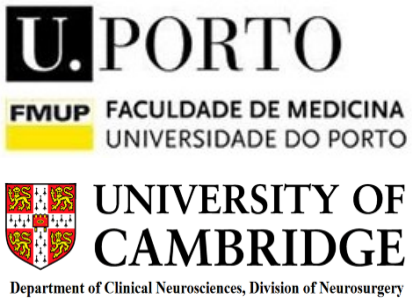

MULTIMODAL BRAIN MONITORING AND EVALUATION OF CEREBROVASCULAR REACTIVITY AFTER SEVERE HEAD INJURY

MARIA **CELESTE** PINHEIRO **DIAS** FERREIRA

THIS DISSERTATION IS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY AND EUROPEAN DOCTORATE
DOCTORAL PROGRAMME IN NEUROSCIENCES
FACULTY OF MEDICINE, UNIVERSITY OF PORTO

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PORTO | 2015

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text.
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título	*Multimodal Brain Monitoring and Evaluation of Cerebrovascular Reactivity After Severe Head Injury*
autor	*Celeste Dias*
edição	*do autor*
isbn	978-989-20-5529-9
ano	*2015*

"philosophy tells us how to proceed when we want to find out what may be true, or is most likely to be true, where it is impossible to know with certainty what is true. The art of rational conjecture is very useful in two different ways. First: often the most difficult step in the discovery of what is true is thinking of a hypothesis which may be true; when once the hypothesis has been thought of, it can be tested, but it may require a man of genius to think of it. Second: we often have to act in spite of uncertainty, because delay would be dangerous or fatal; in such a case, it is useful to possess an art by which we can judge what is probable."

in *The Art of Rational Conjecture*, Bertrand Russell

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Ao Henrique

Aos meus filhos, Catarina e Tiago

Aos meus Pais

À minha Família

To Henrique

To Catarina e Tiago

To my Parents

To my Family

AGRADECIMENTOS

Em primeiro lugar, agradeço a todos os pacientes e seus familiares que aceitaram participar neste estudo.

De modo especial e com muita honra, gostaria de agradecer aos meus supervisores Prof. José Artur Paiva e Prof. Marek Czosnyka. Estou muito reconhecida pelo tempo inestimável que eles dedicaram a este projeto de doutoramento. É difícil expressar a minha gratidão por todas as suas contribuições que tornaram esta experiência produtiva e estimulante. Sem o seu apoio e orientação constantes, seria impossível concretizar este trabalho.

Sem a amizade e enorme ajuda dos meus colegas da Unidade de Cuidados Neurocríticos, Eduarda Pereira, Elisabete Monteiro, Isabel Maia, Silvina Barbosa, Sofia Silva e Teresa Honrado, este estudo nunca poderia ter sido concluído. Gostaria também de agradecer o apoio que recebi dos outros meus colegas do Serviço de Medicina Intensiva, do Serviço de Neurocirurgia e do Serviço de Neurorradiologia.

Agradeço reconhecidamente a todos os enfermeiros e técnicos da Unidade de Cuidados Neurocríticos pela sua motivação e compromisso com este projeto.

Ao Prof. António Cerejo o meu obrigado especial pelas discussões frutíferas e preocupações clínicas que partilhamos e pelos muitos planos e ideias que em conjunto temos vindo a realizar.

Um agradecimento com amizade para os membros do Group of Brain Physiscs, University of Cambridge, UK, especialmente Dr Peter Smielewski, Dra Zofia Czosnyka, Marcel Aries, Corien Weersink, Xiuyun Liu, Georgios Varsos, Joseph Donnelly e Christian Zweifel. Gostaria também de agradecer ao Prof. John Pickard cuja experiência e conhecimento foi uma fonte de motivação.

Agradeço também aos colegas do Departamento de Matemática da Universidade do Porto, particularmente à Prof. Ana Paula Rocha, Prof. Ana Rita Gaio, Prof. Óscar Felgueiras e Maria João Silva pelo seu conhecimento especializado e colaboração na análise estatística.

Para os engenheiros de software Albano Sousa, Telmo Fonseca, Ricardo Sal e Carla Ávila um obrigado especial pela sua boa vontade e apoio, que foi fundamental para resolver os problemas da área da informática e engenharia biomédica.

Finalmente, gostaria de agradecer à minha Família pelo carinho, compreensão, paciência e apoio moral. Henrique, Catarina e Tiago, vocês são a minha força. Eu amo-vos.

ACKNOWLEDGEMENTS

Firstly, I would like to thank all the patients and their relatives who have consented to participate in this study.

Most importantly with great honour, I wish to thank my supervisors Prof. José Artur Paiva and Prof. Marek Czosnyka. I appreciate the priceless time they dedicated to this project. It is difficult to overstate my gratitude for all their contributions to make my PhD experience productive and stimulating. Without their constant support and guidance it would be impossible to materialise this work.

Without the friendship and enormous help of my colleagues from the Neurocritical Care Unit, Eduarda Pereira, Elisabete Monteiro, Isabel Maia, Silvina Barbosa, Sofia Silva e Teresa Honrado this study could never have been completed. I would also like to acknowledge the support that I have received from the other colleagues from the Intensive Care Department, Department of Neurosurgery and Department of Neuroradiology.

I am also extremely grateful to all the nurses and technical staff at the Neurocritical Care Unit for their motivation and commitment with this project.

I am indebted to Prof. António Cerejo, with whom I shared fruitful discussions and clinical concerns and with whom many plans and ideas came to be realised.

A friendly thank to the colleagues from the Brain Physics Group, University of Cambridge, UK especially Dr Peter Smielewski, Dr Zofia Czosnyka, Marcel Aries, Corien Weersink, Xiuyun Liu, Georgios Varsos, Joseph Donnelly and Christian Zweifel. I would also like to thank Prof. John Pickard whose experience and background was a source of motivation.

I am also indebted to the colleagues from the Mathematical Department of University of Porto, especially Prof. Ana Paula Rocha, Prof. Ana Rita Gaio, Prof. Óscar Felgueiras and Maria João Silva for their expert knowledge and collaboration in statistics.

To the software engineers Albano Sousa, Telmo Fonseca, Ricardo Sal and Carla Ávila a special thank for their willingness and support which was invaluable in helping me to solve informatics and biomedical engineering problems.

Finally, I would like to thank my Family for their affection, understanding, patience and moral support. Henrique, Catarina and Tiago you are my strength. I love you.

TABLE OF CONTENTS

RESUMO

SUMMARY

RESUMO

A moderna organização das Unidades de Cuidados Neurocríticos, equipadas com monitorização complexa e aplicações informáticas de recolha e integração de dados, proporciona um ambiente ímpar na área da bioinformática e uma oportunidade única para estudar in vivo os mecanismos fisiopatológicos da lesão cerebral aguda e os efeitos de tratamento, como num laboratório clínico. A Monitorização Cerebral Multimodal, com técnicas avançadas de avaliação da reatividade cerebrovascular, da oxigenação e química cerebral e do fluxo sanguíneo cerebral (FSC) permite a definição em tempo real de alvos fisiológicos usados para individualizar terapêutica e contribuir para melhorar o prognóstico do Traumatismo Cranio-Encefálico (TCE).

Esta complexidade requer abordagem multidisciplinar e, portanto, esta tese contém três dimensões: populacional, metodológica e clínica.

O estudo populacional de 10 anos de admissão hospitalar por TCE confirmou a observação empírica que a lesão cerebral traumática continua a ser um problema de saúde relevante em Portugal. Apesar da diminuição global das admissões hospitalares por TCE, as tendências observadas na idade média dos doentes, na necessidade de cuidados intensivos, nos procedimentos neurocirúrgicos e na taxa de mortalidade, todas cresceram.

A dimensão metodológica abrangeu a revisão sistemática da monitorização cerebral, a aprendizagem da bioinformática aplicada ao neurointensivismo e a aplicação da avaliação da reatividade cerebrovascular em tempo real, como base da implementação da infraestrutura técnica e do desenvolvimento do protocolo de tratamento e investigação. A formação e motivação da Equipa da Unidade para compreender o algoritmo da pressão de perfusão cerebral (PPC) ótima e o empenho na sua correta aplicação foram cruciais para a condução da investigação clínica.

A dimensão clínica incluiu um estudo piloto prospetivo onde se investigou a relevância da monitorização cerebral multimodal para determinar o alvo da "PPC ótima" e reconhecer precocemente os fenómenos cerebrais e sistémicos responsáveis por lesão secundária. A avaliação da autorregulação cerebral mostrou-se útil para identificar a PPC ótima e o manuseamento guiado por este valor associou-se a melhoria de resultados. A redução de FSC e a perturbação da autorregulação que ocorreram durante surtos de hipertensão intracraniana foram rapidamente recuperados com manuseamento adequado. Ademais, interessantes e novas questões surgiram sobre a autorregulação cerebral e renal que parecem estar ligadas entre si e relacionadas com o prognóstico dos doentes com TCE.

SUMMARY

The organization of a modern Neurocritical Care Unit with complex monitoring and computerized data collection provides a unique environment of neural bioinformatics and an opportunity to study pathophysiological mechanisms of acute brain lesion and the effect of treatment, as in a clinical laboratory. Multimodal Brain Monitoring with advanced techniques assessing cerebrovascular reactivity, brain oxygenation and chemistry and cerebral blood flow allow real-time definition of physiologic end points that may be used to customize goal-directed therapy and contribute to improve outcome from severe traumatic brain injury (TBI).

This complexity requires multidisciplinary approach, therefore the thesis has three dimensions: population, methodological and clinical.

The 10-years retrospective population study of TBI hospital admissions in Portugal confirmed the empirical observation that head injury continues to be a relevant health problem. Though incidence of traumatic brain injury admissions have decreased, trends of numbers describing patient's age, indication for intensive care treatment, neurosurgical procedures and mortality rate, all have increased.

The methodological section includes a systematic review of brain monitoring, neurocritical care bioinformatics and cerebrovascular reactivity evaluation at bedside in order to assemble the technical infrastructure and develop the management protocol. Neurocritical Care Unit staff motivation in learning the optimal cerebral perfusion pressure (CPP) algorithm and its commitment to its accurate application was crucial to conduct the clinical research.

The clinical section included a prospective study where the relevance of multimodal brain monitoring, targeting "optimal CPP" and early recognition of brain and systemic phenomenon responsible for secondary injury was investigated. Assessment of cerebral autoregulation proved useful to identify an optimal CPP and patient's management at this CPP was associated with better outcome. The reduction of cerebral blood flow and autoregulation impairment that occurred during surges of intracranial hypertension showed rapid recovery after adequate treatment. Furthermore, new questions have emerged about potential brain and kidney autoregulation link. We managed to demonstrate that better cerebral autoregulation was significantly correlated with augmented renal clearance in TBI patients and associated with better outcome.

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Marek Czosnyka and Celeste Dias. Role of Pressure Reactivity Index in Neuro Critical Care (Chapter 21). In Neuroanesthesia and Cerebro-Spinal Protection. Uchino, Hiroyuki, Ushijima, Kazuo, Ikeda, Yukio (Eds.) Springer. ISBN 978-4-431-54489-0 *(in press)*.

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Abstract and e-poster presentation at the meeting of the Neurocritical Care Society, Seattle, September 2014. Dias C, Silva MJ, Pereira E, Maia I, Barbosa S, Silva S, Honrado T, Cerejo A, Aries M, Smielewski P, Paiva J-A, Czosnyka M. Optimal Cerebral Perfusion Pressure management at bedside: medical and nursing compliance to CPP target based on continuous evaluation of autoregulation. Abstract book 255.

Abstract and e-poster presentation at the meeting of the Neurocritical Care Society, Seattle, September 2014. Dias C, Gaio AR, Moreira E, Barbosa S, Cerejo A, Donnelly J, Felgueiras O, Smielewski P, Paiva J-A, Czosnyka M. Kidney-Brain link in Traumatic Brain Injury Patients ? Abstract book 254.

ABBREVIATIONS

ABP	ARTERIAL BLOOD PRESSURE
$AVDO_2$	ARTERIOVENOUS OXYGEN TENSION DIFFERENCE
BOLD-MRI	BLOOD OXYGEN LEVEL DEPENDENT-MRI
CaO_2	ARTERIAL OXYGEN CONTENT
CBF	CEREBRAL BLOOD FLOW
CBFx	CEREBRAL BLOOD FLOW REACTIVITY INDEX
CBV	CEREBRAL BLOOD VOLUME
CSF	CEREBRAL SPINAL FLUID
CI	CONFIDENCE INTERVAL
$CMRO_2$	CEREBRAL METABOLIC RATE FOR OXYGEN
CO	CEREBRAL OXIMETRY
COx	CEREBRAL OXIMETRY REACTIVITY INDEX
CPP	CEREBRAL PERFUSION PRESSURE
CPPopt	OPTIMAL CEREBRAL PERFUSION PRESSURE
CT	COMPUTED TOMOGRAPHY
CVR	CEREBRAL VASCULAR RESISTANCE
DRG	DIAGNOSIS RELATED GROUP
$ETCO_2$	END-TIDAL CO_2
GCS	GLASGOW COMA SCORE
GOS	GLASGOW OUTCOME SCALE
HTS	HYPERTONIC SALINE
ICD-9	INTERNATIONAL CLASSIFICATION OF DISEASES
ICP	INTRACRANIAL PRESSURE
INE	INSTITUTO NACIONAL DE ESTATISTICA
IQR	INTERQUARTILE RANGE
ISS	INJURY SEVERITY SCORE
LLA	LOWER LIMIT OF AUTOREGULATION
MAP	MEAN ARTERIAL BLOOD PRESSURE
MR	MORTALITY RATE
MRI	MAGNETIC RESONANCE IMAGING
NCCU	NEUROCRITICAL CARE UNIT
NIRS	NEAR INFRARED SPECTROSCOPY
ORx	OXYGEN REACTIVITY INDEX

ORxs	OXYGEN REACTIVITY INDEX SHORT
PaO_2	ARTERIAL OXYGEN TENSION
$PaCO_2$	ARTERIAL CARBON DIOXIDE TENSION
PAx	PULSE AMPLITUDE INDEX
PET	POSITRON EMISSION TOMOGRAPHY SCAN
$PbtO_2$	BRAIN TISSUE OXYGEN TENSION
PRx	PRESSURE REACTIVITY INDEX
RAP	INDEX OF CEREBROSPINAL COMPENSATORY RESERVE
SAPS II	SIMPLIFIED ACUTE PHYSIOLOGY SCORE II
SD	STANDARD DEVIATION
TBI	TRAUMATIC BRAIN INJURY
TCE	TRAUMATISMO CRANIO-ENCEFÁLICO
TDF	THERMAL-DIFFUSION FLOWMETRY
TRISS	TRAUMA AND INJURY SEVERITY SCORE
ULA	UPPER LIMIT OF AUTOREGULATION
WHO	WORLD HEALTH ORGANIZATION
Xe-CT	XENON-ENHANCED CT FOR CBF EVALUATION
YPLL	YEARS OF POTENTIAL LIFE LOST

LIST OF FIGURES

LIST OF TABLES

LIST OF DEFINITIONS

Autoregulation	The intrinsic capacity of the cerebral vasculature to provide constant cerebral blood flow by changing cerebral vascular resistance, over a wide range of cerebral perfusion pressure.
Cerebral Perfusion Pressure	The driving force of blood flow through the cerebrovascular bed. In clinical practice, it is calculated as the difference between mean arterial blood pressure and mean intracranial pressure.
Optimal CPP (CPPopt)	Value of cerebral perfusion pressure according to the best achievable state of autoregulation calculated with PRx.
Cerebrovascular Reactivity	Changes in cerebral vascular resistance in response to vasodilatory or vasoconstrictive stimuli such as arterial pressure, partial pressure of arterial blood gases, or due to drug effects.
Pressure Reactivity	The response of the diameter of blood vessels to a change in transmural pressure.

AIM AND HYPOTHESES

AIM AND HYPOTHESES

The main aim of this research project was to evaluate the impact of optimal CPP-oriented clinical management of acute brain lesion with multimodal brain monitoring. To accomplish this objective we studied patients with severe traumatic brain injury admitted to the neurocritical care unit and requiring standard and advanced neuromonitoring.
Working hypotheses tested in the course of my PhD project are divided into three dimensions: population, methodological and clinical.

TRAUMATIC BRAIN INJURY HOSPITAL ADMISSION IN PORTUGAL

The evolution of epidemiological dimensions of adult TBI patients admitted in Portuguese hospitals during the last decade is very poorly known. In fact, reliable characterization of healthcare resource utilization due to TBI, including ICU admission, neurosurgical procedures and their impact on mortality or morbidity are scarce. Nevertheless, TBI continues to be considered as "a silent epidemic" with a considerable socio-economic impact and being a major cause of morbi-mortality, often leading to permanent disability.
HYPOTHESIS 1: Hospital health care resource utilization due to adult traumatic brain injury in the last decade in Portugal is changing but TBI still remains an important health problem.

MONITORING OF CEREBROVASCULAR PHENOMENA IN TBI PATIENTS

Intracranial hypertension, which frequently occurs after TBI, is one of the most damaging aspects of acute brain lesion and is independently associated with poor outcome. Intracranial hypertension may develop due to vascular or nonvascular mechanisms. The nonvascular mechanisms include oedema, increased mass lesion and increased resistance to cerebral spinal fluid outflow. The vascular mechanisms include active cerebral vasodilation (such as plateau waves), passive distension in the absence of autoregulation and venous outflow obstruction. Intracranial hypertension is accompanied by worsening of brain compliance and cerebral metabolic and haemodynamic disturbances evolving to progressive secondary injury. Monitoring of these secondary insults may be helpful in patients with TBI.
HYPOTHESIS 2: During spontaneous cerebrovascular phenomena such as plateau waves of intracranial pressure specific changes in cerebral hemodynamic indices occur.

HYPOTHESIS 3: Management of intracranial hypertension with hypertonic saline can be monitored and explained with multimodal brain monitoring.

CEREBRAL AUTOREGULATION AND OPTIMAL CPP

Autoregulation is frequently disturbed after TBI. There are several approaches suitable for continuous determination of autoregulation at bedside, but the cerebrovascular pressure reactivity index (PRx) is the best validated one. Based on the fact that intact autoregulation is associated with favourable outcome, it would probably be beneficial to follow the individual autoregulatory curve calculated at bedside and to manage CPP according to the best achievable state of autoregulation (optimal CPP) estimated with PRx. *HYPOTHESIS 4: Optimal CPP management is possible to be conducted prospectively at bedside using pressure reactivity index analysis, and shows a potential to improve outcome following TBI.*

AUTOREGULATION AND SYSTEMIC PATHOPHYSIOLOGY AFTER TBI

The injured brain is more vulnerable to ischemic conditions such as hypotension and hypoxia that could lead to increased neurological damage. On the contrary, neural and humoral control of physiological systems in the body is affected by TBI. There are observable changes in the physiological functioning of the brain and body following TBI involving cerebral autoregulation, autonomic nervous system and cardiovascular, pulmonary and renal systems. Understanding the systemic effects of brain injury may provide some unique and distinctive perspectives as to the effective management after TBI.

HYPOTHESIS 5: Disturbance of cerebral autoregulation is associated with systemic pathophysiology especially with kidney function.

INTRODUCTION

TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) or Head Injury are defined as brain and head injuries caused by external trauma (1). Together, they are a major cause of mortality and permanent disability, often considered as a silent epidemic (2), responsible for relevant consumption of health care resources (3).

The annual incidence of TBI is estimated at up to 500 per 100,000 in the U.S. and Europe. Over 200 per 100,000 individuals are admitted to hospitals each year in Europe (4). According to epidemiological surveillance the nature of TBI is changing over time. The World Health Organization (WHO) predicts that deaths from road traffic incidents (primarily due to TBI) will double between 2000 and 2020 in low- and middle income countries (WHO/OMS, 2009) and that in developed countries the occurrence of TBI will mainly increase in people aged over 60 years.

In Portugal, the incidence of TBI is difficult to ascertain, but between 1996 and 1997, according to Santos, ME *et al*, was 137 per 100,000 (5). From national statistical data published in the webpage of Instituto Nacional de Estatistica (INE), one can read that the years of potential life lost (YPLL) as well as mortality rate (MR) due to traffic accidents are decreasing (Figure 1).

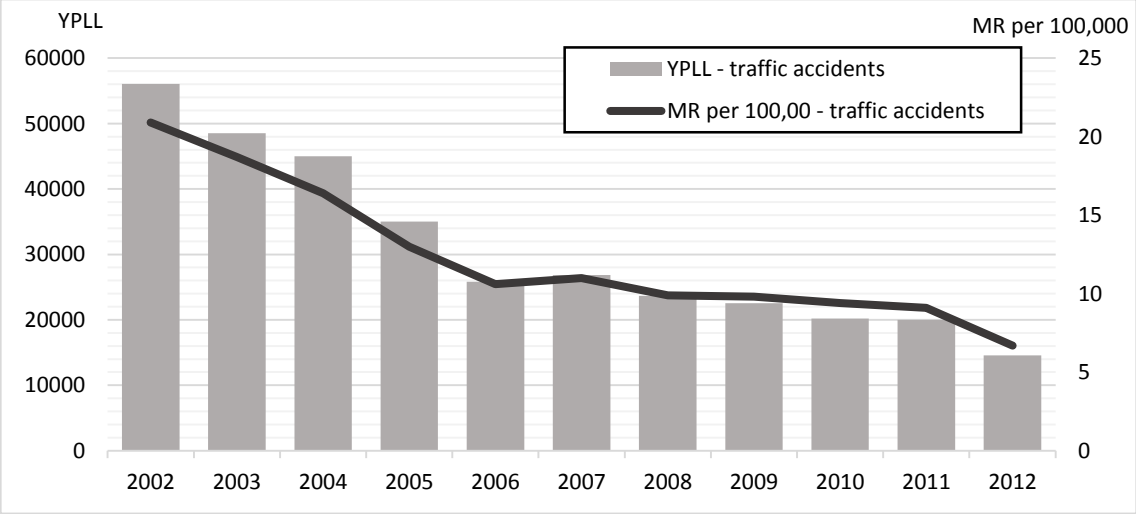


Figure 1 - Years of potential life lost (YPLL) and mortality rate (MR) due to traffic accidents per 100,000 in Portugal from 2002 to 2012 (from INE public statistical data).

We retrospectively studied health records included in the National Diagnosis Related Groups (DRG) Database of adult patients admitted to Portuguese hospitals with ICD-9 (International Classification of Diseases) diagnostic codes of TBI from 2000 to 2010. Based on a large cohort with a broad study period, we concluded that overall hospital admissions due to TBI decreased, but since 2007 stabilized on average around 5525 cases per year. The type of patients and the external cause of TBI has also shifted from younger to older people and from traffic accidents to falls. Moreover, moderate / severe TBI, hospital mortality and ICU admission percentages slightly increased over time (Figure 2).
The results of this study were published in Acta Medica Portuguesa, *(Publication I)*.

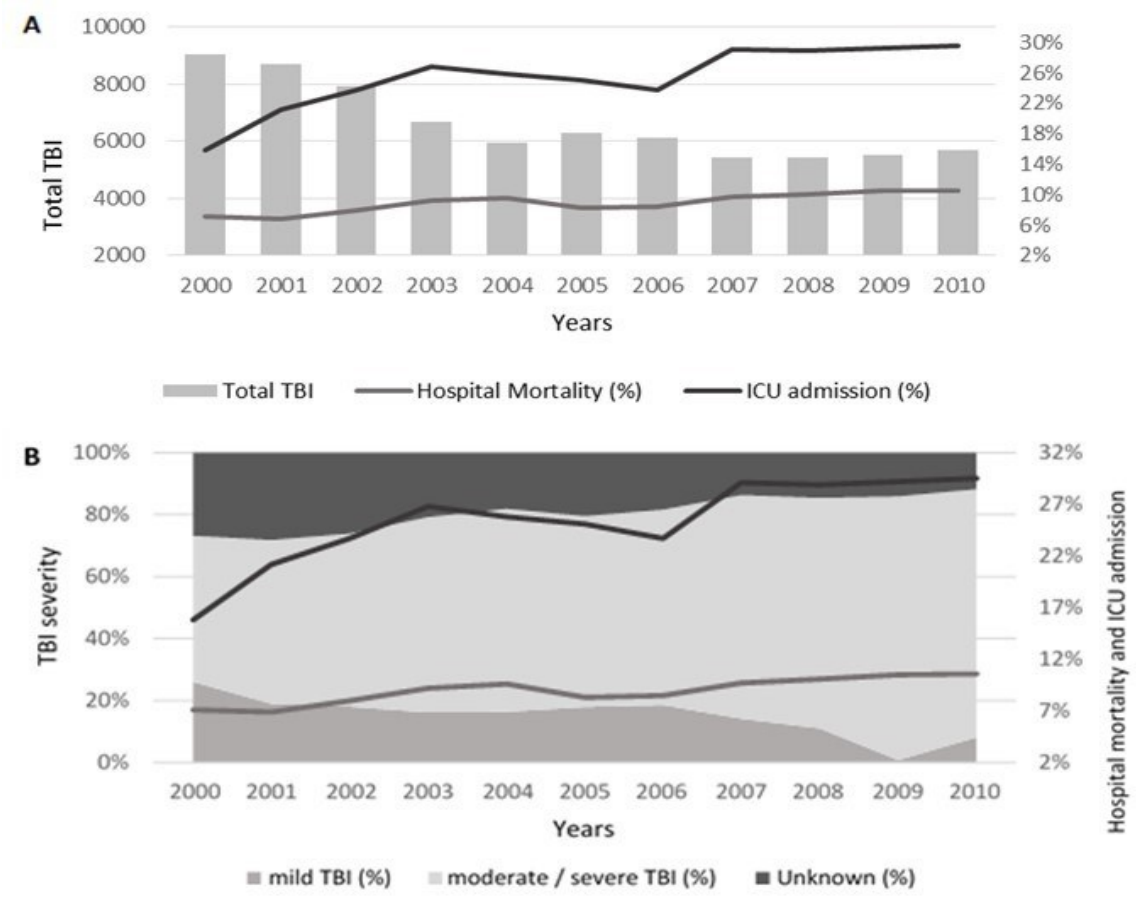


Figure 2 – A. Total number of hospital admissions due to TBI from 2000 to 2010 (grey bars), hospital mortality (grey line) and Intensive Care admission percentages (black line). B. Severity of TBI hospital admissions from 2000 to 2010 (mild - light grey area, moderate to severe – grey area and unknown – dark grey area) and percentage of hospital mortality and ICU admission (grey line and black line, respectively) (*from* National DRG statistical data).

NEUROCRITICAL CARE AND MULTIMODAL BRAIN MONITORING

Severe TBI is a very dynamic process that requires a continuum of acute care. From this point of view neurocritical care management starts in the pre-hospital period, at the scene of the accident, extends through the emergency department, the radiology department, and the operating room before patients are admitted to the Intensive Care Unit (6).

The importance of management of primary lesion and the early identification of secondary insults after TBI is well established and the aim of the intensive care management is to anticipate, prevent and treat timely. The phrase "TIME IS BRAIN" emphasizes the vulnerability of the human brain and the urgency of therapeutic interventions (7).

Neurocritical care is an evolving subspecialty of intensive care medicine (8).A dedicated multidisciplinary team of health professionals: nursing, supervision of ICU care by neurointensivists and involvement of senior neurosurgeons, together with implementation of protocols incorporating recommendations is likely to have a positive impact on patient management and outcome (9). Guidelines for management of TBI have contributed to significant changes in practice (10, 11). Conversely, neurocritical care progressed from primary control of intracranial pressure (ICP) and maintenance of cerebral perfusion pressure (CPP) to a multidimensional approach of neuronal rescue and protection based on clinical evaluation, laboratory findings, imaging studies and continuous multimodal brain monitoring (12). To prevent further damage to vulnerable brain, especially during the early posttraumatic phase, specific knowledge is essential. An in-depth understanding of linked pathophysiologic cascades must be accompanied by dedicated neuromonitoring.

The organization of modern neurointensive care units with complex monitoring and computerized data collection provides a unique environment of neurocritical care bioinformatics (13, 14) and an opportunity to study pathophysiological mechanisms of acute brain lesion and the effect of treatment, as in a clinical laboratory (Figure 3).

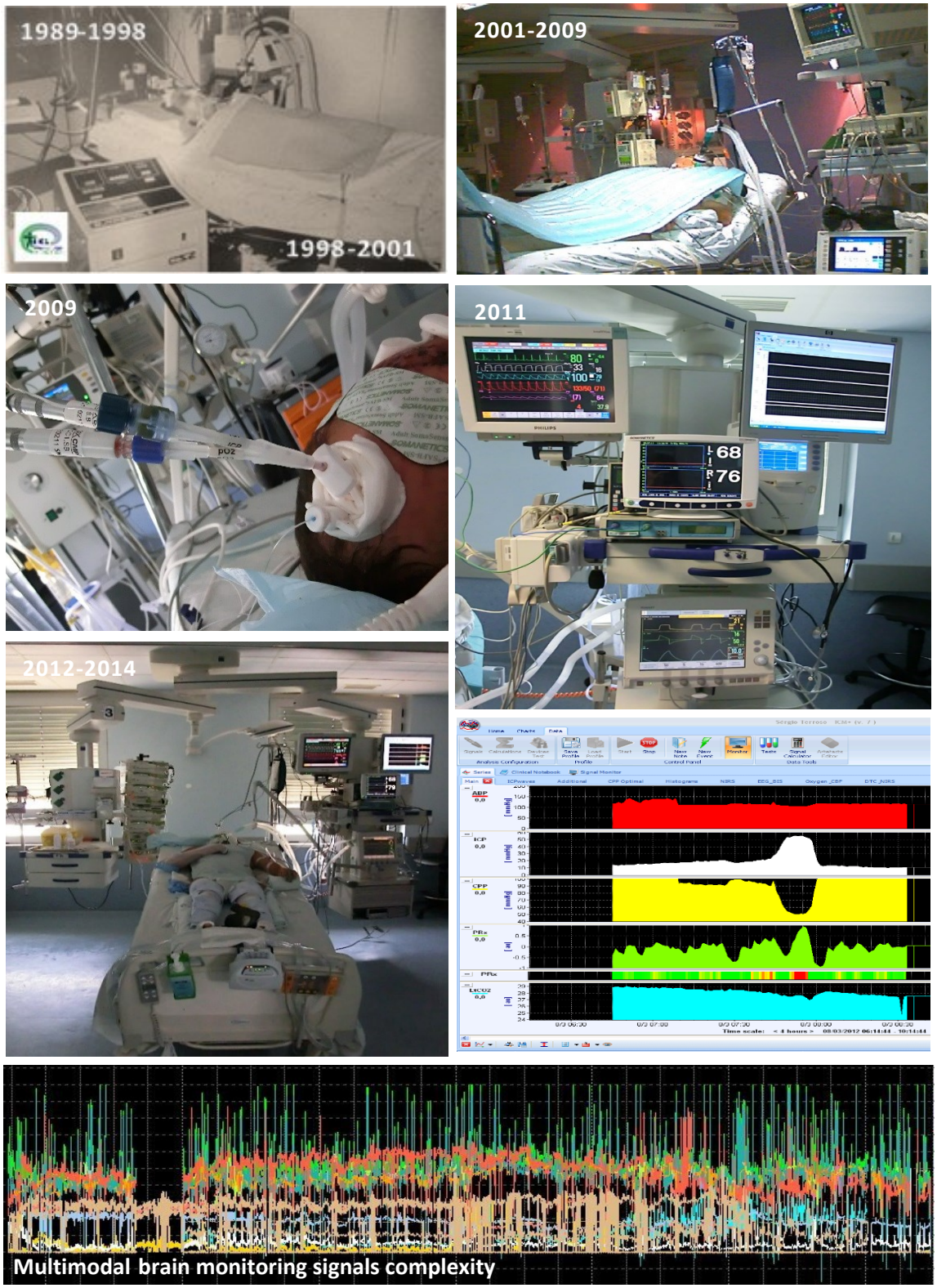


Figure 3 - The neurocritical care environment evolution over time. Neurocritical Care Unit and multimodal brain monitoring in Centro Hospitalar São João from 1989 to 2014.

INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE

INTRACRANIAL PRESSURE

Intracranial pressure (ICP) is derived from cerebral blood flow (CBF), cerebrospinal fluid (CSF) circulation and volumetric changes in brain tissue within the stiff skull (15).

In 1950, Janny published the first clinical studies about ICP (16), extended and supplemented by Lundberg in 1960 with report of accurately measurement of ICP amplitude and waveforms in both normal and pathological conditions (17, 18).

Since then ICP monitoring has become a vital part in the management of patients with head injury. The most reliable methods of ICP monitoring are:

- ventricular catheters, considered to be a ‘‘golden standard’’ method of measure global ICP. Ventricular catheters allow recalibration and therapeutic drainage of CSF but have significant complications including haemorrhage, occlusion and infection.
- Intraparenchymal fiberoptic (Camino, Integra, Plainsboro, USA) or microtransducer probes (Codman, DePuySinthes, Massachusetts, USA) have a minimal associated risk of complications, but can only be calibrated before insertion. Drift over time is usually small, however it cannot be corrected during monitoring.

Normal range value of ICP for an adult in supine position is 0 -15 mmHg.
Critical values of ICP may vary between individual patients but current consensus is to treat ICP exceeding the 20-25 mmHg threshold (12, 19). Intracranial hypertension may develop due to vascular or nonvascular mechanisms. The nonvascular mechanisms include oedema, increased mass lesion and increased resistance to CSF outflow. The vascular mechanisms include active cerebral vasodilation, passive distension in the absence of autoregulation and venous outflow obstruction. Regardless the mechanism, it is between 20 and 30 mmHg, where mortality rate starts to increase with ICP (20, 21).

Continuous ICP analysis should be considered in a dynamic sense taking into account its spontaneous and adaptive variations, namely ICP waves and dynamic of autoregulation. ICP waveform has three components that can be quantified by spectral analysis or studied in time-domain (22-24). These components are related to vascular oscillations, either directly such as the *pulse waves* and *slow waves*, or indirectly such as *respiratory waves* (Table 1).

Table 1 - Classification of Intracranial Pressure (ICP) waveforms.

Types of ICP waves	Frequency Hz	Oscillation cpm	Amplitude mmHg
rapid waves			
pulse waves	0.666-3	40-180 (=HR)	7-15
respiratory waves	0.133-0.333	8-20 (=RR)	
slow waves	0.005-0.055	0.3-3	
A waves (infra B)	occasional	occasional	40-100
B waves	0.083-0.033	0.5-2	up to 20
C waves (ultra B)	0.066-0.133	4-8	up to 50

(*adapted from Lemaire et al, ActaNeurochir, 2002*). HR – heart rate; RR – respiratory rate

ICP PULSE WAVE: ICP pulse waveform has a fundamental frequency equal to the heart rate and consists of three peaks named P1, P2 and P3 and one notch that are related to arterial pulse and brain compliance. P1 (percussion wave) represents systolic arterial pulsation, P2 (tidal wave) reflects intracranial compliance, P3 represents venous wave and the notch results from closure of the aortic valve. In normal conditions, P1 > P2 >P3, but when brain compliance starts to decrease, the amplitude of P2 increases and may exceed P1. This phenomenon is known as “rounding” or as “monotonous” appearance of the ICP waveform (25) (Figure 4).

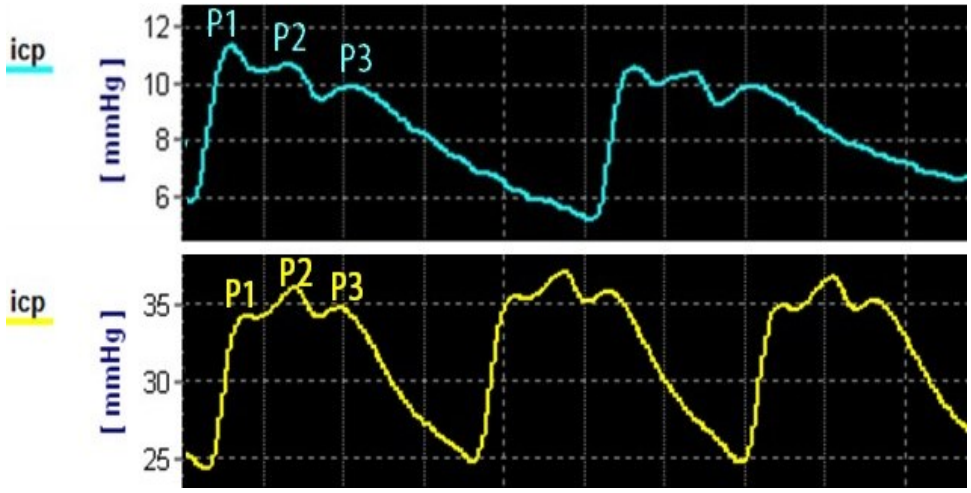


Figure 4 - Intracranial Pressure (ICP) pulse waveform and its three pulsatile components (P1, P2, P3). P1 the ‘‘percussion’’ wave, P2 the ‘‘tidal’’ wave and P3 the dicrotic notch. Under normal values of ICP the three peaks relate with each other as P1 > P2 > P3. When brain compliance decreases and ICP starts to rise, the waveform modifies with an increase in amplitude followed by an inversion of P2/P1 ratio.

ICP A-WAVES: A-waves or “plateau waves” are defined as sudden and relevant increases in ICP up to 40-100 mmHg with duration of 5 to 20 minutes (26) (Figure 5). Plateau waves are associated with working cerebrovascular reactivity and low cerebrospinal compensatory reserve (27) related to several acute or chronic brain pathologies such as head injury (28), spontaneous subarachnoid haemorrhage (29, 30), intracerebral haemorrhage (30), tumours (31), benign intracranial hypertension (30) and craniosynostosis (32). The top of the plateau wave is characterized by a decrease in CVR that accompanies the increase in CBV and a decrease in CPP, $PbtO_2$ and CBF. Concomitantly cerebrovascular reactivity indices that evaluate pressure and oxygen reactivity (PRx and ORx) are affected (33). Plateau waves are associated with worse outcome if intracranial hypertension is sustained (longer than 30–40 min) and should be actively treated (28).

