Investigating Cerebral Autoregulation in Traumatic Brain Injury via Simultaneous Measurements of Intracranial Pressure, Arterial Blood Pressure and relative Cerebral Blood Flow

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Abstract

Traumatic Brain Injury (TBI) can alter the brain's ability to maintain its supply of oxygen and metabolites by disrupting autoregulatory mechanisms that maintain constant cerebral blood flow. Impaired cerebral autoregulation can result in brain hypoxia leading to morbidity and mortality so maintenance of cerebral blood flow after injury is of paramount importance. Currently, this is managed using limited information and various assumptions, so there is significant interest in developing better correlates for impaired or intact cerebral autoregulation. In this study we simultaneously measure cerebral blood flow (CBF), intracranial pressure (ICP, measured invasively) and arterial blood pressure (ABP), with the aim of determining useful relationships that can establish the non-invasive measurement of cerebral blood flow in the treatment of TBI.

Introduction

Cerebral Autoregulation (CA) is the complex process whereby the body maintains constant blood flow and therefore constant oxygenation and nutrition provision to the brain. By balancing blood and cerebrospinal fluid (CSF) pressures, CA dynamically stabilises cerebral perfusion pressure (CPP) and hence cerebral blood flow[1].

CA encompasses a broad set of changes to vascular physiology that involves several tissues and cell types[2]. The CA *myogenic mechanism* maintains constant blood flow in the face of changing blood pressure. In response to an increase in ABP, autoregulatory mechanisms sense the stretch in cerebral arteries and arterioles and translate this to a constriction of surrounding arterial smooth muscle, resulting in increased cerebrovascular resistance to offset increased cerebral perfusion pressure. In contrast, using the *metabolic mechanism*, CA senses local changes in blood CO_2, and acts on arterial smooth muscle via nitric oxide pathways causing dilation or constriction, thus changing blood perfusion according to the

local demands of brain metabolism. Additional mechanisms involve neurons or endothelial cells that through a variety of signalling mechanisms can act on smooth muscle tone. The objective of these mechanisms are similar; to maintain constant cerebral blood flow and thus the constant delivery of oxygen and metabolites to the brain in the face of fluctuating arterial blood pressure and cerebral metabolic demand [1,2].

Failure of CA is often seen in severe brain injury and can result in reduced oxygen and nutrient delivery leading to significant morbidity and mortality. By different measures, CA is impaired in 49–87% of TBI patients.[3,4] However it is difficult to ascertain if CA impairment underlies the physiological trends observed clinically. For instance, cerebral hypoperfusion may result from mismatched metabolic demand resulting in loss of consciousness. Ischaemic tissue damage may be compounded by impaired CA resulting in infarct. Monitoring cerebral perfusion is thus a significant part of modern neurointensive care.

Clinical decision making related to CA status is currently informed by mismatches in ICP responses to blood pressure variations: if ICP increases with blood pressure increases, it is assumed that CA is not intact (intact CA maintains constant cerebral blood flow and hence ICP as Bp increases). It remains unresolved whether additional information is available from the relationships between cerebral blood flow, arterial blood pressure, and intracranial pressure, and in what clinical conditions this information is most useful.

Patients with severe TBI are likely to have disrupted CA, but there is at present no widely used method for measuring cerebral perfusion that is non-invasive, accurate, and able to be used continually. The best available method to continuously monitor CBF and its relationship with systemic blood pressure is trans-cranial doppler ultrasound[2] which lacks consistency and lacks the ability to sense blood flow through the microvasculature.

Here, we employ a non-invasive measurement of CBF using Near-Infra-Red Diffuse Correlation Spectroscopy (NIR-DCS) to monitor brain perfusion and CA. We present case studies that are the first of their kind in the UK to combine these signals in the context of traumatic brain injury. We establish that in these subjects, NIR-DCS signal quality is sufficient to extract indices related to the autoregulatory state of the brain, and to permit further investigation into the utility of using non-invasive blood flow measurements in the clinic.

Methods

Ethics

Subjects were recruited in the critical care unit of the Royal London Hospital, London in accordance with a protocol approved by a UK Health Research Authority (IRAS 317751). All study procedures were carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005. Conscious patients gave written and informed consent prior to any data collection. In the case of unconscious patients, assent to participation was obtained from next of kin acting as a

personal consultee or from an independent healthcare professional acting as a professional consultee according to the UK Mental Capacity Act and the Declaration of Helsinki[5].

Measurement

Measurements of cerebral blood flow were obtained using a custom NIR-DCS research instrument provided by CoMind Technologies, London. The instrument contained a laser source and a set of optical detectors that formed a single non-invasive measurement on the forehead. The laser source was regulated to keep its optical output within skin-safety limits defined by established international safety standards (IEC 60825-1:2014). All electronics were housed within a medical-grade cart that met all relevant electrical safety standards (IEC-60601-1). A single bundle of optical fibres was used to carry light from the laser source to a head probe that was placed on the participant's forehead. Light that scattered through the subject's brain was detected by optical fibres integrated into the head-probe, which carried detected light to optical detectors. Stable positioning on the subject's forehead was ensured using medical-grade tape (3M Medical Tape 1509). Head-probe and adhesive tape biocompatibility met relevant safety standards (ISO:10993-10).

