoretically is outside of the vasogenic frequency range associated with CA, but has been proven to provide useful information on cerebrovascular reactivity and patient outcome.^{15,22} Third, due to the retrospective nature of the data we cannot independently analyze the effect of one variable on cerebrovascular reactivity. Therefore, it cannot be completely ruled out that our

results are biased due to concurrent changes of other variables (e.g., concurrent changes in propofol and norepinephrine infusion rates). Fourth, as suggested by a reviewer, it would be useful to consider a Fisher transformation of the LAx and PRx values since these are correlations, and thus bounded by -1 and 1 . We therefore re-evaluated the cross-correlation between norepinephrine and LAx, transforming the LAx values, as well as the derived cross-correlations. We obtained similar conclusions, with the cross-correlations even being almost identical.

Despite these limitations, we believe that our time-series lagged correlation analysis based on real clinical data from a moderate size cohort adds valuable information to the literature on the use of CA in the management of acute brain injury in the intensive care unit.

Conclusion

Dynamic ICP-based measurements of cerebrovascular reactivity in acute brain-injured patients are not affected by gradually adjusted norepinephrine or propofol infusion rates and slow changes in hemoglobin concentration within the typical ranges during intensive care unit admission. It thus seems that future trials on CA-steered management and treatment of CA impairment based on current CA measurement tools may not have to take these variables into account.

Funding Information

This work was supported in part by a Johnson & Johnson Research Chair in Profound analysis of cerebrovascular pressure autoregulation and associated physiological variables in severe traumatic brain injury at KU Leuven University.

Author Disclosure Statement

No competing financial interests exist.

TABLE 1. DESCRIPTION OF PATIENT CHARACTERISTICS

Number of patients	104
Age mean (SD)	48.2 (19.8)
Gender	
Male, <i>n</i> (%)	67 (64%)
Female, <i>n</i> (%)	37 (36%)
GCS median (Q1-Q3)	10 (6 – 14)
Pupil reactivity	
Both reactive, <i>n</i> (%)	75 (72%)
One reactive, <i>n</i> (%)	11 (11%)
None reactive, <i>n</i> (%)	13 (12%)
Unknown, <i>n</i> (%)	5 (5%)
Cardiovascular risk	
Low, <i>n</i> (%)	68 (65%)
Moderate, <i>n</i> (%)	18 (17%)
High, <i>n</i> (%)	18 (17%)
Brain comorbidity	
No, <i>n</i> (%)	92 (88%)
Yes, <i>n</i> (%)	12 (12%)
Type of injury	
TBI, <i>n</i> (%)	91 (88%)
Stroke, <i>n</i> (%)	13 (12%)

SD, standard deviation; GCS, Glasgow Coma Scale; Q1-Q3, interquartile range (IQR); TBI, traumatic brain injury.

TABLE 2. DESCRIPTION OF THE NUMBER OF PATIENTS, NUMBER OF BLOCKS, AND MEAN NUMBER OF BINS PER BLOCK

	<i>Number of patients</i>	<i>Number of blocks</i>	<i>Mean number of bins per block (standard deviation)</i>
Norepinephrine			
LAX	78	441	284.2 (384.8)
PRx	68	218	265.6 (347.0)
Propofol			
LAX	58	223	223.9 (326.5)
PRx	48	63	216.6 (305.3)
Hemoglobin			
LAX	78	177	284.2 (384.8)
PRx	68	106	265.6 (347.0)

For norepinephrine and propofol 5-min bins are described and for hemoglobin 60-min bins are described.

LAX, low-resolution autoregulation index; PRx, pressure reactivity index.