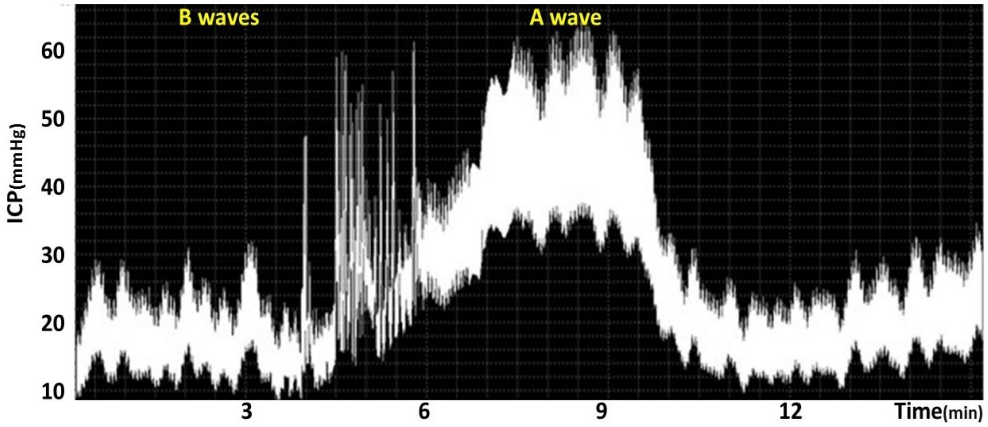


Figure 5 - Examples of slow waves of intracranial pressure type B and type A of Lundberg.

ICP B-WAVES: B-waves are rhythmic oscillations of ICP up to 20 mmHg with frequencies of 0.5-2 cycles per minute (17). B waves are associated with fluctuations of CBF and ABP (34) as well as cerebral oximetry detected with near infrared spectroscopy (35). B-waves may be observed in healthy volunteers (using non-invasive indirect measurement like TCD or NIRS) and in patients with normal pressure hydrocephalus during REM sleep or be associated with snoring and sleep apnoea. These waves may also anticipate “A” waves indicating the need to treat elevated ICP.

ICP C-WAVES: C-waves have a frequency of 4-8/min and low amplitude. They correspond to Traube-Hering-Meyer fluctuations in ABP due to sympathetic tone.

CEREBRAL PERFUSION PRESSURE

Perfusion pressure of an organ is the difference between the arterial input and venous output pressures that drive flow. Cerebral perfusion pressure is defined as the difference between the mean arterial blood pressure at head level and the mean venous pressure of cortical or bridging veins. In pathological conditions ICP exceeds venous pressure and therefore the driving force of intracranial flow becomes the difference between mean arterial pressure and intracranial pressure.

$$CPP=MAP-ICP$$

Consensus Guidelines for the management of severe traumatic brain injury recommend management of CPP between 50-70 mmHg (10, 36).
However, CPP target values have changed over time. Management strategies based on population CPP-target (Rosner concept) (37) have not demonstrated clinical outcome benefit (21, 38) and the alternative approach based on volume-target (Lund concept) (39) might increase the risk of brain ischemia (40, 41).
There are several reasons which may explain this CPP target uncertainty:
- age (42) and previous disease state (43, 44)
- type of acute brain lesion and time course of the disease (45-50)
- ICP higher values and lower limit of CBF autoregulation (51)
- different methodologies of ABP measurement, namely transducer level related to head up elevation (52-54)
- lack of class I evidence to inform the optimal CPP target for any type of acute brain lesion.

Adequate individual CPP targets are therefore difficult to define and one of the leading controversies in neurocritical care today concerns *the optimal CPP goal*.

Detailed information about optimal CPP and CPPopt-target therapy concept are described in a section below.

CEREBRAL OXYGENATION

Management of acute brain injury centred on basic control of ICP and CPP does not prevent cerebral hypoxia in some patients (55). Cerebral oxygenation monitoring evaluates the balance between oxygen delivery and consumption (56) and oxygen guided management could lead to improve neurologic outcome (57). There are several invasive and non-invasive continuous methods of monitoring local or regional brain oxygenation.

BRAIN TISSUE OXYGENATION

Direct measurement of local $PbtO_2$ with an intraparenchymal probe is the golden standard for continuous oxygen monitoring in NCCU. Licox (Integra Neuroscience, Plainsboro, USA), a closed polarographic Clark-type electrode that measures oxygen content around 15 mm^3 of tissue, has been widely used.

Because of brain blood flow and metabolism heterogeneity, normal values depend on the location of the probe. Hence, probes are recommended to be placed in the white matter and post insertion head-CT confirmation is needed to interpret readings.

The normal range is 25-50 mmHg and $PbtO_2$ < 15mmHg is considered the critical threshold for hypoxia (58). The interaction between blood oxygen tension and CBF is an important determinant of $PbtO_2$. In fact, $PbtO_2$ seems to reflect the cumulative value of CBF and the arteriovenous difference in oxygen tension (59, 60).

Brain hypoxia ($PbtO_2$ < 10-15 mmHg) is associated with worse outcome and increases the likelihood of death after severe TBI (61, 62).

Algorithms of $PbtO_2$-directed therapy should incorporate the management of the several causes of tissue hypoxia (hypoxic, anaemic, ischemic, cytopathic and hypermetabolic) (63, 64).

CEREBRAL OXIMETRY WITH NIRS

Cerebral oximetry provides continuous, non-invasive real-time monitoring of changes in regional oxygen saturation of brain tissue by near-infrared spectroscopy (NIRS) technology (65). Near-infrared light at the wavelength range 660-940 nm passes through skin and skull and is absorbed by biological chromophores like Hb and HbO_2 (66). NIRS allows measurements of changes in oxyhemoglobin, deoxyhemoglobin, blood volume, and oxygen availability within the monitored tissue (67). There are several non-invasive cerebral

oximetry devices and in this work we used INVOS 5100C (Covidien, Mansfield, USA) that is widely applied in clinical practice. It uses cutaneous sensors with diodes that emit infrared light at two wavelengths (730 and 810 nm) and a proximal and distal detectors that permit separate data processing of shallow and deep optical signals. The device uses mathematical algorithms and the final value yields a regional venous-weighted percent saturation that represents the balance between frontal cortical O_2 supply and consumption (68). Normal range values is 55-75%. NIRS-derived cerebral oximetry monitoring provides a non-invasive surrogate marker of CBF allowing assessment of autoregulation and calculation of optimal CPP (69-71).

CEREBRAL BLOOD FLOW WITH THERMAL-DIFFUSION FLOWMETRY

Continuous direct bedside monitoring of CBF would be helpful to manage acute brain injury and is a long-standing goal in neurocritical care. The normal range for CBF in the white matter is 18-25 ml/100g/min (72, 73). Classic research with animal stroke models has shown that there are CBF thresholds associated with the cessation of electrocortical activity (18ml/100g/min), cellular membrane failure (10ml/100g/min), and rapid transition to infarction (5ml/100g/min) (74).

Thermal-diffusion flowmetry (TDF) with QFlow 500 probe (Hemedex, Cambridge, USA) is based on thermal conductivity and provides a quantitative measurement of regional CBF. The probe is inserted in the white matter 25 mm below the dura and CBF is calculated around 8 mm^3 of brain tissue. Automatic recalibration of the system occurs within a pre-set time interval (from 2 min to 2 hours) to quantify current thermal properties of the tissue and thus resulting in a 2-5 min interruption of data continuity. No studies have evaluated the CBF thresholds obtained from TDF. However, based on values cited in the literature, it is reasonable to assume an ischemic threshold of 15–18 ml/100g/min.
Regional CBF values obtained with TDF are in good agreement with Laser Doppler flowmetry (the gold-standard technique for instantaneous, continuous, and real-time measurements of regional CBF) and Xe-CT (72). Persistent low TDF-CBF values in the early post injury period is associated with poor clinical outcome in TBI (75). TDF-CBF monitoring values have demonstrated good real-time response of CBF related to vessel occlusion (76), cerebral autoregulation and vasoreactivity (77). Nevertheless, TDF-CBF has several limitations related to baseline shifts of CBF and instability of the thermal field of the

tissue that may occur and influence the accuracy of the measurement method (78, 79). Continuous monitoring of CBF and CPP allows calculation of flow-related autoregulation and estimation of optimal CPP (80).

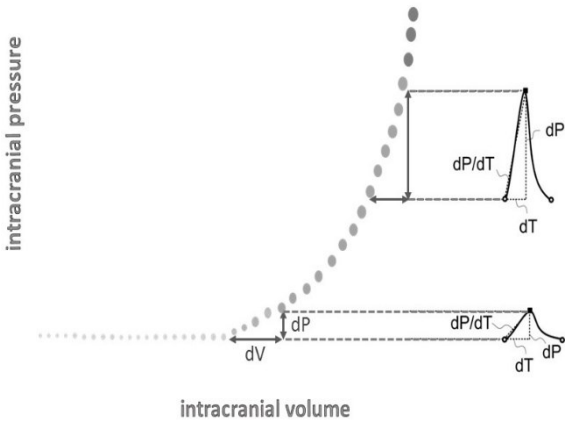
The relevance of multimodal brain monitoring in clinical practice was reviewed and published in the International Journal of Clinical Neurosciences and Mental Health, *(Publication II)*.

PRESSURE AND VOLUME DYNAMICS

BRAIN COMPLIANCE AND PRESSURE VOLUME RELATIONSHIP

Adult intracranial space is composed of three components: approximately 80-85% brain parenchyma, 7-10% cerebral spinal fluid (CSF) and 5-8% cerebral blood volume in vascular network. The Monro-Kellie doctrine states that this global volume within the rigid skull is constant and generates the intracranial pressure (ICP). Changes in any one component are compensated by equivalent changes of another; otherwise ICP will increase. The pressure-volume relationship ($\Delta P/\Delta V$), first described by Langfitt in 1966 (81, 82), is an exponential curve that describes brain elastance and compliance (83) (Figure 6).

Figure 6 - The normal exponential intracranial pressure-volume curve first introduced by Langfitt. At normal intracranial pressure levels, the increase in volume (dV) leads to a small increase in pressure (dP) and hence lower amplitude (lower waveform). With increases in intracranial pressure, the concurrent reduction in intracranial compliance leads to a dramatic increase in pressure even with a small increase in volume (upper waveform). (adapted from Marmarou et al, JNS 1975)



Compensatory reserve of craniospinal space described by pressure-volume curve has three parts (Figure 7):

- a first part with good compensatory reserve with low ICP and low amplitude, despite increase in intracranial volume. ICP waveform presents a normal configuration with P1>P2>P3 (Figure 7, panel A).
- a second part with poor compensatory reserve where the relationship between volume and pressure is nonlinear. In the low range of ICP, but already presenting an important increase in volume (Figure 7, panel B), ICP waveform changes and P2 becomes higher than P1. At this point, (Figure 7, panel C) further small increments of volume trigger significant rise in ICP and amplitude with intracranial hypertension and high P2/P1 ratio.

- a third part with disturbed cerebrovascular response with very high ICP (Figure 7, panel D), collapse of vascular bed and low CPP.

Information about brain compliance can also be obtained as proposed by Czosnyka (84) by calculating the linear correlation coefficient (R) between mean ICP (P) and ICP pulse amplitude (A), designated RAP index. RAP = 0 shows a good pressure-volume compensatory reserve (Figure 7, panel A), RAP = +1 denotes low compensatory reserve (Figure 7, panel C) and RAP = -1 indicates exhausted compensatory reserve with cerebrovascular derangement (Figure 7, panel D).

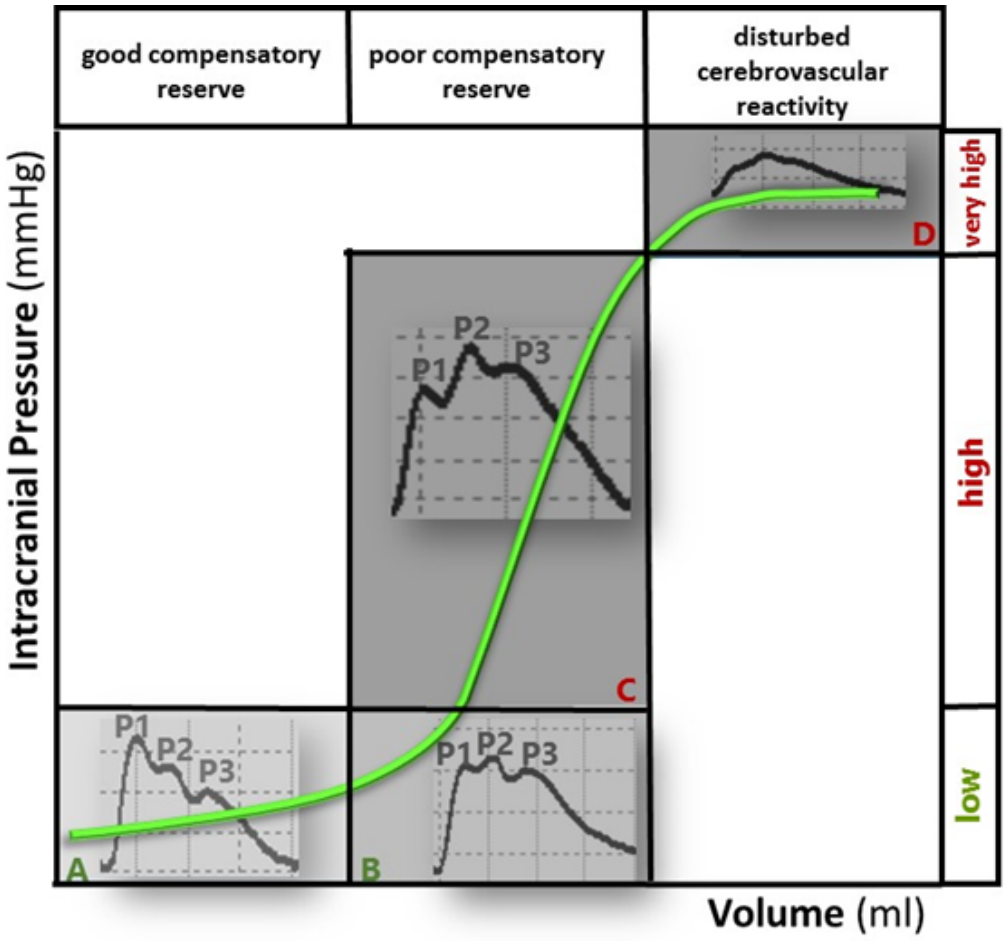


Figure 7 - Brain compensatory reserve and pressure-volume curve. Relationship between pulse waveform, mean intracranial pressure and elastance. A. good compensatory reserve with low ICP and low amplitude, despite increase in intracranial volume. ICP waveform presents a normal configuration with P1>P2>P3. B. In the low range of ICP, but already presenting an important increase in volume, ICP waveform changes and P2 becomes higher than P1. C. further small increments of volume trigger significant rise in ICP and amplitude with intracranial hypertension and high P2/ P1 ratio. D. disturbed cerebrovascular response with very high ICP, collapse of vascular bed and low CPP. *(adapted from Balestreri et al, ActaNeurochir, 2004)*

CEREBRAL BLOOD FLOW AND CEREBROVASCULAR REACTIVITY

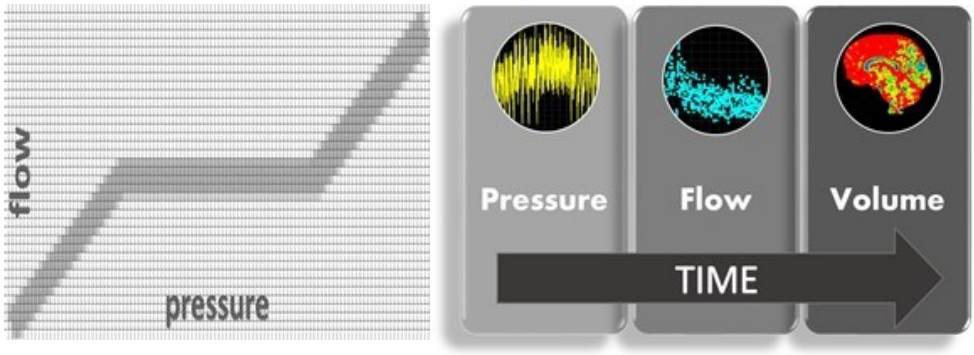


Figure 8 – Pressure / flow curve with autoregulation plateau, first described by Lassen in 1959. The relationship between pressures, flow and volume helps to understand the intracranial fluids dynamics of blood and cerebrospinal fluid over time.

CEREBRAL BLOOD FLOW

Preservation of adequate cerebral blood flow is vital to normal brain functioning. The brain has a high metabolic rate and accounts for almost 20% of total body oxygen consumption and 25% of glucose utilization. It has no metabolic storage and is unable to maintain its integrity through anaerobic metabolism. Therefore, it depends on a constant blood flow of nearly 15% of cardiac output (56).

In the nineteenth century, Theodor Meynert hypothesized for the first time that the partial hyperaemia seen in cortical areas was an indication of their partial awaking – functional hyperaemia. In spite of this observation, the modern era of CBF knowledge started in the sixties with the work of Niels Lassen and David Ingvar (Figure 8) (85, 86). These studies relate anatomical vascular structure with function and intrinsic and extrinsic regulation (87).

Global CBF is approximately 50 ml/min/100g of tissue, but local CBF varies from 50-75 ml/min/100g in gray matter to 25-45 ml/min/100g in white matter. Under normal circumstances, CBF remains almost constant and makes instantly adjustments to neuronal metabolic demands. Strong evidence of neuronal function and vascular coupling has been obtained with in vivo methods (88-90). This need for continuous and adapted flow to

demands is regulated by a variety of mechanisms of cerebrovascular reactivity, which remains incompletely understood:

- neurovascular coupling due to metabolic demands (91)
- autoregulation due to changes in cerebral perfusion pressure and cerebrovascular resistance (60, 92, 93)
- vasoreactivity related to carbon dioxide, pH and blood oxygen content (94, 95)
- intrinsic and extrinsic autonomic nerve activity (96)
- vasoactive humoral factors produced by endothelium, neurons and glial cells, namely adenosine, oxygen and nitrogen reactive species, purines, ions such as potassium, prostanoids and some neurotransmitters
- reactivity to drugs such as acetazolamide.

CEREBROVASCULAR REACTIVITY

Cerebrovascular reactivity reflects the changes in cerebral vascular resistance in response to vasodilatory or vasoconstrictive stimuli such as arterial pressure, partial pressure of arterial blood gases, or due to drug effects. Understanding the normal mechanisms of cerebrovascular reactivity that regulate cerebral blood flow (CBF) and the modifications induced by acute brain lesion and medical interventions is fundamental to the adequate management of neurocritical patients.

AUTOREGULATION

Cerebrovascular autoregulation was first described by Lassen (97) as the inherent capacity of active adjustment of cerebral vascular resistance (CVR) to maintain flow despite the variations of arterial blood pressure. Latter this definition was extended by including cerebral perfusion pressure (CPP) instead of arterial blood pressure (ABP).
Classically, over a wide range of CPP from 50 to 150 mmHg (93, 98, 99), CVR increases to assure constant CBF (plateau region). The lower inflection point is designated lower limit of autoregulation (LLA) and the upper inflection point is the upper limit of autoregulation (ULA). Outside the range of autoregulation flow becomes pressure dependent and arteriolar diameter varies passively (Figure 9).

Contemporary research indicates a far more pressure-passive CBF than the classical definition with a narrower plateau region and less efficacious buffering capacity against decreases than increases in CPP (100). In fact, the mechanism of autoregulation has hysteresis, i.e., the brain defends more effectively against acute hypertension than hypotension. Additionally, the pressure limits of autoregulation vary with age (101, 102) and pathologic conditions such as chronic arterial hypertension (103) or acute brain lesion (47). Autoregulation is also modulated by mechanisms that cause cerebral vasoconstriction and vasodilation.

$$CBF = \frac{CPP}{CVR}$$

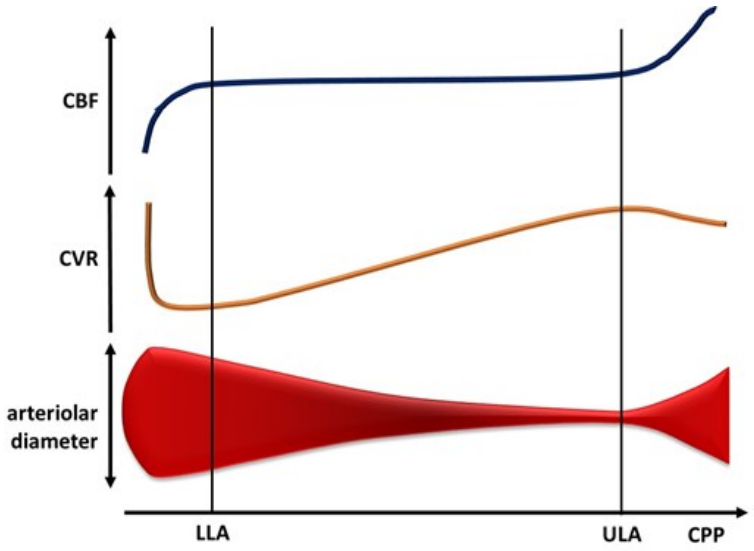


Figure 9 – CBF (cerebral blood flow), CVR (cerebrovascular resistance) and arteriolar diameter variation with CPP (cerebral perfusion pressure). (*adapted from Paulson et al*)

VASOREACTIVITY

Vasoreactivity is defined as the cerebrovascular resistance response to changes in arterial carbon dioxide pressure ($PaCO_2$), arterial oxygen pressure (PaO_2) and arterial oxygen content (CaO_2).

CO_2 – VASOREACTIVITY: Hypercapnia produces vasodilation, increases cerebral blood volume (CBV) and decreases CVR, whereas hypocapnia produces vasoconstriction. Both large intracranial and pial arteries respond to CO_2 oscillations: large vessels are the "first-line" defence of CBF and small subarachnoid pial vessels modulate regional blood flow. Within a $PaCO_2$ range from 20 to 100 mmHg a change in 1 mmHg of $PaCO_2$ induces a 4% average change in CBF (104) (Figure 10).

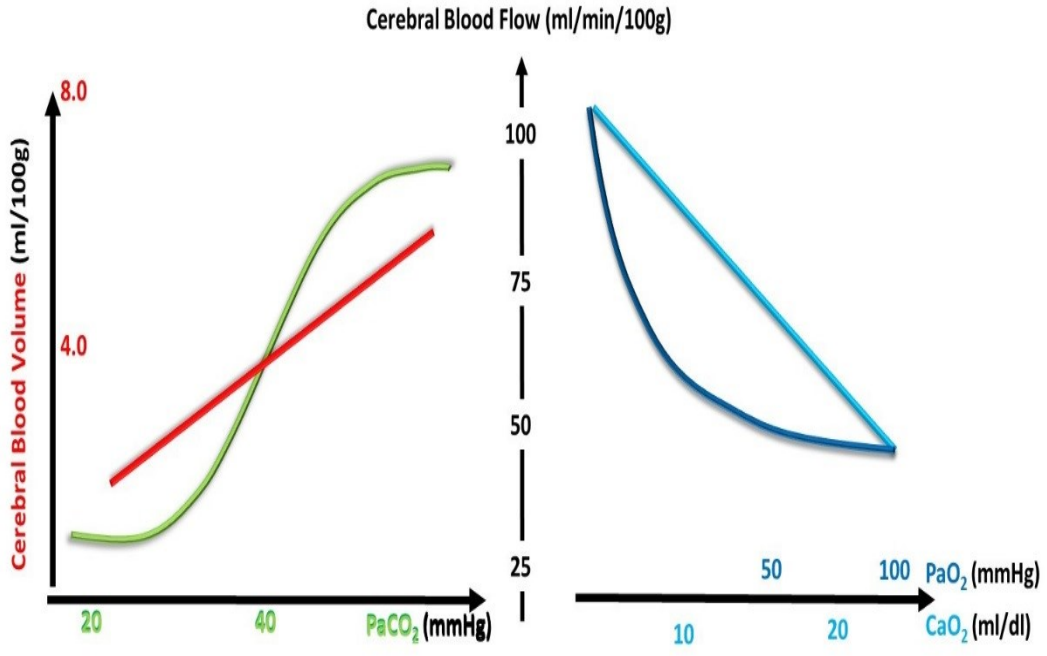


Figure 10 - Left chart: comparison of the response of cerebral blood flow (CBF green line; ml/min/100g) and cerebral blood volume (CBV red line; ml/100g) to arterial carbon dioxide tension ($PaCO_2$). Right chart: comparison of the response of cerebral blood flow to arterial oxygen tension (PaO_2; dark blue line) and oxygen arterial content (CaO_2; light blue line).

O_2- VASOREACTIVITY: CBF increases with PaO_2 below 50 mmHg but response to oxygen is controlled by CaO_2 rather than PaO_2. Inverse relationship between blood haematocrit and CBF seems to be a function of oxygen delivery (105).

Cerebrovascular reactivity to hypoxia is dependent on basal $PaCO_2$: decreases with hypocapnia and increases with hypercapnia.

Vasoreactivity and autoregulation are not independent mechanisms: progressive hypotension impairs the response of cerebral circulation to changes in $PaCO_2$ and progressive increase in $PaCO_2$ narrows the autoregulatory CPP range. In the figure 11 we present an example of recovery of autoregulation evaluated at bedside with cerebrovascular

pressure reactivity (PRx) after mild hyperventilation and without changing CPP. Further detailed information about PRx is presented in next sections.

Disturbed autoregulation may coexist with intact CO_2-vasoreactivity (dissociated vasoparalysis) and in some acute disease states, autoregulation may be regained by induced hypocapnia (106).

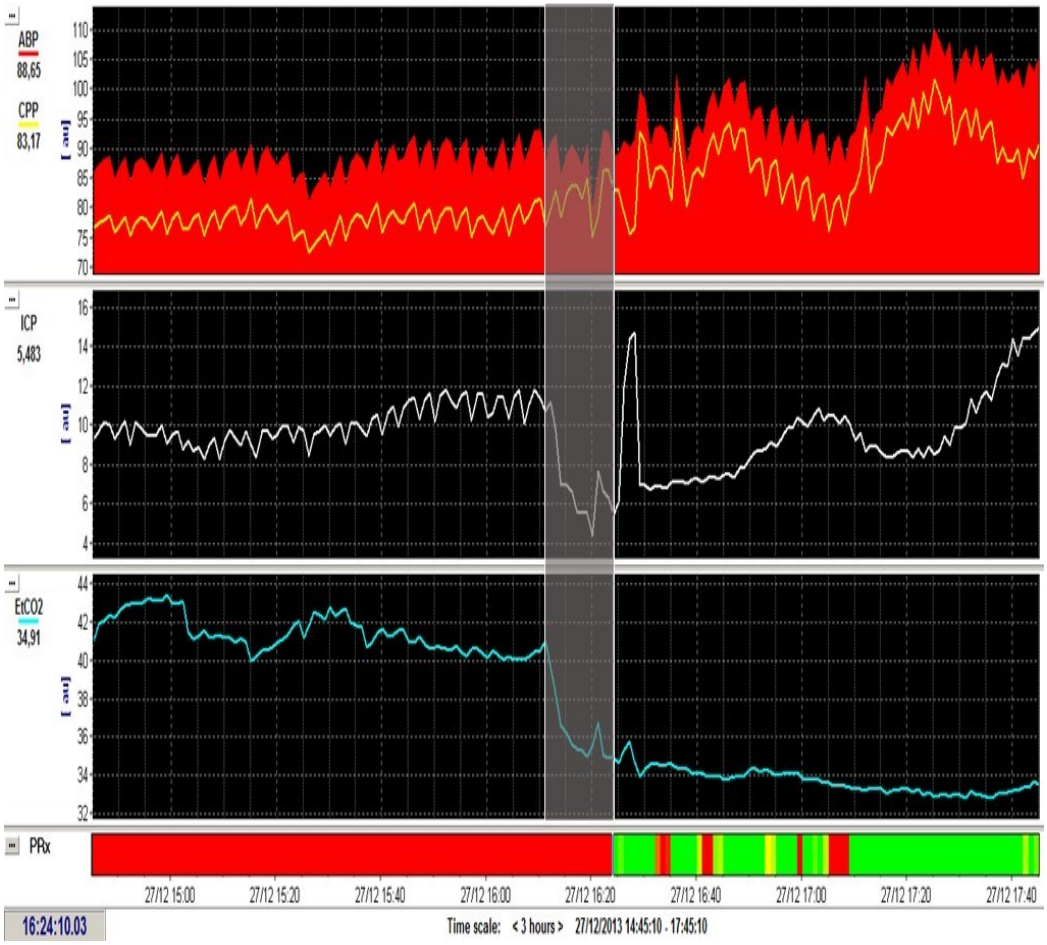


Figure 11– Autoregulation evaluated with pressure reactivity index (PRx) recovered after mild hyperventilation, maintaining cerebral perfusion pressure. PRx red bar means autoregulation impairment and PRx green bar means working autoregulation. ABP (arterial blood pressure; red area), CPP (cerebral perfusion pressure; yellow line), ICP (intracranial pressure; white line), $ETCO_2$ (endtidal carbon dioxide; blue line).

ASSESSMENT OF CEREBROVASCULAR REACTIVITY

Cerebrovascular reactivity assessment may be performed applying different methods of measuring or estimating CBF (non-invasive *vs* invasive, global *vs* regional *vs* local) and using different stimulus (fluctuations of arterial blood pressure, metabolic changes and IV injection of drugs). Evaluation of cerebrovascular reactivity may be intermittent or continuous. Cerebrovascular reactivity may also be measured as static *vs* dynamic. While the static method evaluates relative blood flow changes in response to a steady-state change in the CPP, the dynamic method measures the response during a rapid change in CPP or ABP. The ratio of the change in cerebral blood flow in response to a change in the vasoactive stimulus defines the *static rate* (105). It is most frequently evaluated with non-invasive global intermittent methods of quantifying CBF such as Xe^{133} CT-scan, CT perfusion, BOLD-MRI or PET-scan. The *dynamic rate* of cerebrovascular reactivity is evaluated with continuous methods of quantifying CBF (thermal-dilution flowmetry) or surrogates (CPP, $PbtO_2$, cerebral oximetry with NIRS or TCD) and calculated with time-domain (moving correlation coefficient) (107, 108) or frequency-domain (transfer function analysis) (109) algorithms.

An overview of the methods that can be applied for CBF assessment and the type of vasoactive stimulus most frequently used are presented in Table 2 and Table 3, respectively.

Table 2 - Overview of indirect (I) and direct (D) methods for cerebral blood flow (CBF) assessment

CBF assessment		Mostly continuous	Intermittent
Invasive	global	I:cerebral perfusion pressure (CPP)	
	local	I:brain tissue oxygenation ($PbtO_2$) D:thermal-dilution flowmetry (td-CBF)	I:Microdialysis
Non-invasive	global		D:Xe^{133} CT-scan D:CT perfusion I:BOLD-MRI D:PET
	regional	I:cerebral oximetry (CO) with NIRS I:Transcranial Doppler	

Table 3 – Vasoactive stimulus most frequently used to assess cerebrovascular reactivity.

Vasoactive stimulus*		
ABP or CPP changes	**Metabolic changes**	**IV Drugs**
spontaneous ABP or CPP fluctuations	inspired CO_2	acetazolamide
carotid compression	breath-holding	
thigh cuff release	cognitive tasks	
lower body negative pressure		
hand grip		

*(110-112).

INDICES OF CEREBROVASCULAR REACTIVITY WITH TIME-DOMAIN MONITORING

For the present thesis we studied cerebral autoregulation using continuous assessment of cerebrovascular reactivity with time-domain analysis and moving correlation algorithms (71, 108, 113, 114). For calculation of continuous indices of autoregulation the stimulus signals used were spontaneous fluctuations of ABP or CPP and the comparator signals were ICP for PRx, ICP amplitude for PAx, $PbtO_2$ for ORx, CO for COx and TDF-CBF for CBFx. Briefly, all signals were time averaged using a window of 10 seconds and afterwards the moving linear correlation coefficient between stimulus signal and comparator signal was calculated using a 5 min-window with an update every 10 seconds (Figure 12).

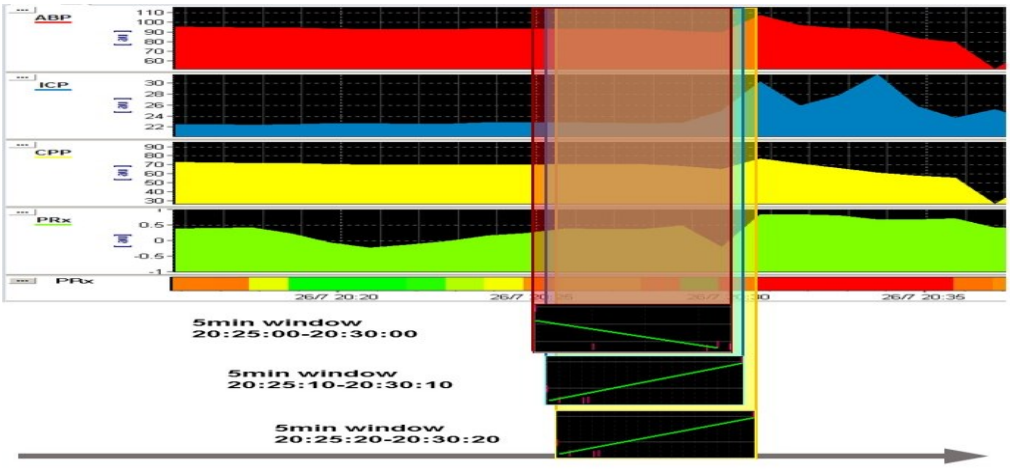


Figure 12– Example of moving linear correlation window of 5 min (300 sec) for arterial blood pressure (ABP) and intracranial pressure (ICP) with an update every 10 seconds and time series plot of the correlation coefficient (PRx; pressure reactivity index).

In a reactive vascular system, these indices are supposed to be close to zero or negative, while positive values close to one signify impaired reactivity.

PRESSURE REACTIVITY INDEX: PRx uses ICP as a surrogate of cerebral vascular resistance changes and hence CBF fluctuations in response to ABP changes (107, 108, 115). In 1997 it was introduced for the first time, using a computer-based approach to continuously calculate and monitor PRx (108). Cerebrovascular pressure reactivity does not necessarily reflect cerebral autoregulation but correlates well with indices of autoregulation based on transcranial Doppler ultrasonography (116) and in PET studies (117, 118). A positive time averaged (period longer than 30 minutes) above 0.25 signifies passive reactive vascular bed, while a PRx < 0 indicates normal autoregulation (20). The prognostic significance of PRx in TBI has been demonstrated in several studies, in which abnormal PRx was clearly associated with high ICP, low CPP, low GCS on admission and poor outcome at 6 months (119-121). PRx may be used to continuous monitoring of autoregulation and define individual lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA), helping target optimal CPP (122, 123) (Figure 13).

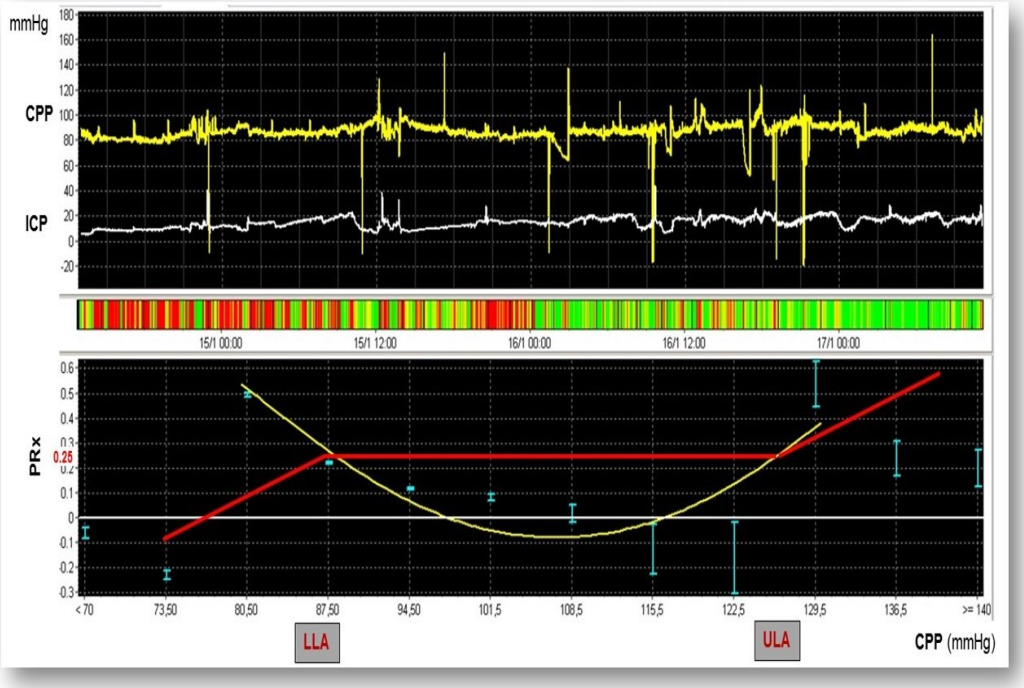


Figure 13 - Intracranial pressure (ICP), cerebral perfusion pressure (CPP), and pressure reactivity index (PRx). Continuous monitoring of autoregulation and definition of individual lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA) to target optimal CPP during NCCU management.