Subjects were included in the study if they were undergoing invasive ICP monitoring alongside arterial-line measurements of ABP as standard medical care. Additional exclusion criteria included subjects with radiological evidence of a severely compromised skull (including via decompressive hemicraniectomy), and subjects with machine-regulated cardiac output (e.g. Cardiopulmonary Bypass).

Arterial Blood Pressure was measured invasively using an arterial catheter interfaced to a **(what make)** transducer for the duration of routine clinical monitoring. Intracranial pressure was measured invasively using an intraparenchymal pressure transducer (Raumedic Neurovent-P). Both signals were collected and monitored continuously through a clinical patient monitor (Mindray BeneVision N1). For the purposes of research data collection, ICP and CBF were duplicated as analog voltages sent from the Mindray and read into a custom digitiser device, sampled at 100 Hz and co-aligned with CBF signals in the same timebase.

Analysis

Analog signals representing ICP, ABP, were digitised at 100 Hz whilst CBF was digitised at 20 Hz. Raw patient data was streamed to a hard-drive, transferred to a secure server within the hospital, stored according to best-practice clinical data security and GDPR regulations, and analysed on-site using custom software written in Python.

Cerebral Blood Flow was estimated using NIR-DCS data by fitting the unnormalized temporal electric field autocorrelation decay of detected light to a model of the correlation diffusion equation under the assumption that scatterer dynamics follow Brownian motion[6,7]. After incorporating constant values for tissue reduced scattering and absorption (μa: 0.1 cm^{-1}, μs': 9.0 cm^{-1}), this model outputs a particle diffusion coefficient (D_B in mm^2/s), which is proportional to CBF[8]. All raw time-series of ABP, ICP and BFI are available upon reasonable request.

Results

Measurements were obtained from two subjects admitted to the hospital for treatment following Traumatic Brain Injury (TBI). In both subjects, ICP and ABP were monitored continuously using invasive probes as part of routine clinical monitoring. In addition to routine monitoring, the same ICP and ABP signals were captured alongside CBF using theNIR-DCS research instrument in a semi-continuous fashion over a number of hours in each patient.

The data were inspected to determine whether it was of sufficient quality to enable further investigation. The data quality of ICP and ABP data was consistently high resulting in well resolved pulsatile waveforms resting on top of slower fluctuations. The CBF signals (as measured via NIRS-DCS) were considerably noisier, as is expected for non-invasive optical measurements, but nonetheless showed clear cardiac pulsatility on top of slower fluctuations. Examples are provided in **Figure 1A and Figure 1B**), and full time-series plots are provided in Supplementary Data.

Intact cerebral autoregulation buffers CBF from fluctuations in ABP. To test if this was evident in our data we correlated ABP and CBF, which we call the Flow Reactivity Index (FRx) to determine if there was any relationship between them. In Subject 1 we observed a positive correlation (Pearson's R^2=0.63) between CBF and ABP as is evident in **Figure 2A**. This compares to the weaker correlation observed between CBF and ICP (Pearson's R^2=0.36, **Figure 2B**).

Discussion

We have presented case studies that demonstrate that it is now possible to investigate cerebral blood flow using Near-Infra-Red Diffuse Correlation Spectroscopy (NIR-DCS) alongside invasive clinical measurements of ABP and ICP. NIR-DCS data was of sufficient quality to identify expected pulse waveform features of CBF representing the characteristic cardiac pressure waves, and measurements over multiple timescales showed correlated fluctuations between the three signals. Together these data indicate that it is technically possible to simultaneously measure ABP, BFI and ICP, unlocking the potential to measure clinical meaningful correlations between them.

The health of Cerebral Autoregulation can be indicated by the Cerebrovascular pressure reactivity; the ability of vascular smooth muscle to respond to changes in cerebral perfusion pressure. This has been previously measured by relating ABP to ICP to produce the Pressure Reactivity Index (PRx), or by relating ABP to transcranial doppler to measure the mean-flow index (Mx)[9], to laser speckle doppler to produce a laser doppler index (LDx)[10], or to cerebral oximetry to produce a cerebral oximetry index (COx)[11]. Here, we directly compare measurements of CA using pressure reactivity and flow reactivity and found in preliminary analysis that correlations between BFI exist with both ABP and ICP.

By increasing this case study and collecting many consecutive hours of data per subject, it may be possible to estimate the optimal CPP by establishing a 'U-shaped' relationship

between PRx and CPP[12]. Finding a similar minimisation in the relationship between FRx and CPP would potentially open new avenues for using CBF measurements to guide clinical decision making.

References

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Figure 1: Example time-series of data collected in this study.
Arterial Blood Pressure (ABP), Intracranial Pressure (ICP) and Cerebral Blood Flow (CBF) were simultaneously measured for each subject. A) Comparison of CBF, ABP and ICP on the time-scale of minutes. Raw traces are filtered using a moving average applied over segments of 10 seconds. B) Comparison of raw pulsatile waveforms from CBF, ABP and ICP.

