

25 years of intracranial pressure monitoring after severe traumatic brain injury: a retrospective, single-centre analysis.

Joseph Donnelly MBChB^{1,2}; Marek Czosnyka PhD^{1,3}; Hadie Adams MD¹; Danilo Cardim PhD¹; Angelos Koliass MD, PhD¹; Frederick A Zeiler MD⁴; Andrea Lavinio MD⁴; Marcel Aries MD, PhD^{1,5}; Chiara Robba MD^{4,6}; Peter Smielewski PhD¹; Peter JA Hutchinson MBBS, PhD¹; David K Menon MD, PhD, FMedSci⁴; John D Pickard MChir, FMedSci¹; Karol P Budohoski MD, PhD¹

1. Brain Physics laboratory; Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, United Kingdom
2. Department of Anaesthesiology, University of Auckland, Auckland, New Zealand
3. Institute of Electronic Systems, Warsaw University of Technology, Warsaw, Poland
4. Department of Anaesthesia, Department of Medicine, University of Cambridge, Cambridge, United Kingdom
5. Department of Intensive Care, University of Maastricht, Maastricht University Medical Center, Maastricht, Netherlands
6. Department of Neuroscience, University of Genoa, Genoa, Italy

Acknowledgements: The authors would like to thank Geert Meyfroidt and Jon Coles for feedback on scientific content of the paper. JD is supported by a Woolf Fisher Scholarship (New Zealand). These studies were supported by National Institute for Healthcare Research (NIHR, UK) through the Acute Brain Injury and Repair theme of the Cambridge NIHR Biomedical Research Centre, an NIHR Senior Investigator Award to DKM, and an NIHR Research Professorship to PJA. Authors were also supported by a European Union Framework Program 7 grant (CENTER-TBI; Grant Agreement No. 602150)

Disclosures: MC receives part of licensing fees for ICM+, owned and distributed by Cambridge Enterprise Ltd; paid lectures for Integra Lifescience Speakers' Bureau; and is an unpaid member of Board of Directors of Medicam Ltd, UK. DKM has had consultancy, research collaboration, or trial data monitoring interactions with Solvay Ltd; GlaxoSmithKline Ltd; Brainscope Ltd; Ornim Medical; Shire Medical, and Neurovive Ltd; Calico Inc; Pfizer Ltd; Pressura Ltd; Glide Pharma Ltd; and

NeuroPro Ltd. However, none of these are relevant to the current manuscript. PS receives part of licensing fees for the software ICM (Cambridge Enterprise Ltd, Cambridge, UK) used in this project for data collection and data preprocessing.

Key words: Traumatic brain injury, intracranial pressure, cerebral haemodynamics, autoregulation

Abstract

Introduction: Intracranial pressure (ICP) monitoring is considered a standard of care after severe traumatic brain injury (TBI) and has been monitored, along with clinical outcome, for over 25-years in Addenbrooke's hospital, United Kingdom. This time period has also seen changes in management strategies with the implementation of protocolled specialist neurocritical care, expansion of neuromonitoring techniques, and adjustments of clinical treatment targets. In this study, we investigate the changes in intracranial monitoring variables over the this period.

Methods: Data from 1146 TBI patients requiring ICP monitoring were analyzed. Monitored variables included ICP, cerebral perfusion pressure (CPP), and the cerebral pressure reactivity index (PRx). Data were stratified into 5-year epochs spanning the 25 years from 1992 to 2017.

Results: CPP increased sharply with specialist neurocritical care management ($p < 0.0001$) (introduction of a specific TBI management algorithm) before stabilizing from 2000 onwards. ICP decreased significantly over the 25 years of monitoring from an average of 19 mm Hg to 12 mm Hg ($p < 0.0001$). The mean number of ICP plateau waves and the number of patients developing refractory intracranial hypertension both decreased significantly. Mortality did not significantly change in the cohort (22%).

Conclusions: We demonstrate the evolving trends in neurophysiological monitoring over the past 25 years from a single, academic neurocritical care unit. ICP and CPP were responsive to the introduction of an ICP/CPP protocol while PRx has remained unchanged.

Introduction

Because the management of severe TBI in the acute phase is focused on reducing further injury from insults such as raised ICP or impaired CPP¹, ICP monitoring has become an established standard of care in the management of TBI². Through the pioneering work of Janny, Lundberg and Jennett³⁻⁵ in the middle of the 20th century, clinical ICP monitoring was promoted as a method to optimize the management after TBI. At Addenbrooke's Hospital (Cambridge, UK), continuous, computer supported (i.e. all data were saved digitally for post-processing) intracranial monitoring was introduced in 1991 and thus has been running for over 25 years.

Despite a paucity of positive randomized trials, the management of severe TBI has evolved significantly over the last 50 years. While the first neurosciences intensive care units were opened in 1932 in Johns Hopkins Hospital (USA) and in the National Hospital for Nervous Diseases (UK) in 1954, it was not until the 1980's and 1990's that the largest academic institutions were equipped with intensive care units to treat TBI patients. People pioneering computer supported monitoring paved a way to recognition of ICP analysis as a complex and clinically relevant signal⁶. In the UK, recognition of the importance of preventing cerebral hypoxia and hypotension led to several significant changes in TBI management. First, a transfer of care for TBI patients from the neurosurgical ward to a specialist neurosciences intensive care unit. Second, a focus on ICP and CPP through a dedicated CPP/ICP management algorithm⁷ and multimodal brain monitoring. Furthermore, national major trauma units were established to facilitate rapid access to specialized care.