Retrospective studies show that PRx is a strong independent predictor of outcome and favourable outcome reaches its peak when CPP is maintained close to optimal CPP (124). Although the retrospective data in support of individualized, PRx-guided optimal CPP therapy are convincing and were referenced in the latest Guidelines for the Management of Severe Traumatic Brain Injury (36) and in the recent Consensus Conference on Multimodality Monitoring in Neurocritical Care (12), prospective data are lacking. Multicentre clinical trials are now being planned to assess the potential benefit of PRx-guided optimal CPP therapy in traumatic brain injury patients.

PRESSURE AMPLITUDE INDEX: The PAx is defined as the moving correlation coefficient between ABP and ICP pulse amplitude (125). The pulse amplitude conveys relevant information about intracranial vascular tone and compliance which are functions of cerebrovascular reactivity (126). The PAx also differentiated between fatal and non-fatal outcomes and can be used to determine optimal CPP. It has been shown that PAx is potentially a more robust estimator of cerebrovascular reactivity at lower values of ICP than PRx, namely when the brain is very compliant, as after decompressive craniectomy or open ventricular drainage (127).

OXYGEN REACTIVITY INDEX: The brain tissue oxygen tension ($PbtO_2$) can be used to create an autoregulation index because its values may be interpreted as a surrogate of local CBF (78), in spite it also reflects the arteriovenous difference in oxygen tension. The oxygen reactivity index (ORx) is the moving correlation coefficient between $PbtO_2$ and CPP (113, 128). The reports about correlation between PRx, ORx and outcome for patients with head injury show discordant results either with positive correlation (113) or with no relevant correlation (129). However, these published papers use different methodologies of measuring $PbtO_2$ with different dynamic properties and, therefore, ORx values of different probes should not be interchanged and analysed as equivalent (130, 131).

CEREBRAL OXIMETRY REACTIVITY INDEX: The cerebral oximetry (CO) measured by cerebral haemoglobin oxygenation saturation (rSO_2) with transcranial NIRS may be used as a continuous non-invasive surrogate of CBF. Modern NIRS machines can detect spontaneous low-frequency oscillations (slow waves) and CO can be used for the continuous assessment of cerebral autoregulation. The COx (other authors also call it TOx) is a moving linear correlation coefficient between CPP and spontaneous slow waves of cerebral oximetry measured by NIRS (71, 123). COx (and TOx) can detect impaired cerebral autoregulation (69).

CEREBRAL BLOOD FLOW REACTIVITY INDEX: Similarly to the other indices, flow reactivity index (CBFx) may be continuously calculated using the values of CBF measured with thermal-diffusion probe. The CBFx (or FRx) is a moving linear correlation coefficient between CPP and TDF-CBF (114).

The following section presents the methods of calculation of cerebrovascular reactivity indexes in greater detail.

OPTIMAL CEREBRAL PERFUSION PRESSURE

In the past decades more emphasis has been directed toward CPP thresholds in TBI patients. Injured brain may present signs of ischemia if CPP remains below 50 mmHg and in contrast raising the CPP above 70 mmHg may be associated with hyperaemia. Current TBI management protocols are based on a combination of CPP-oriented (37), ICP-oriented (132) and/or oxygenation-oriented therapy (64) but this approach is likely an oversimplification of the complex secondary pathophysiology. Autoregulation indices based on ICP (PRx), mean blood flow velocity (Mx), brain tissue oxygenation (ORx, ORxs), cerebral oximetry (TOx, COx) and cerebral blood flow (CBFx) may be helpful in defining optimal therapeutic strategies (133). These descriptors of autoregulation exhibit a U-shaped curve when plotted against CPP (108), in which the nadir of the descriptor distribution represents the reference point for autoregulation and the arms of the parabolic curve denote deviation from 'best autoregulation' possibly leading to ischemic or hyperaemic CBF(Figure 14).

In 2002, Steiner *et al.* demonstrated that it is possible to calculate an "optimal" CPP value (CPPopt) at bedside using continuous evaluation of PRx (122). The CPPopt corresponds to the CPP value at which PRx reaches its lowest (optimal) value in an individual patient and over time. Furthermore, Steiner et *al.* based on their findings proposed a protocol for an autoregulation-oriented management of severe TBI patients with optimization of CPP.

More recently, in 2012 Aries et *al.* published a retrospective analysis of long-term monitoring data of TBI patients using an improved and automatic CPPopt calculation with a homogeneous software methodology (ICM+: www.neurosurg.cam.ac.uk/icmplus) (Figure 15). The new algorithm incorporated automatic updating of CPP using continuous monitoring of PRx. The U-shaped curve fitted a 4h-long moving window updated every minute. The CPPopt value was presented as a dynamically changing variable and was continuously calculated for more than 80% of time. Continuous metrics of the distance between real CPP and CPPopt was

associated to outcome: too low CPP increased mortality, too high CPP increased disability and CPP around CPPopt related to favourable outcome (134).

The concept of "optimal CPP" therapy was prospectively applied during the clinical investigation for this dissertation and an article with the description of the methodology and results was recently accepted for publication for Neurocritical Care Journal *(Publication V).*

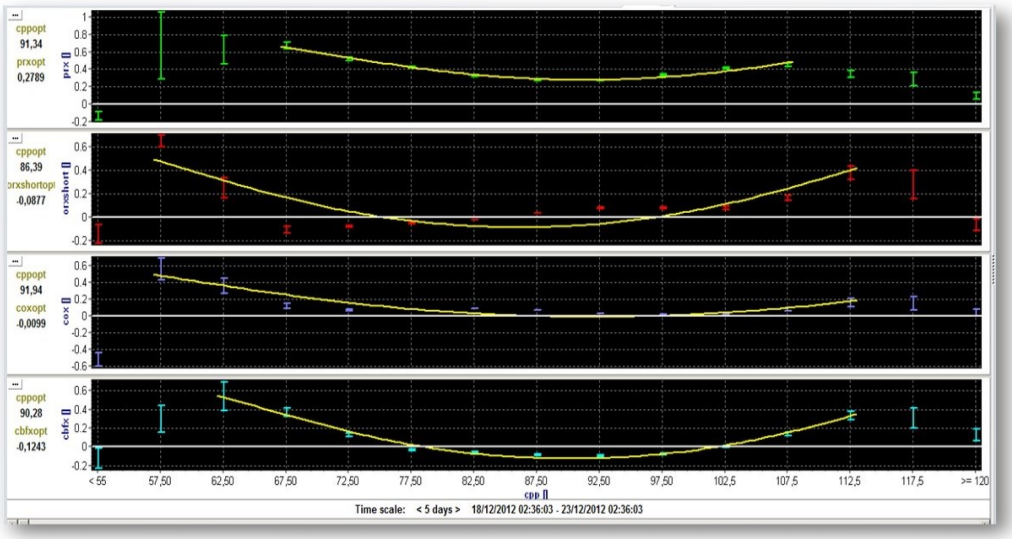


Figure 14 - U-shaped curve distribution of cerebrovascular reactivity indices PRx (pressure reactivity index), ORxs (oxygen reactivity index), COx (cerebral oximetry index) and CBFx (cerebral blood flow index) plotted against CPP (cerebral perfusion pressure) for an individual patient.

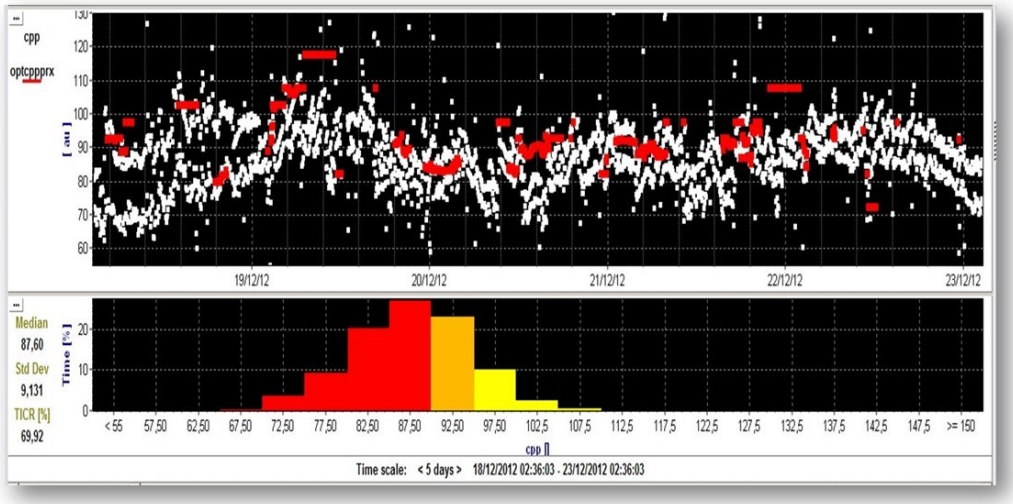


Figure 15 - Visual continuous metrics of the distance between real cerebral perfusion pressure (CPP; white dots) and optimal CPP (CPPopt; red dots) (upper chart). Time histogram of CPP (red area CPP below CPPopt, orange area CPP-CPPopt = 5 mmHg and yellow area CPP-CPPopt > 5mmHg (lower chart).

MATERIAL, METHODS AND DATA ANALYSIS

MATERIAL, METHODS AND DATA ANALYSIS

Local Research Ethics Committee has accepted research protocol and written informed consent was obtained from the next of kin.

PATIENTS

INCLUSION CRITERIA

- Adult patients with severe TBI (GCS ≥ 8) admitted to the NCCU of the Intensive Care Department of Centro Hospitalar São João, between July 2011 and January 2013 with clinical indication for standard and advanced multimodal brain monitoring.

EXCLUSION CRITERIA

- Pregnancy or inability to obtain written informed consent.
- Lack of equipment available for advanced brain monitoring with $PbtO_2$ and CBF.

SAMPLE POPULATION

The study population included 18 consecutive patients (16 males, 89%) with mean age of 42 (SD 16) years old. The median baseline GCS was 6 (IQR3) and 3 patients with GCS > 8 had subsequent deterioration requiring intensive care treatment. The mean SAPS II was 45 with predicted mortality of 36%. Mean length of stay (LOS) in the NCCU and hospital was 26 (SD 12) and 53 days (SD 37) respectively. Mortality rate at 28 days was 17% (3 patients) and median GOS (135) at 6 month was 3.

The initial CT-scan Marshall score (136) distribution was: 6 patients with diffuse injury type II, 3 patients with diffuse injury type III, 4 patients with diffuse injury type IV and 5 patients with non-evacuated lesions.

Before NCCU admission 4 patients were submitted to craniotomy for hematoma drainage, 3 patients needed early decompression and 3 had non-neurosurgical procedures. During NCCU stay, 1 patient had an extraventricular drainage and 2 more patients went for late decompression due to refractory intracranial hypertension. The total time (hours) for standard and advanced multimodal brain monitoring with median and (IQR) was: ICP and CPP 5521h (283;169), CO 4229h (214;137), $PbtO_2$ 4048h (203;129) and CBF 2339h (119;107). More detailed clinical information is available in Table 4.

Patient order	Patient ID	age	GCS	SAPSII	SAPSII mortality prediction	head-CT Marshall Score	Surgery	other procedures	NCCU LOS	monitoring time (hours)					Hosp LOS	Follow-up 28 days	cause of death	GOS 6M
										ICP	CPP	$PbtO_2$	CO	CBF				
1	MAGT	37	3	57	62%	VI	Eye Surgery		36	217	217	168	168	18	58	alive		5
2	EFS	64	4	48	41%	II	No Surgery		14	322	322	278	278	185	14	dead	MOF	1
3	SVC	33	4	48	41%	VI	No Surgery		31	498	498	430	430	350	47	alive		3
4	JAMS	42	12	32	13%	IV	Decompressive Craniectomy		19	273	273	165	204	38	37	alive		4
5	ECFS	44	4	45	35%	VI	Decompressive Craniectomy		31	402	402	219	299	162	65	alive		2
6	PEMR	23	7	32	13%	II	No Surgery		22	146	146	121	121	53	31	alive		4
7	AHCM	65	10	57	62%	VI	Craniotomy SDH drainage		27	284	284	202	225	170	59	alive		4
8	JHBM	44	8	32	13%	II	No Surgery		26	437	437	418	512	148	34	alive		5
9	VISC	25	4	44	33%	III	No Surgery		31	127	127	98	98	79	118	alive		3
10	JAFC	21	7	36	18%	IV	Orthopedic surgery	EVD	35	281	281	210	228	100	126	alive		3
11	RMCC	24	4	42	29%	VI	Craniotomy SDH drainage		17	237	237	194	199	61	61	alive		3
12	APL	40	7	41	27%	III	Late Decompressive		16	346	346	239	246	175	16	dead	brain ischemia	1
13	FS	60	7	58	64%	IV	Decompressive Craniectomy		27	358	358	93	83	75	33	alive		3
14	JMBS	55	6	50	46%	II	Craniotomy SDH drainage		15	187	187	131	117	61	24	alive		4
15	JVP	66	4	36	18%	II	Craniotomy SDH drainage		20	435	435	307	223	155	45	alive		3
16	RMBP	20	4	48,0	41%	III	Late Decompressive	ECMO	65	528	528	498	501	370	138	alive		5
17	MAS	48	3	60	68%	IV	Partial Enterectomy		20	258	258	203	203	138	20	dead	brain ischemia	1
18	AABA	40	11	35	17%	II	No Surgery		10	183	183	73	93	0	19	alive		4

Table 4 – Demographic data of patients included in the clinical investigation.

Abbreviations: GCS (Glasgow Coma Score), SDH (subdural hematoma), EVD (external ventricular drainage), ECMO (extracorporeal membrane oxygenation), MOF (multiple organ failure), GOS (Glasgow outcome scale), ICP (intracranial pressure), $PbtO_2$ (brain tissue oxygen tension), CO (cerebral oximetry), TDF-CBF (thermal diffusion cerebral blood flow)

NEUROCRITICAL CARE UNIT AND PATIENT MANAGEMENT

NEUROCRITICAL CARE UNIT

Patients were managed in the Neurocritical Care Unit (NCCU) of the Intensive Care Department at Centro Hospitalar São João. The modern NCCU is located in the 8th floor since 2009 and has two main clinical areas for intensive and high-dependency care. The purpose-built unit has allocated 10 beds for the intensive care area and 6 for the high-dependency area and provides 24 hour clinical coverage.

The NCCU is staffed with intensivists with different backgrounds (Anaesthesia, Internal Medicine and Infectious Diseases) and nurses who are specially trained and understand the complexities of caring for patients with neurological injuries. Our treatment team also includes psychologists, physical therapists, and nutritionists. The NCCU team is completed by a dedicated neurosurgery consultant and attending neurology and neuroradiology.

The NCCU is equipped with state-of-the-art bedside equipment for intensive care, with multimodal brain monitoring (ICP, CPP, $PbtO_2$, CO and TDF-CBF), clinical data management system (B-ICU®) and neuromonitoring integration data system (ICM+®).

Over 800 patients are treated each year on the NCCU. More than 95% have neurological or neurosurgical related diagnoses (major trauma, isolated head and spinal trauma, subarachnoid and intracerebral haemorrhage, acute severe ischemic stroke, uncontrolled epilepsy, central nervous system infection and neurosurgical postoperative care).

GENERAL PATIENT MANAGEMENT

All patients were managed with NCCU protocol driven therapy aimed at maintaining ICP < 20 mmHg and guided CPP management (Figure 16).

During the study period patients were sedated with continuous infusions of propofol and/or midazolam and fentanyl to achieve a Richmond Agitation-Sedation Scale (RASS) score between zero and -5 (137) and adequate analgesia. Artificial ventilation was applied with lung protective criteria, $PaCO_2$ levels between 35-40 mmHg and normoxia. At our NCCU, patients are treated with 30º head up elevation and CPP is continuously calculated with ABP transducer located at heart level (53).

When possible, we guided CPP management using the bedside optimal CPP values calculated with ICM+ according to pressure reactivity index (CPPopt). If CPPopt was not available, we kept CPP between 50-70 mmHg in accordance to Brain Trauma Foundation Guidelines (36).

Normothermia, correction of electrolyte and glucose imbalance and control of seizures were also standard elements of treatment.

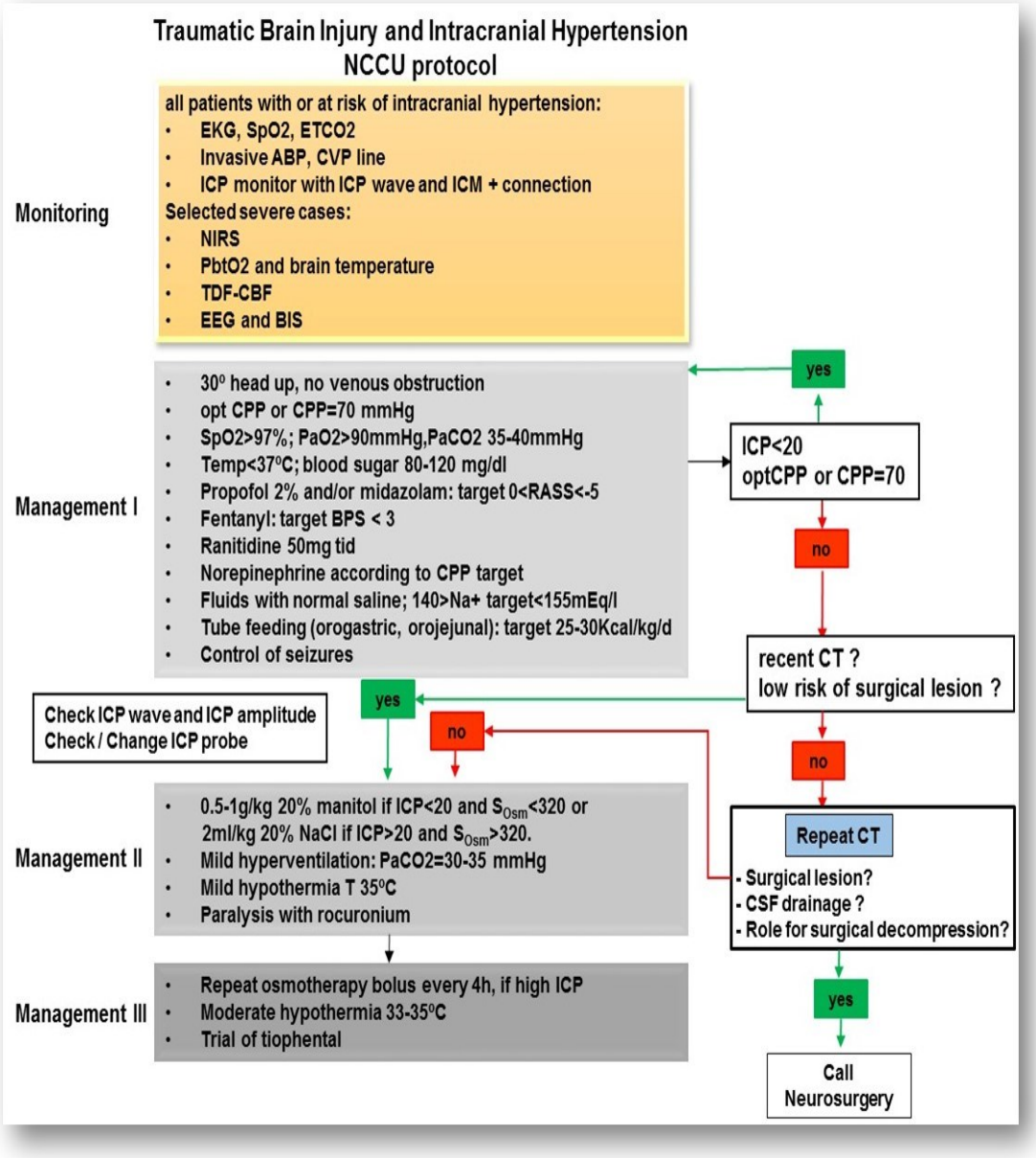


Figure 16 - Neurocritical Care Unit (NCCU) protocol for Traumatic Brain Injury and Intracranial Hypertension Management. Optimal Cerebral Perfusion Pressure (CPPopt) evaluated continuously at bedside with cerebrovascular reactivity index and Intracranial Pressure (ICP) control below 20 mmHg are primary targets.

Abbreviations: EKG (electrocardiogram), SpO_2 (pulse oximetry), $ETCO_2$ (endtidal carbon dioxide), ABP (arterial blood pressure), CVP (central venous pressure), ICP (intracranial pressure), ICM+ (multimodal brain monitoring software), NIRS (cerebral oximetry with near infrared light), $PbtO_2$ (brain tissue oxygen pressure), TDF-CBF (thermal diffusion cerebral blood flow), EEG (electroencephalogram), BIS (bispectral index), CPP (cerebral perfusion pressure), CPPopt (optimal CPP), PaO_2 (arterial oxygen pressure), $PaCO_2$ (arterial carbon dioxide pressure), Temp (temperature), RASS (Richmond agitation-sedation scale), BPS (behavioural pain scale), Na+ (serum sodium), CT (computerized tomography), CSF (cerebral spinal fluid).

CPP MANAGEMENT

CPPopt was determined in individual patients as described by the recent published method of Aries *et al* (134). The software generates automatically a curve with CPPopt value that is continuously displayed at the bedside and both are updated every minute. In addition, we formulated three extra criteria before accepting the suggested automatic displayed CPPopt value: (a) at least 75% of time good recordings of ABP and ICP values had to be available in the 4 hr calculation window, (b) average PRx values had to be < 0.25 the past 4hrs (defined as a period with intact cerebrovascular pressure reactivity) (20) and (c) dedicate the staff to study the CPPopt curve and overrule the automatic CPPopt value and take the CPP value with most negative PRx value covered by the curve. U-shaped, ascending and descending curves were accepted in case the overall PRx<0.25. An illustrative example is shown in Figure 17. To achieve higher CPPopt values CPP augmentation was managed with fluids and/or norepinephrine infusion according to hemodynamic assessment and to lower CPPopt values vasopressor therapy was decreased, intracranial hypertension treated or sedation increased.

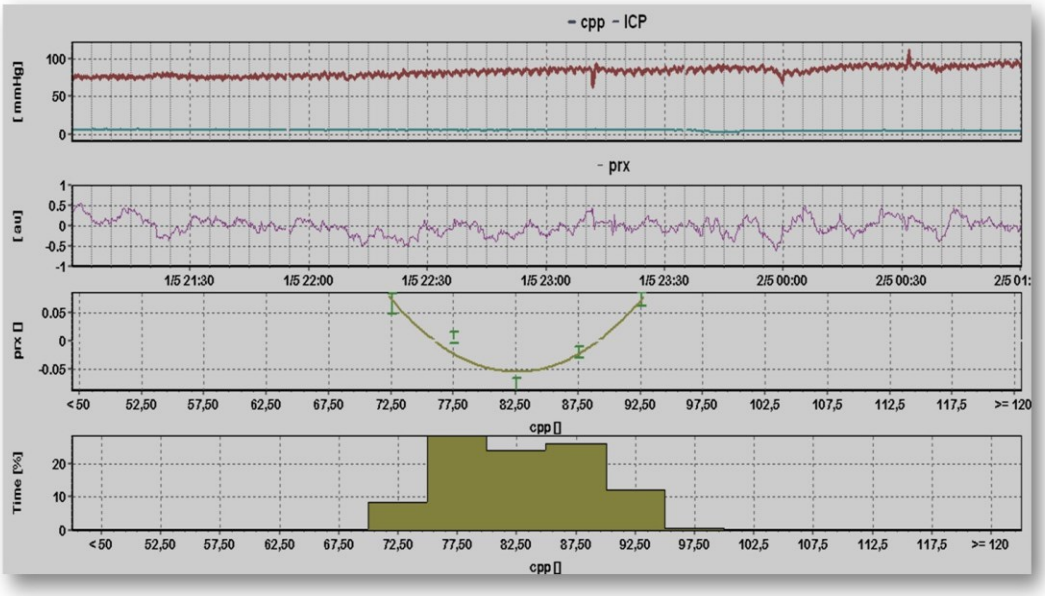


Figure 17- Screenshot of ICM+® software panel with 4h-trend charts for visual decision of optimal cerebral perfusion pressure according to pressure reactivity index (CPPopt). First chart: CPP (cerebral perfusion pressure) and ICP (intracranial pressure); second chart: pressure reactivity index (PRx); third chart: PRx/CPP plot for evaluating CPPopt and fourth chart: percentage of 4h time spent within CPP interval. Criteria of decision for CPPopt: (first chart) 4h-trend with more than 75% of reliable CPP and ICP data; (second chart) PRx < 0.25; (third chart) CPP curve with PRx < 0.25 and CPPopt defined 82.5 mmHg; (fourth chart) CPP targeted according to CPPopt.

INTRACRANIAL HYPERTENSION MANAGEMENT

Episodes of intracranial hypertension (ICP > 20 mmHg) were treated initially with first-tier therapy (deep sedation, paralysis, normothermia, mild hyperventilation and when possible cerebral spinal fluid drainage after insertion of extra ventricular drain). In cases of plateau waves of ICP diagnosis we preferably applied a short hyperventilation period to stop the vasodilatory cascade. If ICP remained above 20 mmHg for more than 20 minutes, osmotherapy was administered (20% mannitol or 20% hypertonic saline bolus) (138-142). Refractory intracranial hypertension was managed with second-tier therapy (hypothermia, profound hyperventilation and surgical decompression) (143, 144) (Figure 16).

MONITORING PARAMETERS, SENSORS, EQUIPMENT, AND SOFTWARE

BASIC VITAL SIGNS MONITORING

ELECTROCARDIOGRAPHY, PULSE OXIMETRY WITH PLETYSMOGRAPHY, NASOPHARYNGEAL TEMPERATURE, MICRO-STREAM END-TIDAL CO_2 and arterial blood pressure were continuously monitored with Philips Intellivue MP70 multiparameter monitor (Philips medical systems, Eindhoven, the Netherlands).

ARTERIAL BLOOD PRESSURE: invasive arterial blood pressure was monitored from radial, brachial or femoral artery with arterial catheters (Arterial Leader-cath, Vygon, Ecouen, France) using a pressure monitoring kit (Combitrans single pressure monitoring kits, BBraun, Melsungen, Germany). Mean arterial blood pressure was continuous calculated (ABP=(sABP+2*dABP)/3)) and displayed by the Philips MP70 monitor. ABP units: mmHg.

STANDARD BRAIN MONITORING

INTRACRANIAL PRESSURE: intracranial pressure was monitored using intraparenchymal probes with a single bolt (Codman microsensor ICP transducer, DePuySinthes, Massachusetts, USA) and ICP EXPRESS® Monitoring System (Codman, DePuySinthes, Massachusetts, USA). ICP pressure and pulse waveform was transferred to Philips monitor with Codman-Philips pressure cable.

CEREBRAL PERFUSION PRESSURE: cerebral perfusion pressure was continuously calculated (CPP=ABP-ICP) and displayed by the Philips MP70 monitor. CPP units mmHg.

ADVANCED BRAIN MONITORING

We used a triple lumen bolt (Licox CMP Triple Lumen Monitoring System, Integra Neurosciences, Plainsboro, USA) for intraparenchymal probes to monitor partial pressure of brain tissue oxygenation, brain temperature and cerebral blood flow with thermal-diffusion flowmetry (Figure 18).

Figure 18 – Basic Vital Signs and Multimodal Brain Monitoring Set.

BRAIN TISSUE OXYGENATION: brain tissue oxygenation was assessed using a flexible polarographic Clarke-type microcatheter (Licox oxygen catheter micro-probe model CC1.SB, Integra, Plainsboro, USA). $PbtO_2$ probes have 0.8mm in diameter and a sensitive region approximately of 5 mm in length and 13 $mm^2$of tissue section. Calibration data is

stored on a smart card supplied with each $PbtO_2$ probe. After insertion, the probe run-in time may be up to 2 hours. The insertion depth of the probe was 30 mm (from dura level to catheter tip). $PbtO_2$ units: mmHg.

BRAIN TEMPERATURE: brain temperature micro probe is a type K thermocouple catheter with 0.8 mm diameter (Licox temperature probe C8.B, Integra, Plainsboro, USA). Temperature measurement accuracy at 37ºC is ±0.2ºC The brain temperature must be supplied to the Licox monitor because $PbtO_2$ is automatically adjusted for temperature (probe $PbtO_2$ sensitivity change with temperature is approximately 4% per ºC). Temperature units: ºC. The Licox CMP Monitor (Integra, Plainsboro, USA), used for oxygen and temperature measurements, displays a digital reading but data were sent to the ICM+ software.

THERMAL-DIFFUSION FLOWMETRY OF CBF: the TDF-CBF sensor consists of a flexible polyurethane catheter of 0.9 mm diameter with a thermistor embedded at the distal tip and a temperature sensor located 8 mm proximal (QFlow 500 Bowman flow sensor, Hemedex, Cambridge, USA). Regional cerebral blood flow is quantified within the 8 mm diameter thermal field generated by the active thermistor which is heated approximately 2ºC above baseline. The power required to stabilize the thermal field is proportional to the thermal dissipation and therefore to the regional CBF. The sensor should be located intraparenchymal, in the white mater, approximately 25-30 mm below the dura.
The Bowman Perfusion Monitor displays CBF values, brain temperature and delta and tissue thermal conductivity value (K Value). CBF units: ml/100g/min.

All intraparenchymal probes were inserted in the white matter in a region at risk of ischemia (penumbra area around contusions or diffuse axonal injury) and their location was confirmed with CT scan.

CEREBRAL OXIMETRY: cerebral haemoglobin oxygenation index (rSO_2) named as cerebral oximetry was monitored with bilateral near-infrared spectroscopy sensors with dual wavelength design (adult cerebral sensors, Covidien, Mansfield, USA) positioned at the forehead and with INVOS 5100C equipment, (Covidien, Mansfield, USA). CO units: %.

DATA CAPTURE AND SOFTWARE

ICM+® SOFTWARE: data were collected digitally using ICM+ software developed by Dr. P. Smielewski and Prof. M. Czosnyka (Cambridge Enterprise, UK, http://www.neurosurg.cam.ac.uk/icmplus) (108, 145-147). Serial communication protocol (RS232), either with direct connection to COM ports or using USB-to-Serial Converter (Aten UC232A), was used to acquire waveforms of ICP, ABP, ECG, CO_2 from Phillips MP70 Intellivue monitors, brain tissue oxygenation ($PbtO_2$) and temperature from Licox monitors, near infrared spectroscopy cerebral haemoglobin oxygenation index (rSO_2) from INVOS monitors, and cerebral blood flow (TDF-CBF) from Hemedex monitors at their respective sampling rates offered by the monitors (ranging from 0.2 Hz for rSO_2, to 125Hz for pressures, and 500Hz for ECG waves). All the data samples were synchronised to the computer time, and resampled to 250 Hz prior to further processing.

DERIVED PARAMETERS AND CONTINUOUS INDICES OF AUTOREGULATION

MEAN VALUES: all data mean values were continuously calculated using an average filter with a window of 10 seconds.

PRX - PRESSURE REACTIVITY INDEX: PRx was determined based on Czosnyka *et al* method (108) by observing the response of ICP to slow spontaneous fluctuations in ABP. The calculations were performed with 10 s averages of ABP and ICP over a 10s-moving window of 5 min length.

PAX – PULSE AMPLITUDE INDEX: was calculated using 10 s averages of ABP and corresponding pulse amplitude of ICP over a 10s-moving window of 5 min length (125).

ORX AND ORXS- OXYGEN REACTIVITY INDEX: The ORx is the moving correlation coefficient between CPP and $PbtO_2$. We used a time window of 60 min as described by Jaeger *et al* (113), but for the purpose of this work we also defined a ‘‘short’’ version of this index, termed ORxs, calculated over a period of 5 min and 10s-moving window. With this new calculation we intended to study brain oxygenation reactivity within the same time window resolution of the other indices and compare both oxygen response dynamics.

COX - CEREBRAL OXIMETRY INDEX: The NIRS-derived cerebral oxygenation, COx was calculated as the 10s-moving coefficient correlation between CPP and CO (bilateral brain regional saturation average) over 5 min window (71).

CBFX – CEREBRAL BLOOD FLOW INDEX: The CBFx is a moving correlation between CPP and CBF, with window length of 5 min moving every 10 s (114).

DATA ANALYSIS

ICM+ DATA ANALYSIS

All ICM+ files with monitoring data from patients were visually studied both raw data files (Figure 19) and main data files. PRx and CPPopt was continuously calculated at bedside with the automatic algorithm described in previous paragraphs but the other cerebrovascular reactivity indexes and related CPP values were calculated offline. To achieve this objective all the raw data files were reanalysed with a new ICM+ profile incorporating the required calculations.

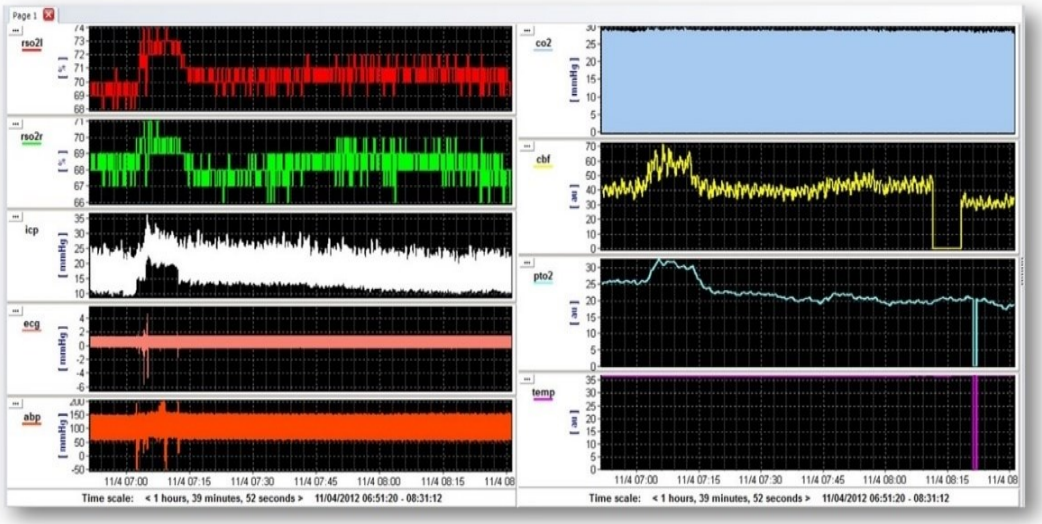


Figure 19 – Example of a screenshot with raw data of left and right cerebral oximetry (rSO_2l and rSO_2r), intracranial pressure (ICP), electrocardiogram (ECG), arterial blood pressure (ABP), endtidal carbon dioxide (CO_2), cerebral blood flow (CBF), brain tissue oxygen pressure ($PbtO_2$) and brain temperature during a period of 1h and 39 min.

To perform the specific analysis of monitoring data according to the objectives of the published papers we used ICM+ “quick stats tool” and “script lab tool” to summarize data for further evaluation with more powerful statistical software (Figure 20).

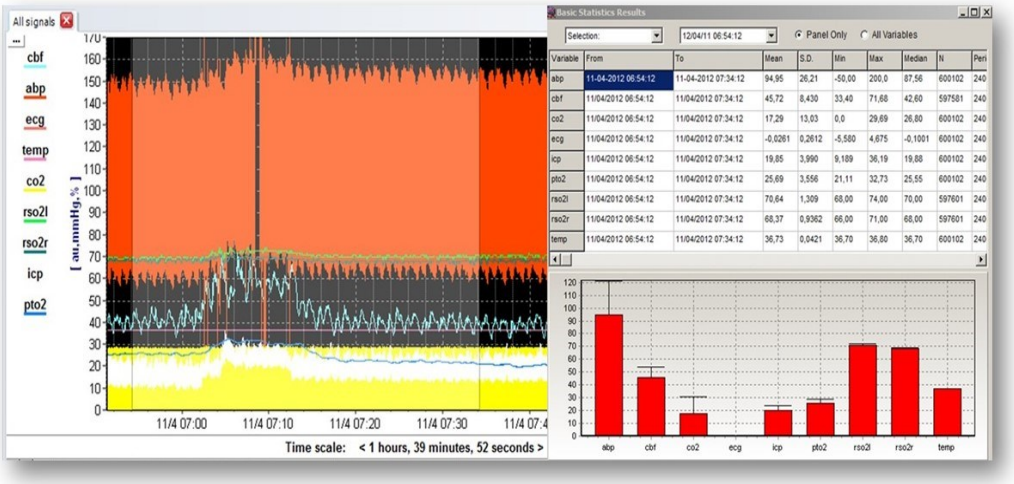


Figure 20 - ICM+ software screenshot with raw data of multiple brain parameters and results from “quick stats tool”.

STATISTICAL ANALYSIS

Statistical analysis was performed using either SPSS commercial IBM software SPSS 20 (IBM, IL, USA) or R language environment software for statistical computing (148).

The distribution of all data samples was checked for normality using Shapiro-Wilk test. Depending on the distribution either parametric or non-parametric statistical tests were used.

For time series analysis we used linear regression models such as generalized least squares method or linear mixed-effects for repeated measurements.

Where applicable, methods of measurement were compared using the approach described by Bland and Altman.

The specific statistical methods used in individual projects and publications are described in detail in the written articles.

