Accepted manuscript

Statistical Signal Properties of the Pressure-Reactivity Index (PRx)

Sophie Kelly[1], Steven M Bishop[2], Ari Ercole[2*]

[1]Clinical School, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

[2]Department of Anaesthesia, University of Cambridge, Cambridge, UK

[*]Corresponding author

Mailing address for correspondence:

University of Cambridge Division of Anaesthesia

Box 93 Addenbrooke's Hospital

Hills Road

Cambridge CB2 0QQ

UK

Email: ae105@cam.ac.uk

Keywords: Cerebral autoregulation; Traumatic brain injury; PRx; Statistical properties; Bias; Fisher transform.

Abstract

Objectives: The pressure-reactivity index (PRx) is defined in terms of the moving correlation coefficient between intracranial pressure (ICP) and mean arterial pressure (MAP) and is a measure of cerebral autoregulation ability. Plots of PRx against cerebral perfusion pressure (CPP) show U-shaped behaviour- the minimum reflecting optimal cerebral autoregulation (CPPopt). However U-shaped behaviour may also occur by chance. To date there has been no evaluation of the statistical properties of these signals.

Materials and Methods: We simulated PRx/CPP distributions using synthetic ICP and MAP signals from Gaussian noise with known cross-correlation. We calculated the statistical distribution of extrema in the PRx/CPP relationship.

Results: The calculation of PRx on random data is statistically biased to show a U-shaped behaviour when the signals are positively cross-correlated (equivalent to PRx>0). For PRx<0, the bias is towards inverse U-shaped behaviour. We demonstrate that this bias is eliminated by Fisher transforming the PRx data before CPPopt analysis.

Conclusions: Cross-correlated signals are biased to show a U-shaped distribution. A "CPPopt-like" behaviour will be observed more often than not even from random ICP and MAP signals that do not exhibit autoregulation unless PRx is Fisher transformed. Care must be taken in interpreting CPPopt in terms of physiology calculated from untransformed data.

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability[1]. Intracranial pressure (ICP) and Cerebral Perfusion Pressure (CPP) monitoring is fundamental to the intensive care of patients with TBI in order to prevent secondary brain injury. Current guidelines for the management of severe TBI recommend maintaining ICP below 22mmHg and CPP between 60-70mmHg[2]. However TBI is highly heterogeneous and fixed thresholds do not account for this. Therapies to sustain cerebral perfusion can also be associated with harm. In particular, excessive CPP may exceed autoregulatory capacity increasing intracranial blood and oedema volumes.

Management of patients based on the state of their cerebral autoregulation has been suggested. Cerebral autoregulation may remain intact over a narrowed range of CPP or be abolished after TBI[3][4]. It has been suggested that such individualized CPP therapy is more appropriate[3][5].

One attractive method for quasi-continuous autoregulation assessment is the cerebrovascular pressure reactivity (PRx). PRx is defined as the moving Pearson correlation coefficient between 30 consecutive 10second averaged values (=5minute window) of mean arterial pressure (MAP) and ICP. Averaging suppresses pulse and respiratory transients[5]. PRx can provide a useful approximation of the state of autoregulation validated against both TCD and PET studies[6][7]. Software is available for the continuous determination of PRx at the bedside[4].

Disturbed pressure reactivity leads to a more positive PRx and is of interest. PRx has been shown to be a more reliable predictor of mortality than ICP thresholds[6][8]. Plotting mean PRx over a moving 4hr window against 5mmHg bins of CPP reveals a U-shaped relationship[4]. The point for which PRx is the lowest is determined by curve fitting. This point defines the optimal CPP (CPPopt), representing the CPP for which autoregulation is best preserved.

CPPopt appears to be clinically significant. Retrospective observational studies have demonstrated patients managed away from CPPopt were associated with worse clinical outcome[3]. Recent data suggested excess mortality for patients managed below CPPopt and

excess severe disability for those managed above[4]. True causality is not yet established; nevertheless the concept of autoregulation-personalised treatment is attractive. The technique is technically feasible. Whilst CPPopt can be identified approximately 70% of the time[4], improved curve fitting heuristics and novel visualization techniques can aid appreciation of trends and overcome gaps in the data[9].

PRx is a derived parameter obtained from relatively complex calculations. The statistical properties of PRx measurements are not immediately obvious, but it is important to be sure that there are no biases affecting subsequent analyses. Successive PRx / CPP measurements form a distribution. However if MAP and ICP are correlated/anticorrelated, this distribution moves because mean PRx increases/decreases. Because PRx is limited to values between -1 and +1 the distribution becomes asymmetrical because of a ceiling effect and this may introduce spurious apparent U-shaped relationships between PRx and CPP.