The primary aim of this study was to describe the time related changes of intracranial physiology (as measured by ICP, CPP, and cerebrovascular pressure reactivity (PRx) over the past 25-year period in a single academic institution in relation to incremental changes in management strategies.

Methods

Patients

The data in this study was gathered during a retrospective analysis of data collected prospectively from 1146 head-injured patients admitted to the Addenbrooke's Hospital Neurocritical Care Unit between 1991 and 2017. TBI patients with a clinical need for intracranial pressure monitoring and computerized signal recordings were included for analysis. The computerized data storage protocol was reviewed and approved by the local ethics committee of Addenbrooke's Hospital, Cambridge University and the neuro critical care unit User's Group. Use of computer-recorded data was approved by NCCU Users' Committee and conducted before 2000 as a part of anonymous clinical audit. After 2000, national ethical approval was obtained (30 REC 97/291).

Inclusion criteria were: TBI; computerised invasive monitoring of ICP and ABP for at least 12 hours, admission Glasgow Coma Scale (GCS) and mortality data available. Of the 1146 TBI patients with monitoring data, 1112 patients were included for subsequent analysis.

Although data on total TBI admissions are not available over the 25 year period, during the period between 2002 and 2017, 2241 patients were admitted to the unit with TBI, of which 1100 had ICP monitors inserted. 569 of the 1100 ICP monitored patients had computerised ICP monitoring (52%). While some patients in the cohort would be categorized into the moderate TBI group on basis of initial GCS, these patients deteriorated and subsequently required invasive intracranial monitoring and therefore were included in the analysis. Patients were managed according to contemporaneous TBI guidelines. Between 1991 and 1993 patients were managed within the Department of Neurosurgery and general Intensive Care Unit if ventilatory or organ support was needed. A dedicated 12 bed Neurocritical Care Unit was opened in 1994 which was later expanded to 21 beds in 2010 followed by transformation to a major trauma unit and further expansion to 23 beds in 2011.

A protocol aimed at keeping CPP > 70 mm Hg and ICP < 20 mm Hg using step-wise medical and surgical management was implemented in 1994. In 2003, modifications to ICP and CPP targets were introduced (reduction of CPP target to CPP > 60 mm Hg) followed by restricting hyperventilation (end-tidal pCO₂ range adjusted from 4-4.5 kPa to 4.5-5 kPa; figure 1). Introduction of multimodal monitoring including microdialysis and brain tissue oxygenation (P_{BT}O₂) occurred in 2002 and 2004 respectively. Assessment of the PRx was a part of multimodal monitoring since 1996, however, it was included in clinical assessment (to assist with prognostication) of TBI in only 1999. Furthermore, since 2012, autoregulation based CPP targets have been available to try to optimize management as a secondary parameter at the clinicians discretion. In 2015, blood pressure zeroing was changed from the level of the right atrium to the level of foramen of Monro, as estimated by tragus level.

All patients were sedated, intubated, and ventilated. The step-wise ICP management included positioning and head elevation, prevention of hypotension and hypoxia and maintenance of end-tidal pCO₂ levels, sedation, muscle paralysis, ventriculostomy, osmotic agents, induced hypothermia, barbiturate coma and decompressive craniectomy. CPP was maintained at target levels using intravenous fluids, vasopressors and inotropes. Tight glucose management was achieved with insulin sliding scale, with target blood glucose levels of between 6 and 8 mmol/L. Seizure management was achieved using phenytoin and levetiracetam as appropriate. Initial Glasgow Coma Scale was obtained for each patient pre sedation. Patients without point breakdown of GCS were included as data for patients before electronic medical records frequently had only total GCS score. Mortality was assessed at 6-months post injury.

Data acquisition

ICP was monitored with an intraparenchymal micro-sensor inserted into the frontal cortex (Codman ICP MicroSensor, Codman & Shurtleff, Raynham, MA) and arterial blood pressure was monitored in the radial or femoral artery (Baxter Healthcare CA, USA; Sidcup, UK) with a zero calibration at the level of the right atrium (1992-2015) and at the foramen of Monro (2015-2017). Between 1992 and 1996 data trends (one-minute time averages) were collected with non-propriety ICM software developed in-house and one-minute trends were stored⁸. From 2002 -2017 data were collected using ICM+©, (Cambridge Enterprise,

Cambridge, UK-<http://www.neurosurg.cam.ac.uk/icmplus>). PRx was monitored from 1996 onwards. PRx was calculated as the Pearson correlation of 30 consecutive 10-second average values of ABP and ICP. CPP was calculated as ABP- ICP. A 10-second average was used to reduce the influence of respiratory and pulse waveforms. A 300-second moving window was used to generate continuous PRx values.

For each patient, the mean values of ICP, CPP, and PRx were calculated for the duration of monitoring. Indicators of secondary insult were obtained using the percentage time with ICP above 20 mm Hg, percentage time with CPP below 60 mm Hg, and percentage time PRx > 0.25. Plateau waves were identified as an increase in ICP above 40 mm Hg, associated with a significant decrease in CPP, for between 5 and 60 minutes. Severe refractory intracranial hypertension was defined here as an increase in ICP over 40 mm Hg for at least 1 hour.

