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Temporal characteristics of the Licox brain tissue oxygenation probe and implications for the future: new strategies for advanced neuromonitoring

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5) Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see below). Retrospective studies require a statement regarding IRB approval.

This study was performed as part of a retrospective Cleveland Clinic IRB (25-933), using previously acquired time-series PbtO2 and CPP patient data (from 2019-2020).

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Abstract (298 words)

Background: Neuromonitoring devices use correlation indices of patient physiology that may compare data with format differences between devices. Cerebrovascular autoregulation can be monitored using the Oxygen Reactivity Index (ORx), a correlation between partial pressure of brain tissue oxygenation ($PbtO_2$) and cerebral perfusion pressure (CPP). We examined temporal characteristics of data from a $PbtO_2$ probe used commonly in the neurological intensive care unit to monitor cerebrovascular autoregulation and applied these findings retrospectively to patient data to estimate their impact.

Methods: Partial pressure of oxygen (pO_2) data were collected using a Licox $PbtO_2$ probe (Integra Lifesciences, Princeton, NJ) and an Integra CMP monitor (Version 1). The probe was equilibrated to room air (pO_2 = 159 mmHg at sea level), followed by an instantaneous change in ambient pO_2 by immersion into a carbonated solution (~6 g CO_2/liter; pO_2 ~ 0 mmHg), followed by a return to room air.

A complex curve was fitted to the experimental data and used to transform CPP data recorded previously from a patient over one week to the same temporal characteristics as the $PbtO_2$ data. The raw and transformed CPP curves were then compared to the raw $PbtO_2$ data.

Results: Licox probe data followed a quadratic transitioning to a long time-constant asymptotic exponential curve after the probe was moved from low pO_2 to high pO_2. Compared to raw CPP data, transformed patient CPP data during a period of impaired cerebrovascular oxygen reactivity exhibited a much stronger correlation with $PbtO_2$.

Conclusions: We mitigated a significant temporal issue with $PbtO_2$ data and dramatically improved correlations between CPP and $PbtO_2$ during periods of impaired cerebrovascular oxygen reactivity. Our findings have profound implications for the calculation of ORx and may be applicable to other monitoring systems and data types to enhance the value of information routinely collected in clinical settings.

Keywords

cerebrovascular autoregulation, cerebral perfusion pressure, neuromonitoring, traumatic brain injury, brain tissue oxygenation, oxygen partial pressure

INTRODUCTION

Advanced neuromonitoring is employed for a variety of severe brain pathologies, including traumatic brain injury (TBI), a leading cause of death and disability. There were approximately 214,000 TBI-related hospitalizations in 2020 and 69,000 TBI-related deaths in 2021.[1] Advanced neuromonitoring has proven its worth in the intensive care of brain-injured patients but tremendous opportunity remains for advancement and refinement.

Advanced neuromonitoring involves the collection and display of simultaneous streams of high frequency, high fidelity data (e.g., mean arterial pressure [MAP], intracranial pressure [ICP]), which scientists and clinicians compare and correlate as valid indices of patient physiology. However, the neuromonitoring devices may not produce instantaneous measurements of current patient physiology. For example, blood pressure data from the General Electric Carescape patient monitor (GE Healthcare, Chicago, IL) used by Cleveland Clinic in 2019 and 2020 was recorded as time-averaged data every 5 seconds. The same data collected today from a Philips Intellivue patient monitor (Philips, Cambridge, MA) is recoded as time-averaged data over 1 second. While the data provided by each of these devices is reliable, indices of patient physiology that are dependent on comparing data from different devices may not be valid if the data has been recorded with different temporal bases. In addition, as companies improve their monitors and probes via hardware and/or software upgrades, the data format (e.g., data fidelity or time-averaging scale) may change year-to-year for the same device. Understanding the effects of the differences in how the data is recorded is critical if valid interpretations are to be obtained when analyzing disparate data streams.