Furthermore, the distribution of PRx with CPP depends on the statistical signal properties of the MAP / ICP waveforms. Statistical fluctuations in these signals can have a complex long-range autocorrelation and it is known that the spectral properties (or equivalently degree of self-similarity/signal complexity) of physiological recordings reflects the underlying homeostatic burden/reserve. This can vary with physiological stress or manipulation[10] and so may vary with time and can be highly prognostic[11]. This signal autocorrelation further distorts the distribution of PRx / CPP measurements and could be another source of bias.

A common (but not universal) heuristic is to first Fisher transform PRx to “normalize” its distribution before assessing for a CPPopt minimum. However the use of the Fisher transformation to remove the ceiling effect of correlated data has not been investigated. This simulation investigates whether the Fisher transformation is necessary to remove the distribution bias of the data and to produce a curve from which a meaningful CPPopt can be calculated.

In this study, we present Monte Carlo simulations characterising the statistical properties of PRx as a function of CPP looking for potential sources of U-shaped bias that may confound / distort any true underlying autoregulation behaviour. In particular, we examine the effect of different levels of correlation between MAP and ICP. Furthermore, we examine the influence

of autocorrelation on bias. Finally, we study the effect of Fisher transformation on any such bias.

Materials and Methods

MAP and ICP signals were synthesised from white noise. A degree of first-order lagged autocorrelation was then introduced into both MAP and ICP signals according to Equation 1.

$$y(t) \longmapsto (1-\phi).y(t) + \phi.y(t-1)$$

(Equation 1)

The parameter ϕ was tuneable simulating different degrees of memory in the signal varying between -1 (antipersistent) and +1 (persistent).

Correlation was subsequently added to ICP according to Equation 2.

$$ICP \longmapsto \rho.MAP + \sqrt{1-\rho^2}.ICP$$

(Equation 2)

Thus ρ represents an underlying correlation between the two signals. Crucially, this correlation does not imply any autoregulation; ρ is not a function of CPP. Thus, whilst we expect PRx to be non-zero for non-zero ρ, there should be no U-shaped behaviour in the PRx/CPP relationship if the CPPopt calculation is unbiased.

In order to test this null hypothesis, we calculated PRx as the moving window Pearson correlation coefficient from our synthetic signals analogously with clinical practice. PRx values so obtained were evenly binned against mean CPP for the window period and a quadratic fit performed to this mean PRx/CPP data (Equation 3 where *U*, *V* and *W* are fitted parameters).

$$PRx = U.CPP^2 + V.CPP + W$$

(Equation 3)

We extracted the quadratic parameter, U, from the fit as a measure of the curvature of the PRx/CPP relationship with 1000-fold repetition to obtain a mean/standard deviation. This was repeated for different values of $\rho \in [-1, +1]$ and $\phi \in [-1, +1]$.

To examine the effect of the Fisher transform on the statistical properties of PRx, we additionally transformed the calculated PRx values before our quadratic fit using Equation 4.

$$PRx \mapsto \frac{1}{2}\ln\left(\frac{1+PRx}{1-PRx}\right)$$

(Equation 4)

Calculations were carried out using MATLAB Release 2015b (The MathWorks Inc, Natick, Massachusetts, United States) on Linux. Code was optimised to run in parallel on 16x3.3GHz Intel Xeon cores with a total of 32GB RAM, (typical runtime ~23hrs).

Results

Figure 1 shows how the quadratic parameter, *U*, varies with correlation parameter ρ for white noise ICP / MAP ($\phi = 0$). For $\rho = 0$, *U* is close to zero. For increasing positive ρ (ICP and MAP are correlated) *U* becomes positive and non-zero, demonstrating a U-shaped tendency to the PRx / CPP relationship. Since the ICP and MAP signals are simulated from correlated noise only, without any autoregulation behaviour, this represents a U-shaped bias.

For ρ below zero, *U* is negative/non-zero meaning that there is, on average, an inverted U-shaped bias for situations where PRx is negative. For $\rho = \pm 1$ the parameter *U* becomes zero since PRx is exactly ± 1 for all CPP.

Figure 2 shows analogous data to Figure 1, but in this case, the simulated PRx values were first Fisher transformed before fitting a quadratic curve against CPP. Within errors, the relationship of *U* against ρ is seen to be abolished.