Statistical analyses

Overall time trends in physiologic variables were investigated graphically by fitting a generalized additive model to the mean physiological variables vs date-time of monitoring. Means, counts, and proportions across 5-year epochs (from 1992-2017) were analysed with a one-way ANOVA, negative binomial regression and the chi-squared test respectively. Holms method was used to adjust for multiple comparisons. All data analysis was performed using the R language for statistical computing⁹ with the following packages: 'MASS', 'dplyr', 'ggplot'¹⁰⁻¹².

Results

Summary data are shown in table 1. 1112 patients were included in the current analysis with a mean age of 38. 867 were male and the majority (776) were severely injured on initial GCS assessment. The remainder had a secondary neurological deterioration. The mean duration of monitoring was 114.08 (sd 102.15) hours and 248 (22.3%) died. Figure 1 highlights important changes to the intensive care management over the past 25 years.

When mean values of ICP are plotted against time of injury, a consistent decrease from values around 19 mm Hg to below 12 mm Hg are observed over the 25-year period (figure 2). The measured CPP showed a distinct increase from ~70 mm Hg in 1994 to above 80 mm Hg in 2000 followed by a gradual reduction and stabilization over the next 15 years at ~ 75 mm Hg. In the final 2 years, measured CPP decreased by ~7 mm Hg. PRx remained stable throughout the years of monitoring (1996-2017).

Statistical analysis confirmed significant effects of time (stratified into five year epochs) for CPP and ICP (including a decrease in number of plateau waves and incidence of refractory intracranial hypertension) but not PRx (figure 3). There was an increase in age of monitored patients over time, however, no change in mortality nor GCS (figure 4). The percentage of monitored patients undergoing decompressive craniectomy was 30% and did not significantly change over the period when data was available (1997 to 2017). Estimated CPP at brain level after post-hoc adjustment of 10 mm Hg were made (approximately the difference in the height of the hydrostatic column between the heart and the tragus with the patient at 30 degrees head up tilt¹³) is shown in figure 5.

Discussion

Of the multiple incremental changes in TBI management over the past 25 years in this single institution, the introduction of specialized neurocritical care and goal directed therapy had the most pronounced effects on monitored physiology (year 1994, figure 2) resulting in increased CPP, decreased ICP, less plateau waves and less time spent outside of ICP or CPP targets. The subsequent introduction of microdialysis, brain tissue oxygenation monitoring or changes in pCO₂ targets and ventilation strategies did not seem to have major immediate effects on ICP, CPP or PRx. Despite an increasing age of the monitored cohort, the mortality has remained low (~22%).

Decreasing mean ICP

The mean ICP decreased over the 25-year period by 8 mm Hg and the percentage of time with ICP over 20 mm Hg also decreased from a mean value of > 30% of monitoring time to < 10%. Because increased ICP is related cerebral blood flow and metabolism^{14,15}, effective treatment of raised ICP is a prime directive of neurocritical care after TBI¹⁶. However, defining a precise ICP that warrants treatment is difficult; it is likely the threshold for a damaging ICP will depend on how long the ICP is raised, and whether other cerebral physiologic markers are also impaired¹⁷⁻¹⁹. Notwithstanding, the threshold of ICP used in this centre was 20 mm Hg for escalating treatment.

The decrease seen in ICP over the years could indicate an increase in frequency in treatments, an increase in efficacy of treatments or perhaps a decrease in the 'baseline' ICP of the monitored cohort. Unfortunately, due to the retrospective nature of the data we do not have exact data on the specific treatments and their timings in each patient. However, the rate of decompressive craniectomy did not change significantly over the past 20 years. Despite the lack of positive trials on ICP lowering interventions that could be responsible for the results (other than the recent RESCUEicp trial for decompressive craniectomy²⁰), the management of TBI has undoubtedly evolved in most neurotrauma centres, including Addenbrooke's Hospital. Such changes have included preference of hypertonic saline over mannitol; use of multimodal monitoring including better access to EEG allowing for more individualized treatment in difficult cases (including seizure management, glucose supplementation, etc.), more rapid access to imaging and treatment of space occupying lesions. Furthermore, with an aging population the age distribution has shifted, albeit modestly, to older patients, potentially contributing to the lower ICP.

Increasing CPP

The increase in CPP between 1994-1999 is particularly striking and is an example of how the introduction of a management protocol can directly affect patient physiology. CPP oriented therapy developed from the works of Rosner who proposed that maintaining CPP at slightly higher values may decrease the stimulus for vasodilatory ICP waves and thus lead to a more stable ICP^{21,22}. Against this background it is interesting to note that the average number of plateau waves per patient decreased after the introduction of CPP oriented therapy (figure 2). It became apparent several years after the promotion of CPP

oriented therapy, that maintaining high levels of CPP, although effective in preventing secondary insults as measured by jugular bulb oxygen saturation, had no significant effect on neurological outcome possibly due to acute lung injury related to the use of vasopressors and fluids required to maintain an increased CPP²³. Subsequently most institutions, including Addenbrooke's Hospital, and the Brain Trauma Foundation²⁴ changed their guidelines to reflect these findings. The decrease of CPP threshold to CPP > 60 mm Hg can be again seen in the time trends in figure 2.

Finally, a 7 mm Hg dip in displayed CPP seen after 2015 can be explained by a change in practice, whereby the position of the zero level for the ABP transducer was changed from the level of the right atrium to the level of the foramen of Monro (figure 2) to give a clearer indication of the perfusion pressure at the level of the brain²⁵. Interestingly, when a post-hoc correction of 10 mm Hg is applied, the highest CPP levels were experienced after 2015 perhaps indicating increased use of vasopressors (however this data is unavailable).