In this study, we examined the response of a brain tissue oxygenation ($PbtO_2$) monitor used commonly in the neuro-ICU to changes in the environmental partial pressure of oxygen (pO_2) to determine its temporal characteristics and how these characteristics impact the $PbtO_2$ data stream that caregivers use to treat patients. In addition, we applied these findings retrospectively to patient data to illustrate the importance of this effect, which has not been previously reported. In this paper, we show that fully understanding the mechanisms of these temporal characteristics is critical if appropriate comparisons are to be made between the raw $PbtO_2$ data stream and other data streams (which may have their own temporal bases/responses).

Of particular interest here is how the understanding and application of these temporal effects relates to the concept of cerebral autoregulation as it pertains to $PbtO_2$ and Cerebral Perfusion Pressure (CPP) (CPP = MAP

minus ICP). When a patient's cerebrovascular oxygen reactivity index (ORx) is impaired, the $PbtO_2$ tends to increase and decrease with CPP, and, when the ORx is intact, the $PbtO_2$ is not dependent on CPP. This means that an improved understanding of the temporal effects of how the data is recorded might improve an analysis of periods of time when ORx is impaired, because a true comparison of the corresponding data streams would be expected to improve the strength of the relationship. Meanwhile, when the ORx is intact, the dependency of $PbtO_2$ on CPP is not expected to strengthen because $PbtO_2$ is not dependent on CPP.

METHODS

Laboratory pO_2 data was collected using a common $PbtO_2$ probe (Licox, Integra Lifesciences, Princeton, NJ) and an Integra Licox CMP (Catheter MicroProbe) monitor (original version). This Licox CMP monitor was used on patients at Cleveland Clinic in 2019 and 2020.

The Licox $PbtO_2$ probe was equilibrated to room air (pO_2 = 159 mmHg at sea level). Then, an instantaneous change was made to the pO_2 by immersing the probe into a carbonated solution (~6 g CO_2/liter)[2] with a much lower pO_2 (~0 mmHg) (Dr. Pepper; Keurig Dr Pepper, Plano, TX) due to the presence of dissolved CO_2. Carbonated beverages have been used previously in other studies, with no effects noted by added colors, corn syrup, or other ingredients.[2-4] Once the pO_2 value stabilized, a second instantaneous change was made to the pO_2 by returning the probe to room air. Data collection continued until the pO_2 had stabilized again, and this measurement was then repeated several times, and the experimental data was studied.

In our experiment, the pO_2 data was recorded every 2 seconds, and the resulting data was averaged over three trials. We then accurately fitted a complex curve to the resulting data. This curve fit was then used to implement a method to transform a data stream from one which does not contain the temporal characteristics of the Licox probe, into one which does contain the temporal characteristics of the Licox probe.

We applied this data transformation to patient raw CPP data obtained at Cleveland Clinic on a patient from 2020. Transformed CPP data with the same temporal characteristics as the recorded $PbtO_2$ data were compared before data transformation/after data transformation CPP traces to the patient's $PbtO_2$ trace. We chose an example region where the patient's ORx was believed to be impaired (which meant that $PbtO_2$ was correlated with CPP) and also an example region where the ORx was believed to be intact (when the $PbtO_2$ was not dependent on CPP).

This study was performed as part of a retrospective Cleveland Clinic IRB (25-933), using previously acquired time-series $PbtO_2$ and CPP patient data (from 2019-2020). The CPP data was acquired via a GE Carescape monitor (GE Healthcare, Chicago, IL) which fed a Moberg Component Neuromonitoring System (CNS) (Natus Medical Inc., Middleton, WI), which recorded the mean time-averaged data at 0.2 Hz. The $PbtO_2$ data was acquired via a Licox CMP Monitor and associated Licox $PbtO_2$ probe, which also fed a Moberg CNS that recorded the data at 0.5 Hz.

RESULTS

Figure 1 shows the known steady-state (blue curve) in our pO_2 experiment which cannot be reproduced experimentally because of the temporal characteristics of the probe. The pO_2 data was recorded every 2 seconds, and the resulting data (green) was averaged over three trials. The measured pO_2 data trace exhibits a multi-minute exponential time-constant because it takes several minutes for the pO_2 data to asymptotically stabilize.[5] An exponential curve does not fit the data well during the initial period of the pO_2 transition. Instead, a quadratic function that smoothly transitions into an asymptotic exponential was used as a basis for modeling the $PbtO_2$ probe's response. The red curve is the result of choosing appropriate curve fit parameters which transformed the blue steady-state curve into a curve which closely matched the green experimental curve.