Figure 3 shows the effect of changing the degree of autocorrelation ϕ, for a fixed $\rho = 0.6$ (chosen so that *U* is approximately maximal in figure 1). The U-shaped bias is seen to reduce

slightly with increasing positive autocorrelation. For negative autocorrelation, U is found to increase dramatically.

Discussion

Our simulations demonstrate that PRx is statistically biased to display U-shaped behaviour, centred on the mean value of CPP, in the absence of autoregulation. The direction and magnitude of this U-shape depends on the degree and sign of the cross-correlation between MAP and ICP. This consideration is important: For positively correlated signals (such as occurs with a generally pressure-passive ICP/MAP relationship), this could distort the true autoregulatory minimum or even introduce a spurious CPPopt. For negatively correlated ICP/MAP (as might be expected on average for an autoregulating system), the U-shape bias is inverted which may serve to distort or abolish the true autoregulatory minimum.

In Figure 1, it is noteworthy that the relationship is not symmetrical $\rho = \pm 1$, the maximum U being greater than the minimum. This results from inherent correlation between ICP and CPP since CPP=MAP-ICP. Repeating the simulations for the ICP/MAP relationship (as opposed to the clinically important case of ICP/CPP) removes the asymmetry.

Conclusions

We show that PRx/CPP is statistically biased and this applies to any similar parameter from two correlated time series). Furthermore this bias is exacerbated if the signals are autocorrelated with antipersistence. Since changes in autocorrelation and signal complexity are known to occur in the face of physiological perturbation, the U-shaped bias is therefore expected to be dependent on physiological stress. We recommend that the Fisher transform is always used before analysing such data. This rescales the Pearson correlation coefficient in such a way as to normalise its distribution.

Acknowledgements

The authors would like to acknowledge M Czosnyka and P Smielewski for support and useful discussions.

References

[1] Maas AI, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, Hill S, Legrand V, Sorgner A; CENTER-TBI Participants and Investigators. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery. 2015;76(1):67-80.

[2] Brain Trauma Foundation Guidelines, 4th Ed. 2016. https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf. Accessed 31 October 2016

[3] Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit. Care Med. 2002;30, 733–8.

[4] Aries MJH, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, Hutchinson PJ, Brady KM, Menon DK, Pickard JD, Smielewski P. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012;40, 2456–63.

[5] Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: Facts, myths, and missing links. Neurocritical Care 2009;10, 373–86.

[6] Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997;41, 11–19.

[7] Steiner LA, Coles JP, Johnston AJ, Chatfield DA, Smielewski P, Fryer TD, Aigbirhio FI, Clark JC, Pickard JD, Menon DK, Czosnyka M. Assessment of cerebrovascular autoregulation in head-injured patients: A validation study. Stroke 2003;34, 2404–9.

[8] Lazaridis C, DeSantis SM, Smielewski P, Menon DK, Hutchinson P, Pickard JD, Czosnyka M. Patient-specific thresholds of intracranial pressure in severe traumatic brain injury. J. Neurosurg. 2014;120, 893–900.

[9] Aries MJ, Wesselink R, Elting JW, Donnelly J, Czosnyka M, Ercole A, Maurits NM, Smielewski P. Enhanced Visualization of Optimal Cerebral Perfusion Pressure Over Time to Support Clinical Decision Making. Crit Care Med. 2016;44(10):e996-9.

[10] Bishop SM, Yarham SI, Navapurkar VU, Menon DK, Ercole A. Multifractal analysis of hemodynamic behavior: intraoperative instability and its pharmacological manipulation. Anesthesiology. 2012;117(4):810-21.
[11] Gao L, Smielewski P, Czosnyka M, Ercole A. Cerebrovascular Signal Complexity Six Hours After Intensive Care Unit Admission Correlates with Outcome After Severe Traumatic Brain Injury. J Neurotrauma. 2016. doi:10.1089/neu.2015.4228.

Figure Captions

Figure 1. Plot of fitted quadratic parameter U (arbitrary units x 10^{-5}) against ICP/MAP correlation strength ρ. Positive values of *U* suggest a U-shaped tendency between ICP and CPP, negative values represent an inverted U-shape.

Figure 2. Equivalent plot to Figure 1 for Fisher transformed PRx. Unlike the untransformed case, there is no longer a demonstrable U-shape bias for any value of ρ.

Figure 3. Parameter *U* (logarithmic scale) as a function of autocorrelation ϕ for simulated ICP/MAP data with fixed $\rho = 0.6$. For zero autocorrelation, this corresponds to a value of *U* near the maximum seen in Figure 1. The bias is reduced slightly for increasing positive autocorrelation (persistence). However with negative autocorrelation (anti-persistent data), the U-shaped bias increases dramatically.