TABLE 3. NOREPINEPHRINE CROSS-CORRELATIONS WITH LAX OR PRx; 5-MIN BINS

Lag	Norepinephrine - LAX 5 min		Norepinephrine - PRx 5 min	
	CC (95% CI)	p Value	CC (95% CI)	p Value
0	-0.006 (-0.021;0.009)	0.2003	-0.013 (-0.036;0.010)	0.0958
1	-0.001 (-0.015;0.014)	0.8673	0.005 (-0.020;0.029)	0.5671
2	0.007 (-0.005;0.020)	0.0587	0.000 (-0.021;0.022)	0.9637
3	-0.002 (-0.015;0.011)	0.5709	-0.001 (-0.022;0.019)	0.8367
4	0.002 (-0.010;0.013)	0.6162	-0.001 (-0.019;0.018)	0.9226
5	0.002 (-0.009;0.014)	0.5358	0.006 (-0.013;0.025)	0.3324
6	-0.003 (-0.015;0.008)	0.3450	-0.008 (-0.026;0.010)	0.2138
7	0.000 (-0.012;0.012)	0.9547	0.003 (-0.014;0.021)	0.5628
8	-0.000 (-0.011;0.010)	0.9133	0.000 (-0.017;0.017)	0.9778
9	0.002 (-0.009;0.013)	0.5781	0.001 (-0.016;0.019)	0.8561
10	0.003 (-0.008;0.014)	0.3921	-0.001 (-0.018;0.017)	0.9084
11	-0.006 (-0.017;0.005)	0.0670	0.003 (-0.014;0.021)	0.5837
12	0.005 (-0.006;0.015)	0.1681	-0.001 (-0.018;0.016)	0.8605
13	-0.004 (-0.015;0.007)	0.2812	-0.002 (-0.019;0.015)	0.7663
14	0.005 (-0.005;0.016)	0.1140	-0.002 (-0.019;0.014)	0.6704
15	-0.006 (-0.016;0.003)	0.0356	0.005 (-0.012;0.022)	0.3707
16	-0.001 (-0.011;0.009)	0.6797	-0.004 (-0.021;0.012)	0.4700
17	0.007 (-0.004;0.017)	0.0498	0.010 (-0.007;0.027)	0.0801
18	-0.003 (-0.013;0.007)	0.3615	-0.007 (-0.022;0.007)	0.1544
19	-0.000 (-0.010;0.010)	0.9071	-0.002 (-0.018;0.014)	0.7495
20	0.001 (-0.009;0.011)	0.7871	-0.003 (-0.019;0.013)	0.6374
21	-0.000 (-0.010;0.009)	0.8837	0.008 (-0.007;0.024)	0.1323
22	-0.001 (-0.011;0.008)	0.6352	-0.005 (-0.019;0.009)	0.3080
23	0.004 (-0.006;0.013)	0.1932	-0.001 (-0.016;0.013)	0.8217
24	-0.002 (-0.011;0.008)	0.5861	0.001 (-0.013;0.015)	0.8340

The average pairwise correlation (of the cross-correlations) between the lags equaled 0.072 and 0.361 resulting in adjusted alpha levels = 0.0014 and 0.0044 for LAX and PRx, respectively. Based on these adjusted alpha levels, none of the correlations were significant.

LAX, low-resolution autoregulation index; PRx, pressure reactivity index; CC, cross-correlation; CI, confidence interval.