As part of the curve fit, the exponential time constant was determined to be approximately 140 seconds, indicating that the probe response rises to 63% of its final asymptotic value after almost two and a half minutes. If a caregiver is interested in second-to-second or even minute-to-minute $PbtO_2$ patient monitor values, this multi-minute time constant is significant.

This curve fit was then used to implement a method to transform a data stream from one which does not contain the temporal characteristics of the Licox probe, into one which does contain the temporal characteristics of the Licox probe. Note that the asymptotic nature of the exponential means that the curve fit extends to infinity. We used an industry standard ~6 half-length times (~15 minutes of data in this case) to be able to accurately and practically transform the data. The reader will note that our data transformation works very well, because there is an excellent match between the experimental data we measured (green) and the modeled data (red) which was derived from the curve fit. We then applied this data transformation to patient

raw CPP data obtained at Cleveland Clinic in 2020, to obtain CPP data with the same temporal characteristics as the $PbtO_2$ data, and we compared the before/after CPP traces to the $PbtO_2$ trace.

Figure 2 shows a heatmap of approximately one week of $PbtO_2$ vs CPP data for our patient. You will see that when the CPP is below approximately 75 mmHg, the $PbtO_2$ vs CPP part of the graph has a positive gradient, which means the $PbtO_2$ appears to be dependent on the CPP, and this positive correlation implies that the ORx is impaired. Data from this part of the graph was used to illustrate what happens when the $PbtO_2$ probe's temporal effects are taken into account for a region when the ORx is impaired. You will also see that when the CPP is above approximately 80 mmHg, the $PbtO_2$ vs CPP part of the graph is mostly flat, which means the $PbtO_2$ appears to not be dependent on the CPP, and data from this part of the graph was used to illustrate what happens when the $PbtO_2$ probe's temporal effects are taken into account for a region when the ORx was intact.

Impaired Oxygen Reactivity

Figure 3D is an extension of the 1-hour graph to 5 hours. You will see that the brain tissue oxygenation autoregulation status appears to be completely impaired most of the time (because the curves match very well), but there are some instances when $PbtO_2$ is not as dependent on CPP.

Figure 4 depicts a patient recording over 9 hours. In Figure 4A, the CPP data (blue) and the $PbtO_2$ probe data (green) are shown during a period when the $PbtO_2$ vs CPP curve is roughly flat in Figure 2B and the cerebrovascular oxygen reactivity is considered intact. $PbtO_2$ is not correlated with CPP over most of this period. Note that at approximately hour 7, when the CPP temporarily falls to below 50 mmHg, the $PbtO_2$ becomes temporarily strongly correlated to CPP, suggesting that the cerebrovascular oxygen reactivity is no longer intact. CPP then returns to values above 80 mmHg and intact cerebrovascular oxygen reactivity is reestablished. There are three upward $PbtO_2$ spikes at hours ~2.5, ~3.8 and ~5.0 – these are believed to be suctioning events where the ventilator's fraction of inspired oxygen (FiO_2) is turned up to 100% for one minute at a time. Figure 4B is the same plot except modeled CPP data is shown (red). Again, $PbtO_2$ is not well-correlated with CPP over most of this period, and the red and green curves do not match (except when the CPP temporarily fell below 50 mmHg).

DISCUSSION

In this study, we investigated the response of the Licox $PbtO_2$ probe to an instantaneous change in $PbtO_2$ in a lab setting (Fig. 1). Our results show the Licox probe's response exhibits a complex time-average (a quadratic curve transitioning to an asymptotic exponential curve) over several minutes.