Unchanged pressure reactivity

Pressure reactivity in this single centre cohort did not change over time (figure 2). Secondary indices such as PRx derived from continuous monitoring of ICP and ABP can be useful for monitoring various aspects of physiology^{26,27}. PRx has been proposed as a measure of cerebral autoregulation and has the pragmatic advantage over other more direct methods, in that it can be calculated continuously over time²⁸. PRx has been demonstrated to related to patient outcome after TBI (worse autoregulation, worse outcome), has been validated in experimental models against gold-standard static autoregulation analysis and has been shown to correspond with the PET based static rate of regulation in adult TBI patients²⁹⁻³¹.

Although we have the ability to easily monitor cerebral autoregulation, our ability to improve it is at present limited. Despite early promise of some drugs such as statins³², there are currently none in use for improving autoregulation. In addition, autoregulation can be affected by many physiological and treatment factors including, CO₂, arterial glucose, red blood cell transfusion and body temperature³³⁻³⁶. Altering physiological conditions has been proposed as a method to improve overall autoregulation and in this light, the concept of CPP_{optimal} may prove useful³⁷⁻⁴¹. With this method, the CPP at which autoregulation is the most efficient is actively targeted through the careful titration of vasopressors. Despite conceptual promise, its use in clinical practice has been limited⁴² due to the lack of prospective clinical studies demonstrating either its safety, or its efficacy.

Nevertheless, as cerebral autoregulation is intrinsically linked to CPP and hence ICP, one could argue that incremental changes in either of these parameters, as well as good neurocritical care with adequate ventilatory support and maintained systemic homeostasis should have exerted beneficial effect on PRx. The obtained results, together with the confirmed independent association of PRx with outcome, suggest there is still room for developing interventions targeting cerebral autoregulation

Admission patient characteristics and mortality

Despite the increasing age and steady initial GCS over the 25 years, mortality in the analyzed cohort did not significantly change (figure 4). While this may have been contributed to by the sustained improvement in ICP, and better control of CPP, it should be appreciated that patient outcome and in particular mortality are influenced by not only ICP, but also factors not assessed in this study. These factors include the severity of extracranial injuries, co-morbidities, the severity of the primary insult, involvement of critical structures such as the brain stem, as well as patient factors and wishes with respect to withdrawal of care. Indeed, the importance of ICP (and CPP) monitoring after head injury has been challenged with the publication of the BEST TRIP trial⁴³. It has not been our institutional policy, however, to abandon ICP monitoring. Rather ICP is used in combination with multimodal monitoring in an interdisciplinary effort (neurointensivists, neurosurgeons, and neurologists) to obtain maximal information about the intracranial physiology and guide specialized therapies.

While the limited nature of the current database prevents detailed analysis of outcome trends over time, our institutional outcomes compare favorably with published data where mortality after severe TBI typically exceeds 25-30%^{20,43-45}. Indeed a review of severe TBI outcomes in the last 150 years Stein et al.⁴⁶ demonstrated that while mortality after head injury decreased significantly in the periods between 1970 - 1990 there was no significant improvement in mortality after 1990, which remained static at around 35%. The reasons for the improvements before 1990 are likely related to the introduction of neurocritical care for head injury patients with good haemodynamic and ventilatory management avoiding hypotension and hypoxemia, rapid access to CT scanning and surgery if required⁷. Since 1995, Brain Trauma Foundation Guidelines have been published⁴⁷⁻⁴⁹ and Major Trauma Networks have been set up⁵⁰ in an attempt to unify care after severe TBI. Some reports suggest improved outcomes with increasing adherence to the Brain Trauma Foundation Guidelines^{51,52}.

In the UK, neurosurgery services have been centralized since 1948 and therefore volumes and guideline adherence are typically high. Previous UK-based studies have demonstrated reducing mortality over time when all patients with TBI were taken into account⁵³ and good overall performance when confronted with prediction models⁵⁴. Our data does not strictly confirm this improving trend, however, direct comparison is impossible, as only a selected cohort of patients requiring prolonged computerised intracranial monitoring and neurocritical care was selected for this analysis. Nevertheless, our data, as well as similar studies from other locations^{44,55} confirm that it has proven difficult to clearly reduce mortality after severe TBI. Potential reasons for a stagnant mortality rate despite an apparent improved neurocritical care and access to neurosurgery include an aging population, better prehospital survival in patients previously dying on the scene, and an increasing frequency of multitrauma or high velocity accidents.

Limitations

Due to the retrospective nature of this study, the collection of detailed patient outcome assessment, and characterization of patient injury severity (pupil reactivity, CT findings,

pre-hospital insults etc.) was not possible. Therefore, inferences from patient outcome results must be treated cautiously. However, the main purpose of the study was to document changes in trends in the monitored physiological parameters and as such, the available ICP, CPP and PRx data suffice to address the research question. Furthermore the modest percentage of patients with ICP monitoring captured in the this study (51%) raises the possibility of inclusion bias. In addition, information regarding treatment on a patient-by-patient level may aid in the interpretation of this monitoring data. Unfortunately, such data was unavailable in this database.

Conclusions

In over 1100 patients we demonstrate the evolving trends in neurophysiological monitoring over the past 25 years from a single, academic neurocritical care unit. ICP and CPP were responsive to the introduction of an ICP/ CPP goal directed therapy while cerebrovascular pressure reactivity has remained unchanged. Although we treat increasingly older patients, mortality seems to remain unchanged and low.