TABLE 4. PROPOFOL CROSS-CORRELATIONS WITH LAX OR PRx; 5-MIN BINS

Lag	Propofol - LAX 5 min		Propofol - PRx 5 min	
	CC (95% CI)	p Value	CC (95% CI)	p Value
0	0.004 (-0.017;0.026)	0.5255	0.013 (-0.026;0.053)	0.2934
1	-0.003 (-0.028;0.021)	0.6614	-0.009 (-0.052;0.035)	0.5324
2	-0.013 (-0.035;0.009)	0.0594	-0.016 (-0.057;0.025)	0.2299
3	0.007 (-0.011;0.025)	0.1912	0.027 (-0.014;0.068)	0.0366
4	-0.005 (-0.023;0.013)	0.3639	-0.013 (-0.052;0.025)	0.2779
5	-0.001 (-0.020;0.017)	0.8098	0.013 (-0.020;0.046)	0.2097
6	-0.001 (-0.016;0.014)	0.8457	-0.014 (-0.044;0.016)	0.1399
7	0.008 (-0.008;0.024)	0.1228	0.002 (-0.018;0.022)	0.7600
8	-0.004 (-0.020;0.012)	0.4163	-0.003 (-0.030;0.024)	0.7099
9	-0.003 (-0.019;0.014)	0.6132	-0.000 (-0.027;0.026)	0.9737
10	-0.006 (-0.024;0.011)	0.2529	-0.006 (-0.035;0.023)	0.5182
11	0.014 (-0.003;0.030)	0.0091	0.007 (-0.020;0.034)	0.4172
12	-0.001 (-0.017;0.015)	0.8345	-0.003 (-0.033;0.028)	0.7726
13	-0.003 (-0.017;0.011)	0.5000	-0.000 (-0.026;0.025)	0.9712
14	-0.007 (-0.021;0.008)	0.1362	-0.001 (-0.026;0.025)	0.9170
15	-0.000 (-0.017;0.017)	0.9760	-0.008 (-0.033;0.017)	0.3373
16	0.003 (-0.015;0.020)	0.6514	0.012 (-0.019;0.043)	0.2270
17	0.004 (-0.012;0.020)	0.4322	-0.006 (-0.033;0.020)	0.4533
18	-0.003 (-0.016;0.011)	0.5453	-0.003 (-0.026;0.020)	0.6882
19	-0.001 (-0.016;0.014)	0.8188	0.003 (-0.022;0.027)	0.7283
20	-0.003 (-0.017;0.011)	0.5293	-0.011 (-0.035;0.012)	0.1370
21	0.004 (-0.008;0.016)	0.3056	0.010 (-0.009;0.030)	0.1010
22	0.000 (-0.015;0.015)	0.9519	-0.011 (-0.034;0.012)	0.1277
23	0.001 (-0.015;0.016)	0.9165	0.013 (-0.009;0.036)	0.0667
24	-0.005 (-0.017;0.008)	0.2525	-0.010 (-0.036;0.015)	0.2061

The average pairwise correlation (of the cross-correlations) between the lags equaled 0.084 and 0.136 resulting in adjusted alpha levels = 0.0015 and 0.0018 for LAX and PRx, respectively. Based on these adjusted alpha levels, none of the correlations were significant.

LAX, low-resolution autoregulation index; PRx, pressure reactivity index; CC, cross-correlation; CI, confidence interval.