We modeled this response (Fig. 1) and applied the model to patient CPP data (Fig. 1) to compare the resulting data to $PbtO_2$ data which has these temporal characteristics inherently built-in. Note that it is not known how uniform the Licox probe temporal characteristics are to one another, which could be regarded as a source of error when we apply a recent probe's response to patient data which was acquired 6 years ago. Based on the $PbtO_2$-CPP heatmap (Fig. 2), we examined a region of data (low CPP) when the patient was believed to have impaired ORx, and also a data region (high CPP) when the patient was believed to have intact ORx.

In the impaired autoregulation lower CPP data region, we showed the overlaid original CPP and $PbtO_2$ traces (Fig. 3B~1 hour), followed by the overlaid modeled CPP and $PbtO_2$ traces (Fig. 3C). The former figure (Fig. 3B) can be regarded as being somewhat invalid for comparison purposes on time scales of less than 15 minutes because the two data traces do not contain the same temporal characteristics (the temporal characteristics of the Licox $PbtO_2$ probe last of the order ~15 minutes). The latter figure (Fig. 3C) represents a valid comparison because each overlaid data trace now contains the same temporal characteristics.

We also extended the overlay of the modeled CPP and $PbtO_2$ data traces in figure 10 from ~1 hour to ~5 hours (Fig. 3D). In Figure 3D we can see there are some regions in this lower CPP region where the near-perfect match (and dependency between CPP and $PbtO_2$) is temporarily lost, before it reestablishes again. We believe it is quite likely that this is the result of nursing interventions such as ventilator adjustments. Understanding deviations such as these will be the focus of future studies.

In the intact ORx higher CPP data region, we showed the overlaid CPP and $PbtO_2$ traces using both the raw CPP (Fig. 4A) and the transformed CPP (Fig. 4B). Since the $PbtO_2$ is not believed to be dependent on CPP in this region, the relationship between the two variables is clearly not strong in either graph. Of note, a large ICP spike at hour 7 resulted in a large CPP drop, down to a CPP level where we believe ORx is impaired. As expected, when the CPP dropped, a dependency with $PbtO_2$ was temporarily established, before the CPP

returned to pre ICP-spike levels. We assume that a nursing intervention, or perhaps some physiologic transient, caused the ICP spike.

The match between the modeled CPP and $PbtO_2$ curves in Figure 3C is somewhat remarkable. We expected the match to improve when the temporal characteristics model was implemented, but we did not expect the two curves to be synchronized and correlated to this degree. The degree of match has several implications, notably:

1) Our temporal characteristics implementation should be thought of as a data correction. The remarkable resulting match between CPP and $PbtO_2$ means that when this patient has impaired ORx, the two CPP and $PbtO_2$ data traces are almost perfectly synchronized.
2) The remarkable match means that it is not possible to make any other significant data correction which would improve the match. This means that no other potentially unknown significant data corrections exist. For example, any significant difference in the temporal characteristics for our measured-in-the-lab Licox probe and that for our patient from 6 years ago cannot exist.
3) For the first time, valid comparisons of CPP and $PbtO_2$ can now be made on short timescales. This has important implications for the calculation of ORx, the correlation between CPP and $PbtO_2$.
4) A valid ORx could have important clinical implications for the clinical utility of $PbtO_2$. An improved and valid ORx could allow for a quick and accurate assessment of the status of brain tissue oxygenation cerebrovascular autoregulation. This is for future studies.
5) The vastly improved timing precision of the calculation suggests that it may be possible in the future to identify when ORx changes occur at time-scales of seconds, which changes are beneficial, and what clinical actions may affect ORx. This is for future studies.

CONCLUSIONS

In this study, we identified previously unreported critical temporal characteristics in Licox $PbtO_2$ data which affect any attempt to compare $PbtO_2$ to other data streams on short (~less than an hour) timescales. We then took these temporal characteristics into account in a patient whose data was acquired several years ago, a patient which appeared to have impaired ORx at low CPP, and intact ORx at high CPP. In a low CPP region, if we took these temporal characteristics into account, we found regions of data where there was now a near

perfect, synchronized match between the transformed CPP and the raw $PbtO_2$. In a high CPP region where we believe the ORx was intact, this was not the case. Even then, within this high CPP region of data, there was a temporary large ICP spike which drove the CPP down to the impaired ORx CPP-level, and a near perfect, synchronized match between CPP and $PbtO_2$ was temporarily established, before CPP returned to the intact ORx level. The identification and implementation of the Licox probe's temporal characteristics has profound implications for the calculation of ORx and future brain tissue oxygen autoregulation assessments, and possible clinical use of these assessments.