Figure 1

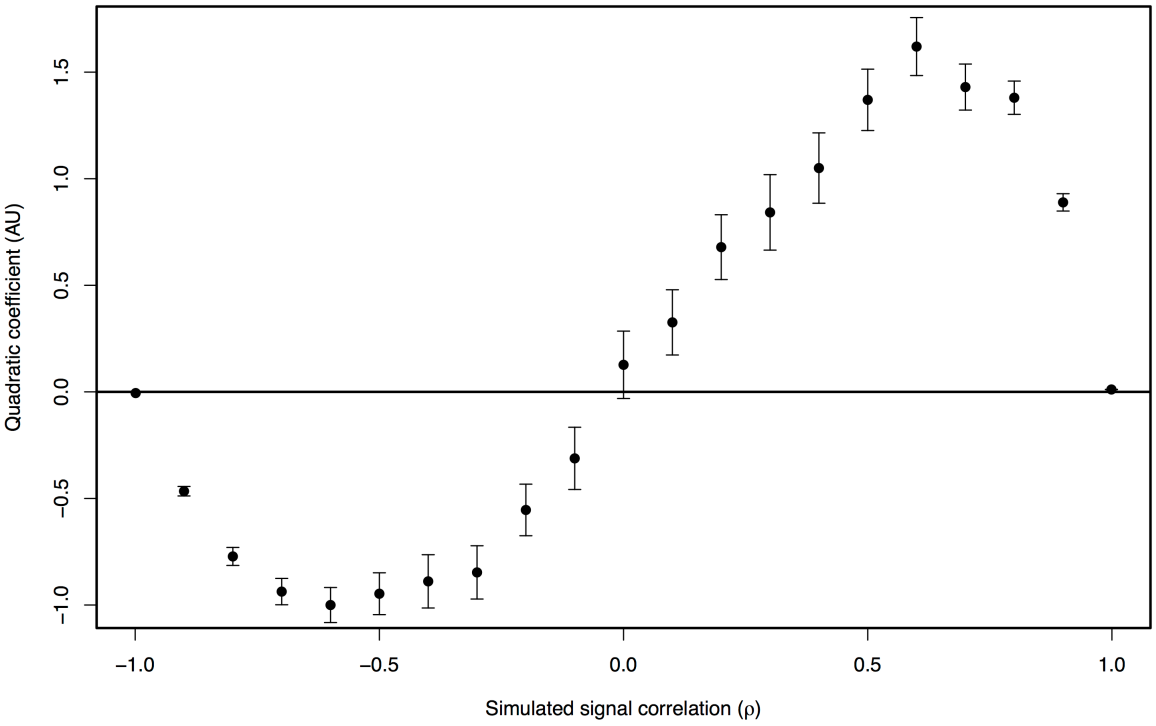

Quadratic coefficient (AU)
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.0
−0.5
0.0
0.5
1.0
Simulated signal correlation (ρ)