PUBLICATIONS

TRAUMATIC BRAIN INJURY IN PORTUGAL: TRENDS IN HOSPITAL ADMISSIONS FROM 2000 TO 2010

Dias, C, Rocha, J, Pereira, E, Cerejo, A

Acta Med Port 2014 May-Jun;27 (3):349-356

Traumatic Brain Injury in Portugal: Trends in Hospital Admissions from 2000 to 2010

ARTIGO ORIGINAL

Traumatismo Crânio-Encefálico em Portugal: Tendências em Doentes Internados de 2000 a 2010

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Acta Med Port 2014 May-Jun;27(3):349-356

ABSTRACT

Introduction: Traumatic brain injury has a considerable socio-economic impact, being a major cause of morbi-mortality, often with permanent disability. We sought to characterize health resource utilization of adult traumatic brain injury patients in Portugal between 2000 and 2010.

Material and Methods: Retrospective study of medical records of adult patients with ICD9 diagnostic code of traumatic brain injury included in the National Diagnosis Related Groups Database from 2000–2010. Descriptive statistical analysis was performed and trends during the decade were evaluated.

Results: We analysed 72 865 admissions to 111 hospitals, 64.1% males, mean age 57.9 ± 21.8 years (18-107). We found a decrease in number of traumatic brain injury in younger patients and an increase in older ones. The number of traffic accidents decreased and the number of falls increased. There was an increase of moderate to severe traumatic brain injury admissions: 47.2% in 2000 / 80% in 2010. Patients admitted in Intensive Care have nearly doubled (15.8% *vs* 29.5%) as well as the number submitted to neurosurgical procedures (8.2% *vs* 15.2%). Total mortality increased from 7.1% to 10.6%.

Discussion: The decrease of traumatic brain injury may be associated with the trauma prevention campaigns, road network improvement and health politics. The increase in mortality may be related to better pre-hospital care, enabling more severe cases to arrive in-hospital alive, and although treated more frequently in Intensive Care and requiring more neurosurgical procedures, they end up having higher mortality. Also this may be due to an increase in patients' age and worse pre-morbid status.

Conclusion: Traumatic brain injury in Portugal is changing. Although hospital admissions due to global traumatic brain injury have decreased, mortality rate has increased.

Keywords: Intensive Care Units; Brain Injuries; Hospitalization; Portugal.

RESUMO

Introdução: O traumatismo crânio-encefálico tem um impacto sócio-económico considerável, sendo uma importante causa de mobi-mortalidade, frequentemente causador de incapacidade permanente. Procuramos caracterizar a utilização dos recursos de saúde de adultos com traumatismo crânio-encefálico em Portugal entre 2000-2010.

Material e Métodos: Estudo retrospectivo de registos de adultos com código ICD9 de traumatismo crânio-encefálico incluídos na Base-de-Dados Nacional de Grupos Diagnósticos Homogéneos de 2000-2010. Realizamos uma análise estatística descritiva e avaliamos as tendências durante a década.

Resultados: Analisamos 72 865 admissões em 111 hospitais, 64,1% do sexo masculino, idade média de 57,9 ± 21,8 anos (18-107). Encontramos uma diminuição no número de traumatismo crânio-encefálico em pacientes jovens e um aumento nos mais velhos. O número de acidentes de trânsito diminuiu e o número de quedas aumentou. Houve um aumento de traumatismos crânio-encefálicos moderados-graves internados: 47,2% em 2000 / 80% em 2010. O número de admissões em Cuidados Intensivos quase duplicou (15,8% *vs* 29,5%), assim como o número de procedimentos neurocirúrgicos efectuados (8,2% *vs* 15,2%). A mortalidade total aumentou de 7,1% para 10,6%.

Discussão: A diminuição do traumatismo crânio-encefálico observada pode estar associada com as campanhas de prevenção rodoviária, melhoria da rede rodoviária e políticas de saúde. O aumento da mortalidade poderá ser explicado pelo melhor atendimento pré-hospitalar, permitindo que casos mais graves cheguem ao hospital com vida e, embora tratados com mais frequência em Cuidados Intensivos e exigindo procedimentos neurocirúrgicos, vêm a falecer. Por outo lado, o aumento da idade dos doentes presumivelmente com maiores co-morbilidades associadas ao envelhecimento também estará a contribuir para a maior mortalidade.

Conclusão: O traumatismo crânio-encefálico em Portugal está a mudar. Embora as admissões hospitalares por traumatismo crânio-encefálico tenham diminuído, a mortalidade aumentou.

Palavras-chave: Unidades de Cuidados Intensivos; Traumatismos Crânio-Encefálico; Hospitalização; Portugal.

INTRODUCTION

Traumatic head injury and traumatic brain injury (TBI) are defined as head and brain injuries caused by external trauma.[1] Together, they are a major cause of consumption of health services as well as for mortality, morbidity and permanent disability,[2] often considered a silent epidemic with a considerable socio-economic impact world-wide.[3] A systematic review of TBI epidemiology of 14 European countries from 1980-2003, derived an aggregate hospitalized plus fatal TBI incidence rate of about 235/ 100 000 person-years,[4] but there were large variations in the reports.[5]

Over the past 20 years a remarkable progress in the management of TBI, especially in critical care units, has

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Recebido: 03 de Outubro de 2013 - Aceite: 02 de Fevereiro de 2014

been achieved with periodically revised treatment guidelines available since 1996.[6]

Epidemiological reports from different regions of Europe and United States have revealed changes in trends during the last decades.[1,7-10] Traumatic head and brain injury prevention and management policies need reliable information about incidence, demographic and etiology. This information is not always readily available, particularly in southern Europe countries like Portugal. Also, epidemiological variations and resource availability need to be accessed to better adapt and reform Health Services and referral systems.

Through this study, the authors intend to provide epidemiological characterization and resource utilization trends of TBI adult patients admitted in Portuguese hospitals from 2000 to 2010.

Currently, in Portugal, there are no reliable epidemiological estimates of patients with severe TBI admitted to hospital or trends of use of hospital resources, including ICU, and their impact on mortality.

MATERIAL AND METHODS

Study design

For study simplification purposes, traumatic head injury will be encompassed in the designation TBI.

We performed an observational, descriptive study of traumatic brain injury patients in the adult Portuguese population, admitted to the 111 hospitals that composed the National Health Service (NHS) hospitals during the study period. Trauma patients may be first admitted in any of these Hospitals and the admission generally takes place within a relatively short distance of where the accident occurred. Usually, the emergency medical teams that are deployed to trauma care, access the need to transport TBI patients to the major neurosurgical trauma referral centres. During this period, a total of 15 hospitals had Neurosurgical teams available for the treatment of TBI patients. After the acute phase, patients can be transferred back to the hospital of the area of residence for continued care.

Data collection

We analyzed the medical registry of the National Diagnosis Related Groups (DRG) database of all trauma patients with associated TBI admitted to hospital from January 1st 2000 to December 31st 2010. Only adult patients (> 18 years) were selected for analysis. Selection of TBI patients was made by diagnosis using the International Disease Classification, 9th Edition (ICD9-CM) with codes 800 until 804 and 850 until 854.

Due to lack of clinical data on DRG registries, TBI severity classification based on ICD-9 codes could only be made considering skull fracture, duration of loss of consciousness and presence of intracranial lesion due to trauma (contusion, laceration or any kind of haemorrhage). With this limitation in mind, we graded TBI as mild (TBI 1), including concussions, with no cranial fractures or intracranial lesions, no loss of consciousness or when loss of consciousness was present with less than 30 minutes duration; moderate to severe (TBI 2-3) if skull fracture was present, loss of consciousness for more than 30 minutes or intracranial lesion due to trauma was present; when ICD-9 codes did not allow classification, TBI severity was deemed unknown.

Registry data collected also included demographic characteristics (age, gender), in-hospital stay duration, mortality and destination after discharge, admission in an ICU or need for neurosurgical procedure. Admissions were considered if patient was discharged after a day. Since data anonymity was an issue, all demographic characteristics were referred to hospital admission episodes and not to individual patients. The enrolled patients were divided into four age groups: 18-40 years, 41-60 years, 61-80 years, and > 80 years for sub-analysis.

We considered patients to have been admitted to ICUs if it was registered on the DRG infirmary code at any point of their hospitalization, or had an ICD-9 procedure code related to ICU management such as mechanical ventilation, tracheal intubation or tracheostomy (9604, 9605, 967x, 311-312x).

Patients with a neurosurgical procedure were also identified using the ICD-9 procedure codes (012x, 013x, 014x, 015x, 016, 02x).

TBI etiology was divided into 5 major categories: traffic accidents excluding two-wheeled vehicles (E81x to E825x (except all codes ending in 2, 3, 6 or 7) and E8299); traffic accident involving two-wheel vehicles (E81x to E825x ending in 2, 3 and 6 and E8261); falls (E880x to E888x, E9293, E987x); run-over (E81x to E825x 8261 ending in 7, E8257, E8260, E8270, E8280, E8290); others (all other codes), when a code could not be integrated in the previous categories or was not registered.

Ethics statement

Due to the observational nature of this study, no randomization or therapeutic intervention was made, and all information was gathered retrospectively. Ethical question surrounding patient identity and confidentiality was resolved before data collection by the Regional Health Administration Services, by removing any data that would allow patient identification or personal information visualization through other data source.

Data analysis and statistics

The DRG database was provided in digital format in xls format for Microsoft Windows Excel. Descriptive statistics analysis was performed with SPSS software (v.16, SPSS Inc. Chicago, IL).

RESULTS

We recorded a total of 90 406 Emergency Department (ED) admissions from 111 hospitals with a TBI ICD9-CM code. A total of 72 865 were adults (> 18 years), with male preponderance 1,8M: 1F. Mean age of 57.9 ± 21.8 years. Moderate to severe traumatic TBI (TBI 2-3) represented the

majority of patients, with 1/5 of patients with insufficient data as to grade severity. In-hospital admission of more than one day represented 78.8% of all patients. Total mortality rate was of 6375 (8.7%) and more than half of patients were discharged home. Almost 25% of patients were admitted to ICUs and 12.3% had a neurosurgical procedure performed (Table 1).

Demographic data

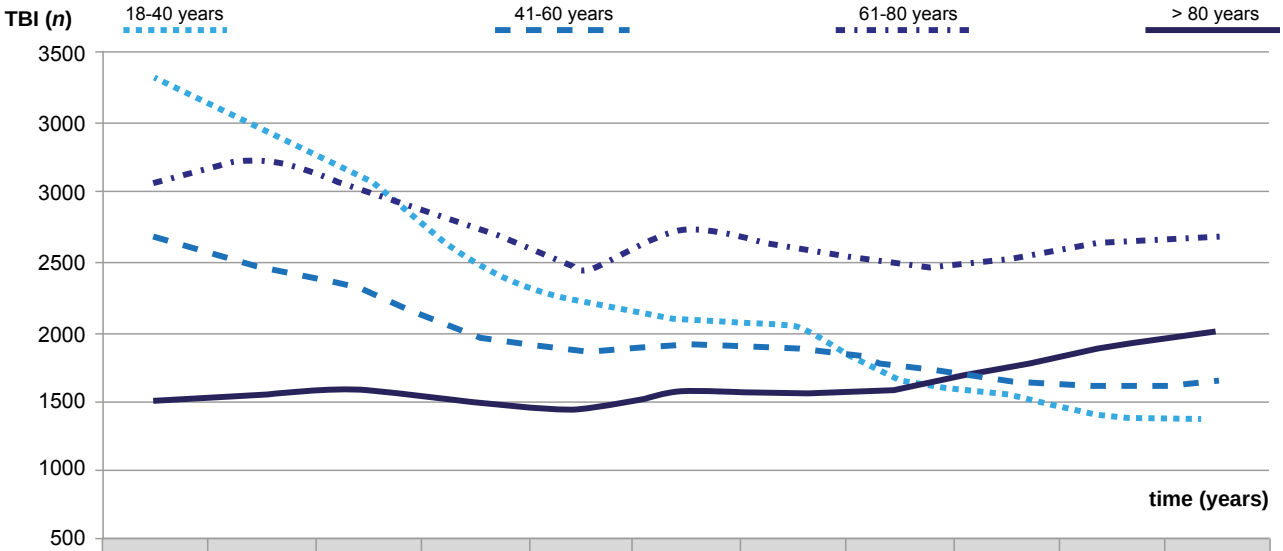
Throughout the decade, there has been a sustained decrease in the number of total TBI admissions (Fig. 1). Mean age has continuously risen, from 52.2 years in 2000 to 65.1 years in 2010 (Table 2), maintaining a male preponderance above 60% (data not shown).

TBI severity and external causes

During the study period, there has been a clear tendency for severity increase as shown by the progressive reduction of registered mild TBI (TBI 1) and a marked growth of moderate to severe TBI (TBI 2-3) rates. Cases

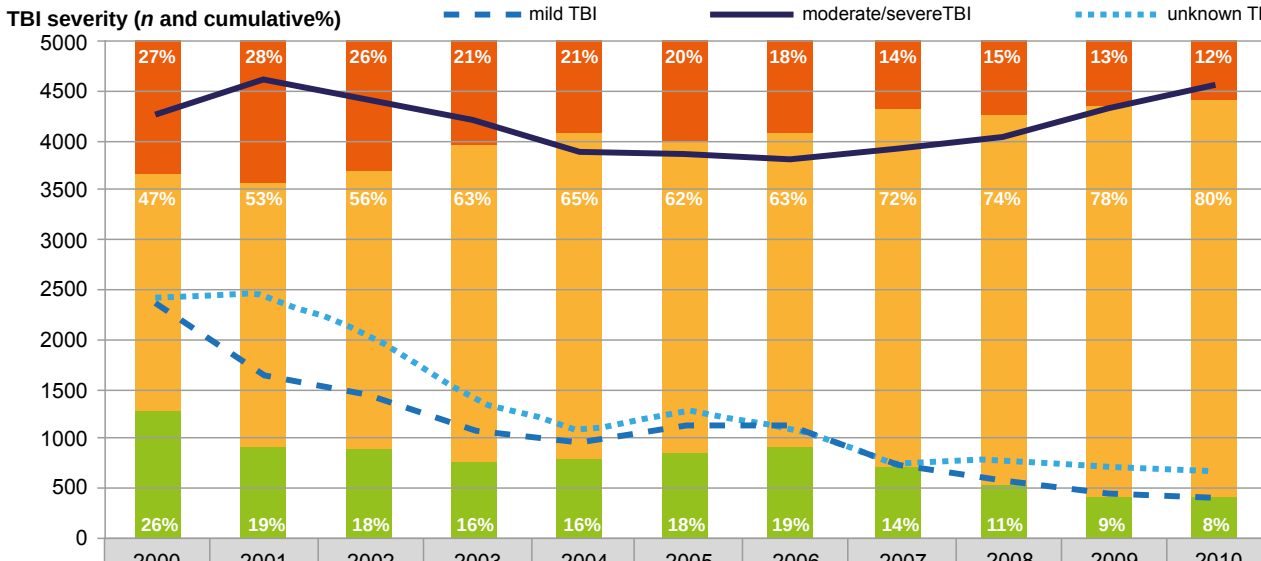
Table 1 - General characterization of patients and hospital admissions

TBI hospital admissions (> 18 years)	
Total	**72865**
Male	46709 (64.1%)
Age – mean ± SD and range (years)	57.9 ± 21.8 18-107 yr
TBI severity	
Mild TBI (TBI 1)	12112 (16.6%)
Moderate to severe TBI (TBI 2-3)	45991 (63.1%)
Unknown	14762 (20.3%)
Hospital length of stay (total) - mean ± SD and range (days)	9.3 ± 19.1 (0-1048)
Hospital length of stay (TBI 2-3) - mean±SD and range (days)	12.4 ± 22.4 (0-1048)
ICU admissions (total)	**17964 (24.7%)**
Neurosurgical procedures (total)	8988 (12.3%)
Mortality	6375 (8.7%)
Home discharge	42431 (58.2%)
Other institutions	23136 (31.8%)
Other/unknown	923 (1.3%)



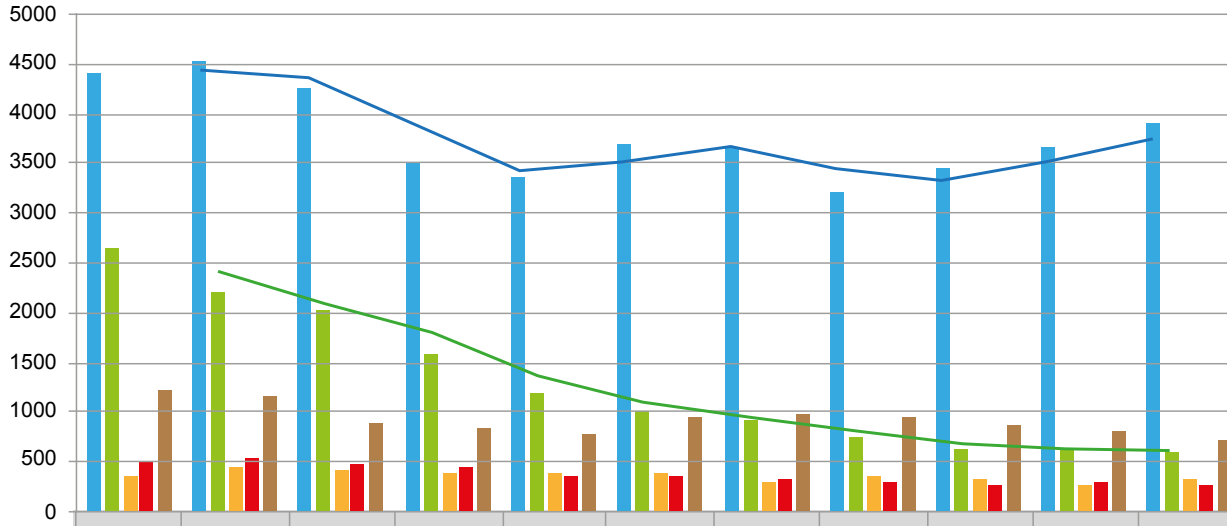
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
18-40 yr	3297	2958	2572	1965	1693	1583	1538	1135	1041	886	885
41-60 yr	2178	1943	1802	1462	1360	1412	1395	1232	1145	1097	1140
61-80 yr	2580	2760	2491	2245	1960	2228	2118	1977	2002	2150	2179
> 80 yr	1012	1054	1069	1005	957	1068	1057	1095	1249	1397	1493
Total	9067	8715	7934	6677	5970	6291	6108	5439	5437	5530	5697

Figure 1 - Variation of TBI hospital admissions by age group from 2000 to 2010.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
unknown TBI	2431 (27%)	2454 (28%)	2073 (26%)	1388 (21%)	1081 (21%)	1288 (20%)	1121 (18%)	743 (14%)	793 (15%)	718 (13%)	672 (12%)
moderate/ severe TBI	4272 (47%)	4607 (53%)	4424 (56%)	4207 (63%)	3909 (65%)	3873 (62%)	3848 (63%)	3925 (72%)	4042 (74%)	4327 (78%)	4557 (80%)
mild TBI	2364 (26%)	1654 (19%)	1437 (18%)	1082 (16%)	980 (16%)	1130 (18%)	1139 (19%)	771 (14%)	602 (11%)	485 (9%)	468 (8%)

Figure 2 - TBI severity per year (total number and cumulative rate).



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Falls 57%	4395	4499	4222	3505	3348	3677	3659	3206	3440	3633	3885
Traffic accident (except 2 wheels) 19%	2650	2175	2002	1565	1167	990	895	709	603	605	572
Traffic accident (2 wheels) 5%	337	413	394	382	359	361	287	322	319	236	292
Run-over 5%	492	498	440	418	347	337	297	262	239	269	249
Others/Unkown 14%	1193	1130	876	807	749	926	970	940	836	787	699

Figure 3 - External cause of TBI per year.

Table 2 - TBI demographics and management (Hospital length of stay, ICU admission and neurosurgical procedures) and mortality per year

Year	Gender (Male)	Mean Age ± SD (yr)	Hospital lenght of stay (days ± SD)	ICU admission	Neurosurgical procedure	Total Mortality and rate
2000	596 (65.7%)	52.2 ± 21.8	6.6.±.12.1	1432 (15.8%)	742 (8.2%)	641 (7.1%)
2001	5752 (66.0%)	53.7 ± 22.0	7.9 ± 16.9	1846 (21.2%)	779 (8.9%)	602 (6.9%)
2002	5174 (65.2%)	54.6 ± 22.0	7.8 ± 17.3	1880 (23.7%)	647 (8.2%)	632 (8%)
2003	4365 (65.4%)	56.4 ± 22.0	9.3 ± 17.0	1790 (26.8%)	746 (11.2%)	617 (9.2%)
2004	3937 (65.9%)	56.9 ± 21.8	9.8 ± 23.6	1543 (25.8%)	846 (14.2%)	572 (9.6%)
2005	3993 (63.5%)	58.5 ± 21.5	9.3 ± 19.6	1579 (25.1%)	851 (13.5%)	523 (8.3%)
2006	3763 (61.6%)	58.6 ± 21.4	9.3 ± 18.5	1449 (23.7%)	805 (13.2%)	519 (8.5%)
2007	3436 (63.2%)	61.0 ± 20.9	11.3 ± 22.6	1581 (29.1%)	921 (16.9%)	530 (9.7%)
2008	3399 (62.5%)	62.6 ± 20.9	11.2 ± 21.4	1572 (28.9%)	910 (16.7%)	551 (10.1%)
2009	3442 (62.2%)	64.6 ± 20.3	11.6 ± 20.6	1613 (29.2%)	874 (15.8%)	583 (10.5%)
2010	3487 (61.2%)	65.1 ± 20.0	11.1 ± 22.4	1679 (29.5%)	867 (15.2%)	605 (10.6%)

impossible to be classified through registry (unknown TBI) have diminished considerably (Fig. 2).

Considering external causes of TBI, falls were the most frequent cause of TBI throughout the years and the only etiology to register a considerable increase in frequency in recent years. Two-wheeled traffic accident maintained around a 5% frequency but a considerable and continuous decrease was noticed in all other causes, especially in traffic accidents. Unclassified causes of TBI also decreased throughout the study period (Fig. 3).

Management and mortality

As previously mentioned, total in-hospital admissions have decreased (Fig. 1), but duration of hospitalization, ratio of ICU treated patients and patients submitted to neurosurgical procedures has almost doubled (Table 2). Total mortality rate in ICU treated patients was 21.9% and in patients submitted to neurosurgical procedure was 16.7% (data not shown in table). Mortality according to TBI severity was 1.1% (130 patients) for TBI 1, 12.9% (5 951 patients) for TBI 2-3 and 2.0% (294 patients) in the unknown severity class (data not shown). A slight increase in total mortality rates was noticed throughout the years (Table 2).

Analysis by age group

On age sub-analysis TBI was more frequent in the 61-80 group, followed by 18-40, 41-60 and older than 80 years. Male preponderance is only inverted in patients older than 80 years. Hospitalization duration is also higher in the 61-80 group and TBI severity seems to increase in the eldest groups, as happens with mortality. Traffic accidents decreased in older age groups and falls have a considerably higher expression, being the main cause of TBI in patients > 80 years. Rate of ICU admissions decreased with age, but were never under 20%. Inversely, neurosurgical procedures are increasingly performed in older age groups. The rate of home discharge also increased with age (Table 3).

The age distribution along the decade is shown in Fig. 1, with an important decrease in TBI numbers in younger age groups and an increase in the elder.

DISCUSSION

TBI in-hospital admissions - Demographics

The results of our study clearly show that TBI in Portugal is evolving and there are some identified trends that may be important for Health Services planning and organization.
We report a clear decrease in total number of TBI in hospital admissions, confirming trends already demonstrated in other European countries.[5,8] Male preponderance is maintained throughout the decade as expected when comparing other population based studies.[2,5,11] An exception to this was found in the age group > 80 years-old. Here we find a female preponderance, perhaps due to higher life expectancy of women and, therefore, a larger contribution in the composition of older age groups.[12]

Mean age of our population (57.9 years) was higher than reported in other European studies, although most of them only included severe TBI patients.[5,7,9] This fact may be explained because mean age was calculated taking into account all hospital admissions without excluding readmissions or hospital transfers, since ethical criteria did not allow us to identify duplications in the data base. We point out that ageing of Portuguese population during the last decade, with an important demographic pyramid inversion[13] may have also contributed to this finding. Finally, by including all grades of TBI and excluding pediatric population, mean age was biased to higher values**.** Although an incidence analysis was not possible in our study, reports of a trend inversion, with increased incidence in older age groups and decrease in younger ones has also

Table 3 - TBI Characterization (*n*, %) by age group

Age group (years)	18 - 40	41 - 60	61 - 80	> 80
Total	**19553 (26.8%)**	**16166 (22.2%)**	**24690 (33.9%)**	**12456 (17.1%)**
Gender male	15594 (79.8%)	11960 (74%)	14264 (57.8%)	489 (39.3%)
Hospital lengh of stay (days)	8.8 ± 22.8	9.5 ± 19.3	9.7 ± 17.6	9.1 ± 15.2
TBI severity				
Mild TBI (TBI 1)	374 (19,2%)	2855 (17,7%)	3556 (14,4%)	1954 (15.7%)
Moderate to severe TBI (TBI 2-3)	10583 (54,2%)	9891 (61,1%)	16946 (68,6%)	8571 (68.8%)
Unknown	5223 (26,7%)	3420 (21,2%)	4188 (17,0%)	1931 (15.5%)
External Cause				
Traffic accident excluding 2 wheel vehicles	7687 (39,3%)	3229 (20%)	2607 (10,6%)	410 (3.3%)
Traffic accident with 2 wheels vehicles	2140 (10,9%)	886 (5,5%)	606 (2,5%)	70 (0.6%)
Falls	5405 (27,6%)	8417 (52,1%)	17203 (69,7%)	10444 (83.8%)
Run-over	849 (4,3%)	987 (6,1%)	1616 (6,5%)	396 (3.2%)
Other	3249 (16,6%)	2382 (14,7%)	2232 (9%)	884 (7.1%)
Unknown	233 (1,1%)	265 (1,6%)	426 (1,7%)	252 (2%)
ICU admission	5366 (27,4%)	4257 (26,3%)	5779 (23,4%)	2562 (20.6%)
Neurosurgical procedure	1800 (9,2%)	1816 (11,2%)	3589 (14,5%)	1783 (14.3%)
Mortality	1241 (6,3%)	1131 (7%)	2344 (9,5%)	1659 (13.3%)
Home discharge	10715 (54,8%)	9254 (57,2%)	14568 (59%)	7456 (59.9%)

been reported in northern Europe,[10] rendering our findings, in an older population, more credible.

TBI in-hospital admissions (severity, length of stay and external causes)

Accompanying the previous reported demographic trend, there seems to be an increase in TBI severity with moderate to severe TBI (TBI 2-3) admitted to hospital reaching 80.0% in 2010. This may be associated not only with the higher number of TBI in older patients,[10] but also to a more efficient pre-hospital emergency care as well as better institutional referral. Thus, more patients with severe TBI, who would have previously died before arriving at hospital, are now being admitted and treated.

As expected and presented in Table 1, the mean length of stay of TBI 2-3 patients is higher than total mean length of stay. Hospital length of stay has increased considerably and an explanation may also be found in the increasing age and severity of TBI patients. This trend is in accordance to data previously reported.[10]

External causes of TBI have changed over the study period. An increase in falls may be explained by an older, ailing population whereas a decrease in traffic accidents,[14] where typically younger age groups would be at greater risk of TBI, may be related to the improvement of traffic conditions and road safety. Similar results have been previously published.[7-9,15]

TBI in-hospital admissions - Management and mortality

Total mortality increased during the study period despite more patients being treated in ICUs or submitted to neurosurgical procedures in 2010 in comparison to 2000. There was an expected increase in mortality in keeping with TBI severity. The unknown TBI severity patients only had a 2.0% mortality, similar to the TBI 1 mortality, which leads us to speculate that this group may share more characteristics with TBI 1 patients, than with TBI 2-3. This trend was also reported in a recent multi-centre study.[7] ICU mortality was higher than global mortality as can be expected due to the severity of TBI. Better treatment did not mean less mortality. The increase of age and consequently comorbidities may have promoted a raise in mortality, despite optimization of treatment and surgical intervention[15]. When compared with a European study of severe TBI,[9] our ICU mortality was similar (31.7% *vs* 29.5%). The comparison, however, is deficient due to methodological differences. The increase in ICU admissions and use of neurosurgical procedures in treating TBI may be responsible in part for the increase in

length of hospital stay noted during the period evaluated.

Although mortality increased throughout this period, current treatment options, including implementation of clinical practice guidelines, have proven to benefit survival and outcome.[6] So, presumably, severe TBI patients that survive do so in better conditions and longer. Also contributing to this may be the technological developments in health services encountered in the first decade of this century and the rise in their consumption. As severity of TBI patients admitted to hospital increases, so does the availability of these resources, permitting treatment of patients in a more differentiated environment.

In our analysis there was a slight reduction in ICU admissions with older age. The majority of ICUs are not dedicated solely to neurologic patients; thus, the investment in older TBI patients may be secondary when comparing younger patients with other ICU manageable conditions. Rates of neurosurgical procedures, however, increased with age. A possible explanation may be found not only in the higher availability of resources but also by the increasing severity of TBI demanding surgical intervention.

Finally, although severity and mortality is higher in older patients, the proportion of home discharge increases with age. This could be partly justified by a probability of a worse functional recovery after the injury.

Final remarks

To date, this is one of the few studies that provides an analysis of the evolution of TBI in Portugal, and indeed it identified trends in the population composition and TBI etiology, as well as revealing an increase in the number of patients treated with more intensive and invasive modalities. The authors stress the large cohort, including data from 111 hospitals in a period of 11 years.

The importance of this database revision is concerned about reporting epidemiologic evidence that is lacking, especially in southern European countries. In spite of this, some limitations to the analysis must be addressed. First, this is an observational study with retrospective analysis of the DRG database that collects coded information of clinical records. The diagnostic and procedural information was based on ICD-9 codes, which can have several levels of detail, depending on the quality of information provided to the encoder and the number of encoders involved; during the 11 years thousands of encoders were involved in the process. Nevertheless, across the years, we noticed a reduction in the number of 'unknown severity' when classifying TBI that may be associated with an improvement in the quality of registry. It has been reported that codification errors tend to under identify moderate to severe cases of TBI.[16] In our study, with ICD-9, it seems that the opposite happened. We may argue that some multiple trauma patients may have mild TBI or concussion that was neglected by the encoder faced with other more severe diagnosis. Also, patients that recur to ED due to accidents or other events may also have minor head injuries that are under-reported.

Since we didn't have access to validated severity score scales, our severity grading system was oriented by the clinical characteristics encoded, including intracranial injury, presence of bone fracture and duration of loss of consciousness and was based on other international grading scales.

Bearing all these considerations in mind, the data collected must be analysed cautiously. Our interpretation was based on the trends over the years and not on absolute frequencies. Most studies address only severe TBI or are single-hospital based thus limiting the understanding of the epidemiology of this 'silent epidemic'.[3] In an effort to provide a more complete and real picture of TBI in Portugal, our study attempted to include all adult patients admitted to all hospitals of the Portuguese National Health Services during the first decade of the 21st century.

CONCLUSION

In conclusion, our work was based on a large cohort with a broad study period, and provided information that until now was missing. During the decade 2000-2010, TBI hospital admissions have decreased in frequency but mean age increased. Trends in etiology of TBI are shifting from traffic accidents to falls, manifesting the need to pay special attention to older age groups and implementing preventive measures to reduce TBI. Primary prevention of road accidents seems to be working, but we need to improve global accessibility for old people. Utilization of ICU resources and neurosurgical procedures is more widespread but mortality rates have also grown. During the study period, mortality rates have increased, possibly due to the increase of TBI severity, but also Portuguese pre-hospital care improved resulting in previously lethal cases arriving alive at Hospital and, although treated more frequently in ICUs and requiring more neurosurgical procedures, still they end up having higher mortality. In the future, a better quality of registry and codification may lead to collection of data that will permit not only evaluation of trends but also to determine precise frequency, incidence and severity needed to better adjust resources to our population.

ACKNOWLEDGMENT

The authors wish to thank the collaboration of the Health Systems Central Administration and Northern Regional Health Administration for providing us with the data in which this study was based.

CONFLICTS OF INTEREST

None stated.

FUNDING SOURCES

No funding was provided to conduct this study.

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MULTIMODAL BRAIN MONITORING IN NEUROCRITICAL CARE PRACTICE

Dias, C

IJCNMH 2014; 1(Suppl. 1):S08

INTERNATIONAL JOURNAL OF
CLINICAL NEUROSCIENCES
AND MENTAL HEALTH

REVIEW

Multimodal brain monitoring in neurocritical care practice

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Special Issue on Neurosonology and Cerebral Hemodynamics

Abstract

The management of severe acute neurological patients is a constant medical challenge due to its complexity and dynamic evolution. Multimodal brain monitoring is an important tool for clinical decision at bedside. The datasets collected by the several brain monitors help to understand the physiological events of acute lesion and to define patient-specific therapeutic targets. We changed from pure neurological clinical evaluation to an era of structure and image definition associated with instrumental monitoring of pressure, flow, oxygenation, and metabolism. At each time, we want to assure perfect coupling between energy deliver and consumption, in order to ensure adequate cerebral blood flow and metabolism, avoid secondary lesion, and preserve normal tissue.

Continuous monitoring of intracranial pressure, cerebral perfusion pressure, and cerebrovascular reactivity with transcranial Doppler, allows us to predict cerebral blood flow. However, adequate blood flow means not only quantity but also quality. To study and avoid tissue hypoxia we start to use methods for evaluation of oxygen extraction, such as oxygen jugular saturation, cerebral transcutaneous oximetry or measurement of oxygen pressure with intraparenchymal probes. To better understand metabolic cascade we use cerebral microdialysis to monitor tissue metabolites such as glucose, lactate/pyruvate, glycerol or cytokines involved in the acute lesion. Multimodal brain monitoring in neurocritical care practice helps neurointensivists to better understand the pathophysiology of acute brain lesion and accomplish the challenge of healing the brain and rescue lives.

Keywords: Multimodal brain monitoring, Intracranial pressure, Cerebral oximetry, Cerebral oxygenation, Cerebral blood flow, Cerebral microdialysis, Cerebrovascular reactivity indexes, Neurocritical care.

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Citation: Dias, C. Multimodal brain monitoring in neurocritical care practice. IJCNMH 2014; 1(Suppl. 1):S08

Received: 01 Sep 2013; Accepted: 29 Oct 2013; Published: 09 May 2014

Introduction

The main purpose of neurocritical care is to fight brain cell death, giving adequate flow, oxygen, and glucose in order to promote neuronal, endothelial, and glial cell recovery to ensure neuronal function. Although clinical evaluation of comatose patients is still one of the foundations of clinical neuroscience, the neurological findings of adverse events appear too late in time. Multimodal brain monitoring may give crucial, real-time information about the dynamic evolution of brain lesion, allowing to avoid secondary injury, recognize adverse events, and improve individualized management of severe acute neurological patients admitted to Neurocritical Care Units (NCCU) [1].

Basic neuromonitoring

Intracranial pressure, cerebral perfusion pressure, and autoregulation

Intracranial pressure (ICP) is derived from cerebral blood flow (CBF) and cerebrospinal fluid (CSF) circulation within the stiff skull [2]. The most reliable methods of ICP monitoring are ventricular catheters and intraparenchymal probes. An intraventricular drain connected to an external pressure transducer is still considered to be a "golden standard" method of measure global ICP. Ventricular catheters allow recalibration and therapeutic drainage of CSF but have significant complications, including hemorrhage, occlusion and infection. Intraparenchymal fiberoptic or microtransducer probes have a minimal associated risk of complications, but can be calibrated only before insertion although the sensitivity drift over time is very small. Critical values of ICP may vary between individual patients but current consensus is to treat ICP exceeding the 20 mmHg threshold [3].

International guidelines for traumatic brain injury (TBI) recommend that ICP should be monitored in patients with Glasgow Coma Scale (GCS) score <8, with an abnormal head CT scan; or patients with GCS score <8 with a normal head CT scan if two or more of the following characteristics are present: age over 40 years, systolic blood pressure <90 mmHg or motor posturing [4, 5]. Recently, Chesnut et al. [6] published the results of the first randomized trial of ICP monitoring in patients with severe TBI. Six months after injury, patient groups had similar scores on functional status and cumulative mortality. For intensivists the strongest clinical implication of this trial is that we need to understand that the true value of ICP is more than a number and should become part of a multimodality approach to targeted therapy [7, 8].

ICP beat-to-beat waveform consists of three components named P1, P2, and P3 that are related to arterial pulse and brain compliance (**Figure 1**). P2 over P1 is a sensitive (99%) but not specific (1-17%) predictor of ICP subsequent increase [9]. Continuous ICP and arterial blood pressure monitoring allow calculation of cerebral perfusion pressure (CPP=ABP-ICP). CPP is the driving force of CBF and the principal determinant of cerebrovascular reactivity to pressure, named cerebral autoregulation. The normal cerebral arterial bed actively reacts to small fluctuations in arterial blood pressure in order to maintain constant CBF over a wide range of CPPs (from approximately 50–150 mmHg). When reactivity is normal the changes in ABP produce an inverse change in cerebral blood volume and hence ICP, but when reactivity is disturbed, changes in ABP are passively transmitted to ICP. Computational methods for continuous assessment of cerebral autoregulation were introduced more than a decade ago and they evaluate dynamic relationships between slow waves of ABP or CPP and ICP or flow velocity [10]. Examples of these methods are moving correlation coefficient, phase shift, or transmission (either in time- or frequency-domain).

The pressure reactivity index (PRx) is calculated as the moving correlation coefficient between 30 consecutive, 10 seconds averaged data points of ICP and ABP [11, 12]. A positive PRx (>0.2) signifies passive reactive vascular bed, while a PRx <0.2 means normal autoregulation. PRx may be used to continuous monitoring of autoregulation and define individual lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA), helping target optimal CPP [13, 14] (**Figure 2**). Retrospective studies show that favorable outcome reaches its peak when CPP is maintained close to optimal CPP [15].