While our findings are limited to $PbtO_2$ data obtained with specific equipment, our findings may be applicable to other monitoring systems and data types to enhance the value of information routinely collected in clinical settings.

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Figure Legends

Figure 1: Modeling the $P_{bt}O_2$ probe response to an instantaneous change in pO_2

Plots depicting theoretical instantaneous data (blue) (for comparison), *$P_{bt}O_2$ experimental data (green) recorded by the monitor after the instantaneous change in pO_2*, and the modeled response (red) to the theorized instantaneous change in the pO_2 data.

Figure 2. Heatmap of PbtO2 vs CPP

The underlying heatmap uses the colors of the rainbow to show the data which was recorded over approximately one week. The black crosses represent the PbtO2 average and its standard deviation for each 5mmHg slice of CPP.

Figure 3. Example of Impaired Cerebrovascular Oxygen Reactivity

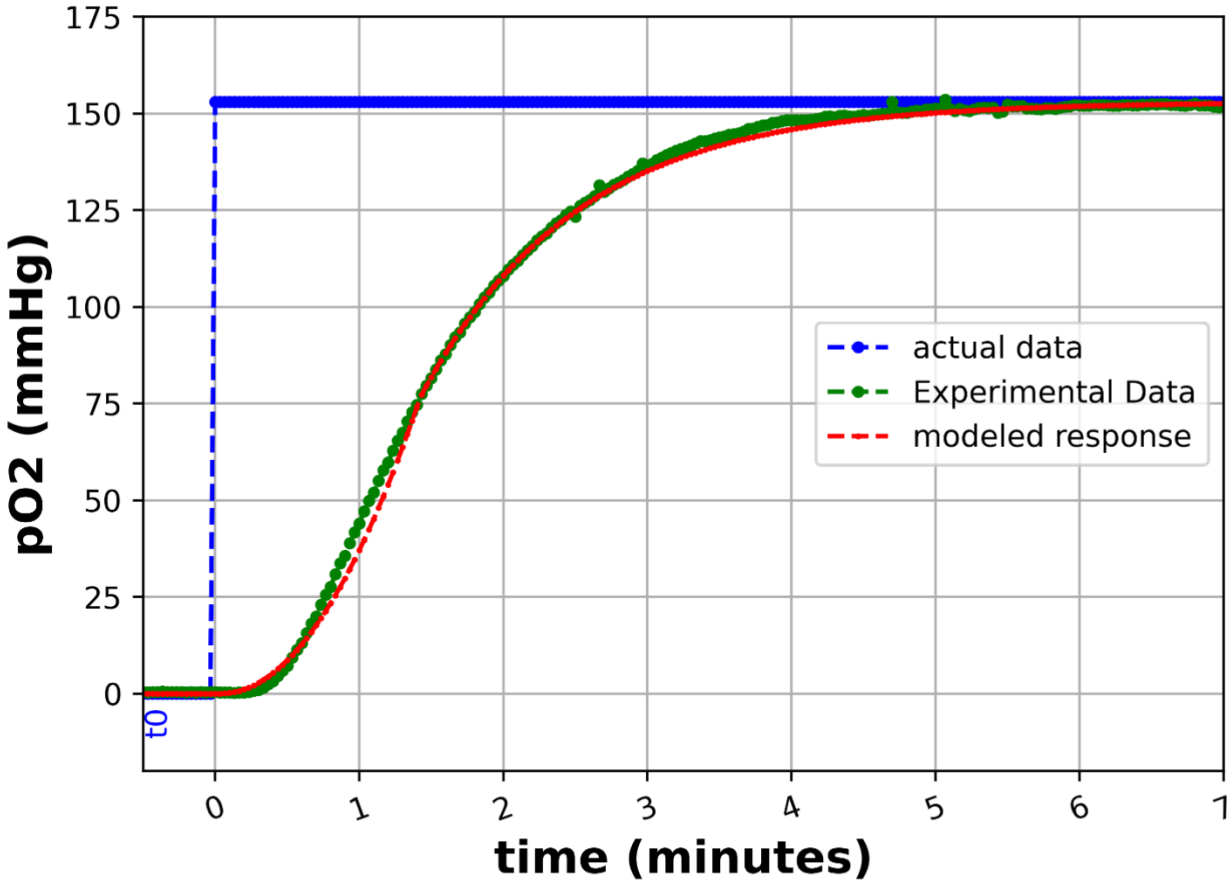
Original and modeled CPP data and $PbtO_2$ probe data produced from a TBI patient data when the cerebrovascular oxygen reactivity index was impaired. A. 50 minutes of CPP data (blue) and overlaid $PbtO_2$ data (green) recorded from a TBI patient. B. The modeled CPP data (red) (using the quadratic and exponential curve fit) and raw CPP data (blue). C. Modeled CPP data (same as in B, in red) and $PbtO_2$ probe data (green) show extremely close correlation, indicating poor cerebrovascular oxygen reactivity. D. Modeled CPP data and $PbtO_2$ probe data in the same patient over an expanded 5-hour period. Periods of close correlation and poor correlation correspond to impaired and intact cerebrovascular oxygen reactivity, respectively.