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Figure and table legends

Table 1 **Patient demographics; long-term monitoring trends after TBI**

ICP intracranial pressure; CPP cerebral perfusion pressure; PRx pressure reactivity index.

Figure 1 Severe TBI management at Addenbrooke's Hospital over 25 years of ICP monitoring. Over the past 25 years, there have been several changes in the way severe TBI patients have been managed. Before 1994 patients were managed in a neurosurgical annex whereas after 1994 the specialist neurocritical care was opened and a specific ICP/ CPP protocol was instituted. Modifications to monitoring parameter targets, and the addition of further neuromonitoring modalities have also occurred. ABP arterial blood pressure; CPP cerebral perfusion pressure; ICP intracranial pressure; NCCU neurocritical care unit.

Figure 2 Changes in TBI neuromonitoring variables over 25 years- ICP (top), PRx (middle) and CPP (bottom) (n=1112; generalised additive model with 95% confidence limits). ICP decreases from just below 20 mm Hg to below 12 mm Hg while CPP increases shortly after 1995 from below 70 to greater than 80 mm Hg around 2000. PRx remains unchanged throughout the 20 years it has been monitored. Key changes in management are indicated by the dotted lines and refer to (in chronological order): Change from ward to NCCU based care (1994); introduction of brain oxygen and metabolism monitoring, relaxation of CO₂ and CPP targets (2002-2004), designation of major trauma unit (2012); and switch from ABP transducer zero at heart to brain level (2015). ICP intracranial pressure; PRx pressure reactivity index; CPP cerebral perfusion pressure.

Figure 3 Changes in TBI intracranial monitoring variables over 25 years (error bars represent 95% confidence interval) - ICP, plateau waves, refractory intracranial hypertension, PRx and CPP. ICP decreases and CPP increases were statistically significant over time. The mean number of plateau waves and the proportion of patients developing severe refractory intracranial hypertension (defined here as ICP >40 for greater than 1 hour) decreased over time. PRx remained unchanged. ICP intracranial pressure; PRx pressure reactivity index; CPP cerebral perfusion pressure.

Figure 4 Changes in TBI age, GCS and mortality over 25 years. The age (mean with 95% confidence limits) of patients has significantly increased over time while initial GCS and mortality at 6-months have not significantly altered. GCS Glasgow coma scale.

Figure 5 Changes in CPP corrected to estimate CPP at level of tragus. (n=1112; generalised additive model). When a 10 mm Hg correction is made for the approximate height of the hydrostatic column between the heart and the tragus in the 30 degrees head up

position, it is apparent that the highest CPP levels have occurred since switching the zero level of the transducer from the heart to the tragus level CPP cerebral perfusion pressure (2015).

Tables and Figures

Table 1 Patient demographics; long-term monitoring trends after TBI

	Overall
n	1112
Age [years] (mean (sd))	37.96 (17.24)
Sex = male (%)	867 (78.0)
GCS <= 8 (%)	
No	275 (24.7)
Yes	776 (69.8)
NA	61 (5.5)
Decompressive craniectomy (%)	
No	620 (55.8)
Yes	267 (24.0)
NA	225 (20.2)
ICP [mm Hg] (mean (sd))	15.96 (9.33)
CPP [mm Hg] (mean (sd))	76.84 (11.72)
PRx [a.u.] (mean (sd))	0.07 (0.17)
Plateau wave presence (%)	383 (34.4)
Mean number of plateau waves (mean (sd))	1.90 (5.30)
Severe refractory intracranial hypertension presence (%)	94 (8.5)
Mortality (%)	248 (22.3)

ICP intracranial pressure; *CPP* cerebral perfusion pressure; *PRx* pressure reactivity index.