Oxygenation and cerebral blood flow

Brain resuscitation based on basic control of ICP and CPP does not prevent cerebral hypoxia in some patients [16]. Cerebral oxygenation monitoring evaluates the balance between oxygen delivery and consumption [17] and oxygen guided management could lead to improved neurologic outcome [18]. There are several invasive and non-invasive continuous methods of monitoring regional or global brain oxygenation and avoid secondary lesion due to hypoxia (jugular venous bulb oximetry, brain tissue oxygenation, and transcutaneous cerebral oximetry with near infrared spectroscopy).

Brain tissue oxygen pressure

Brain tissue oxygenation pressure (PbtO2) represents the interaction between plasma oxygen tension and CBF [19]. Direct measurement of local PbtO2 with an intraparenchymal probe is becoming the gold standard for oxygen monitoring in NCCU. PbtO2 probes are placed in the white matter and post-insertion head CT confirmation is needed to interpret readings. The normal range is 25-50 mmHg and PbtO2 <15 mmHg is considered the critical threshold for hypoxia [20, 21]. Algorithms of PbtO2-directed therapy should incorporate the management of the several causes of tissue hypoxia (hypoxic, anemic, ischemic, cytopathic, and hypermetabolic) [22] (**Table 1**). Similarly to PRx, the index of tissue oxygen reactivity (ORx), calculated as the correlation coefficient between PbtO2 and CPP, can be

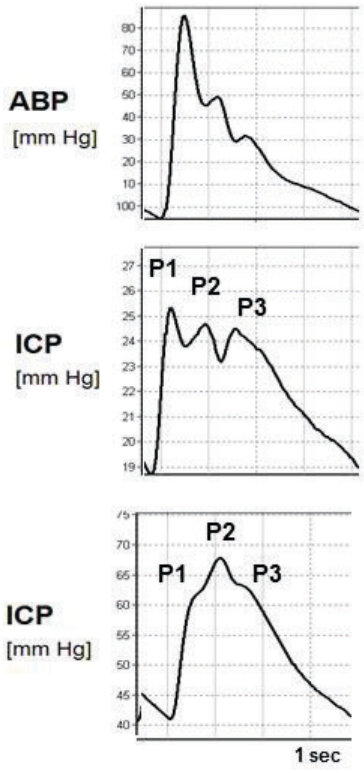

Figure 1. Arterial blood pressure (ABP) and Intracranial Pressure (ICP) waveform. P1 (percussion wave) represents systolic arterial pulsation, P2 (tidal wave) reflects intracranial compliance and P3 (dicrotic wave) represents venous wave that result from closure of aortic valve. In normal conditions, P1 > P2 >P3, but when brain compliance starts to decrease, the amplitude of P2 increases and may exceed P1.

used as an indicator of CBF autoregulation [23]. The concepts of cerebrovascular pressure reactivity and oxygen reactivity are related as high CPP should be avoided if it does not yield improvement in brain tissue oxygenation [24].

Transcranial Doppler and thermal diffusion flowmetry

Continuous direct monitoring of CBF would be helpful to manage acute neurologic patients. Transcranial Doppler ultrasonography (TCD) is a non-invasive method to assess flow velocity as a surrogate of cerebral blood flow. TCD is more frequently used in the diagnosis of vasospasm or hyperemia, but may also be used as a tool to monitor the regulatory reserve of cerebral vasculature to changes in ABP, CO_2, and transient hyperemic response test [25-27]. Thermal diffusion flowmetry (TDF) is based on thermal conductivity and provides a quantitative measurement of regional CBF. Probes are inserted in the white matter, 25 mm below the dura and the normal range is 18-25 ml/100g/min [28]. Continuous monitoring of CBF with TDF and CPP allows calculation of flow-related autoregulation index [29].

Cerebral metabolism and electrical function

Brain metabolism can be assessed by hourly microdyalisis measurement of cell substrates (glucose), metabolites (lactate, pyruvate, glycerol), and neurotransmitters (glutamate) in the extracellular fluid [30]. Normal ranges are described in **Table 2**. Cerebral microdyalisis detects early hypoxia and ischemia and increases the therapeutic window to avoid secondary lesion. However, remains to be established if treatment-related improvement in biochemistry translates into better outcome after acute brain injury [31].

Continuous electroencephalography (cEEG) with or without video surveillance is becoming more widespread in the NCCU [32]. Modern cEEG approaches include quantitative analysis of total power, relative alpha variability and asymmetry detection. The most common indications are: detection of nonconvulsive seizures or status epilepticus, assessment of depth of sedation, detection of ischemia and characterization of clinical signs such as rigidity, tremors, eye deviation, agitation and otherwise unexplained variations of ABP and heart rate [33].

Table 1. Causes of brain tissue hypoxia and management.

Etiology	Pathophysiology	Management of brain tissue hypoxia
Hypoxic	Low PaO_2 Low SaO_2	Lung recruitment and FiO_2 increase Improve O_2 delivery and Hb dissociation curve
Anemic	Low Hb concentration	Red blood cell transfusion
Ischemic	Hypotension, low CPP Hyperventilation Vasospasm Shunt Low cardiac output Dysperfusion	Increase ABP or CPP Increase CO_2 Vasodilation (systemic or local) Treat SIRS or sepsis Improve cardiac output Reduce brain edema
Cytotopathic	Low oxygen extraction Hb high affinity Mitochondrial dysfunction	Improve O_2 delivery Improve Hb dissociation curve
Hypermetabolic	High metabolism	Increase sedation, treat seizures, decrease temperature

ABP = Arterial blood pressure; CPP = Cerebral perfusion pressure; Hb = Hemoglobin

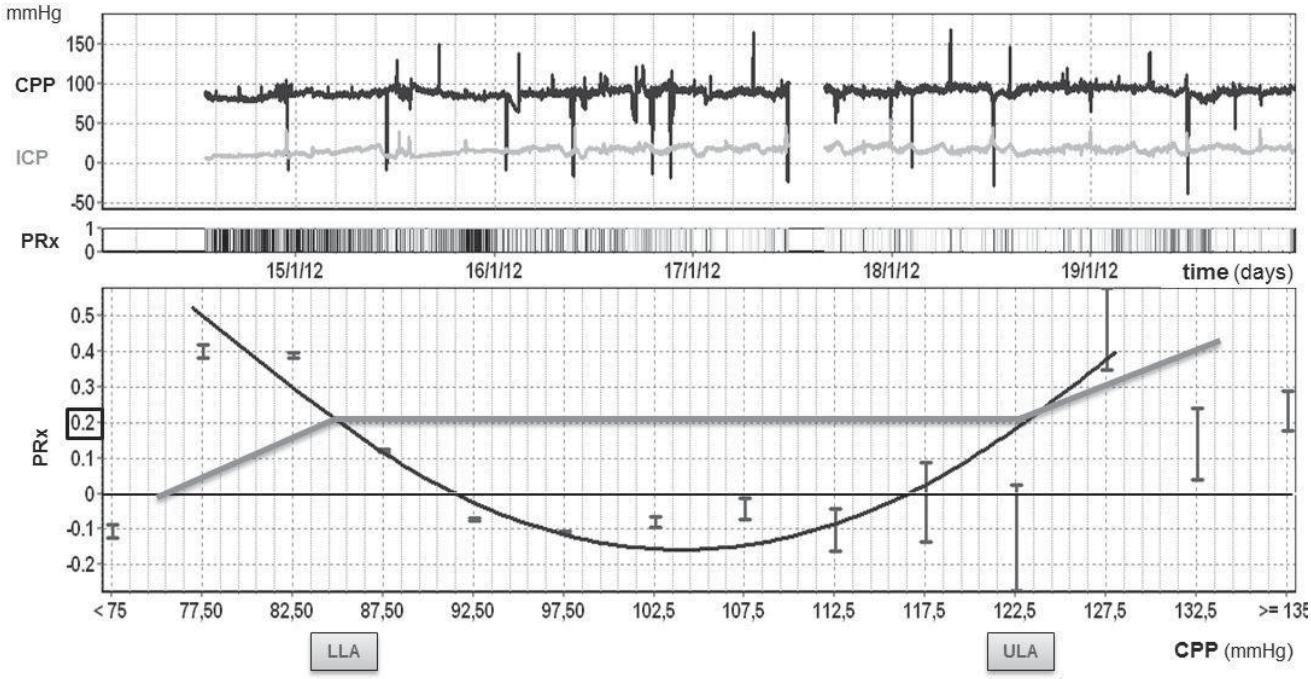

Figure 2. Intracranial pressure (ICP), cerebral perfusion pressure (CPP), and pressure reactivity index (PRx). Continuous monitoring of autoregulation and definition of individual lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA) to target optimal CPP during ICU management.

Conclusion

Multimodal brain monitoring increases the therapeutic window and helps to target treatment avoiding excess or lack of interventions, decreasing cerebral secondary lesions, and systemic complications. Clinical information systems and integrated brain monitoring graphical trends show that pathologic readings precedes clinical deterioration and therefore are an important tool to support proactive medical decision in daily neurocritical care practice.

Abbreviations

ABP: Arterial blood pressure; CBF: Cerebral blood flow; cEEG: Continuous electroencephalography; CSF: Cerebrospinal fluid; CPP: Cerebral perfusion pressure; GCS: Glasgow coma scale; ICP: Intracranial pressure; LLA: Lower limit of autoregulation; NCCU: Neurocritical care units; ORx: Oxygen reactivity index; PbtO2: Brain tissue oxygenation pressure; PRx: Pressure reactivity index; TBI: Traumatic brain injury; TCD: Transcranial Doppler ultrasonography; TDF: Thermal diffusion flowmetry; ULA: Upper limit of autoregulation

Competing interests

The authors declare no conflict of interest.

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Table 2. Cerebral microdialysis normal range of biomarkers and metabolism failure interpretation.

Microdialysis concentration	Normal range	Monitoring interpretation
Glucose	1.5-2.0 mmol/l	Hypoglycemia, cerebral hyperglycolysis Hypoxia, ischemia,
Lactate / Pyruvate ratio	>20-25	Cellular redox state, hypoglicemia Hypoxia, ischemia
Glycerol	>100 µmol/l	Cell membrane degradation Hypoxia, ischemia
Glutamate	>15-20 µmol/l	Excitotoxicity Hypoxia, ischemia

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PRESSURES, FLOW, AND BRAIN OXYGENATION DURING PLATEAU WAVES OF INTRACRANIAL PRESSURE

Dias, C, Maia, I, Cerejo, A, Varsos G, Smielewski, P, Paiva, J-A, Czosnyka, M

Neurocrit Care (2014) 21:124–132

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-013-9918-y

ORIGINAL ARTICLE

Pressures, Flow, and Brain Oxygenation During Plateau Waves of Intracranial Pressure

Celeste Dias · Isabel Maia · António Cerejo · Georgios Varsos · Peter Smielewski · José-Artur Paiva · Marek Czosnyka

Abstract
Background Plateau waves are common in traumatic brain injury. They constitute abrupt increases of intracranial pressure (ICP) above 40 mmHg associated with a decrease in cerebral perfusion pressure (CPP). The aim of this study was to describe plateau waves characteristics with multimodal brain monitoring in head injured patients admitted in neurocritical care.
Methods Prospective observational study in 18 multiple trauma patients with head injury admitted to Neurocritical Care Unit of Hospital Sao Joao in Porto. Multimodal systemic and brain monitoring of primary variables [heart rate, arterial blood pressure, ICP, CPP, pulse amplitude, end tidal CO_2, brain temperature, brain tissue oxygenation pressure, cerebral oximetry (CO) with transcutaneous near-infrared spectroscopy and cerebral blood flow (CBF)] and secondary variables related to cerebral compensatory reserve and cerebrovascular reactivity were supported by dedicated software ICM+ (www.neurosurg.cam.ac.uk/icmplus). The compiled data were analyzed in patients who developed plateau waves.
Results In this study we identified 59 plateau waves that occurred in 44 % of the patients (8/18). During plateau waves CBF, cerebrovascular resistance, CO, and brain tissue oxygenation decreased. The duration and magnitude of plateau waves were greater in patients with working cerebrovascular reactivity. After the end of plateau wave, a hyperemic response was recorded in 64 % of cases with increase in CBF and brain oxygenation. The magnitude of hyperemia was associated with better autoregulation status and low oxygenation levels at baseline.
Conclusions Multimodal brain monitoring facilitates identification and understanding of intrinsic vascular brain phenomenon, such as plateau waves, and may help the adequate management of acute head injury at bed side.

Keywords Multimodal brain monitoring · Intracranial pressure · Plateau waves · Cerebral perfusion pressure · Cerebrovascular reactivity · Head injury

Introduction

"Sudden rises in intracranial pressure" (ICP) were first described by Janny in 1950 [1] but the term "plateau waves" or "A waves" was introduced by Lundberg in 1960 [2]. Plateau waves were defined as sudden and relevant increases in ICP up to 40–100 mmHg with duration of 5–20 min [3]. However, the duration of plateau waves should not be considered as a strict criterion particularly that in many centers elevations of ICP are actively treated. Plateau waves are associated with working cerebrovascular reactivity [3] and low cerebrospinal compensatory reserve [4] related to several acute or chronic brain pathologies such as head injury [5], spontaneous subarachnoid hemorrhage [6, 7], intracerebral hemorrhage [7], tumors [8], benign intracranial hypertension [7], and craniosynostosis [9].

These tidal ICP elevations are accompanied by a decrease in cerebral perfusion pressure (CPP = MAP–ICP), which in turn may decrease brain blood flow and

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Published online: 27 September 2013

tissue oxygenation [10]. The theoretical model for the underlying mechanism of sudden increase in ICP is a vasogenic positive feedback loop triggered by active vasodilation, increase in cerebral blood volume (CBV) leading to elevation of ICP and decrease of CPP [3]. The reverse of the cycle may arise spontaneously or due to medical management with a vasoconstrictive stimulus that decreases CBV, and restores normal ICP and CPP [3, 11].

Acute intracranial hypertension is an important cause of secondary lesion in neurocritical care patients that should be avoided. To pursue this objective at bedside we need to understand better, and if possible anticipate this phenomenon, in order to reduce its negative impact on brain oxygenation and cerebral blood flow (CBF). Analysis of the ICP time pattern combined with multimodal brain monitoring may provide important information not only about cerebral perfusion and autoregulation reserve but also about cerebral hemodynamics combined with cerebral oxygenation. In this paper we describe the course of plateau waves in traumatic brain injury (TBI) patients using multimodal systemic and brain monitoring with primary variables such as heart rate (HR), arterial blood pressure (ABP), ICP, CPP, pulse amplitude, end tidal CO_2 ($ETCO_2$), brain temperature, brain tissue oxygenation pressure ($pbtO_2$), transcutaneous near-infrared spectroscopy for cerebral oximetry (CO—mean values between left and right side monitoring) and CBF with thermal diffusion method. By using the information derived from these signals we exploit the use of some hemodynamic indices in order to enhance further our insight on cerebrovascular reactivity.

Materials and Methods

Patients

After local research ethics committee approval and with written consent from the patients' next of kin, we prospectively studied 18 consecutive multiple trauma patients (16 male; mean age 42 years; min 20, max 66 years) admitted to the Neurocritical Care Unit at Hospital S. João, Porto. All had head injury with a mean GCS score of 6 (range 3–14) and mean SAPS II score of 45 (predicting mortality of 36 %). On first brain CT scan nine patients had mainly contusions, eight had acute subdural hematomas, one had vasogenic edema, and all had traumatic subarachnoid hemorrhage. During admission four were submitted to craniotomy for hematoma drainage, six went through decompressive craniotomy, and three had non-neurosurgical procedures. Median GOS at 3 month was three with mortality rate 17 %.

Patients were sedated with propofol and/or midazolam and fentanyl and normoventilated. Whenever possible we targeted CPP management for optimal CPP [12] according to the pressure reactivity index (PRx). Otherwise we managed CPP for values >60 mmHg according to Brain Trauma Foundation Guidelines [13]. Patients' physiological variables were continuously monitored (HR, ABP, ICP, CPP, $ETCO_2$, $pbtO_2$, brain temperature, CO, and CBF) for the first 10 days. We used one bolt for intraparenchymal ICP (Codman®) and another triple bolt for intraparenchymal CBF thermal flow sensor (Hemedex®), $pbtO_2$, and brain temperature (Licox®). Sensors were inserted in the penumbra area and their location was confirmed afterward with CT scan. Near-infrared spectroscopy transcutaneous sensors for CO (Covidien®) were used. Furthermore we use ICM+® software to collect data from the several brain monitors and to calculate secondary variables related to cerebral compensatory reserve and cerebrovascular reactivity [14].

Data Analysis

Data monitoring was captured with ICM+® for online and offline analyses. Plateau waves were visually identified during offline analysis. In total 59 plateau waves were studied in eight out the 18 patients, none of them with decompressive craniectomy.

The primary analysis of measured signals included calculation of 10 s averages of HR, ABP, ICP, ICP, ICP pulse amplitude (AMP), CPP, $ETCO_2$, CO, $pbtO_2$, CBF, and cerebrovascular resistance (CVR = CPP/CBF). In addition, we performed secondary analysis calculating indices of brain compensatory reserve and cerebrovascular reactivity using a moving linear correlation approach applied to the primary analysis results. In a reactive vascular system, these indices are supposed to be close to zero or negative, while positive values close to one signify impaired reactivity.

PRx was evaluated using 10 s averages of ICP and ABP over a moving window of 5 min length [15].

Pulse amplitude index (PAx) [16] was calculated using 10 s averages of ABP and corresponding pulse amplitude of ICP over a moving window of 5 min length.

Similarly, for NIRS-derived cerebral oxygenation, index COx was calculated as correlation between CO and CPP over 5 min moving window [17].

Oxygen reactivity index ORx was evaluated between $pbtO_2$ and CPP over an average period of 60 min [18], but we also defined a "short" version of this index, termed ORxshort, calculated over a period of 5 min.

Finally, we defined CBFx as a moving correlation between CBF and CPP, with window length of 5 min.

In addition to the reactivity indices we also calculated a volume pressure compensatory reserve index RAP, defined as a linear correlation coefficient between the amplitude of ICP wave (AMP) and mean ICP. With RAP we can define distinct regions in the volume–pressure curve: a RAP coefficient close to 0 indicates a good compensatory

Table 1 Fundamental (measured) variables and *p* values between baseline, during and after plateau waves (two consecutive 30-min period intervals)

	Baseline	Plateau	Just after	Later
ICP (mean ± SD)	17.39 ± 5.3	47.27 ± 6.47	16.92 ± 6.85	15.51 ± 7.46
p values		***p	NS	NS
p values from plateau to after			***$p = 0$	***$p = 0$
ABP (mean ± SD)	107.85 ± 12.93	108.21 ± 13.97	109.76 ± 12.90	108.56 ± 13.01
p values			NS	NS
p values from plateau to after			NS	NS
CPP (mean ± SD)	90.72 ± 11.37	61.13 ± 14	93.12 ± 13.29	93.18 ± 12.67
p values		***$p = 0$	NS	NS
p values from plateau to after			***$p = 0$	***$p = 0$
AMP (mean ± SD)	2.7 ± 1.25	6.9 ± 2.65	2.92 ± 1.42	2.59 ± 1.08
p values		***$p = 0$	NS	NS
p values from plateau to after			***$p = 0$	***$p = 0$
CBF (mean ± SD)	31.64 ± 30.92	26.18 ± 24.53	41.15 ± 28.31	33.67 ± 33.55
p values from baseline		NS	NS	NS
p values from plateau to after			*$p = 0.03$	NS
CVR (mean ± SD)	4.88 ± 2.78	3.97 ± 2.35	3.64 ± 2.49	5.23 ± 3.80
p values		NS	*$p = 0.02$	NS
p values from plateau to after			NS	NS
CO (mean ± SD)	53.01 ± 8.45	50.06 ± 12.78	50.79 ± 13.11	51.38 ± 10.51
p values		$p = 0.021$	NS	NS
p values from plateau to after			NS	NS
$PbtO_2$ (mean ± SD)	21.38 ± 7.95	16.66 ± 8.67	20.44 ± 7.34	20.68 ± 8.01
p values		**$p = 0.0004$	NS	NS
p values from plateau to after			**$p = 0.002$	*$p = 0.009$
$ETCO_2$ (mean ± SD)	28.12 ± 3.54	29.93 ± 4.15	28.89 ± 3.56	28.26 ± 3.87
p values		**$p = 0.00042$	NS	NS
p values from plateau to after			NS	*$p = 0.001$
HR (mean ± SD)	78.18 ± 17.97	79.9 ± 15.74	79.51 ± 17.90	78.75 ± 18.84
p values		NS	NS	NS
p values from plateau to after			NS	NS
TEMP (mean ± SD)	37.43 ± 0.84	37.4 ± 0.82	37.28 ± 0.85	37.26 ± 0. 90
p values		NS	NS	NS
p values from plateau to after			*$p = 0.01$	*$p = 0.031$

Quoted *p* values are not corrected for multiple comparisons

ICP intracranial pressure, *ABP* arterial blood pressure, *CPP* cerebral perfusion pressure, *AMP* amplitude of ICP, *CBF* cerebral blood flow, *CVR* cerebral vascular resistance, *CO* cerebral oximetry, *$pbtO_2$* pressure of brain tissue oxygenation, *$ETCO_2$* endtidal CO_2, *HR* heart rate, *Temp* brain temperature, *NS* non-significant

reserve with linear relationship between volume and pressure. RAP index around 1 indicates poor compensatory reserve with exponential relationship between volume and ICP. RAP negative at high ICP values indicates exhausted compensatory reserve [4].

To describe the plateau waves we applied time averages of the primary and secondary variables during the plateau phase, within a 30 min interval before the onset and two consecutive 30 min intervals after the wave (just after—first 30 min and later—second 30 min).

In addition, observations of the shape of pulse waveform of ICP were performed. ICP beat-to-beat waveform consists of three components that reflect various aspects of the cerebral vascular bed. The first peak (P1) is the "percussion" wave and is due to arterial pressure being transmitted from the choroid plexus to the ventricle. The second wave (P2), known as the "tidal" wave, is related to brain compliance. The origin of third peak P3 (not always clearly observed) is still a subject for disputes. It is believed to coincide with the closure of the aortic valve and represents

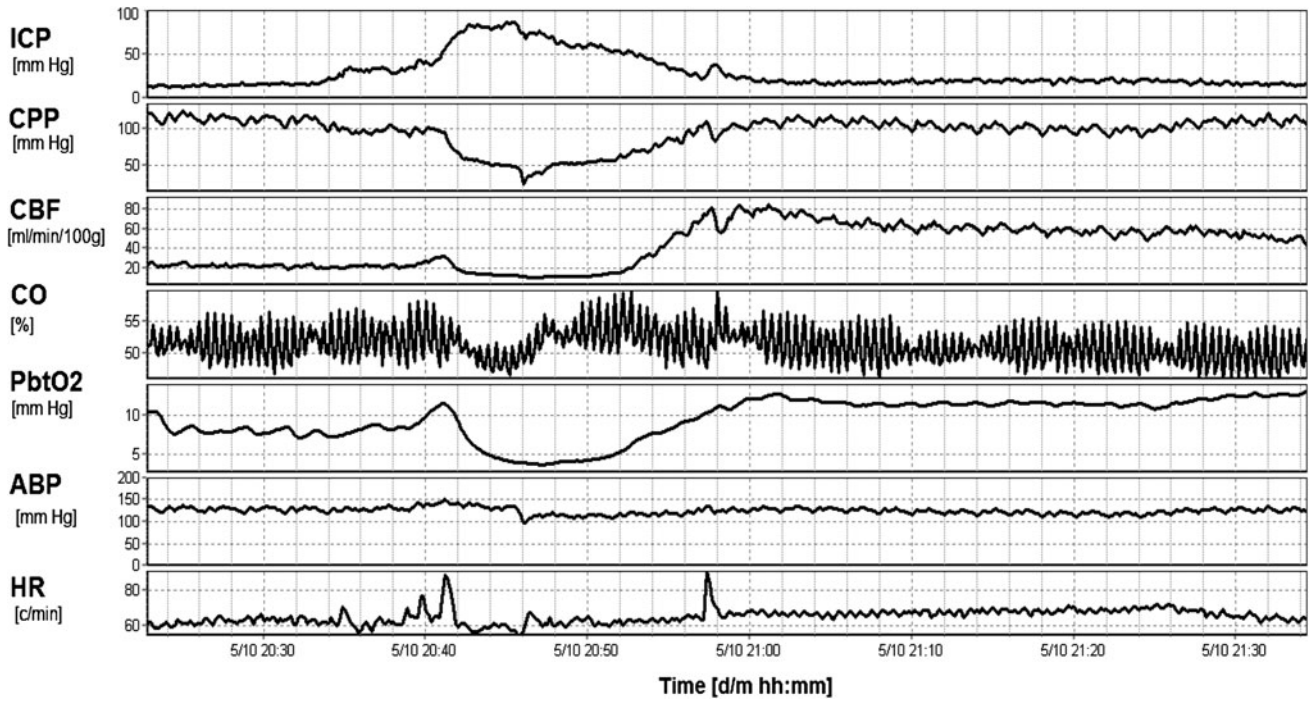

Fig. 1 Example of multimodal brain monitoring recording during plateau wave. Rise in ICP courses with relatively stable systemic variables such as ABP and HR but is accompanied of an important decrease in CPP, CBF, CO, and $pbtO_2$

the dicrotic notch [19]. Under normal conditions of low ICP, the three peaks relate to each other as P1 > P2 > P3. When brain compliance decreases and ICP starts to rise the ICP pulse waveform morphology gradually changes and the P2/P1 ratio eventually becomes greater than 1.0.

Statistical Analysis

The analyses were performed using commercial IBM software SPSS 20®. Data were expressed as mean values, range, and standard deviation (mean ± SD). Normal distribution was established with Shapiro–Wilk test. Repeated measures ANOVA were applied to test the significance of the results comparing baseline values with values obtained during and after plateau waves, between and within subjects. When appropriate, non-parametric Kruskal–Wallis test was used to investigate statistical relationships between the studied variables. Tests were considered statistically significant for p values <0.05.

Results

Plateau Waves and Primary Brain Multimodal Variables

In this study plateau waves occurred in 44 % of the patients. Averaged values of primary variables describing plateau waves are summarized in Table 1. During A waves, HR and ABP remained almost constant as ICP rose from mean baseline of 17.39 ± 5.3 to a mean value of 47.27 ± 6.47. The mean time of ICP values above 40 was 9 min with a range of 2–31 min. During this time, at the top of the plateau wave, mean ICP pulse amplitude (AMP) increased and CPP decreased ($p < 0.0001$). CBF and cerebrovascular resistance decreased and brain oxygenation decreased significantly ($p = 0.0004$) to values below 20 mmHg. Simultaneously, brain hypoxia was detected by CO although with less significant value ($p = 0.021$). We also saw a small increase in $ETCO_2$ between baseline and plateau wave, although highly significant ($p = 0.00042$), which may be responsible for triggering the vasodilatory cascade. Example of shape of plateau wave using multimodal monitoring setup is presented in Fig. 1.

Cerebral Hyperemia After Plateau Waves

After the end of plateau waves, as ICP decreased and CPP recovered, a hyperemic response in 64 % of cases with a statistically significant increase in CBF ($p = 0.03$) and decrease of CVR ($p = 0.02$) was noticed (see Fig 1).

In the hyperemic response after plateau waves CBF increased higher (above 7 ml/min/100 g) if baseline $PbtO_2$ was less than 20 (23 ± 7 vs. 16 ± 7 mmHg; $p = 0.004$, Kruskal–Wallis test). Also higher hyperemia was noted

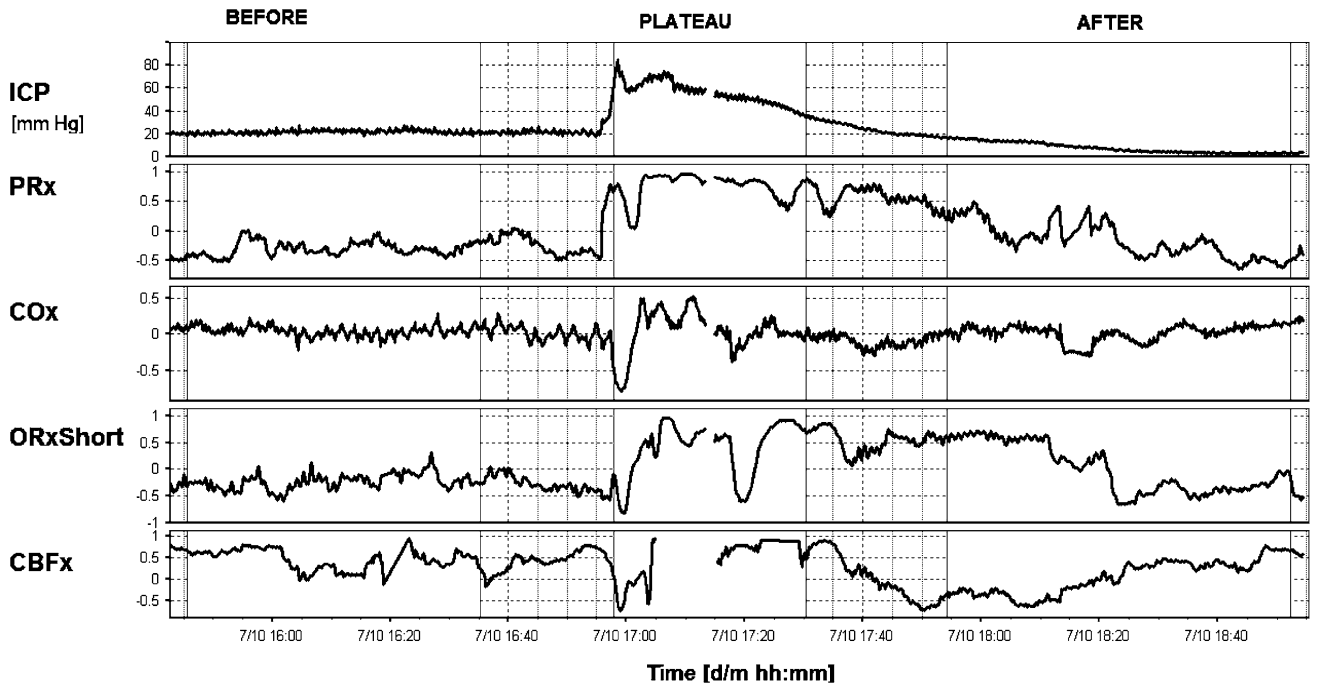

Fig. 2 Plateau wave and cerebral vascular reactivity indexes. During the increase of ICP, PRx changes abruptly from −0.5 to values above 0.5 demonstrating impairment of autoregulation. Oxygenation indexes cerebral oximetry index (COx) and oxygen reactivity index (ORxshort) also reveal derangement of oxygen availability to brain tissue. Cerebral blood flow reactivity index (CBFx) shows blood flow instability with important risk of cerebral ischemia

Table 2 Compensatory volume–pressure reserve and cerebrovascular reactivity indices and *p* values between baseline, during and after plateau waves (two consecutive 30-min period intervals)

	Baseline	Plateau	Just after	Later
RAP (mean ± SD)	0.57 ± 0.18	0.65 ± 0.21	0.59 ± 0.19	0.55 ± 0.22
p values		NS	NS	NS
PRx (mean ± SD)	−0.05 ± 0.27	0.16 ± 0.50	0,02 ± 0.26	0.02 ± 0.31
p values		*$p = 0.02$	NS	NS
PAx (mean ± SD)	0.12 ± 0.30	0.15 ± 0.35	0.16 ± 0.23	0.14 ± 0.24
p values		NS	NS	NS
CBFx (mean ± SD)	0.62 ± 0.26	−0.31 ± 0.39	0.69 ± 0.24	0.006 ± 0.19
p values		NS	NS	NS
COx (mean ± SD)	0.04 ± 0.09	−0.09 ± 0.26	0.03 ± 0.13	0.03 ± 0.13
p values		NS	NS	NS
ORx (mean ± SD)	0.15 ± 0.26	0.26 ± 0.33	0.31 ± 0.31	0.30 ± 0.32
p values		NS	*$p = 0.02$	**$p = 0.03$
ORxShort (mean ± SD)	−0.01 ± 0.15	0.13 ± 0.4	0.07 ± 0.17	0.01 ± 0.17
p values		**$p = 0.04$	**$p = 0.004$	NS

Quoted *p* values are not corrected for multiple comparisons

RAP RAP index between AMP and ICP, *PRx* pressure reactivity index, *PAx* pulse amplitude index, *CBFx* cerebral blood flow reactivity index, *COx* cerebral oximetry reactivity index, *ORx* and *ORxshort* oxygen reactivity index, *NS* non-significant

with lower baseline PRx (0.01 ± 0.21 vs. −0.26 ± 0.23; $p = 0.002$). During hyperemic response, brain oxygenation improved with a slow and sustained increase ($p = 0.002$) and the same tendency was seen in CO, although non-significant. We also noticed a marginal decrease in brain temperature ($p = 0.01$) after plateau wave.

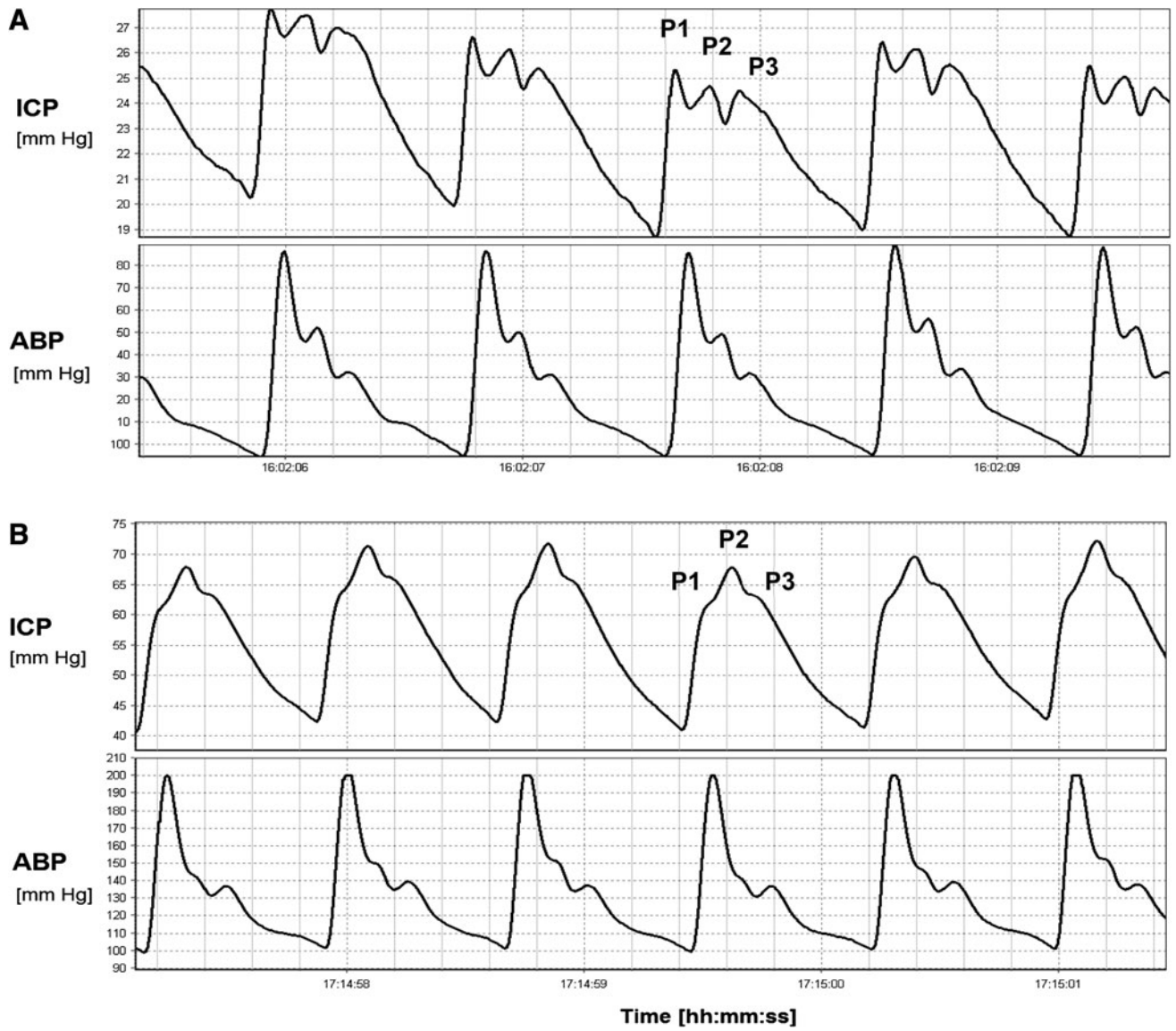

Fig. 3 **a** ICP beat-to-beat waveform and the three pulsatile components. P1 the "percussion" wave, P2 the "tidal" wave, and P3 the dicrotic notch. Under normal values of ICP the three peaks relate with each other as P1 > P2 > P3. **b** When brain compliance decreases and ICP starts to rise, the waveform modifies with an increase in amplitude followed by an inversion of P2/P1 ratio

Association with Cerebrovascular Reactivity and Compensatory Volume–Pressure Reserve

Figure 2 represents an example of plateau wave and secondary variables. As ICP suddenly increases, all indices present important modifications. With the exception of CBFx and COx all other indices (PRx, PAx, ORx, and ORxshort) change reflected deterioration of autoregulation, vascular reactivity, and oxygenation. During plateau waves RAP, a measure of impairment of compensatory volume–pressure reserve, increases but without statistically significance. Cerebrovascular reactivity indices deteriorate with frequent impairment of autoregulation related to a significant increase in PRx ($p = 0.02$). ORxshort also increased significantly ($p = 0.04$) during plateau wave warning of potential brain hypoxia. The index recovers to its baseline values but after some delay (the "just after" values were still significantly increased, at $p < 0.004$). ORx, due to its longer calculation time window (1 h), does not reflect adequately such rapid modifications in cerebral vascular reactivity. CBFx and COx show no significant modification in the majority of patients (Table 2).