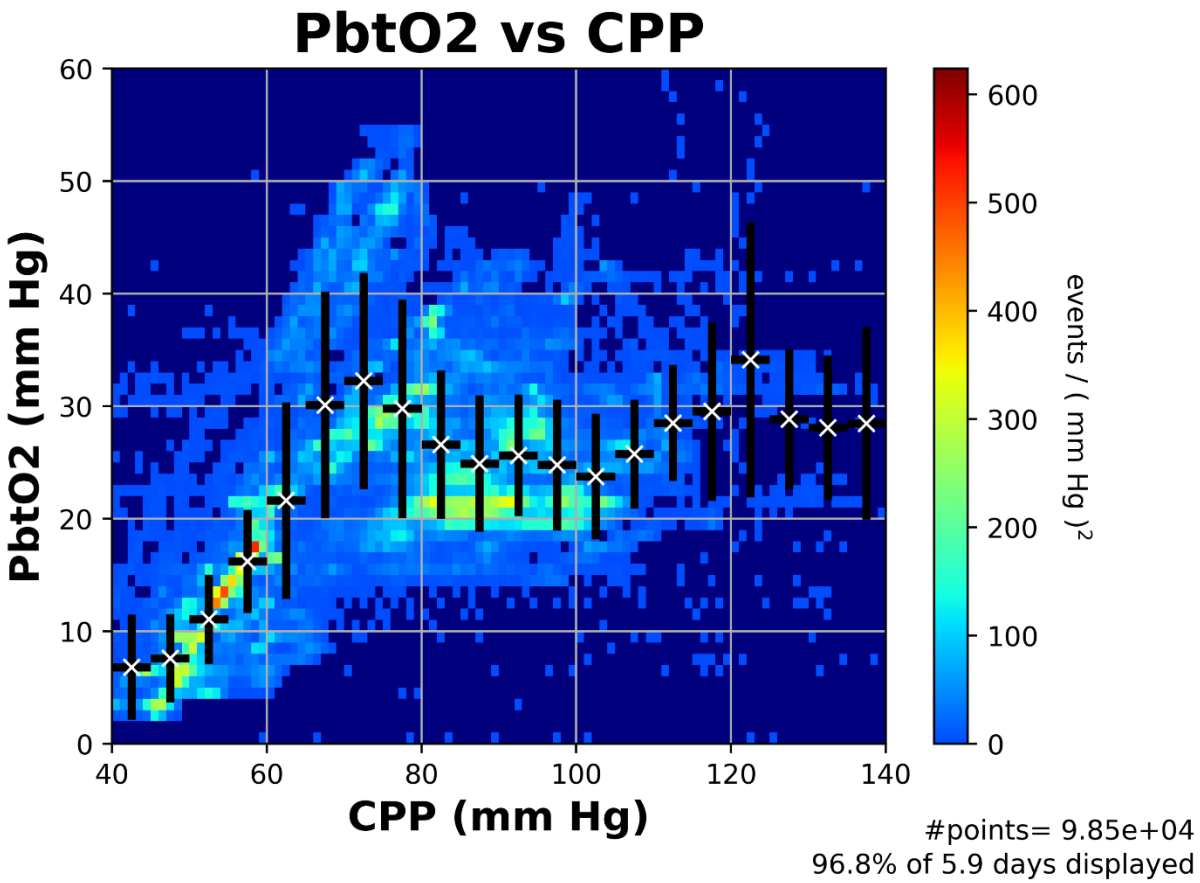
Figure 4. Modeled CPP data and PbtO2 probe data recorded from a TBI patient over 9 hours during a period when cerebrovascular oxygen reactivity was intact.