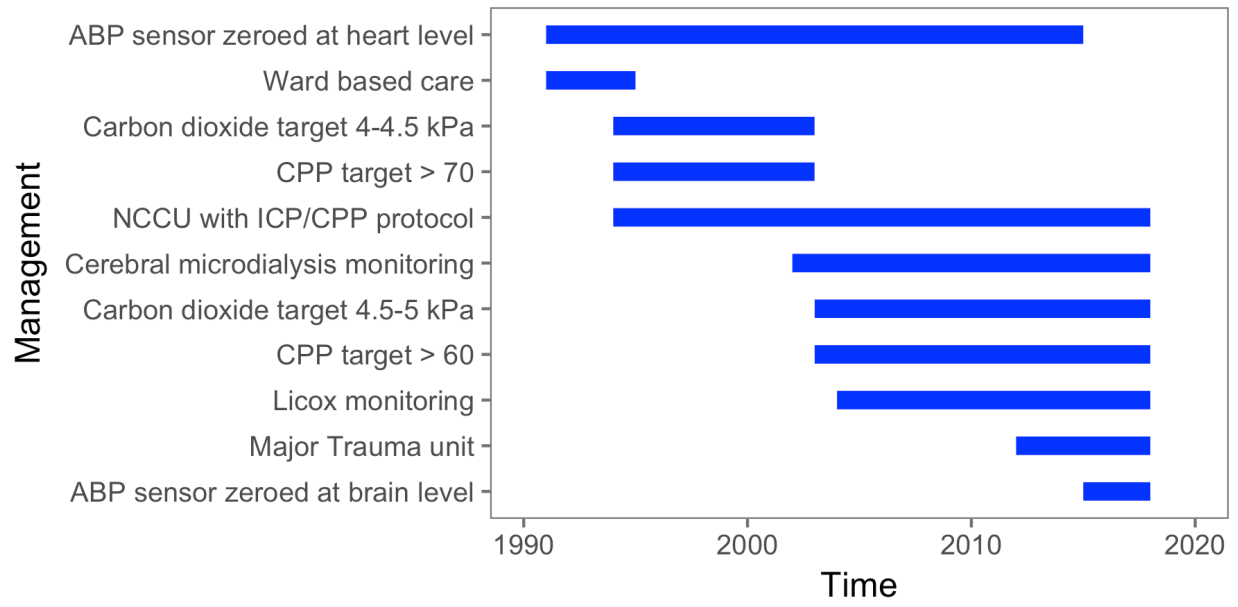


Figure 1

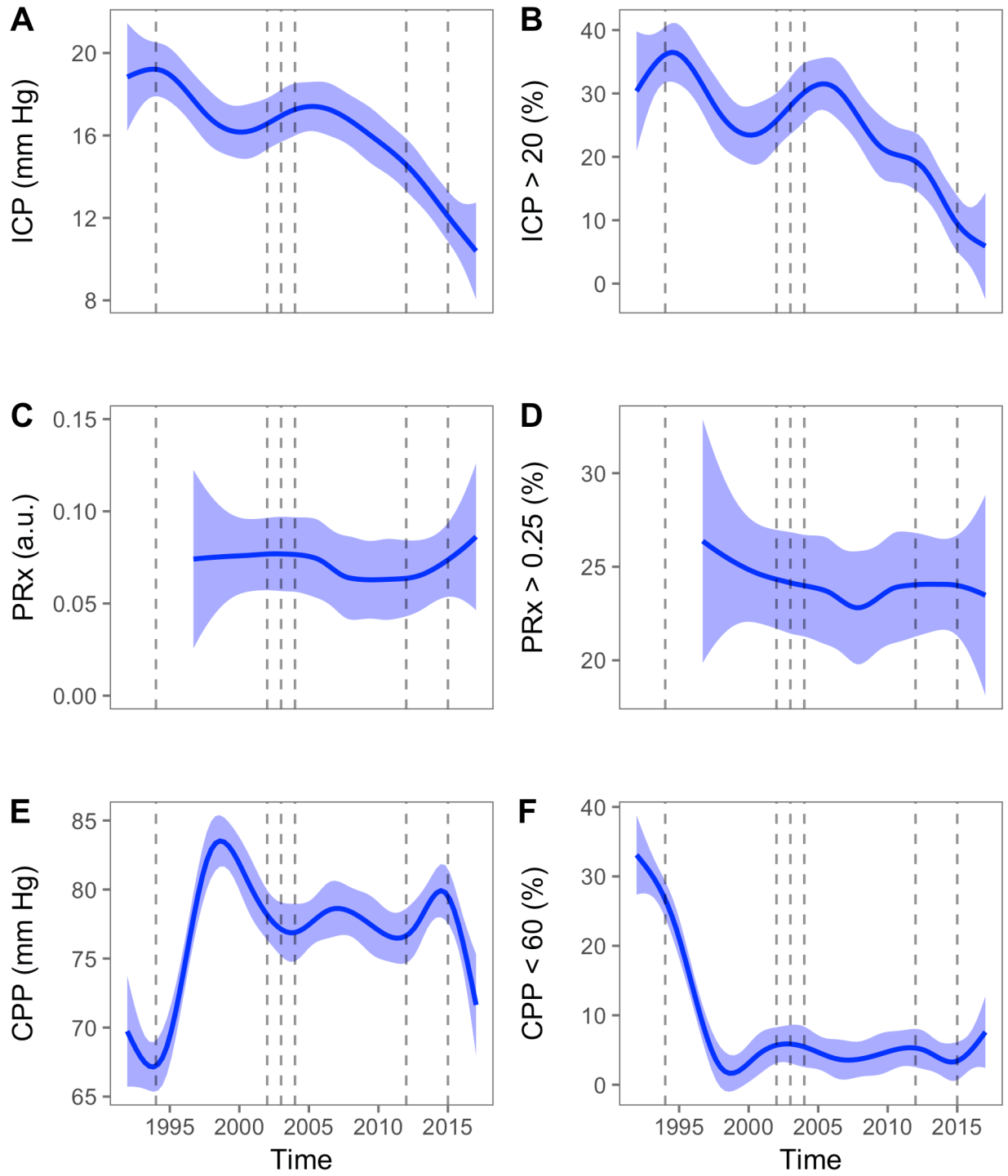