Observation of ICP Pulse Waveform During Plateau Waves

Figure 3 shows an example of change in ICP waveform morphology at baseline (Fig. 3a, P1 > P2 > P3) and

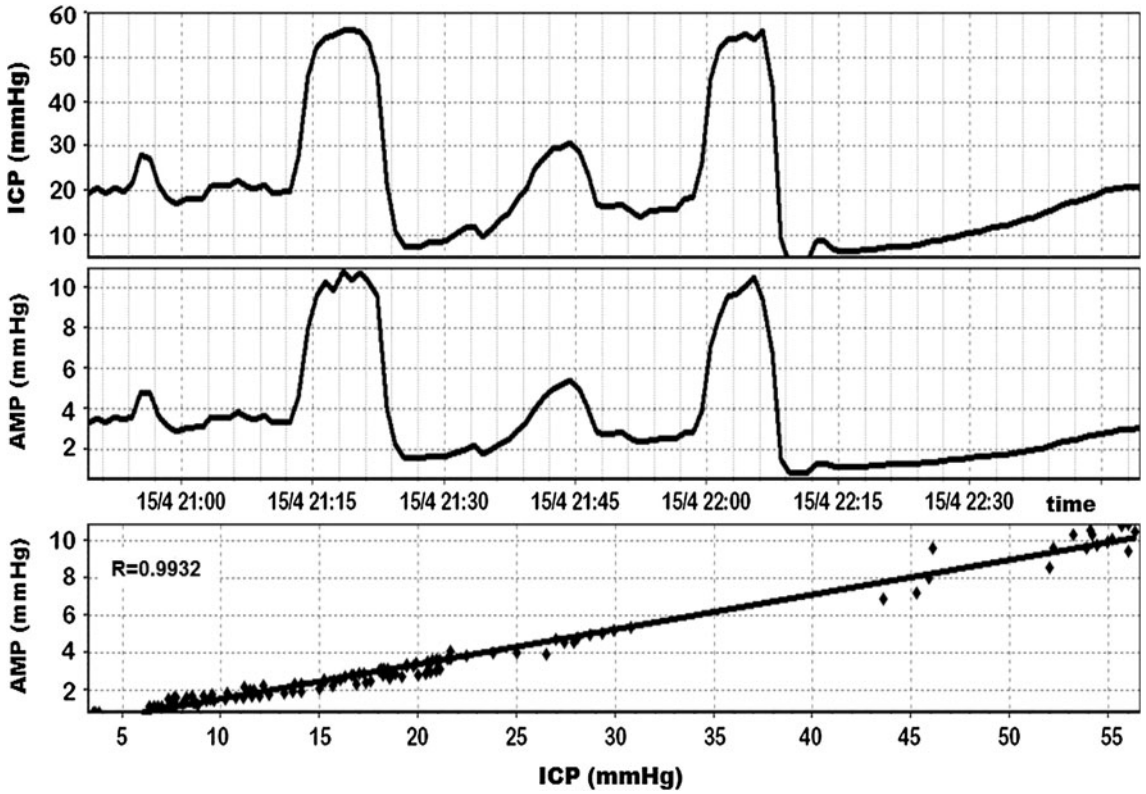

Fig. 4 Correlation between absolute values of ICP during plateau wave and ICP pulse amplitude

during plateau waves (Fig 3b P1 < P2 > P3). During plateau waves increase in ICP pulse amplitude is highly correlated with the mean value of ICP ($r = 0.9932$), as demonstrated by an example shown in Fig. 4.

Plateau Waves Magnitude and Duration

As the duration of plateau waves increased from 5 to 30 min we detected a negative correlation with PRx ($r = -0.46$; $p < 0.003$) which means that the better the autoregulation the longer the duration of plateau waves (Fig. 5a). Using multiple regression analysis we defined a model that explains the magnitude of ICP based on average values of cerebrovascular indexes from the wave plateau period:

$$\text{Increase in ICP} = 8.3\text{O} \times \text{ORx} + 0.37 \times \text{CO} - 8 \times \text{PRx} + 49$$

The lower PRx with the better oxygenation parameters (CO and ORx) the higher magnitude of ICP (Fig. 5b).

Discussion

Plateau waves are frequent cerebrovascular phenomena in TBI, which are not usually associated with worse outcome, unless they are longer than 30 min [5]. Nevertheless, TBI with sustained intracranial hypertension or low oxygenation have poor prognosis [20].

Multimodal brain monitoring and computerized analysis help in early detection of secondary insults at the bedside. It also adds value to retrospective observation in offline analysis, namely during intracranial hypertension [21]. Rises in ICP above 40 mmHg with different causes may appear in TBI patients [22]. It is important to understand their etiology and pathophysiology in order to apply the most adequate treatment. In this study multimodal brain monitoring helped to distinguish and describe plateau waves as sudden rises in ICP triggered by vasodilatory events, such as small oscillations of ABP, brain oxygenation, or arterial CO_2. This vasodilatory cascade leading to an increase in CBV has combined effects on CPP, cerebral oxygenation, and CBF. With our monitoring setup, we were able to detect significant compromise of CPP, decrease of cerebral vascular resistance, CBF, and brain oxygenation. Autoregulation, normally intact before the onset of the plateau wave, was lost during the crest of the wave, as indicated by the PRx. The same pattern was followed by the other cerebrovascular reactivity indexes related to oxygenation reactivity index ORxshort. Plateau waves are not benign phenomena and, at the lower limit of autoregulation (LLA), there is a risk of zero flow due to the collapse of brain vessels [23]. This is particularly relevant in the situations of

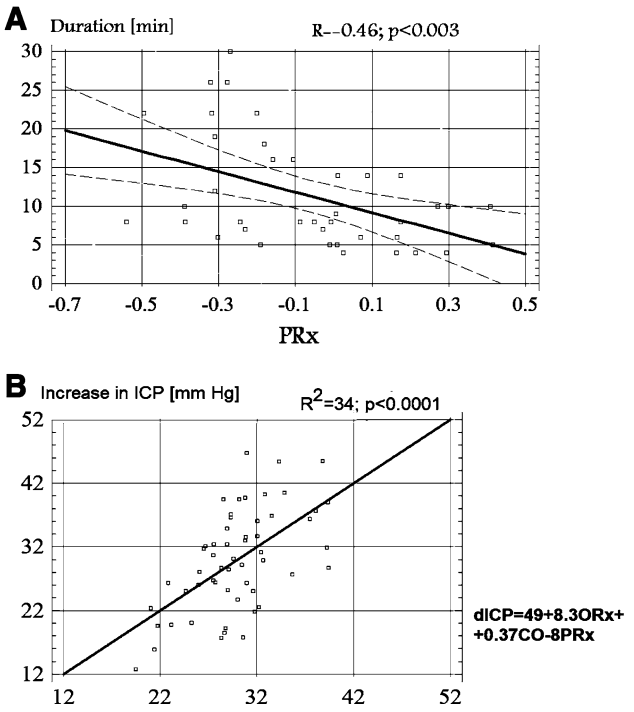

Fig. 5 **a** Significant correlation between PRx and length ($r = -0.46$; $p < 0.003$). **b** Model defined by multiple regression analysis that explains the magnitude of ICP with cerebrovascular indexes for the period of plateau waves

intracranial hypertension with increased LLA [24]. So the impairment of brain oxygenation and autoregulation should be corrected promptly to avoid deleterious consequences on the brain [22].

As stated by Rosner and Becker [3] "the plateau wave is the logical consequence of intact autoregulation interacting with an unstable CPP." Also Czosnyka et al. [22] reported that "plateau waves can be recorded only in patients in whom autoregulation was well preserved at the baseline." In our patients we also demonstrated that the duration and magnitude of plateau waves were greater in patients with more "active" cerebrovascular reactivity.

Plateau waves occur in situations of decreased volume–pressure compensatory reserve. In fact our patients with decompressive craniectomy did not present any plateau waves. Continuous monitoring of ICP and observation of pulse waveform (Fig. 3) at bed side help to understand the individual relationship between volume and pressure for each patient. Increase in pulse amplitude and RAP index indicates shift of the "working point" of in the pressure–volume curve toward the steeper, exponential part, and increase in P2/P1 ratio reflects changes in the brain compliances.

Post-plateau hyperemia was not always present, though it did occur in over half of the cases (64 %). Our results clearly show, not surprisingly, that the highest increases in CBF during the transient hyperemia following the hypoxic insult are associated with the most reactive vascular beds. The better autoregulation status with low oxygenation levels at baseline resulted in the most pronounced hyperemic response.

Conclusions

Multimodal brain monitoring permits early detection of intracranial hypertension episodes. The identification and understanding of intrinsic vascular brain phenomenon, such as plateau waves, may help the adequate management of acute head injury at bed side.

Conflict of interest The software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/imcplus) is licensed by the University of Cambridge (Cambridge Enterprise). Peter Smielewski and Marek Czosnyka have financial interests in a part of the licensing fee. All other authors declare that they have no conflict of interest.

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POST-TRAUMATIC MULTIMODAL BRAIN MONITORING: RESPONSE TO HYPERTONIC SALINE

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J Neurotrauma. 2014 Sep 11. [Epub ahead of print]

NEU-2014-3376-ver9-Dias_1P
Type: Research Article

JOURNAL OF NEUROTRAUMA XX:1–9 (Month XX, 2014)

DOI: 10.1089/neu.2014.3376

Original Research

Post-Traumatic Multimodal Brain Monitoring: Response to Hypertonic Saline

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Abstract

Emerging evidence suggests that hypertonic saline (HTS) is efficient in decreasing intracranial pressure (ICP). However there is no consensus about its interaction with brain hemodynamics and oxygenation. In this study, we investigated brain response to HTS bolus with multimodal monitoring after severe traumatic brain injury (TBI). We included 18 consecutive TBI patients during 10 days after neurocritical care unit admission. Continuous brain monitoring applied included ICP, tissue oxygenation (PtO_2) and cerebral blood flow (CBF). Cerebral perfusion pressure (CPP), cerebrovascular resistance (CVR), and reactivity indices related to pressure (PRx) and flow (CBFx) were calculated. ICM + software was used to collect and analyze monitoring data. Eleven of 18 (61%) patients developed 99 episodes of intracranial hypertension (IHT) greater than 20 mm Hg that were managed with 20% HTS bolus. Analysis over time was performed with linear mixed-effects regression modelling. After HTS bolus, ICP and CPP improved over time ($p < 0.001$) following a quadratic model. From baseline to 120 min, ICP had a mean decrease of 6.2 mm Hg and CPP a mean increase of 3.1 mmHg. Mean increase in CBF was 7.8 mL/min/100 g ($p < 0.001$) and mean decrease in CVR reached 0.4 mm Hg*min*100 g/mL ($p = 0.01$). Both changes preceded pressures improvement. PtO_2 exhibited a marginal increase and no significant models for time behaviour could be fitted. PRx and CBFx were best described by a linear decreasing model showing autoregulation recover after HTS ($p = 0.01$ and $p = 0.04$ respectively). During evaluation, CO_2 remained constant and sodium level did not exhibit significant variation. In conclusion, management of IHT with 20% HTS significantly improves cerebral hemodynamics and cerebrovascular reactivity with recovery of CBF appearing before rise in CPP and decrease in ICP. In spite of cerebral hemodynamic improvement, no significant changes in brain oxygenation were identified.

Key words: Cerebral blood flow; cerebral perfusion pressure; cerebrovascular reactivity; hypertonic saline; intracranial pressure.

Introduction

Recent Best Trip trial[1] gave us a lesson that end-hour instant value monitored intracranial pressure (ICP) cannot improve average mortality after traumatic brain injury (TBI), which stayed at the same dreadfully high level of 40% as without monitoring. This may illustrate that more sophisticated methods of ICP analysis (starting from simple time averaging) should be considered to support management—as suggested later by the first author of the study.[2] Intracranial hypertension (IHT) is a common cause of secondary lesions after TBI[3,4] and may be potentially life threatening.[5,6]

The crisis associated with high ICP in TBI patients depends on multiple intrinsic and extrinsic factors frequently interdependent. The time course of the disease[7] and individual response to acute brain injury contribute to duration and magnitude of ICP peaks. Uncontrolled intracranial hypertension leads to ischemia, brain shift, and herniation. The main objective of treatment is to reduce ICP, recover cerebral perfusion pressure, and improve cerebral blood flow and brain oxygenation. In neurocritical care units, adequate treatment of IHT at bedside is a complex issue. Clinical decisions are supported by the analysis of head computed tomography (CT) and multimodal brain monitoring. In practice this high complexity is often simplified by ''ICP Management Protocols''[8–11] that specify appropriate types and levels of interventions according to the underlying cause and the patient response to treatment. Among all the specific interventions, hyperosmolar therapy is recommended[12] as a non-surgical measure to manage high ICP due to brain edema either with mannitol or hypertonic saline.[13]

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Emerging evidence suggests that small boluses of high concentrations of hypertonic saline (HTS) are very effective in decreasing ICP and increasing cerebral perfusion pressure (CPP).[14–16] However, mechanisms of action of this drug are still unclear, its targets controversial,[17] and there is no consensus about its effects on brain microcirculatory hemodynamics, and oxygenation,[18–20] particularly associated within normal brain or peri-contusional penumbra.[21] In this study, we examined the effect of 20% HTS bolus to treat recurrent IHT on brain hemodynamics through multimodal brain monitoring in the penumbra area.

Methods

Patients

After local ethics committee approval and written consent from the next of kin, 18 consecutive adult multiple trauma patients with severe traumatic brain injury admitted to the Neurocritical Unit (NCCU) at Porto University, Hospital São João, a Level I trauma center, were eligible.

At NCCU admission, all patients had a Glasgow Coma Scale (GCS) score of less than 8 and were sedated with continuous infusion of propofol and/or midazolam and fentanyl and ventilated with mild hypocapnia (partial pressure of carbon dioxide [$PaCO_2$] between 32–35 mm Hg). At our NCCU, patients are treated with 30° head up elevation and CPP is continuously calculated with arterial blood pressure (ABP) transducer located at heart level. When possible we targeted CPP management for optimal CPP [22] looking for autoregulation following pressure reactivity index (PRx) based on a 4 h window time. Otherwise, we managed CPP for values >60 mm Hg according to Brain Trauma Foundation Guidelines. [23] None of the patients were younger than 18, pregnant, or not exhibiting clinical indication for invasive ICP monitoring.

Monitoring

Patients were monitored with heart rate (HR), invasive ABP, ICP, CPP, end-tidal CO_2 ($ETCO_2$), brain tissue oxygenation (PtO_2), brain temperature, and cerebral blood flow (CBF) for the first ten days. We used one bolt for intraparenchymal ICP (Codman®) and another triple bolt for intraparenchymal CBF thermal flow sensor (Hemedex®), PtO_2, and brain temperature probes (Licox®). Sensors were inserted in the penumbra area and their location was confirmed with CT scan. Data acquired from vital signal monitor (Philips®) and brain monitors were continuously collected using ICM+® software to calculate secondary variables related to cerebrovascular reactivity, like PRx and optimal CPP.[24]

Prior to bolus infusion blood gas analysis was collected to measure pH, $PaCO_2$, partial pressure of oxygen (PaO_2), and sodium (Na+). High sodium levels were actively controlled by giving free water through nasogastric or nasojejunal tube according to a target interval of 140–155 mEq/L.

Procedure

We looked for IHT episodes that occurred during the first 10 days after NCCU admission and that were treated with 20% HTS bolus. IHT was defined as ICP above 20 mm Hg for no more than 20 min, in the absence of external stimulus and after correction of pH, PaCO2, PaO2, ABP, and body temperature, according to Brain Trauma Foundation Guidelines.[25] Patients with outbreaks of IHT that is not corrected by the first-tier measures cited were then treated with bolus of 0.5 mL/kg of 20% HTS infused for 30 min.

Data analysis

Primary endpoint for data analysis was the effect of 20% HTS bolus on brain hemodynamics evaluated with multimodal brain monitoring variables. For a secondary endpoint, we checked for the variations of $ETCO_2$ and sodium levels for each bolus during the ten days of the study.

We analyzed 99 bolus of HTS administered to 11 patients out of the 18 consecutive patients enrolled. Seven patients were excluded because they did not receive HTS during the observation period. To analyze the effect of HTS, we first calculated primary variables with a 10-sec average of HR, ABP, ICP, ICP pulse amplitude (AMP), CPP, $ETCO_2$, PtO_2, CBF and cerebrovascular resistance (CVR = CPP/CBF). Additionally, we computed moving Pearson correlation coefficient between 30 consecutive 10-sec averages (5 min), to calculate indices of brain compensatory reserve and cerebrovascular reactivity: pressure reactivity index (PRx: ABP correlated with ICP), and cerebral blood flow index (CBFx: CBF correlated with CPP).

Time averages of all the above mentioned variables were calculated at baseline (60 min previous to drug infusion) and during 210 min after the start of the drug, divided into regular non-overlapping intervals of 30 min. A total of eight consecutive time points were defined (t1 – 60 min baseline, t2 – first 30 min corresponding to drug infusion, t3 to t8 – remaining 30 consecutive min).

Modelling and statistical analysis

Linear mixed-effects (regression) models (LMEM) was used.[26] The observations were grouped according to two levels, namely the individual and the bolus within the individual. This two-level structure was needed as variability was found not only among

Table 1. Patient Demographics and Clinical Characteristics of 11 Patients With 99 Episodes of Intracranial Hypertension After Traumatic Brain Injury Admitted to the Neurocritical Care Unit (NCCU)*

Characteristics	n/*% or mean ± SD or median (range; interquartile range)*
n (patients)	11
Age (years)	40 ± 11
Sex (men)	9/82%
Glasgow Coma Score	6 (3–12; 4)
Mean APACHE/predicted mortality rate	18.3 ± 5.4/32%
Mean ISS/TRISS Predicted mortality rate	42 ± 17.0/49%
Marshall Classification category of 1st head-CT:	
II	3/27%
III	2/18%
IV	4/36%
VI	2/18%
Types of main traumatic brain injury	
Contusions	4/36%
Extra-axial hematomas	4/36%
Diffuse axonal injury	3/27%
NCCU length of stay (total 269 days)	24 ± 9
Hospital mortality at 28 days	27%
Median Glasgow Outcome Scale at 6 months	3 (1–5; 3)
HTS bolus per patient	6 (1–31; 6)[a]

*Second line therapy of high intracranial pressure was accomplished with infusion of 0.5 mL/kg of 20% hypertonic saline.

[a]only 20% of the administrations were above 11 bolus per individual.

SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; ISS, Injury Severity Score; TRISS, Trauma Score and the Injury Severity Score; CT, computed tomography; HTS, hypertonic saline.

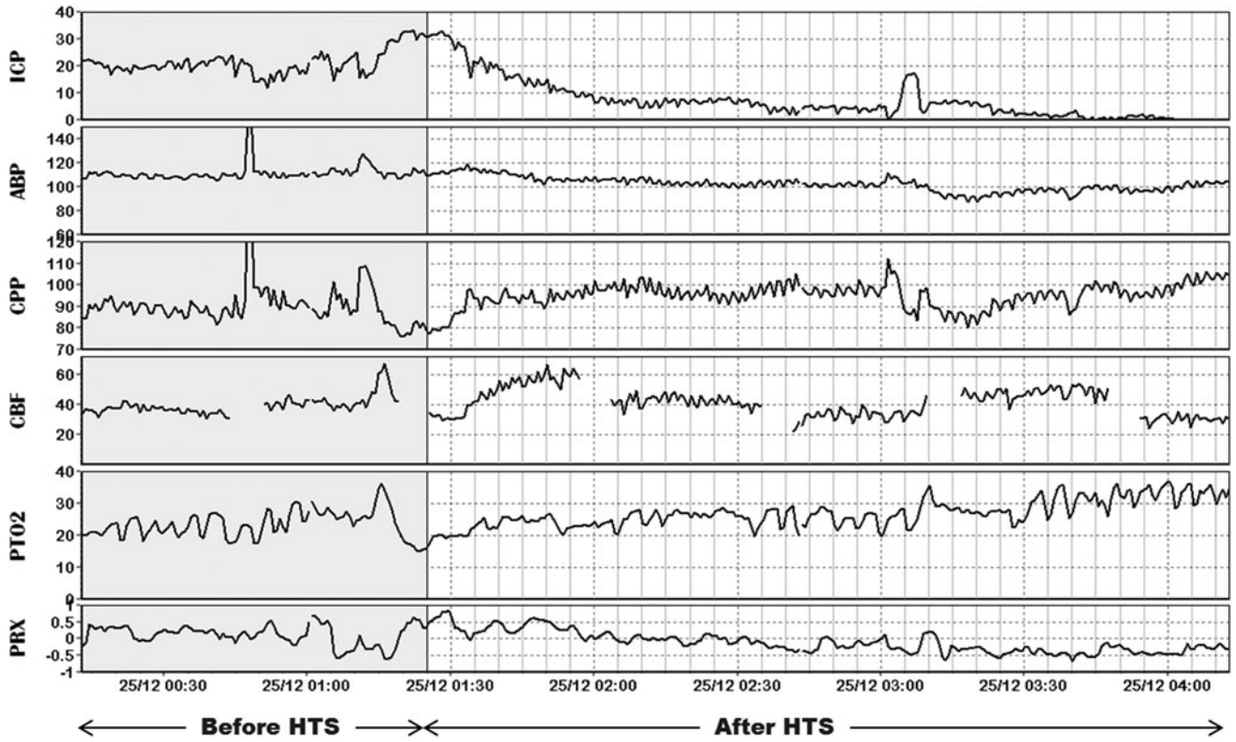

FIG. 1. Example of multimodal brain monitoring data from one patient with intracranial hypertension treated with 0.5 mL/kg of 20% hypertonic saline (HTS) bolus. Intracranial pressure (ICP), arterial blood pressure (ABP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), brain tissue oxygenation (PtO_2), and pressure reactivity index (PRx) are represented. 337 × 203 mm (96 × 96 DPI).

individuals but also within each individual for different boluses across time. Random effects on final models were identified on the intercept only, on the time slope only, or on both of them at the individual, bolus, or individual and bolus level, depending on the response variable. The exception was the model for the secondary endpoint for which we only had one level of grouping (the individual), given that a single measurement of sodium previous to each HTS bolus infusion was taken.

For the identification of the best model, we considered regressions with different random effects structures, residual correlation matrixes and residual variances, and time structures for the mean predictor up to order 2. Due to high multicollinearities, the quadratic terms were always centered. Comparison between models was based on the likelihood ratio test for nested models and on the Bayesian Information Criteria otherwise. Statistical analysis was performed with the R language and software environment for statistical computation, version 2.15.3.[27] Statistical significance was considered at $p < 0.05$.

Results

A total of 11 adult consecutive multiple trauma patients with severe traumatic brain injury (nine males; mean age ± SD, 40 ± 11 years old [range, 21–64]) were analyzed. At hospital admission the median (range; interquartile range) post-resuscitation Glasgow Coma Score (GCS) was 6 (3–12; 4), mean Acute Physiology and Chronic Health Evaluation score 18.3 ± 5.4 (predicted mortality 32%) and mean Injury Severity Score 42 ± 10 (Trauma Score and Injury Severity Score predicted death rate 49%).[28] Patients with first GCS above 8 had secondary neurologic deterioration with indication for intubation, ventilation and ICP monitoring. On first brain CT scan the most frequent Marshall Classification category was IV—diffuse brain injury with midline shift. All patients presented subarachnoid haemorrhage but 4 (36%) had mainly contusions, another four (36%) had extra-axial hematomas and three (27%) had diffuse axonal injury.[29] Before NCCU admission four patients were submitted to craniotomy for hematoma drainage and three had non-neurosurgical procedures. During the study period, two patients went for decompressive craniectomy at Day 2 and Day 5 and from that onwards they did not need HTS bolus any further. Only one patient with extraventricular drainage received HTS bolus. Hospital mortality rate was 27% and median Glasgow Outcome Scale score at six months after discharge was 3. More detailed demographical data is presented in Table 1.

According to the protocol described above, the total number of HTS bolus administered was 99, with a median number of administrations per subject of six, ranging from one to 31, and with only 20% of the administrations per subject being higher than 11.

An example of an individual recording of multimodal monitoring response to HTS documented with ICM+is provided in Figure 1.

The effect of HTS boluses on multimodal brain monitoring parameters over time and across patients was investigated through LMEM. Averaged values of primary and secondary parameters in time are illustrated in Figure 2. This figure does not show statistical significance of variation of evaluated parameters (ICP, CPP, CBF, CVR) in response to saline infusion but suggests a trend. Parameter estimates of the identified models and their statistical significances are presented in Table 2 and additionally illustrated in Figure 3 and Figure 4.

ICP and CPP were expected to improve quadratically over time ($p < 0.001$). The baseline value (t = 1) for ICP was estimated at 20.5 mmHg, then the mean curve decreased until 14.3 mmHg at

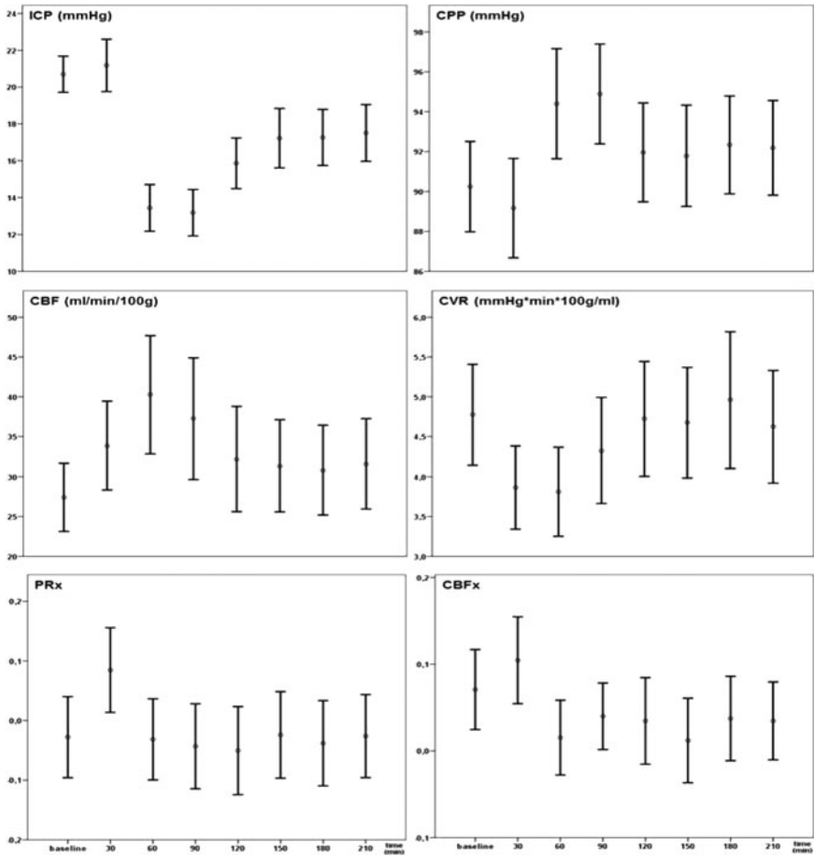

FIG. 2. 95% Confidence intervals for mean values of intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebrovascular resistance (CVR), pressure reactivity index (PRx) and cerebral blood flow index (CBFx) at baseline and along time (210 min) after 20% hypertonic saline bolus (0.5 mL/kg).

TABLE 2. ESTIMATES (AND *P* VALUES WHENEVER ADEQUATE) OF THE CONSIDERED MODELS FOR INTRACRANIAL PRESSURE (ICP), CEREBRAL PERFUSION PRESSURE (CPP), CEREBRAL BLOOD FLOW (CBF), CEREBROVASCULAR RESISTANCE (CVR), BRAIN TISSUE OXYGENATION (PTO2), PRESSURE REACTIVITY INDEX (PRX), CEREBRAL BLOOD FLOW INDEX (CBFX), ENDTIDAL CO_2 ($ETCO_2$) AND SERUM SODIUM

	Fixed-effects						*Random-effects (SD)*			
							At ID level		*At bolus level*	
Variables	*Intr*	p *value*	*time*	p *value*	*(time-4.5)^2*	p *value*	*Intr*	*Time*	*Intr*	*Time*
ICP	16.89	0.00	−0.53	0.05	0.34	0.00	…	0.796	1.936	…
CPP	87.33	0.07	0.18	0.00	−0.20	0.00	8.880	…	5.372	…
CBF	42.29	0.00	0.39	0.27	−0.52	0.00	16.715	…	15.251	…
CVR	3.33	0.00	0.02	0.55	0.04	0.01	1.893	…	1.324	…
PtO_2	24.05	0.00	−0.07	0.25	…	…	6.179	…	4.765	…
PRx	0.09	0.31	−0.01	0.01	…	…	0.274	…	0.181	…
CBFx	0.09	0.00	−0.01	0.04	…	…	…	…	0.075	…
$ETCO_2$	29.36	0.00	0.00	0.96	…	…	4.004	…	1.512	…
Sodium	149.14	0.00	−0.31	0.21	…	…	0.003	…	…	…

ICP (mm Hg); CPP (mm Hg); CBF (mL/min/100 g); CVR (mm Hg*min*100 g/mL); PtO_2 (mm Hg); $ETCO_2$ (mm Hg); Sodium (mEq/L)
Intr: Intercept (time-4.5)^2: quadratic term in time had to be centered (around its sample mean) in order to avoid high multicollinearities.
SD, standard deviation; ID,

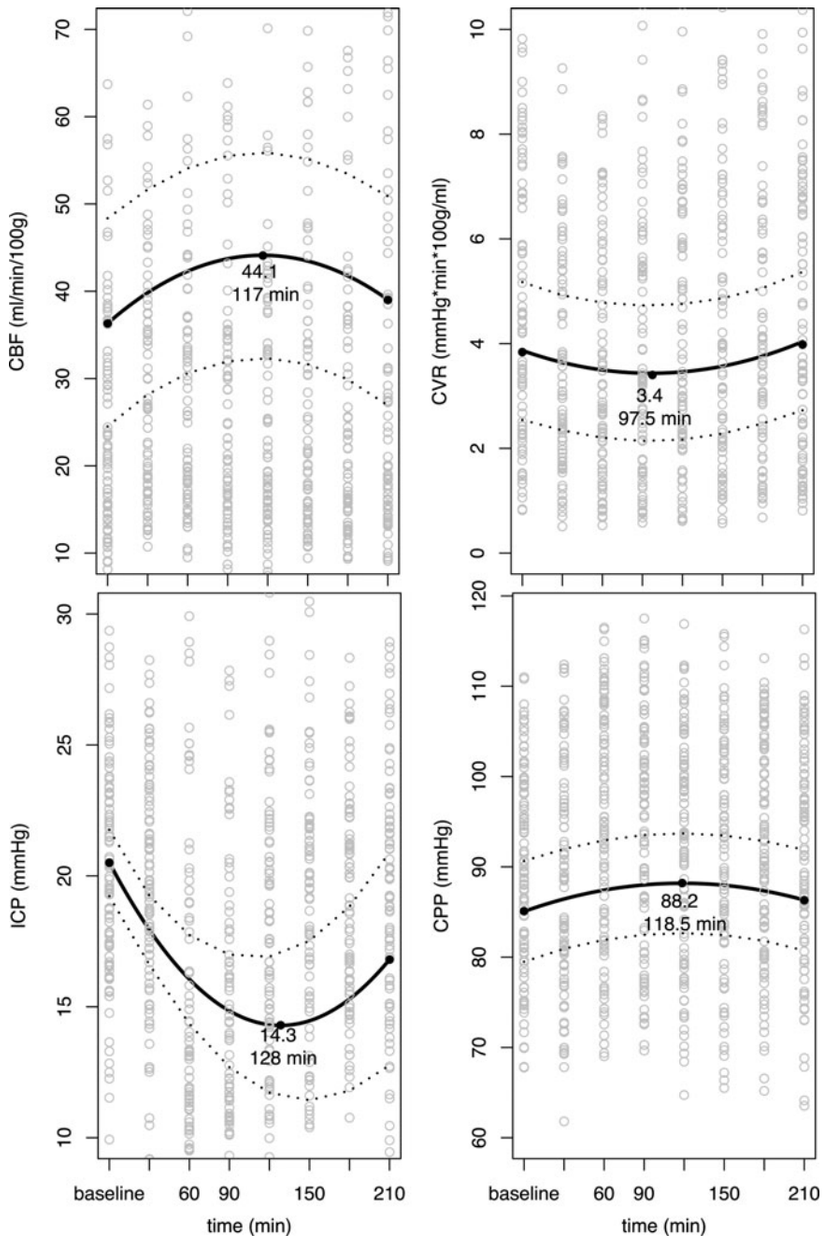

FIG. 3. Estimated mean models for intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebrovascular resistance (CVR) and scattergram of all individual values in response to 20% hypertonic saline bolus (0.5 mL/kg). A total of 8 consecutive time points were defined (60 min interval for baseline, first 30 min corresponding to drug infusion time, and remaining nonoverlapping consecutive 30 min intervals). CVR decreases to a minimum value of 3.4 mm Hg*min*100 g/mL at 97.5 min. CBF reaches the maximum value of 44.1 mL/min/100 g at 117 min. CPP increases to a maximum value of 88.2 mm Hg at 118 min and finally ICP decreases to the minimum value of 14.3 mm Hg at 128 min.

128 min and afterwards, increased again reaching a final value of 16.8 mm Hg. Simultaneously, we identified a significant decrease in ICP pulse amplitude ($p < 0.0001$) and a modification in ICP pulse waveform morphology with a decrease in P2/P1 ratio. Spearman's correlation assessed the relationship between maximum baseline ICP levels and magnitude of ICP responses to HTS infusion. Results revealed that infusions at greater baseline ICP values lead to more significant responses ($r_s = 0.29$, $p < 0.05$). Regarding CPP, the expected (mean) curve was convex with a baseline value of 85.1 mm Hg, a maximum value of 88.2 mm Hg attained at 119 min and a final value of 86.3 mm Hg (Fig. 3). Time for maximum CVR and CBF response was shorter than that for CPP. In fact, CVR decreased significantly from an initial value of 3.8 mm Hg*min*100 g/mL to 3.4 mm Hg*min*100 g/mL at 97.5 min, then increased 0.6 mm Hg*min*100 g/mL until the end ($p = 0.01$). CBF baseline values started at 36.3 mL/min/100 g, then significantly increased to 44.1 mL/min/100 g at 117 min after the HTS bolus and ended up at a value of 39.0 mL/min/100 g ($p < 0{,}001$) (Fig. 3).

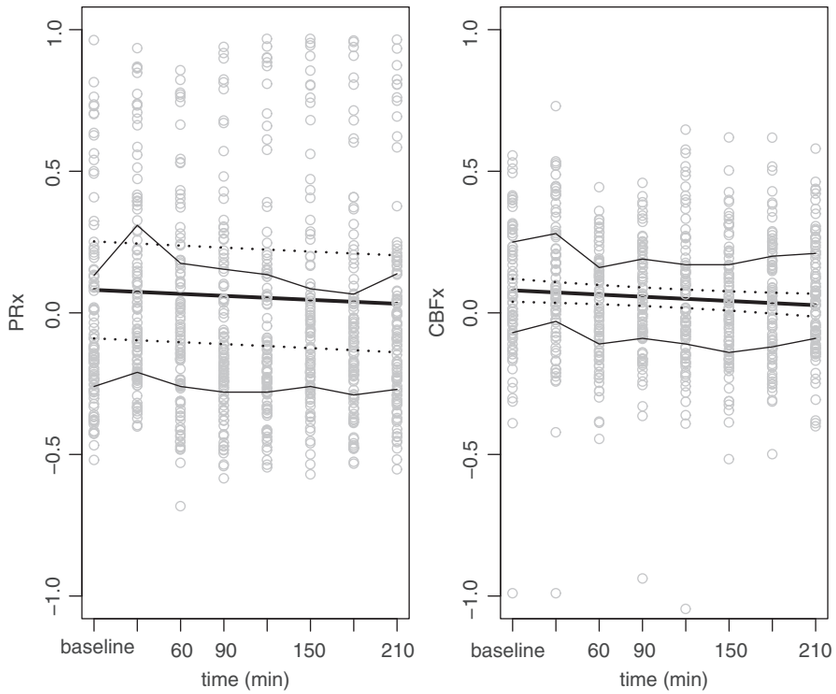

FIG. 4. Mean expected values and correspondent 95% confidence intervals (bold and dotted lines, respectively) and empirical 25th and 75th percentiles (segmented lines) for cerebrovascular pressure reactivity index (PRx) and cerebral blood flow index (CBFx) in response to 20% hypertonic saline (HTS) bolus (0.5 mL/kg). A total of 8 consecutive time points were defined (60 min interval for baseline, first 30 min corresponding to drug infusion time, and remaining nonoverlapping consecutive 30 min intervals). Both PRx and CBFx slopes were statistically significant (PRx, $p = 0.01$; CBFx, $p = 0.04$). On average, autoregulation evaluated with PRx and CBFx showed a slight but steady improvement after HTS infusion.

Cerebral vasodilation and improvement of CBF preceded by more than 2 min the increase of CPP and by 9 min the decrease of ICP. In the first 90 min the augmentation of CBF reached more than 7.5 mL/min/100 g.

No significant models with linear or quadratic time dependencies could be fitted to PtO_2 values.