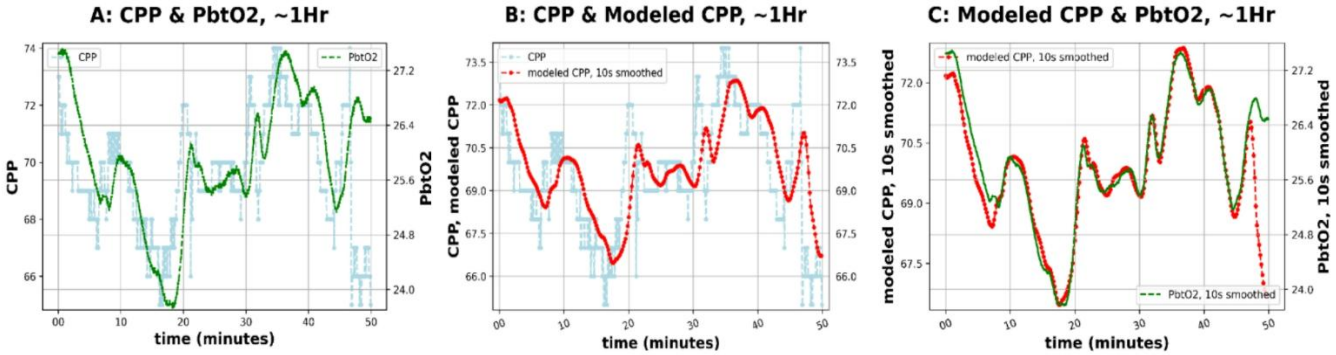
A. ~8 hours of overlaid raw CPP (blue) and PbtO2 (green) data. At the higher CPP values the correlation is clearly weak.

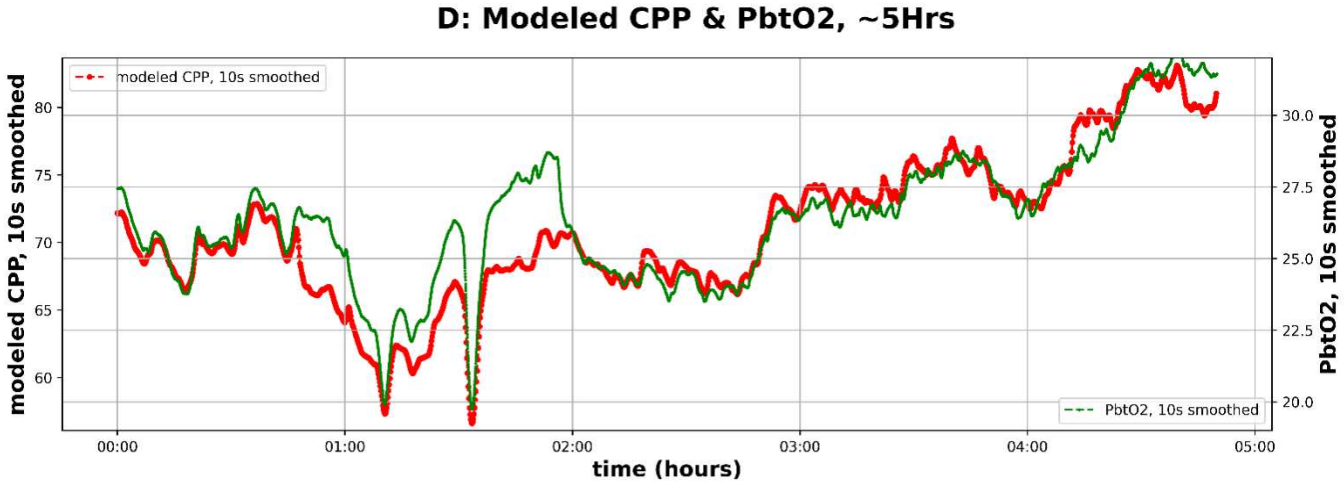
B. Modeled CPP data (red) and PbtO2 probe data (green) over the same period as in A. The correlation of the two traces is weak, indicating intact cerebrovascular oxygen reactivity.