Figure 2

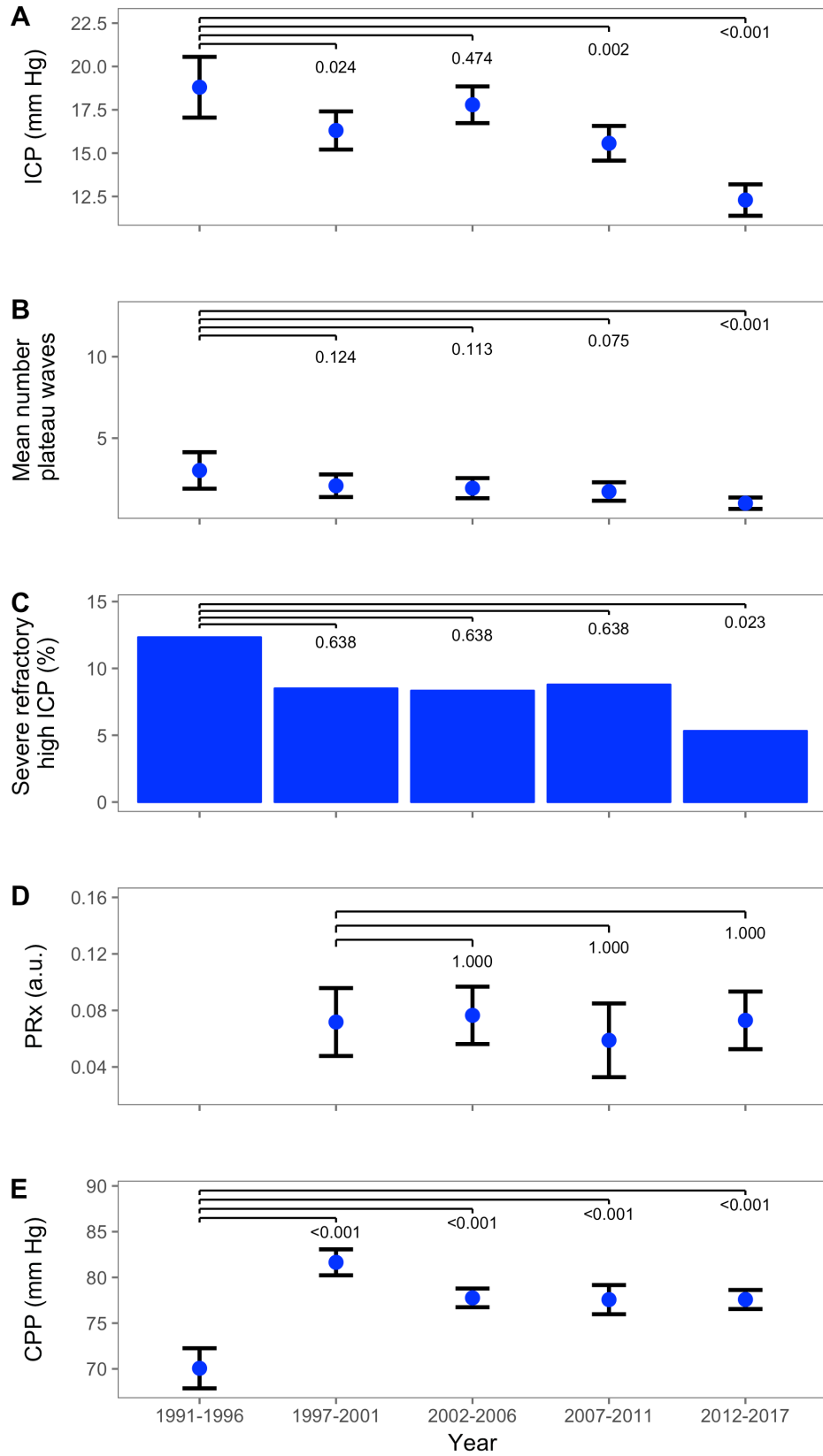


Figure 3