The time behavior of secondary variables, cerebrovascular pressure reactivity index (PRx) and cerebral blood flow index (CBFx), was best described by decreasing linear models. Both slopes were statistically significant (PRx, $p = 0.01$; CBFx, $p = 0.04$). Autoregulation evaluated with PRx index and CBFx indexes impaired during IHT and recovered after HTS bolus staying below 0.2, as represented in figure 4 with empirical 25th and 75th percentiles curves.

During HTS infusion, $ETCO_2$ did not suffer any significant variation ($p = 0.96$).

We used 0.5 mL/kg of 20% HTS that corresponds to 6844 mOsm/Kg and a total amount of 8000 mg of sodium every 40 mL bolus. With repeated bolus, the majority of patients developed hypernatremia with sodium levels between 146–155 mEq/L, but no statistically significant difference was found when sodium peak values were compared with baseline values ($p = 0.21$).

Discussion

Effects of hypertonic saline on pressures (ICP and CPP) and cerebrovascular reactivity (PRx and CBFx)

The ICP-lowering effect of HTS has been demonstrated conclusively in previous studies[13–15]; however, little is known on the effect of HTS on cerebrovascular reactivity. HTS bolus to treat intracranial hypertension aims to reduce brain edema and maintain cerebral perfusion pressure. The osmotic gradient between intravascular and extravascular compartments draws water out of the brain tissue, decreasing total brain volume and preserving intravascular volume. Administration of 20% HTS triggered a relevant decrease in elevated ICP starting immediately after the first 30 min (end of infusion), although the reduction of ICP was more pronounced at 120 min. Mean CPP improved and this improvement lasted for more than 3 h, which may be explained by HTS osmotic effects on the brain and systemic hemodynamics.[30] We also observed a modification in ICP pulse waveform along with a decrease in ICP pulse amplitude. Together, all these changes may reveal the sum of effects of HTS on brain total water content, cerebral blood volume and brain compliance[31] Temporary autoregulation impairment related to intracranial hypertension, significantly recovered after HTS infusion as evaluated with cerebrovascular reactivity indices PRx and CBFx.

Effects of hypertonic saline on cerebral blood flow

In this study, cerebral vascular resistance and cerebral blood flow changes started during the first 30 min, while HTS bolus was still being infused. HTS acts as a relaxant on smooth muscle,[32] causing an early reduction in cerebrovascular resistance. The subsequent increase in CBF also may be explained by the rapid onset of plasma volume expansion induced by the hypertonic solution.[16,33,34] HTS also improves CBF by its rheological effects on red cells and capillary bed.[35–37] We stress the brain hemodynamic properties of HTS as a relevant observation.[38] This increase in CBF

may become even more important and vital when ICP is very high and CPP is below the lower limit of autoregulation approaching critical closing pressure with a high risk of zero flow.[39]

Effects of hypertonic saline on cerebral oxygenation

In spite of the positive effect on brain flow and perfusion, brain tissue oxygenation showed no significant change. We also failed to demonstrate any relationship between trends in pressures or flow and brain oxygen levels. Rockswold and colleauges showed that the effect of HTS treatment on PtO_2, although positive, was not as robust as other brain monitoring parameters.[19] It is widely accepted that fast changes in PtO_2 can be interpreted as a surrogate measure of changes in CBF. In this study, the apparent uncoupling between CBF and PtO_2 may be explained by multifactorial causes considering high baseline level of PtO_2, probes position and HTS effect on peri-focal tissue. Several studies showed the heterogeneity in response of brain tissue oxygenation to different insults in normal brain and penumbra area.[40–43] On the other hand, hypertonic solution decreases total brain water content and total brain volume[44] but may be unable to reduce edema in injured tissue and may even increase the water content within contusion areas.[21,43] Therefore, overall ICP decreases, but pericontusional conditions may remain unchanged or even get worse, causing dysperfusion hypoxia[45] due to the larger distance between capillaries and cells.[41,42,46]

Effects of hypertonic saline and serum sodium levels

Paredes-Andrade and colleagues showed that HTS administration is as effective in reducing intracranial hypertension at high serum as at normal levels.[47] Other authors stated that higher sodium levels correlated with lower ICP.[48] In our sample, natremia state did not influence significantly HTS response. Still, the optimal natremic state for patients with traumatic brain injury is not defined and remains a controversial issue.[49,50]

Study limitations and insights for future investigations

In our study, we prospectively analyzed 99 repetitive intracranial hypertension events treated with HTS bolus, although data were obtained from only 11 patients with unbalanced needs for HTS therapy. Due to sample size restrictions, the models evaluated only the net effect of time at most through quadratic models. Because of the current standard protocol of management of intracranial hypertension at our institution, HTS administration was done as a second-tier therapy to treat IHT. In spite of first-tier treatment standardization, this approach may influence baseline values of cerebral blood flow and oxygenation.

Further research is required to clarify the influence of probes position on regional brain monitoring data, best optimal administration regimen of HTS, and treatment targets adapted to individual patient's brain and systemic monitoring pattern, as well as its impact on morbidity and mortality.

Conclusion

Despite failing to demonstrate a significant increase in brain regional oxygenation, management of intracranial hypertension with 20% HTS bolus recovered autoregulation evaluated with cerebrovascular reactivity indexes and improved cerebral hemodynamics, increasing cerebral blood flow before the rise in perfusion pressure and decrease in intracranial pressure.

Author Disclosure Statement

Ana Rita Gaio and Ana Paula Rocha were partially funded by the European Regional Development Fund through the program COMPETE and by the Portuguese Government through the FCT - Fundação para a Ciência e a Tecnologia under the project PEst-C/MAT/UI0144/2013.

The software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/imcplus) is licensed by University of Cambridge (Cambridge Enterprise). Peter Smielewski and Marek Czosnyka have financial interests in a part of the licensing fee. For the other authors, no conflicting financial interests exist.

Appendix

The Choice of the Statistical Methodology

The rationale followed in our statistical analysis was to reduce the number of hypothesis tests to its minimum and to try to model all the phenomena at once, thus avoiding inflation of the significance level while modeling variability and correlations simultaneously within the fitting process. The data came from a longitudinal prospective study. Therefore, the most adequate methods for the statistical analysis were those from longitudinal analysis. Our design had the additional complexity of having two sources of possible variation—namely, the individual and the bolus. Indeed, variability and nonzero correlations were detected among different individuals and different boluses within the same individual by our mixed effects models.

In our situation, no underlying pathophysiologic formula between the variables of interest was previously known, to the best of our knowledge. As such, we started the modeling from the simplest possible model—the linear one. Whenever possible, we went one step higher and studied quadratic time dependencies. Comparison across models following standard statistical principles (the likelihood ratio test or the Bayesian Information Criterion, as appropriate) were afterwards performed.

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OPTIMAL CEREBRAL PERFUSION PRESSURE MANAGEMENT AT BEDSIDE:

A SINGLE CENTRE PILOT STUDY

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Neurocrit Care. Jan 2015. [Epub ahead of print]

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-014-0103-8

ORIGINAL ARTICLE

Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study

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Abstract
Background Guidelines recommend cerebral perfusion pressure (CPP) values of 50–70 mmHg and intracranial pressure lower than 20 mmHg for the management of acute traumatic brain injury (TBI). However, adequate individual targets are still poorly addressed, since patients have different perfusion thresholds. Bedside assessment of cerebral autoregulation may help to optimize individual CPP-guided treatment.
Objective To assess staff compliance and outcome impact of a new method of autoregulation-guided treatment (CPPopt) based on continuous evaluation of cerebrovascular reactivity (PRx).
Methods Prospective pilot study of severe TBI adult patients managed with continuous multimodal brain monitoring in a single Neurocritical Care Unit (NCCU). Every minute CPPopt was automatically estimated, based on the previous 4-h window, as the CPP with the lowest PRx indicating the best cerebrovascular pressure reactivity. Patients were managed with CPPopt targets whenever possible and otherwise CPP was managed following general/international guidelines. In addition, other offline CPPopt estimates were calculated using cerebral oximetry (COx-CPPopt), brain tissue oxygenation (ORxs-CPPopt), and cerebral blood flow (CBFx-CPPopt).
Results Eighteen patients with a total multimodal brain monitoring time of 5,520 h were enrolled. During the total monitoring period, 11 patients (61 %) had a CPPopt U-shaped curve, 5 patients (28 %) had either ascending or descending curves, and only 2 patients (11 %) had no fitted curve. Real CPP correlated significantly with calculated CPPopt ($r = 0.83$, $p < 0.0001$). Preserved autoregulation was associated with greater Glasgow coma score on admission ($p = 0.01$) and better outcome ($p = 0.01$). We demonstrated that patients with the larger discrepancy (>10 mm Hg) between real CPP and CPPopt more likely have had adverse outcome ($p = 0.04$). Comparison between CPPopt and the other estimates revealed similar limits of precision. The lowest bias (−0.1 mmHg) was obtained with COx-CPPopt (NIRS).
Conclusion Targeted individual CPP management at the bedside using cerebrovascular pressure reactivity seems feasible. Large deviation from CPPopt seems to be associated with adverse outcome. The COx-CPPopt methodology using non-invasive CO (NIRS) warrants further evaluation.

Keywords Traumatic brain injury · Multimodal brain monitoring · Cerebral perfusion pressure · Cerebrovascular pressure reactivity · Optimal cerebral perfusion pressure

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Published online: 08 January 2015

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability among young individuals and worse outcome is associated with ongoing secondary insults [1, 2]. Current Brain Trauma Foundation (BTF) guidelines regarding the management of patients after TBI include the reduction of intracranial pressure (ICP) below 20 mmHg [3] and maintenance of cerebral perfusion pressure (CPP) between 50 and 70 mmHg [4]. Worldwide, several TBI management protocols are based on a combination of CPP-oriented [5] and ICP-oriented [6] therapy. Although the idea of avoiding global hypo- and hyper-brain perfusion was an important step in the management of TBI patients, this approach is likely an oversimplification of the complex secondary pathophysiology. Fixed thresholds may be not compatible with broad heterogeneity of post-TBI brain damage (contusion, hematoma, subarachnoid hemorrhage, and diffuse axonal injury) [7]. The first author of the BEST TRIP trial [8] commented in another article that "the strongest clinical implication of the results is that we shouldn't abandon ICP monitoring but to refine its role in TBI management" and emphasized the need to develop "clinical methods for interpreting ICP in the setting of individual patient care" [9].

Cerebral autoregulation of cerebral blood flow (CBF) is pivotal to the maintenance of normal brain function [10, 11]. Impaired autoregulation leads to secondary damage and is an independent predictor of fatal outcome following TBI [12]. The goal of 'real-time' continuous cerebral autoregulation monitoring is to enable the early detection of potentially harmful events before they cause irreversible damage [13]. Modern computer signal processing of waveforms obtained from multimodal brain monitoring allows calculation of cerebrovascular reactivity indices and therefore evaluation of trends of cerebral autoregulation at bedside [12]. Autoregulation indices based on ICP (PRx) but also other variables included in multimodal brain monitoring scheme: brain tissue oxygenation (ORxs), cerebral oximetry (COx), and cerebral blood flow (CBFx) may be all helpful in defining optimal therapeutic strategies [14]. Recent clinical TBI studies demonstrated that an "optimal" CPP can be calculated at bedside retrospectively, based on continuous evaluation of PRx [12, 15–17]. This flexible target value was called CPPopt and may differ individually, and vary over time. Importantly, deviation for this calculated value was associated with bad outcome [17–21]. Since the end of 2011, we have introduced a pragmatic TBI treatment protocol in our academic NCCU that uses CPPopt instead of the fixed range of CPP advised by the BTF guidelines.

The main aim of this pilot study was to investigate the feasibility of a pragmatic method of CPPopt-guided therapy in severe TBI patients with multimodal brain monitoring. In addition, we evaluated the impact of this new approach on mortality figures. As a secondary aim, we assessed the agreement between online CPPopt (PRx) calculated at bedside and new offline CPPopt estimates retrospectively calculated based on ORxs, COx, and CBFx indices.

Materials and Methods

Type of Study

Retrospective analysis of monitoring records of prospective data collected from a cohort of consecutive severe TBI patients and clinical indication for multimodal brain monitoring. Exclusion criteria included age less than 18 years old and pregnancy. The local research ethics committee approved the protocol and anonymized data collection. Written informed consent from the next of kin was obtained.

Patients

Eighteen consecutive adult multiple-trauma patients with severe TBI admitted to the NCCU at Hospital São João, Porto, Portugal were included in the period between July 2011 and January 2013. Postresuscitation Glasgow Coma Scale (GCS) was used to determine baseline neurological status. Overall disease severity and mortality prediction on admission was calculated with Simplified Acute Physiology Score II (SAPS II). Brain CT characteristics of TBI were classified with the Marshall score [22]. Outcome at 6 months after hospital discharge was assessed with Glasgow Outcome Scale (GOS = 1 death, GOS = 2 persistent vegetative state, GOS = 3 severe disability, GOS = 4 moderate disability, GOS = 5 good recovery) [23].

Multimodal Brain Monitoring

Patients were continuously monitored with ECG, heart rate (HR), invasive arterial blood pressure (ABP), pulse oximetry (SpO_2), end-tidal CO_2 ($ETCO_2$), ICP, CPP, bilateral transcutaneous cerebral oximetry with near-infrared spectroscopy (NIRS), brain tissue oxygenation ($PbtO_2$), and cerebral blood flow (CBF). Real-time cerebrovascular pressure reactivity index (PRx) and CPPopt were calculated and displayed at the bedside. We worked with Philips Intellivue MP70 multiparameter monitor (Philips medical systems, Eindhoven, the Netherlands) to acquire systemic variables and calculation of CPP, NIRS sensors for cerebral oximetry (CO in %) with INVOS 5100C (Covidien, Mansfield, USA), intraparenchymal ICP

probe with bolt from Codman (DePuySinthes, Massachusetts, USA) and a second triple bolt for intraparenchymal CBF thermal QFlow 500 Bowman flow sensor (CBF in ml/min/100 g) from Hemedex (Hemedex, Cambridge, USA), and $PbtO_2$ (in mmHg) and brain temperature (in °C) sensors with Licox (Integra, Plainsboro, USA). We used ICM+ software, version 8.0 (http://www.neurosurg.cam.ac.uk/pages/ICM) to collect data (200 Hz) and to calculate autoregulation estimate (PRx) and associated variable (CPPopt) [24].

Real-Time Bedside Calculation

Ten seconds averages of the physiological variables HR, ABP, ICP, CPP, CO, $PbtO_2$, and CBF were calculated. PRx was calculated as the Pearson correlation coefficient using 10 s averages of ICP and ABP over a moving window of 5 min length with 80 % overlap [25]. CPPopt was determined in individual patients as described by the recent-published method of Aries et al. [17]. A parabolic curve is fitted automatically to the processed CPP-PRx error bar plot using the past 4 h of ICP/ABP data to construct the CPPopt curve. Besides a curve, the software generates automatically a CPPopt value that is continuously displayed at the bedside and both are updated every minute. Our institutional protocol indicated that this value was used to guide CPP in each individual patient at short-term intervals. In addition to the method of Aries et al., we formulated three extra criteria before accepting the suggested automatic-displayed CPPopt value: (a) at least 75 % of time good recordings of ABP and ICP values had to be available in the 4-h calculation window, (b) average PRx values had to be <0.25 the past 4 h (defined as a period with intact cerebrovascular pressure reactivity) [26], and (c) dedicate the staff to study the CPPopt curve and overrule the automatic CPPopt value and take the CPP value with the most negative PRx value covered by the curve. U-shaped, ascending, and descending curves were accepted in case the overall PRx < 0.25. An illustrative example is shown in Fig. 1.

Algorithm of TBI Management

During the study period, all patients were sedated with continuous infusions of propofol and/or midazolam and fentanyl to achieve a Richmond Agitation–Sedation Scale (RASS) score between zero and -5 [27] and adequate analgesia. Artificial ventilation was applied with lung protective criteria, $PaCO_2$ levels between 35 and 40 mmHg, and $PaO_2 > 90$ mmHg. At our NCCU, patients are treated with 30° head up elevation and CPP is continuously calculated with ABP transducer located at heart level [28].

CPP Management

When possible, we guided CPP management using the bedside CPPopt values. When CPPopt was not available, we kept CPP between 50 and 70 mmHg in accordance to BTF Guidelines [29]. See examples presented in Fig. 2. To achieve higher CPPopt values, volume expansion in combination with norepinephrine were used at the discretion of the physician in charge; lower CPPopt values with decreasing vasopressor therapy, treating intracranial hypertension or increasing sedation.

Intracranial Hypertension Management

ICP above 20 mmHg was treated initially with first-tier therapy (deep sedation, paralysis, normothermia, mild hyperventilation, and when possible cerebral spinal fluid drainage after insertion of extra ventricular drain). If ICP remained above 20 mmHg for more than 20 min, osmotherapy was administered (mannitol or hypertonic saline bolus). In cases of refractory intracranial hypertension, second-tier therapy (hypothermia, profound hyperventilation, and surgical decompression) was applied [30]. Further details of the NCCU protocol are presented in the "Appendix" section (Fig. 5).

Retrospective Post Hoc Offline Calculations

Retrospectively, using raw data stored on the hard disk, we calculated analogically to the PRx index, 5 min moving correlation coefficients between CPP and $PbtO_2$ (short oxygen reactivity index (ORxs)), CO (cerebral oximetry index (COx)), and CBF (CBFx) with 80 % overlap. Similarly, using the CPPopt curve-fitting approach, we calculated offline CPPopt according to ORxs (ORxs-CPPopt), COx (COx-CPPopt), and CBFx (CBFx-CPPopt).

Statistical and data analysis

We used the R language and environment software for statistical computing [31]. Continuous variables were expressed as mean values with standard deviations (mean ± SD) or medians and interquartile range (med ± IQR). Discrete variables were presented as counts or percentage. We calculated the total monitoring time for all monitoring variables, the percentage of time during which cerebral vasoreactivity was impaired (defined as PRx > 0.25) [26], percentage of time CPPopt was calculated, and finally the percentage of time during which CPP was below and above CPPopt. Outcome was dichotomized into GOS ≥ 3 and GOS < 3.

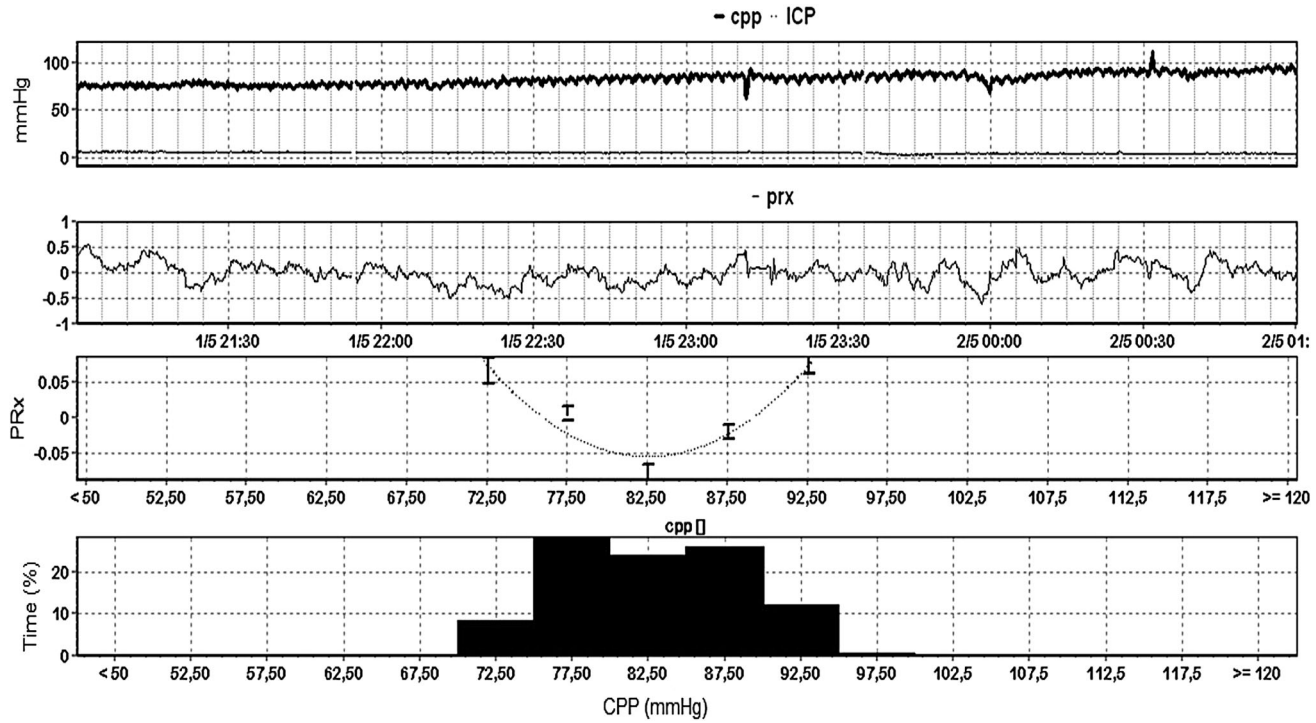

Fig. 1 Screenshot of ICM+® panel with 4-h-trend charts for visual decision of optimal cerebral perfusion pressure according to pressure reactivity index (CPPopt). *First chart*: cerebral perfusion pressure (CPP) and intracranial pressure (ICP); *second chart*: pressure reactivity index (PRx); *third chart*: PRx/CPP plot for evaluating CPPopt; and *fourth chart*: percentage of 4-h time spent within CPP interval. Criteria of decision for optimal CPP based on visual analysis of ICM+ cbarts: (*first chart*) 4-h-trend with more than 75 % of reliable CPP and ICP data; (*second chart*) PRx < 0.25; (*third chart*) CPP curve with PRx < 0.25 and CPPopt defined as 82.5mmHg; (*fourth chart*) CPP targeted according to CPPopt

Normal distribution of all variables was tested with the Shapiro–Wilk test. The non-parametrical statistical method Mann–Whitney–Wilcoxon was applied to calculate differences between continuous variables with non-normal distribution or unequal variance.

To evaluate the feasibility of our pragmatic CPPopt-guided protocol, we calculated the correlation between averaged patients' real CPP and the automatic CPPopt and the limits of agreement using the approach suggested by Bland and Altman [32]. We defined that in case the difference between the averaged flexible CPP target (CPPopt) and averaged patients' CPP (real CPP) was within 5 mmHg; a satisfactory and clinically significant result was reached.

For our secondary aim, we compared the CPPopt value evaluated with PRx and the ones with the three other cerebrovascular reactivity indexes (COx-CPPopt, CBFx-CPPopt, and ORxs-CPPopt) using the Bland–Altman method. We defined a difference of 5 mmHg as evidence of good agreement between multi-modality results [15, 17]. Tests were considered statistically significant for two-sided p values <0.05.

Results

Demographic Data

The study population included 18 patients (16 males, 89 %) with mean age of 42 (SD 16) years old. The median baseline GCS was 6 (IQR 3) and 3 patients with GCS > 8 had subsequent deterioration requiring intensive care treatment. The mean SAPSII was 45 with predicted mortality of 36 %. Mean length of stay (LOS) in the NCCU and hospital was 26 (SD 12) and 53 days (SD 37), respectively. Mortality rate at 28 days was 17 % and median GOS at 6 month was 3. More detailed clinical information is available in "Appendix" section.

Monitoring Data of Whole Period

The total monitoring time with median and IQR numbers in brackets was for ICP and CPP 5521 h (283;169), for CO 4229 h (214;137), for $PbtO_2$ 4048 h (203;129), and for CBF 2339 h (119;107). Mean values for the physiological variables were ICP 13 (SD 4) mmHg, ABP 99 (SD 6)

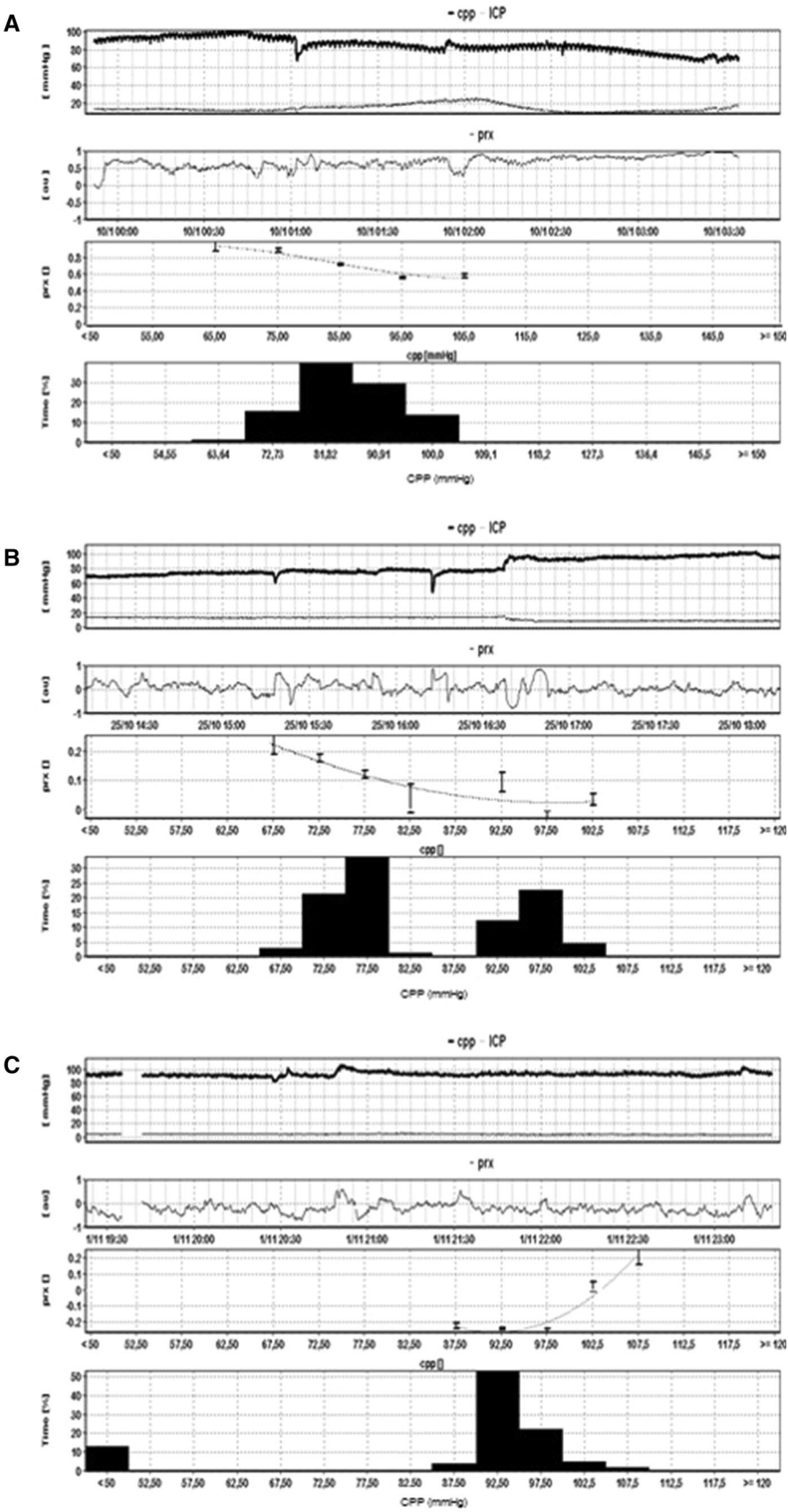

Fig. 2 Three screenshots of ICM+® panel with 4-h-trend charts for visual decision of optimal cerebral perfusion pressure according to pressure reactivity index (CPPopt). *First chart* cerebral perfusion pressure (CPP) and intracranial pressure (ICP); *second chart* pressure reactivity index (PRx); *third chart* PRx/CPP plot for evaluating CPPopt; *fourth chart* percentage of 4-h time spent within CPP interval. **a** Patient with PRx $>$ 0.25 reflecting autoregulation impairment. CPP was targeted according to Brain Trauma Foundation guidelines. **b** Patient with PRx $<$ 0.25 and *descending curve*. CPP was target to the highest value of CPP/PRx plot (97.5 mmHg). **c** Patient with PRx $<$ 0.25 and *ascending curve*. CPP was targeted to the lowest value of CPP/PRx plot (92.5 mmHg)

mmHg, CPP 86 (SD 5) mmHg, CO 56 (SD 19) %, $PbtO_2$ 25 (SD 8) mmHg, and CBF 39 (SD 21) ml/min/100 g.

For CPPopt calculations, the following mean values were obtained: CPPopt 88 (SD 7) mmHg and the percentage of time CPPopt calculation that was available was CPPopt 59 % (IQR 13 %). Eleven patients (61 %) had a CPPopt U-shaped curve, 5 patients (28 %) had either ascending or descending curves, and in 2 patients (11 %) no fitted curve could be defined looking at the total monitoring period.

The mean values of CPP calculated with the other indices were COx-CPPopt 88 (SD 7) mmHg, ORxs-CPPopt 85 (SD 6) mmHg, and CBFx-CPPopt 85 (SD 6) mmHg. The percentages of time CPPopt calculation, according to these indices that were available were 29 % (IQR 17 %) for ORxs-CPP, 22 % (IQR 29 %) for COx-CPP, and 23 % (IQR 19 %) for CBFx-CPP.

PRx and Autoregulation

When we separated the patients into those with preserved cerebrovascular pressure reactivity (PRx < 0.25, $n = 15$) and those with impaired cerebrovascular reactivity (PRx > 0.25, $n = 3$), the mean PRx in the first group was -0.04 (SD 0.13) and in the second group was 0.29 (SD 0.04). The median percentage of time patients in the preserved group spent with impaired cerebrovascular pressure reactivity was 24 % (IQR 16 %) compared to 55 % (IQR 3 %) in the impaired group ($p = 0.007$). Patients in the preserved group had significantly higher GOS compared to the ones with impaired cerebrovascular reactivity ($p = 0.01$). There were no differences in age, SAPSII, and Marshall scores, but patients with overall preserved cerebrovascular pressure reactivity presented with significantly higher GCS ($p = 0.01$) (Table 1).

CPPopt and Outcome

The median fraction of time spent with impaired cerebrovascular pressure reactivity (% of time PRx > 0.25) was greater in patients with adverse outcome (GOS < 3) (median 54 % vs 24 %, $p = 0.06$). Mean real CPP in patients with GOS < 3 was significantly lower than CPPopt when compared to mean real CPP in those with GOS ≥ 3 (87 mmHg vs 103 mmHg, respectively, $p = 0.04$). In the group with adverse outcome, the median difference between real CPP and CPPopt was -6.6 mmHg (IQR 5.3), compared to the median difference of -1.0 mmHg (IQR 5.8) in the group with GOS ≥ 3 ($p = 0.04$) (Fig. 3).

Table 1 Demographic characteristics, monitoring variables, and cerebrovascular pressure reactivity (CV reactivity) status of enrolled patients

	CV reactivity preserved PRx < 0.25	CV reactivity impaired PRx > 0.25	p value	Total
No. patients (%)	15 (83 %)	3 (17 %)	–	18
Age years (mean ± SD)	40 ± 16	52 ± 11	0.173	42 ± 16
SAPS II (mean ± SD)	42 ± 10	48 ± 8	0.172	45 ± 10
GCS median (IQR)	7 (4)	4 (2)	**0.014**	6 (3)
CT Marshall score median (IQR)	3 (3)	4 (2)	0.806	4 (4)
GOS at 6 monts median (IQR)	4 (1)	1 (1)	**0.014**	3 (2)
ABP mmHg (mean ± SD)	98.7 ± 6.6	97.4 ± 3.5	0.678	98.5 ± 6.1
ICP mmHg (mean ± SD)	12.1 ± 3.7	12.4 ± 5.7	0.912	12.1 ± 3.9
CPP mmHg (mean ± SD)	86.2 ± 5.3	85.0 ± 4.6	0.906	86.0 ± 5.1
$PbtO_2$ mmHg (mean ± SD)	25.6 ± 7.8	23.2 ± 6.2	0.427	25.1 ± 7.5
CO % (mean ± SD)	57.8 ± 8.2	48.0 ± 6.5	0.300	56 ± 8.6
CBF ml/100 g/min (mean ± SD)	39.0 ± 20.9	36.3 ± 22.2	0.953	38.5 ± 20.5
$ETCO_2$ mmHg (mean ± SD)	30.1 ± 3.0	31.7 ± 1.2	0.109	30.4 ± 2.8
PRx (mean ± SD)	-0.04 ± 0.13	0.29 ± 0.04	**0.003**	0.01 ± 0.17
CPPopt mmHg (mean ± SD)	87.5 ± 7.7	91.7 ± 5.2	0.374	88.2 ± 7.4
% time PRx > 0.25 median (IQR)	23.4 (15.5)	55.4 (2.8)	**0.007**	25.4 (29.3)

Bold values are statistically significant

SAPS II Simplified Acute Physiology Score II, *GCS* Glasgow coma score, *GOS* Glasgow outcome score, *CT Marshall score* first head CT classification, *ABP* mean arterial blood pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *$PbtO_2$* brain tissue oxygenation, *CO* cerebral oximetry, *CBF* cerebral blood flow, *$ETCO_2$* endtidal CO_2, *PRx* pressure reactivity index, *CPPopt* optimal CPP according to PRx, and *% time PRx > 0.25* percentage of time with PRx > 0.25, *IQR* interquartile range, *SD* standard deviation

p value for Mann–Whitney U test

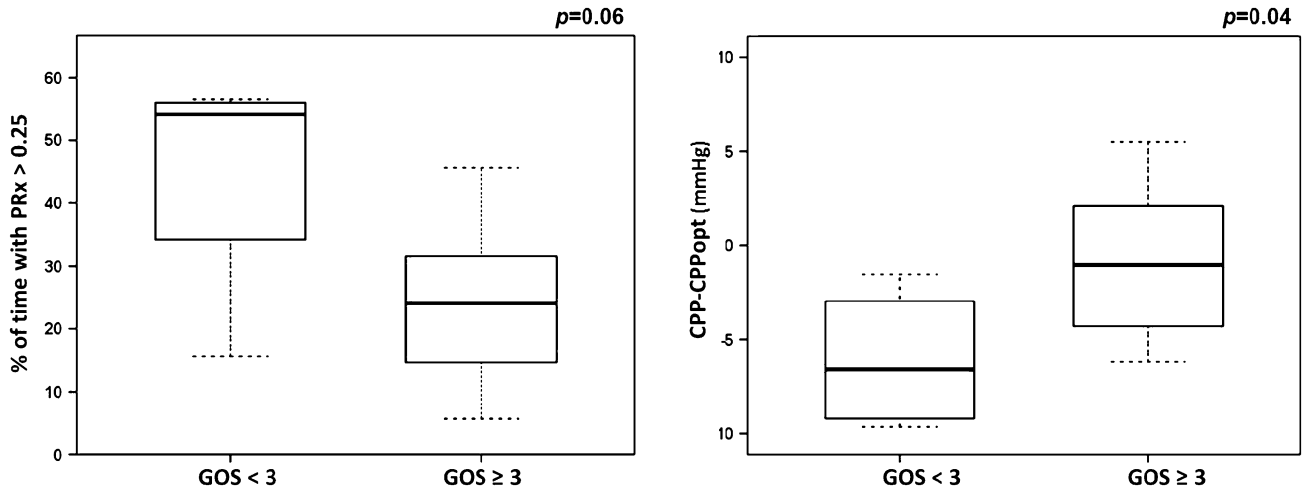

Fig. 3 *Box* and *whisker plots* showing medians and 25th and 75th percentiles of time with cerebrovascular autoregulation impairment (% of time PRx $>$ 0.25) and difference between cerebral perfusion pressure (CPP) and optimal CPP according to pressure reactivity index (CPPopt). Glasgow outcome score (GOS) was dichotomized into GOS $\geq$ 3 and GOS $<$ 3 (adverse outcome: death and persistent vegetative state). The median percentage of time spent with disturbed autoregulation was greater although non-significant in patients with GOS $<$ 3 (median 54.1 %; interquartile range 24.7 %) ($p = 0.055$). Real CPP was significantly lower than CPPopt on patients with adverse outcome ($p = 0.04$). The median difference "CPP-CPPopt" in the adverse outcome group was -6.6 mmHg with interquartile range of 5.3 mmHg, compared to median difference of -1.0 mmHg with interquartile range of 5.8 mmHg in the other group. *p* values were calculated with Mann–Whitney–Wilcoxon test

Real CPP and CPPopt Estimates

Patients' real CPP averaged over the whole monitoring period significantly correlated with CPPopt ($r = 0.83$, $p < 0.0001$). Mean real CPP for all patients was 2.2 mmHg lower than mean CPPopt. The limits of agreement (LOA) between CPP and CPPopt ranged from -10.5 to 6.2 mmHg and limit of precision was 4.2 mmHg (Fig. 4, box A). The limits of agreement between CPPopt and ORxs-CPPopt, COx-CPPopt and CBFx-CPPopt are presented in Fig. 4. The CPPopt and COx-CPPopt mean values had the smallest difference (-0.1 mmHg) and a LOA range of -12.3 to 12.2 mmHg. The limits of precision of the 3 methods compared to CPPopt were all around 6.5 mmHg.

Discussion

In this pilot study, we present data of severe TBI patients managed according to a recently developed individual CPP-oriented algorithm that incorporates feedback from continuous cerebrovascular reactivity measurements (CPPopt) [15, 17]. In our hospital, the CPPopt could be detected in around 60 % of ICP monitoring time. Close values of mean real CPP and mean CPPopt along with significant correlations and a small LOA bias might indicate that target CPPopt values are feasible with application of our algorithm [33]. We emphasize that the learning process of the protocol, degree of medical and nursing compliance, and commitment to this new protocol of targeted CPP seem fairly good.