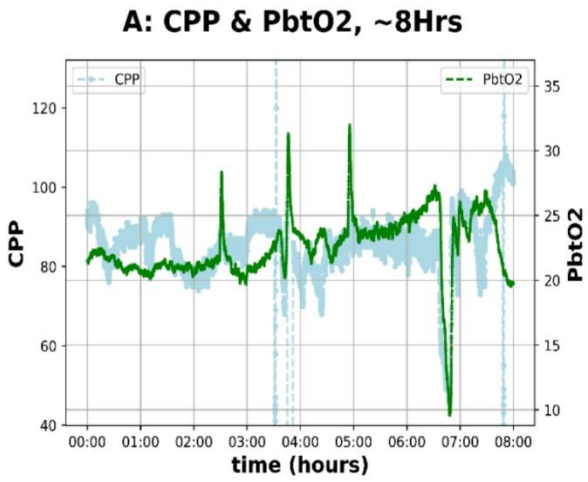
Actual, Experimental & Modeled Data

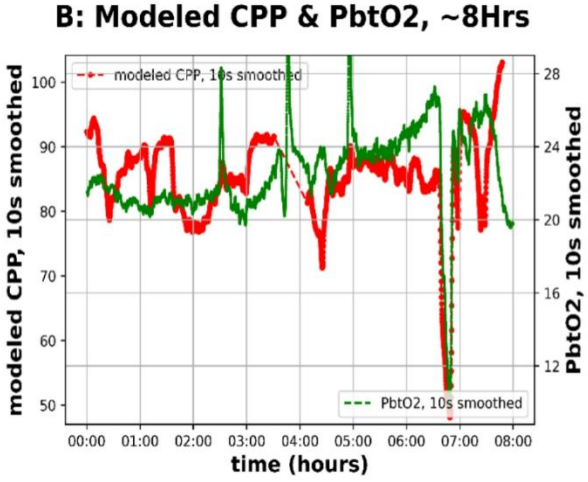



PbtO2 vs CPP
PbtO2 (mm Hg)
CPP (mm Hg)
events / (mm Hg)²
#points= 9.85e+04
96.8% of 5.9 days displayed


A: CPP & PbtO2, ~1Hr
CPP
PbtO2
time (minutes)
B: CPP & Modeled CPP, ~1Hr
CPP
modeled CPP, 10s smoothed
CPP, modeled CPP
time (minutes)
C: Modeled CPP & PbtO2, ~1Hr
modeled CPP, 10s smoothed
PbtO2, 10s smoothed
modeled CPP, 10s smoothed
PbtO2, 10s smoothed
time (minutes)


D: Modeled CPP & PbtO2, ~5Hrs
modeled CPP, 10s smoothed
PbtO2, 10s smoothed
modeled CPP, 10s smoothed
PbtO2, 10s smoothed
time (hours)


A: CPP & PbtO2, ~8Hrs
CPP
PbtO2
time (hours)


B: Modeled CPP & PbtO2, ~8Hrs
modeled CPP, 10s smoothed
PbtO2, 10s smoothed
time (hours)