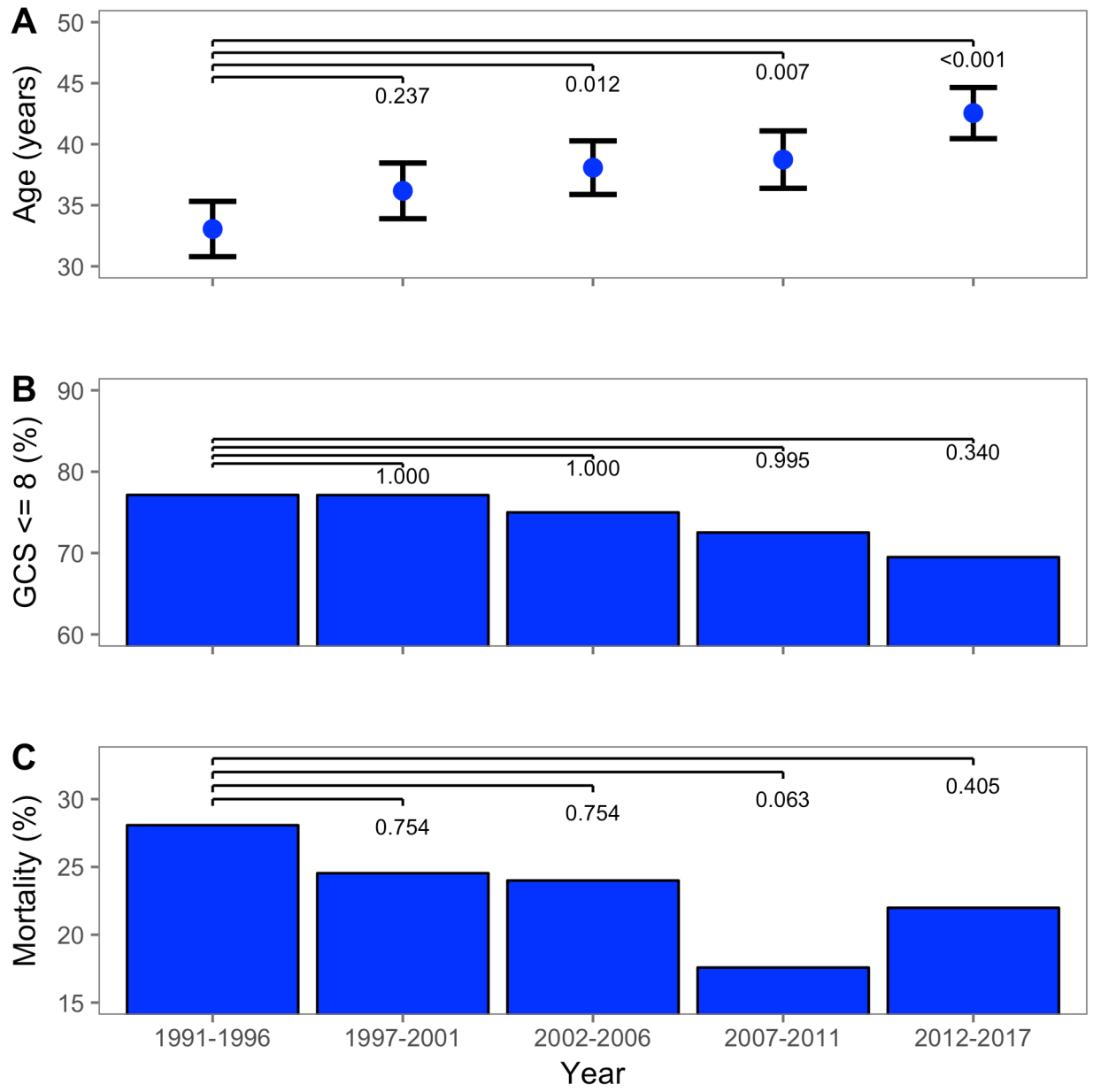


Figure 4

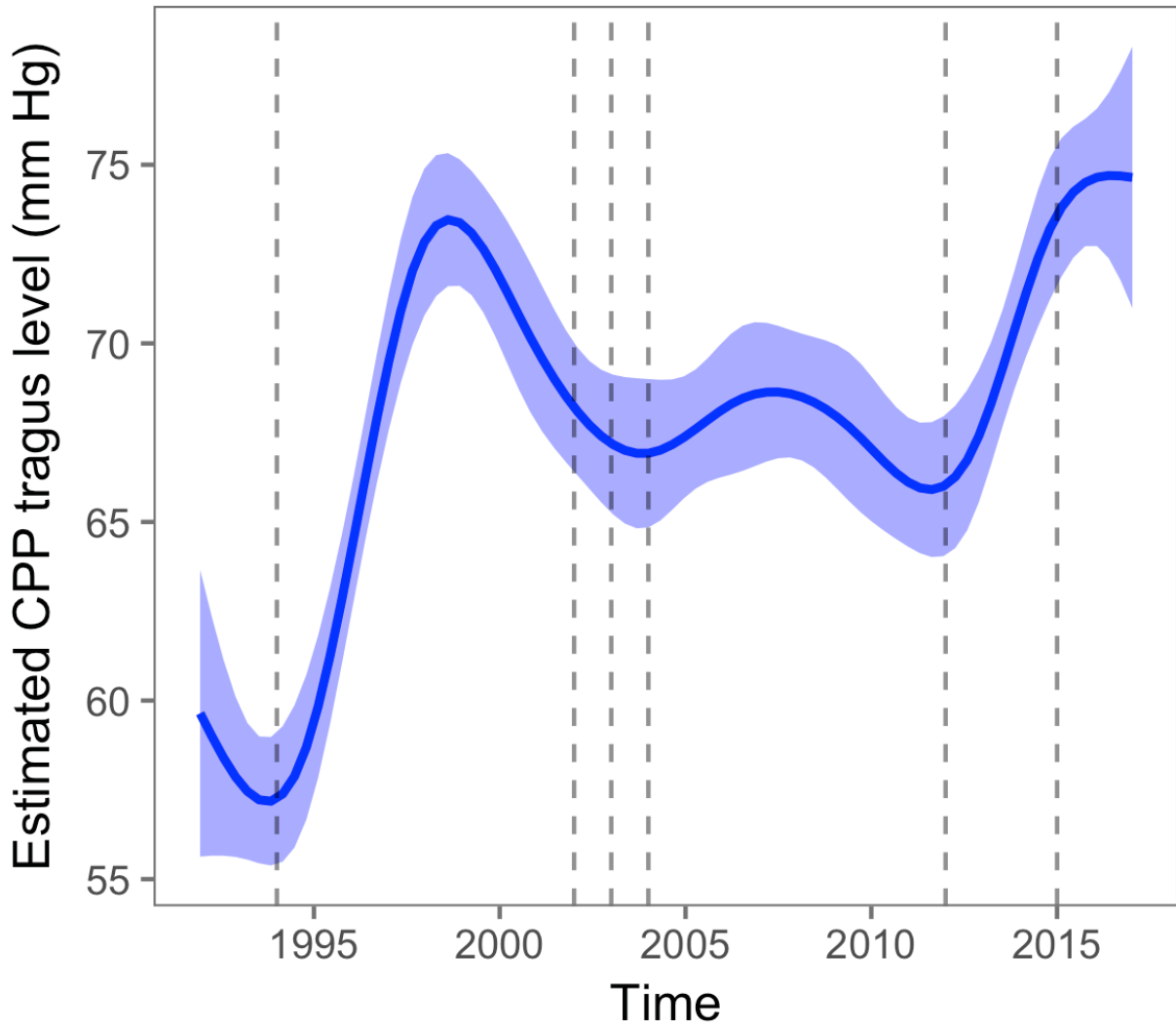


Figure 5