TABLE 5. HEMOGLOBIN CROSS-CORRELATIONS WITH LAX OR PRX; 60-MIN BINS

Lag	Hemoglobin - LAX 60 min		Hemoglobin - PRx 60 min	
	CC (95% CI)	p Value	CC (95% CI)	p Value
1	-0.003 (-0.062;0.057)	0.9026	-0.003 (-0.062;0.057)	0.9026
2	-0.006 (-0.061;0.050)	0.7785	-0.006 (-0.061;0.050)	0.7785
3	0.032 (-0.023;0.087)	0.1065	0.032 (-0.023;0.087)	0.1065
4	-0.026 (-0.079;0.027)	0.1729	-0.026 (-0.079;0.027)	0.1729
5	0.017 (-0.038;0.072)	0.3879	0.017 (-0.038;0.072)	0.3879
6	-0.023 (-0.077;0.031)	0.2345	-0.023 (-0.077;0.031)	0.2345
7	0.028 (-0.022;0.079)	0.1196	0.028 (-0.022;0.079)	0.1196
8	-0.015 (-0.063;0.034)	0.3945	-0.015 (-0.063;0.034)	0.3945
9	0.020 (-0.032;0.072)	0.2837	0.020 (-0.032;0.072)	0.2837
10	-0.014 (-0.066;0.038)	0.4535	-0.014 (-0.066;0.038)	0.4535
11	-0.004 (-0.052;0.044)	0.8234	-0.004 (-0.052;0.044)	0.8234
12	0.008 (-0.040;0.055)	0.6582	0.008 (-0.040;0.055)	0.6582
13	-0.004 (-0.050;0.041)	0.7840	-0.004 (-0.050;0.041)	0.7840
14	0.003 (-0.041;0.046)	0.8691	0.003 (-0.041;0.046)	0.8691
15	-0.015 (-0.060;0.031)	0.3726	-0.015 (-0.060;0.031)	0.3726
16	0.015 (-0.032;0.061)	0.3755	0.015 (-0.032;0.061)	0.3755
17	0.001 (-0.044;0.046)	0.9277	0.001 (-0.044;0.046)	0.9277
18	-0.015 (-0.057;0.027)	0.3078	-0.015 (-0.057;0.027)	0.3078
19	0.012 (-0.032;0.057)	0.4336	0.012 (-0.032;0.057)	0.4336
20	0.002 (-0.045;0.049)	0.9143	0.002 (-0.045;0.049)	0.9143
21	0.001 (-0.044;0.046)	0.9517	0.001 (-0.044;0.046)	0.9517
22	0.000 (-0.043;0.044)	0.9791	0.000 (-0.043;0.044)	0.9791
23	-0.003 (-0.048;0.043)	0.8736	-0.003 (-0.048;0.043)	0.8736
24	0.002 (-0.044;0.048)	0.9080	0.002 (-0.044;0.048)	0.9080
25	-0.009 (-0.056;0.039)	0.6189	-0.009 (-0.056;0.039)	0.6189

The average pairwise correlation (of the cross-correlations) between the lags equaled 0.405 (PRx) and 0.160 (LAX) resulting in adjusted alpha-levels=0.0052 (PRx) and 0.0020 (LAX). Based on these adjusted alpha-levels, none of the correlations were significant.

LAX, low-resolution autoregulation index; PRx, pressure reactivity index; CC, cross-correlation; CI, confidence interval.

TABLE 6. SIGNIFICANCE LEVELS OF CONFOUNDER BASED DIFFERENCES IN MIXED MODEL CROSS-CORRELATIONS OF NOREPINEPHRINE INFUSION RATE, PROPOFOL INFUSION RATE, AND HEMOGLOBIN CONCENTRATION WITH PRX AND LAX

	LAX			PRx		
	Mixed model p value			Mixed model p value		
Noradrenaline	60-min bins	15-min bins	5-min bins	60-min bins	15-min bins	5-min bins
Age	1	0.96	0.78	0.87	1	0.98
Gender	0.98	0.81	0.99	0.98	0.99	1
Brain comorbidity	0.97	0.99	1	0.99	0.99	0.96
GCS	0.99	0.97	0.95	0.86	0.99	0.86
Cardiovascular risk	1	1	0.98	1	1	0.99
Pupil reactivity	0.99	1	0.99	0.98	1	1
Stroke vs. TBI	0.96	1	0.95	1	0.99	1
Propofol						
Age	0.99	1	0.88	0.99	0.98	0.83
Gender	0.99	0.98	0.93	0.99	0.99	0.98
Brain comorbidity	0.93	0.97	0.96	0.88	0.99	0.48
GCS	0.97	0.99	0.84	0.99	0.94	0.88
Cardiovascular risk	1	0.96	0.99	1	0.99	0.96
Pupil reactivity	1	0.93	0.99	0.99	0.99	0.99
Stroke vs. TBI	0.93	1	0.90	0.96	0.91	0.93
Hemoglobin						
Age	0.97	1	0.94	0.97	0.97	0.97
Gender	0.98	0.99	0.71	0.99	0.99	0.99
Brain comorbidity	1	1	0.92	0.99	1	1
GCS	0.99	0.94	0.99	0.97	0.97	0.98
Cardiovascular risk	0.99	1	0.79	1	1	1
Pupil reactivity	1	1	0.99	0.99	0.99	1
Stroke vs. TBI	0.93	0.99	0.73	0.94	0.94	0.94

LAX, low-resolution autoregulation index; PRx, pressure reactivity index; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

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