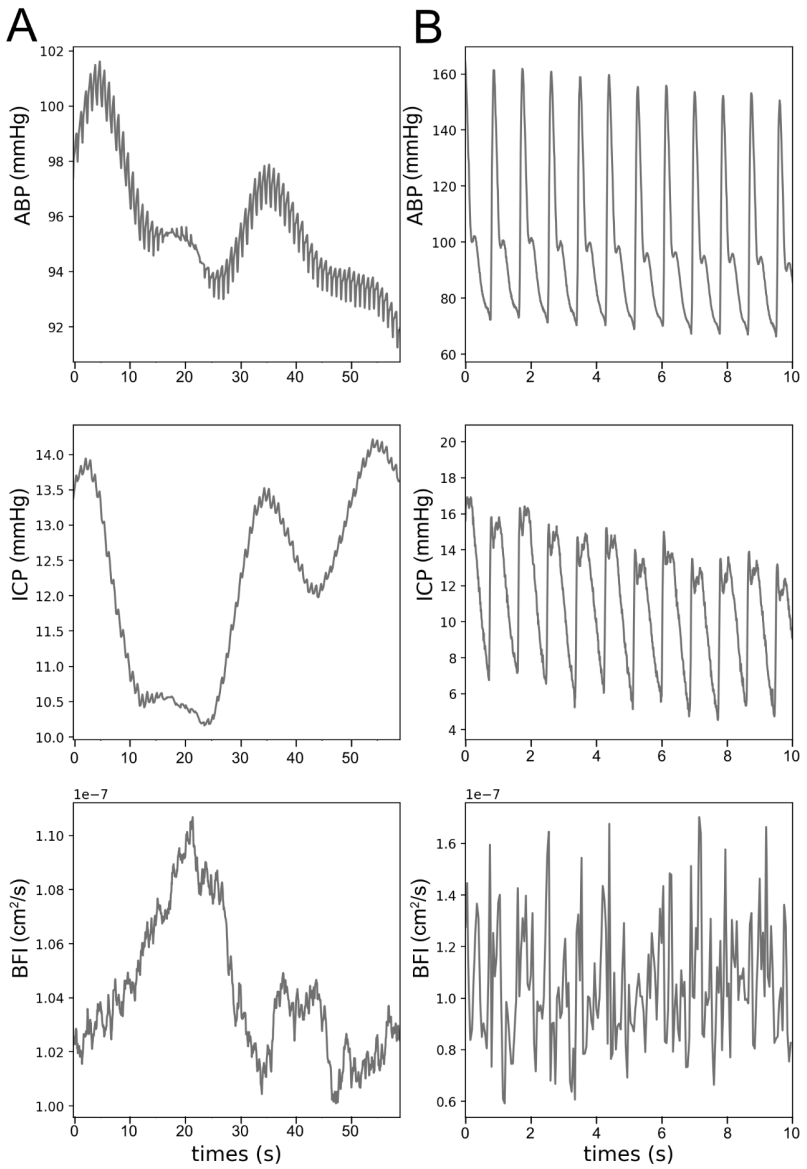
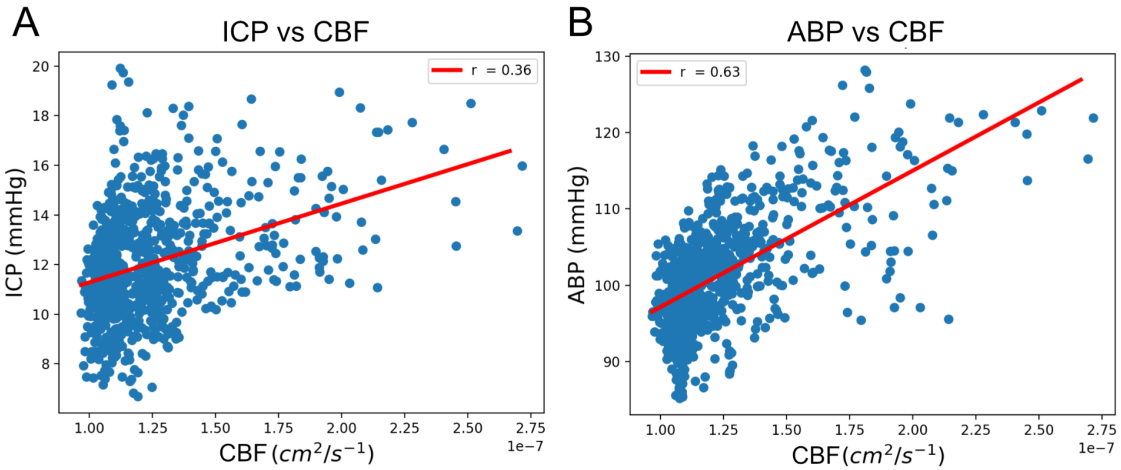
Figure 2: Correlation-based measurements of CA.
A) Correlation between ICP and ABP. B) Correlation between CBF and ABP.