Figure 2

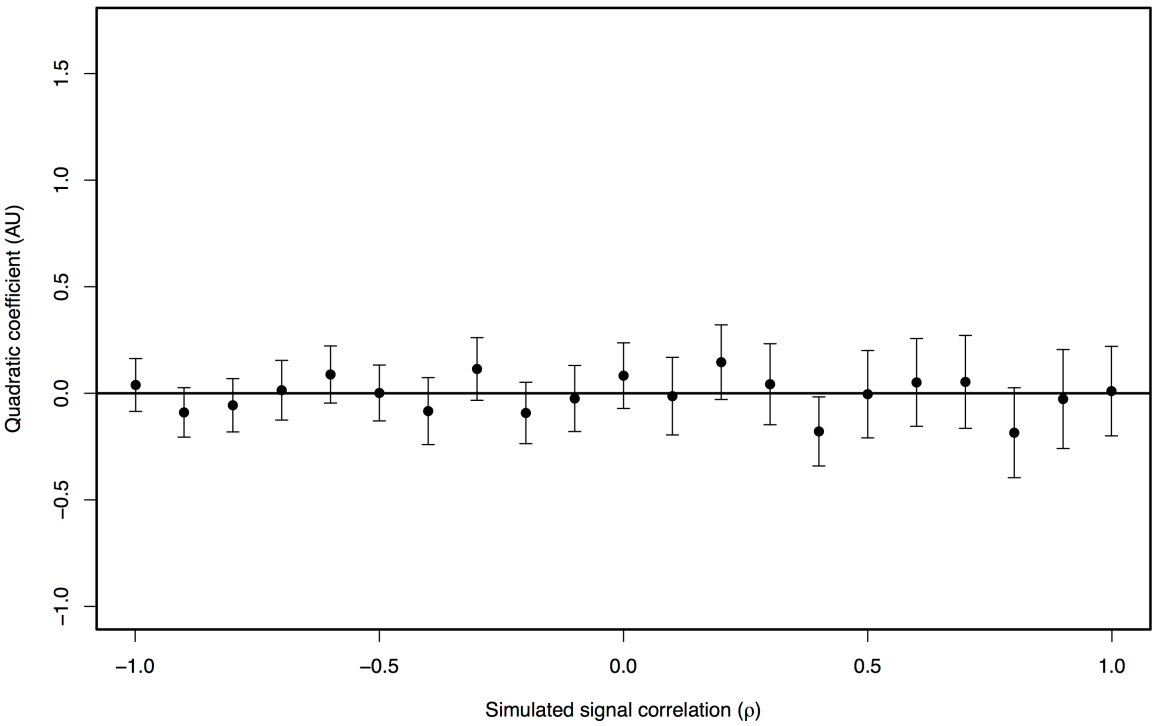
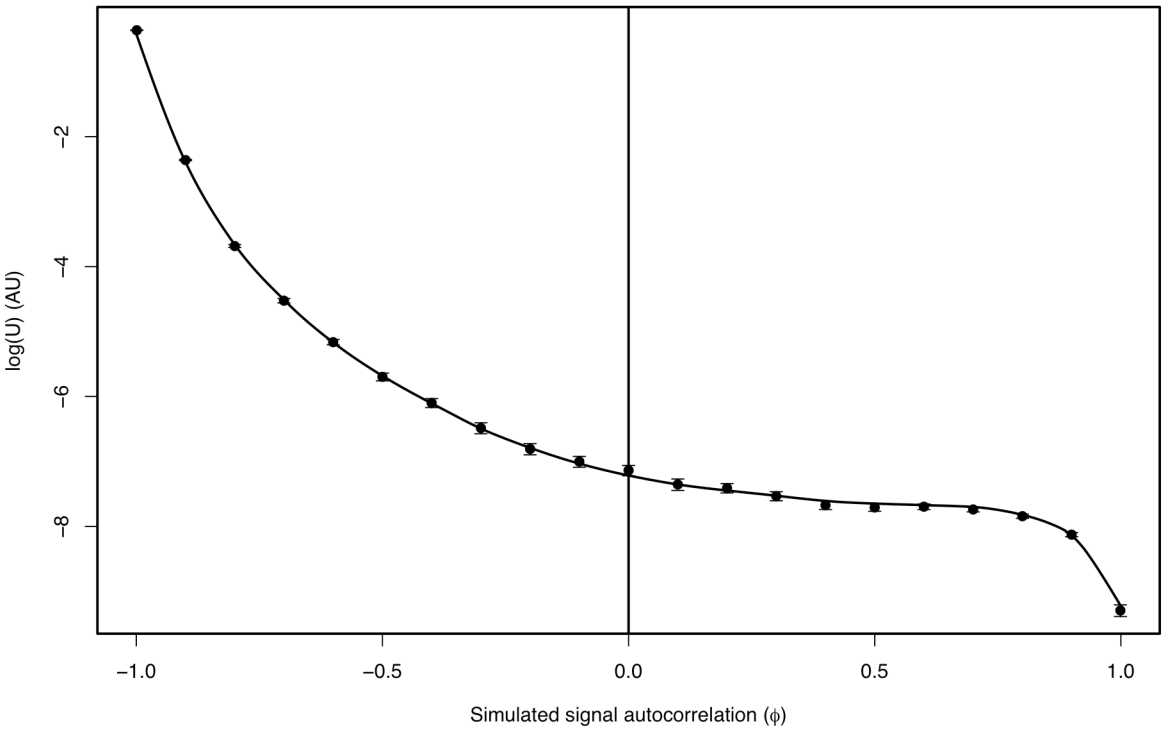

Quadratic coefficient (AU)
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.0
−0.5
0.0
0.5
1.0
Simulated signal correlation (ρ)

Figure 3


log(U) (AU)
−2
−4
−6
−8
−1.0
−0.5
0.0
0.5
1.0
Simulated signal autocorrelation (ϕ)