The patients with overall preserved autoregulation (mean PRx $<$ 0.25) had not only significantly higher GCS but also a better outcome and presented longer periods of intact cerebrovascular pressure reactivity (non-significant result). These results are in agreement with several published studies reporting that the interval duration of impaired autoregulation was associated with poor outcome in head injury [34–36]. We demonstrated that patients with larger discrepancy ($>$10 mm Hg) between real CPP and CPPopt more likely have adverse outcome. This finding stresses the importance of guiding TBI treatment using autoregulation indices in clinical practice. It may be interpreted (but needs confirmation on the larger sample) that any difference between real and target CPP greater than 10 mmHg must be avoided. Multicenter clinical trials investigating the benefit of CPPopt-oriented therapy are warranted.

Comparison of the 4 methods of calculating CPPopt revealed that limits of precision were similar and around 6.5 mmHg. Similar averaged values for CPPopt were obtained. Taken CPPopt (ICP/PRx) as the reference, the lowest bias (-0.1 mmHg) was obtained with COx-CPPopt using non-invasive NIRS. Recent literature showed that slow NIRS waves in TBI patients are synchronous with slow ICP waves which may be a new opportunity for the continuous non-invasive monitoring of cerebrovascular pressure reactivity [37, 38]. Other authors suggested that NIRS can monitor dynamic cerebral autoregulation and be

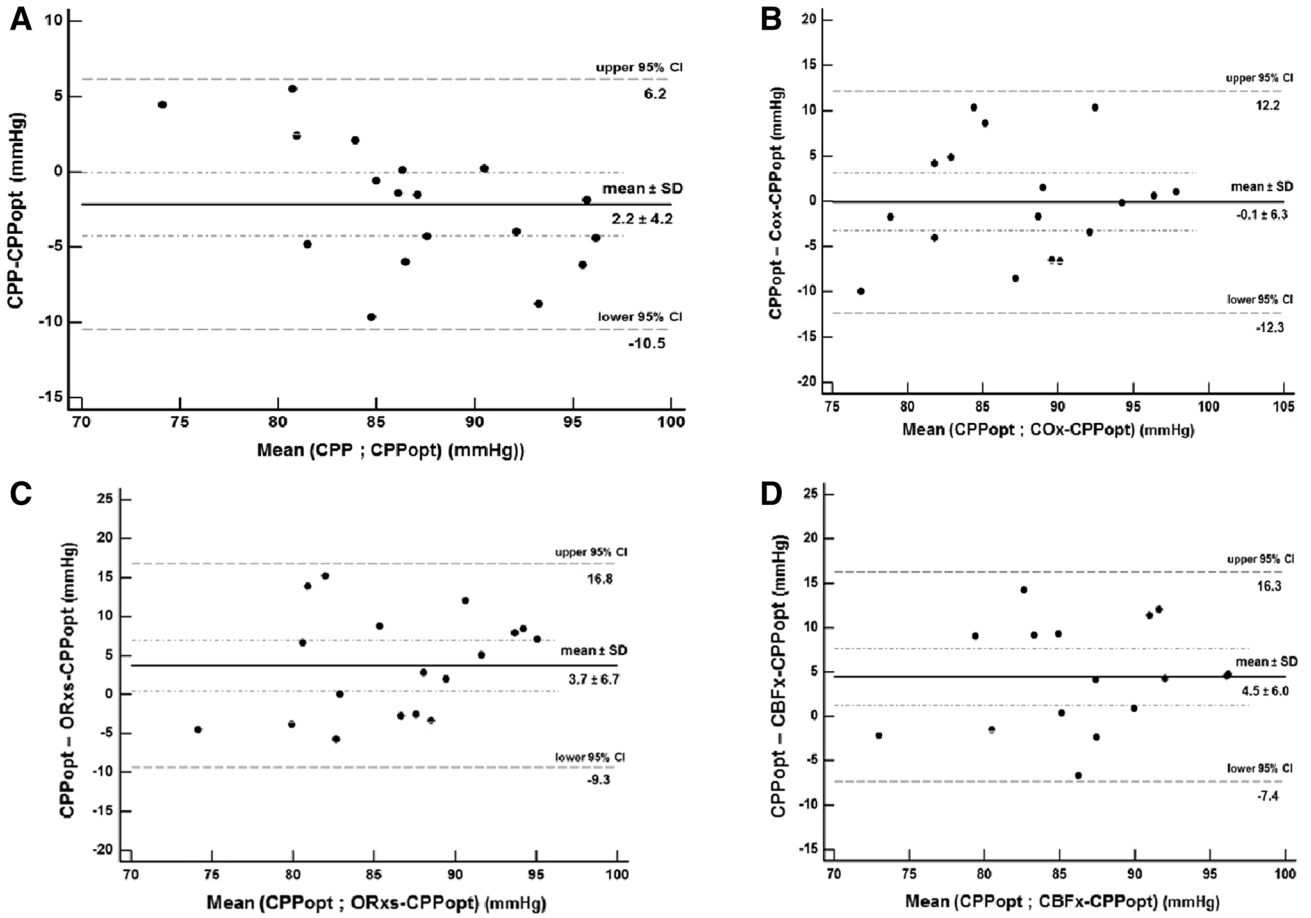

Fig. 4 Bland Altman plot for the comparison of mean paired cerebral perfusion pressure (CPP) and optimal CPP (CPPopt) plotted against their mean difference. Limits of agreement range between the lower and upper 95 % confidence interval (CI) and limits of precision within one standard deviation (SD) of the mean. **a** CPP and CPPopt (CPP evaluated with cerebrovascular pressure reactivity index). The CPP and CPPopt average bias was −2.2 mmHg (−10.5 to +6.2 mmHg). Limit of precision 4.2 mmHg. **b** CPPopt and COx-CPPopt (cerebral oximetry index). The CPPopt and COx-CPPopt average bias was −0.1 (−12.3 to +12.2 mmHg). Limit of precision 6.3 mmHg. **c** CPPopt and ORxs-CPPopt (oxygen reactivity index short). The optCPPprx and optCPPorxs average bias was +3.7 mmHg (−9.3 to 16.8 mmHg). Limit of precision 6.7 mmHg. **d** CPPopt and CBFx-CPPopt (cerebral blood flow index). The CPPopt and CBFx-CPPopt average bias was 4.5 mmHg (−7.4 to 16.3 mmHg). Limit of precision 6.0 mmHg

used for autoregulation-guided therapy [39–42]. However, CPPopt calculation with non-invasive CO (NIRS) needs further evaluation.

Study Limitations

This study is single center and has a small sample size. Still, it is a prospective pilot study of CPPopt-oriented therapy in TBI patients, which results allow authors to envisage further assessment in larger cohorts, with time series analysis and finer discrimination of outcome. The CPPopt window of the ICM+ is updated every minute and the team tried to follow the target value as close as possible. However, the patient's records did not have information about how often the CPP was modified by the staff, and therefore, staff compliance to the algorithm was assessed only with indirect information about CPP, CPPopt, the difference between them, and the percentage of time autoregulation was disturbed. At our NCCU, CPP is continuously calculated with ABP transducer located and calibrated at heart level, and consequently, CPP calculated values have to be interpreted according to head elevation of 30° (the difference in CPP for ABP measured at heart level is 11 mmHg) [28]. Thus, the obtained mean CPP value of 86.0 ± 5.1 mmHg should be probably adjusted to 75 mmHg. Additionally, in 2 patients, we were unable to define all period CPPopt. One possible cause for failing to define it was the narrow range of CPP variation. However, the most frequent cause for intermittent CPPopt failure was periodic intervals of autoregulation impairment with positive values of PRx. As stressed by Lazaridis et al. [43]

autoregulation is not an "all or nothing" phenomenon with a very dynamic nature, not only across patients but also within patients over time. Indeed, in our study, even patients with preserved autoregulation had PRx > 0.25 approximately during 25 % of monitoring time.

Conclusion

The results of this pilot study with severe TBI patients showed that targeted CPP management at bedside with evaluation of cerebrovascular pressure reactivity seems overall feasible. Patients managed at averaged real CPP close to CPPopt seem to have better outcome. The methodology for CPPopt calculation with non-invasive CO (NIRS) warrants further evaluation.

Acknowledgments Authors would especially like to thank all the NCCU Nursing staff for their motivation in learning the optimal CPP algorithm and for the commitment to its correct application.

Conflict of interest The software for brain monitoring ICM+ (www.neurosurg.cam.ac.uk/imcplus) is licensed by the University of Cambridge (Cambridge Enterprise). Peter Smielewski and Marek Czosnyka have financial interests in a part of the licensing fee. All other authors declare that they have no conflict of interest.

Appendix

The initial CT-scan Marshall classification distribution was 6 patients with diffuse injury type II, 3 patients with diffuse injury type III, 4 patients with diffuse injury type IV, and 5

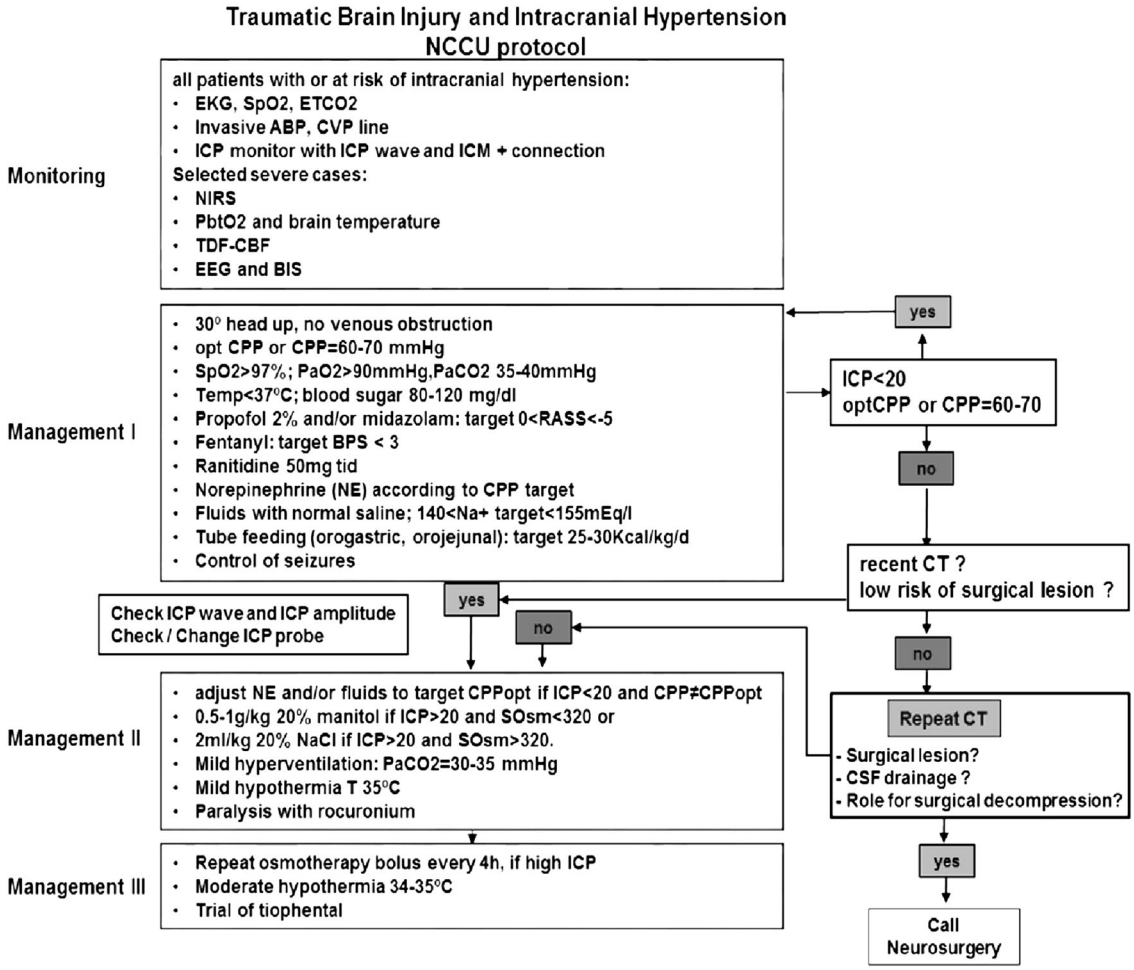

Fig. 5 Neurocritical Care Unit (NCCU) protocol for Traumatic Brain Injury and Intracranial Hypertension Management. Optimal Cerebral Perfusion Pressure (CPPopt) evaluated continuously at bedside with cerebrovascular reactivity index and Intracranial Pressure (ICP) control below 20 mmHg are primary targets. *EKG* electrocardiogram, SpO_2 pulse oximetry, $ETCO_2$ endtidal carbon dioxide, *ABP* arterial blood pressure, *CVP* central venous pressure, *ICP* intracranial pressure, *ICM+* multimodal brain monitoring software, *NIRS* cerebral oximetry with near-infrared light, $PbtO_2$ brain tissue oxygen pressure, *TDF-CBF* thermal diffusion cerebral blood flow, *EEG* electroencephalogram, *BIS* bispectral index, *CPP* cerebral perfusion pressure, *CPPopt* optimal CPP, PaO_2 arterial oxygen pressure, $PaCO_2$ arterial carbon dioxide pressure, *Temp* temperature, *RASS* Richmond agitation–sedation scale, *BPS* behavioral pain scale, *Na+* serum sodium, *CT* computerized tomography, *CSF* cerebral spinal fluid

patients with non-evacuated lesions. Before NCCU admission, 4 patients were submitted to craniotomy for hematoma drainage, 3 patients needed early decompression, and 3 had non-neurosurgical procedures. During NCCU stay, 1 patient had an extraventricular drainage and 2 more patients went for late decompression due to refractory intracranial hypertension.

NCCU protocol for Traumatic Brain Injury and Intracranial Hypertension Management is presented in Fig. 5.

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KIDNEY-BRAIN LINK IN TRAUMATIC BRAIN INJURY PATIENTS?
A PRELIMINARY REPORT

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Neurocrit Care. 2014 Oct 2. [Epub ahead of print]

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-014-0045-1

ORIGINAL ARTICLE

Kidney-Brain Link in Traumatic Brain Injury Patients? A preliminary report

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Abstract
Background Kidney hyperfiltration with augmented renal clearance is frequently observed in patients with traumatic brain injury. The aim of this study is to report preliminary findings about the relationship between brain autoregulation impairment, estimated kidney glomerular filtration rate and outcome in critically ill patients after severe traumatic brain injury.
Methods Data collected from a cohort of 18 consecutive patients with severe traumatic brain injury managed with ICP monitoring in a Neurocritical Care Unit, were retrospectively analyzed. Early morning blood tests were performed for routine chemistry assessments and we analyzed creatinine and estimated creatinine clearance, osmolarity, and sodium. Daily norepinephrine dose, protein intake, and water balance were documented. Time average of brain monitoring data (intracranial pressure, cerebral perfusion pressure, and cerebrovascular reactivity pressure index—PRx) were calculated for 6 h before blood sample tests. Patient outcome was evaluated using Glasgow outcome scale at 6-month follow-up, considering non*fatal* outcome if GOS $\geq$3 and *fatal* outcome if GOS $<$3. Multiple linear regression models were used to study the crude and adjusted effects of the above variables on PRx throughout time.
Results A total of 199 complete daily observations from 18 adult consecutive multiple trauma patients with severe traumatic brain injury were analyzed. At hospital admission, the median post-resuscitation Glasgow coma score was 6 (range 3–12), mean SAPSII score was 44.65 with predicted mortality of 36 %. Hospital mortality rate was 27 % and median GOS at 6 month after discharge was 3. Creatinine clearance (CrCl) was found to have a negative correlation with PRx (Pearson correlation—0.82), with statistically significant crude ($p < 0.001$) and adjusted ($p = 0.001$) effects. For each increase of 10 ml/min in CrCl (estimated either by the Cockcroft–Gault or by Modification of Diet in Renal Disease Study equations) a mean decrease in PRx of approximately 0.01 was expected. Amongst possible confounders only norepinephrine was shown to have a significant effect. Mean PRx value for outcome *fatal status* was greater than mean PRx for *non-fatal status* ($p < 0.05$), regardless of the model used for the CrCl estimation.
Conclusions Better cerebral autoregulation evaluated with cerebrovascular PRx is significantly correlated with augmented renal clearance in TBI patients and associates with better outcome.

Keywords Traumatic brain injury · Cerebrovascular pressure reactivity index · Creatinine · Renal clearance · Outcome

Introduction

Autoregulation of blood flow is the inherent capacity of vascular bed to maintain constant perfusion despite the variations of arterial blood pressure (ABP) and intracranial pressure (ICP), and is an important mechanism to maintain cerebral [1] and kidney [2] blood flow relatively constant. The brain and kidney are highly perfused organs with a low vascular resistance, and hence are exposed to high-volume

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Published online: 02 October 2014

blood flow throughout the cardiac cycle [3]. As O'Rourke and Safar described [4] "These 2 organs throb with each beat of the heart, and their venous efflux, like that of the lungs, retains pulsations transmitted through the capillary network. The brain and kidney are susceptible to influences upstream that may increase fluctuations of pressure and flow, whereas small vessels in other organs are protected by relatively intense vasoconstriction upstream". The hemodynamic parallelism between vascular beds of brain and kidney are described by other authors, acknowledging a putative cerebrorenal connection [5, 6]. Finally, brain and kidney play an important role in maintaining homeostasis by adjusting sodium, fluid tonicity, and water balance [7].

Cerebrovascular autoregulation and kidney function are frequently impaired in patients with traumatic brain injury (TBI) [8]. Conversely, increased glomerular filtration rate with augmented renal clearance (ARC) and polyuria are also frequently observed in patients with TBI [9, 10]. Systemic inflammation after trauma [11], cytokine cascade triggered by brain lesion [12], aggressive fluid resuscitation, use of hypertonic solutions and vasopressor support may promote organ blood flow disruption and excretory function disturbance. The aim of this study is to report preliminary findings about the relationship between brain autoregulation impairment, estimated kidney glomerular filtration rate, and outcome in critically ill patients after severe TBI.

Methods

Patients and Monitoring

We retrospectively performed an analysis of data collected for a prospective cohort of 18 consecutive patients admitted to the Neurocritical Care Unit (NCCU) of the Hospital S. João, Porto, with multiple trauma and severe TBI and clinical indication for ICP monitoring. In the NCCU, all patients were sedated with infusions of propofol and/or midazolam and had continuous analgesia with fentanyl. Mechanical ventilation was performed to achieve normocapnia (PaCO2 35–40 mmHg) and normal oxygenation (PaO2 $>$ 90 mmHg), with lung protective criteria. Patients were continuously monitored for heart rate (HR), invasive ABP, end-tidal CO2 (ETCO2), ICP, and cerebral perfusion pressure (CPP). An intraparenchymal ICP probe with bolt from Codman® was used and CPP was continuously calculated with ABP transducer located at heart level with patients at 30° head-up elevation. Data acquired from vital signal monitor (Philips®) and ICP monitor were continuously recorded using ICM + ® software [13]. Primary analysis of data monitoring waveforms of ABP, ICP, and CPP was done using time-averaged values of 10-s intervals. Cerebrovascular pressure reactivity index (PRx) was calculated using 10-s averages of ICP and ABP over a moving window of 5-min length [14] as correlation coefficient between ICP and ABP. Optimal CPP [15] for autoregulation was calculated following PRx based on a 4 h window time. Whenever possible we targeted management for optimal CPP (optCPP) and when optimal CPP could not be found we managed CPP for values $>$60 mmHg according to Brain Trauma Foundation Guidelines [16]. To achieve optCPP goal, volume expansion and norepinephrine were used when necessary.

Exclusion criteria were age less than 18 years old, pregnancy, or no clinical indication for invasive ICP monitoring. Local ethics committee approval and written consent from the next-of-kin were obtained.

Procedure

The study period elapsed while the patients had an indication to be monitored with ICP. Daily early morning blood tests were performed for routine chemistry assessments, namely Osm—osmolarity, Na + -sodium and Cr—creatinine. As this trial was not designed specifically to examine creatinine clearance (CrCl) in the TBI population, we estimated glomerular filtration rate (GFR) using the Cockcroft–Gault formula (CrCl−CG = (140-age)*body weight/(plasma Cr*72)(*0,85 if female)) [17] and abbreviated Modification of Diet in Renal Disease Study Equation (CrCl−MDRD = (175*(plasma creatinine$^{-1.154}$)*(age$^{-0.203}$)(*0.742 if female; *1.21 if black))) [18]. We also recorded daily norepinephrine dose, protein intake, and water balance.

Time-averaged brain monitoring data was calculated for 6 h before blood sample tests.

Patient outcome was evaluated using Glasgow Outcome Scale (1—death, 2—persistent vegetative state, 3—severe disability, 4—moderate disability, and 5—good recovery) [19] at 6 months after hospital discharge. We classified outcome as a *nonfatal status* if GOS $\geq$ 3 and as a *fatal status* if GOS $<$3.

Data Analysis

We analyzed 199 complete daily observations from the 18 patients, regarding ABP, ICP, CPP, PRx, creatinine, CrCl, norepinephrine dose, protein intake, water balance, sodium, and osmolarity. For one of the individuals, 38 daily observations were available but only the first 23 complete daily observations were retrieved. This cut-off value was essentially established by two criteria: proximity to the highest number of complete daily observations from the other individuals in the sample, and representativeness of the mean of its remaining observations. For the

remaining patients, the number of complete daily values ranged from 3 to 18.

Modeling and Statistical Analysis

Simple univariate regression analysis between whole time-averaged CrCl and PRx was first performed. PRx and CrCl were compared in patients with *fatal* and *nonfatal status*.

To further investigate correlations, multiple linear regression models studied the crude and adjusted effect of CrCl on PRx throughout time. Due to sample size constraints, adjustment was considered for norepinephrine, sodium, protein intake, water balance, and outcome. The generalized least squares method with normally distributed and correlated errors was applied. The best variance–covariance matrix was having an intra-individual time autocorrelation structure of order 1. The method choice was due to the nature of the study: for a given subject, the variables of interest were collected daily for a sequence of several days while ICP was being monitored.

The condition of preserved renal function with creatinine <1.3 mg/dl was also investigated (2 male subjects who developed kidney failure with *fatal status* having 11 complete observations were removed), with the same confounding variables and structure of the variance–covariance matrix.

In all models, graphical analyses were used to assess normality and homoscedasticity of model residuals and no compromising features were detected. Intra-individual and inter-individual variations were also considered by linear mixed-effects models, with observations grouped at the individual level. The obtained models were discarded as less than 4 % of the response variation was explained by the random effects.

Comparison between models was based on the likelihood ratio test for nested models and on the Bayesian information criterion (BIC) otherwise. Statistical analyses were performed with the R language and software environment for statistical computation, version 2.15.3 [20]. Statistical significance was considered at $p < 0.05$.

Results

A total of 18 adult consecutive multiple trauma patients with severe TBI (16 (89 %) males) with mean age 41.7 ± 15.6 years old (range 20–66) were analyzed. At hospital admission the median post-resuscitation Glasgow coma score (GCS) was 6 (range 3–12), and mean SAPSII score was 44.65 with predicted mortality of 36 %. Patients with first GCS above 8 had secondary neurologic deterioration with indication for intubation, ventilation, and ICP monitoring. Hospital mortality rate was 27 % and median GOS at 6 months after discharge was 3. Monitoring time for ICP, CPP, and PRx totalized 6028 h. ICP presented a median value of 11.6 mmHg with a minimum of 1.5 mmHg and a maximum of 44.1 mmHg. CPP varied between 66.1 mmHg and 110.2 mmHg with a median value of 85.3 mmHg. These values should be interpreted taking into account the position of ABP transducer and bed angle as described in the methods [21]. PRx oscillated between -0.7 and 0.84 with a median value of 0.0. Serum creatinine had a median value of 0.6 mg/dl with a minimum of 0.2 mg/dl and a maximum value of 1.7 mg/dl. Estimated CrCl-CG fluctuated between 62 ml/min and 471 ml/min with a median value of 199 ml/min, while estimated CrCl-MDRD varied between 32 ml/min and 519 ml/min with a median value of 173 ml/min. None of the patients had any antecedent of chronic kidney disease and only two patients developed altered kidney function with creatinine >1.20 mg/dl during NCCU admission. ARC or kidney hyperfiltration was defined as CrCl above 130 ml/min. For CrCl estimates, ARC was observed in 16 (88 %) patients, corresponding to 166 (83 %) estimated values of CrCl-CG, and ARC was found in 15 (83 %) patients, corresponding to 137 (69 %) estimated values for CrCl-MDRD. Scattergram and mean values of creatinine, CrCls estimates, and cerebrovascular PRx for each patient are presented in Fig. 1. Serum sodium varied from 129 to 179 mg/dl with a median of 144 mg/dl. Median norepinephrine total daily dose was 32.3 mg ranging from 0 to 145 mg. A complete description of these variables is presented in Table 1.

Univariate regression between mean patient values of PRx and CrCl-CG (respectively CrCl-MDRD) shows a strong negative and significant association. $R = -0.81$ (resp. -0.73), $p < 0.0001$; i.e., higher CrCl is associated with better cerebrovascular reactivity. See Fig. 2.

Amongst norepinephrine, sodium, protein intake, water balance, and outcome, the longitudinal crude effect of clearance creatinine on PRx was only found to be significantly altered by norepinephrine and outcome. The obtained estimates are presented in Table 2. Crude effects were studied with the structure of the variance–covariance matrix that was used in the adjusted-effects model. Obtained 95 % confidence intervals for the correlation parameter and the residual standard error of the adjusted model were (0.2546, 0.5376) and (0.2161, 0.2733).

Both CrCl calculated values were found to have significantly negative (and similar) crude and adjusted effects in the model (Table 2). The model estimated PRx to have a 0.01 mean decrease for each increase of 10 ml/min in CrCl. The effect of fatal/nonfatal status outcome found in the model was statistically similar for the two CrCl calculations: it decreased by 39 % after being adjusted for CrCl-CG and NE, and 32 % for CrCl-MDRD and NE. Regarding

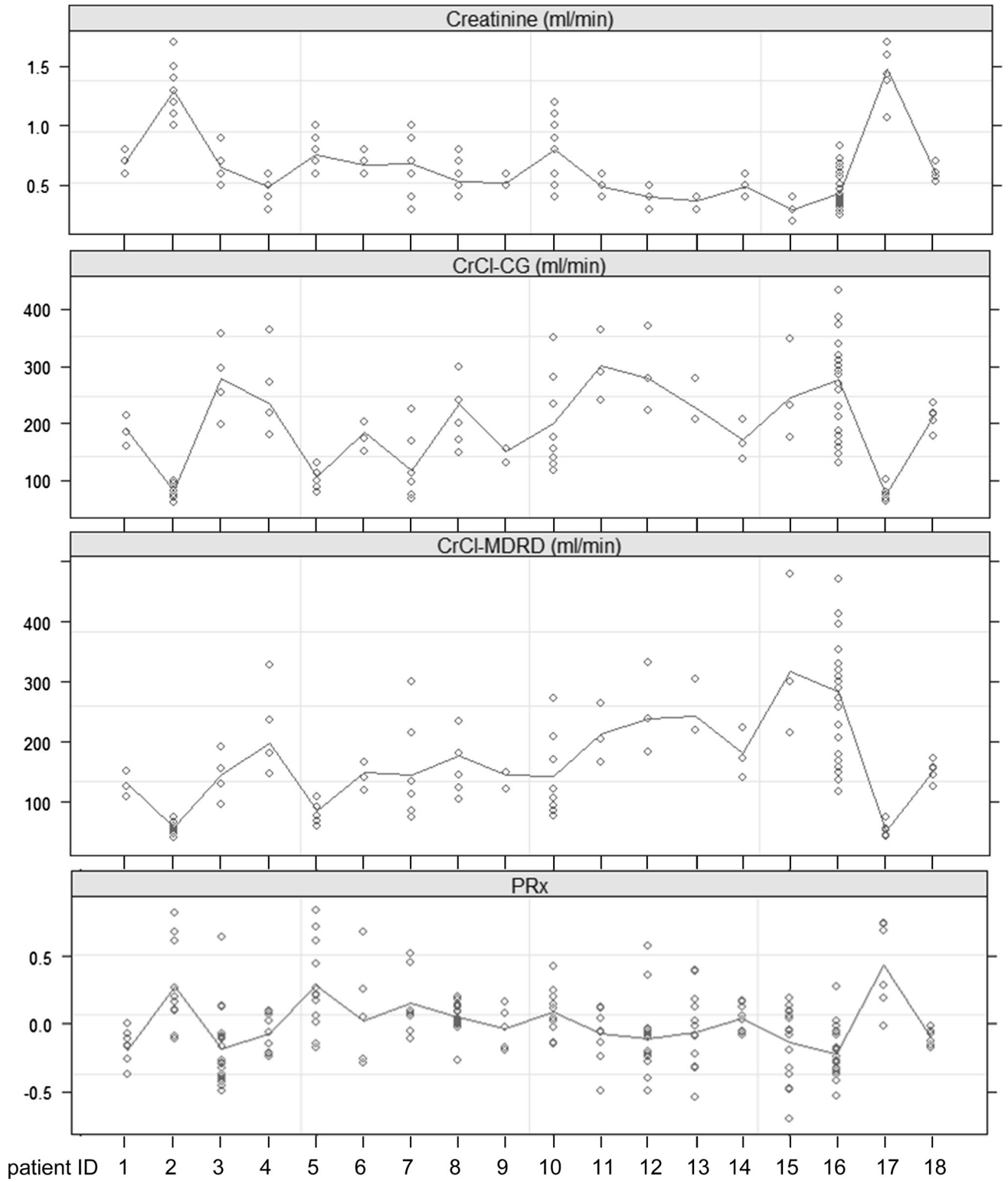

Fig. 1 Individual sample values of creatinine, creatinine clearance estimates calculated with Cockroft-Gault equation (CCl-CG) and modification of diet in renal disease study equation (CrCl-MDRD), and cerebrovascular pressure reactivity index (PRx). Patients are identified from 1 to 18 on the x-axis and solid lines connect mean values. Subjects with Glasgow outcome scale <3 are labeled 2, 5, 12, and 17

Table 1 Patient characteristics (age, Glasgow Coma Score, SAPS II, and Glasgow Outcome Score), and physiological values of intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebrovascular pressure reactivity index (PRx), serum creatinine (creat), calculated creatinine clearance with Cockroft-Gault equation (CCl-CG) and calculated with modification of diet in renal disease study equation (CrCl-MDRD), serum sodium, norepinephrine total dose per day (NE), protein intake (g/d), and water balance (ml/d). Physiological data are presented as median, minimum, and maximum

ID	age	GCS	SAPS II	GOS	ICP mmHg	CPP mmHg	PRx	Creat mg/dl	CrCl-CG ml/min	CrCl-MDRD ml/min	Sodium mEq/l	NE mg/day	Protein intake (g/d)	Water Balance (ml/d)
1	37	3	57	5	15.4	75.0	−0.21	0.7	184	127	144	64.1	64.9	337
			62 %		5.4; 15.9	67.7; 79.4	−0.37; 0.00	0.6; 0.8	161; 215	109; 152	139; 152	0.0; 76.8	0.0; 71.4	−213; 3600
2	64	7	48	1	14.4	84.9	0.20	1.3	81	56	163	69.3	54.7	777
			41 %		12.8; 17.6	74.3; 94.4	−0.11; 0.68	1.1; 1.7	62; 96	32; 75	139; 173	42.5; 240.0	0.0; 76.0	−996; 4092
3	33	4	48	3	7.0	92.8	−0.33	0.6	297	155	143	12.0	72.5	77
			41 %		1.5; 20.6	88.3; 105.1	−0.49; 0.14	0.5; 0.7	255; 357	97; 191	137; 156	0.0; 37.2	27.9; 73.0	−806; 2142
4	42	12	27	4	12.5	88.8	−0.06	0.5	218	29,8	143	42.1	59.2	463
			8 %		8.9; 16.2	79.8; 96.1	−0.24; 0.10	0.3; 0.6	181; 363	148; 329	140; 153	0.0; 92	23.9; 63.4	−1301; 2448
5	44	4	45	2	17.1	85.3	0.21	0.7	113	91	157	13.9	81.1	852
			35 %		6.2; 23.5	73.0; 98.5	−0.18; 0.84	0.6; 1.0	79; 132	60; 109	143; 179	0.0; 49.5	0.0; 100.0	−1725; 3395
6	23	7	32	4	7.5	83.0	−0.10	0.7	189	153,5	144	39.1	55.7	1078
			13 %		1.9; 15.9	75.9; 95.1	−0.29; 0.68	0.6; 0.8	152; 203	120; 167	143; 146	21.9; 62.6	10.0; 72.4	261; 2470
7	65	10	57	4	9.2	85.2	0.07	0.7	105	113	144	41.3	29.2	−991
			62 %		8.0; 13.8	80.8; 90.4	−0.11; 0.45	0.3; 0.9	75; 226	75; 301	135; 148	5.1; 62.7	10.8; 84.5	−2253; 1677
8	44	8	32	4	18.1	81.8	0.06	0.5	240	181	142	38.9	63.4	521
			13 %		5.5; 28.4	66.1; 95.1	−0.27; 0.21	0.4; 0.8	150; 300	105; 234	136; 151	7.2; 67.5	9.5; 67.2	−853; 2368
9	25	3	44	4	13.7	80.4	−0.17	0.5	157	150	146	27.2	8.44	415
			33 %		13.4; 15.1	79.5; 89.3	−0.20; 0.08	0.5; 0.6	131; 157	122; 150	141; 151	4.2; 55.6	0.0; 56.1	−736; 931
10	21	7	36	3	6.7	92.0	0.08	0.9	166	107	163	8.4	47.9	837
			18 %		6.1; 15.5	74.6; 97.6	−0.15; 0.43	0.4; 1.2	117; 351	76; 272	136; 179	1; 145	0.0; 63.7	−1606; 4849
11	24	4	42	3	4.3	84.1	−0.01	0.5	290	204	141	15.4	62.7	521
			29 %		2.4; 15.2	74.2; 94.8	−0.50; 0.13	0.4; 0.6	242; 363	166; 264	136; 151	1.3; 43.7	11.7; 64.0	−1313; 1305
12	40	7	41	1	18.4	101.6	−0.20	0.4	278	238	151	40.3	63.0	866
			27 %		7.0; 44.1	69.9; 106.5	−0.50; 0.58	0.3; 0.5	222; 370	184; 332	144; 176	10.6; 60.0	31.3; 66.7	−981; 2951
13	60	7	58	3	13.1	81.0	−0.04	0.4	208	219	134	20.3	56.5	447
			64 %		5.9; 22.1	71.8; 91.4	−0.54; 0.40	0.3; 0.4	208; 278	219; 306	129; 148	0.0; 45.7	0.0; 68.0	−1480; 1537
14	55	6	50	5	7.0	92.5	0.03	0.5	165	173	138	37.4	55.0	218
			46 %		5.9; 9.6	83.2; 99.1	−0.08; 0.17	0.4; 0.6	138; 207	140; 223	137; 142	10.6; 42.0	0.0; 63.0	−1003; 3170
15	66	4	36	3	10.7	89.7	−0.05	0.3	233	300	138	3.5	66.5	182
			18 %		3.4; 16.2	76.0; 110.2	−0.70; 0.19	0.2; 0.4	175; 349	215; 479	132; 149	0.0; 48.6	29.0; 65.0	−1708; 2490
16	20	4	46	4	8.4	87.6	−0.21	0.3	339	342	149	38.4	63.0	766
			37 %		4.3; 33.7	72.1; 102.4	−0.53; 0.29	0.2; 0.8	131; 471	118; 519	140; 163	0.0; 96.0	0.0; 64.0	−3887; 4831
17	48	3	60	1	3.0	94.4	0.69	1.7	64	52	167	25.8	68.0	1285

Table 1 continued

ID	age	GCS	SAPS II	GOS	ICP mmHg	CPP mmHg	PRx	Creat mg/dl	CrCl-CG ml/min	CrCl-MDRD ml/min	Sodium mEq/l	NE mg/day	Protein intake (g/d)	Water Balance (ml/d)
			68 %		2.0; 6.5	84.6; 99.1	0.29; 0.75	1.1; 1.7	64; 102	43; 75	160; 176	25.2; 64.5	0.0; 74.0	371; 2284
18	40	11	31	3	14.0	84.2	−0.14	0.6	211	158	139	19.3	51.5	−33
			12 %		10.9; 15.0	83.8; 87.5	−0.18; −0.05	0.6; 0.7	179; 219	125; 198	132; 148	14.2; 25.8	4.0; 73.0	−897; 2058

CrCl-CG estimates, the expected PRx value for fatal status outcome was 0.1533 greater than the expected PRx for nonfatal status ($p = 0.023$); whereas for CrCl-MDRD estimates, the expected PRx value for fatal status outcome was 0.1727 greater than the expected PRx for nonfatal status ($p = 0.014$). The breakdown of PRx along CrCl values, both CG and MDRD, are presented in Fig. 3, for each outcome status. Crude and adjusted effects for the variables that were excluded from the final model due to non-significance, namely sodium, protein intake, and water balance, are presented in Table 2. Amongst these variables, sodium was the only one showing a significant crude effect ($p = 0.03$, 0.61, and 0.33, respectively).

The effect of CrCl on PRx was also studied on individuals with sustained normal renal function (16 patients out of 18). Amongst possible confounders such as norepinephrine, outcome, sodium, protein intake, and water balance, only norepinephrine was shown to have a significant effect. The obtained estimates are also presented in Table 2. The 95 % confidence intervals for the correlation parameter and residual standard error of the adjusted model were (0.2606, 0.5384) and (0.2148, 0.2729), respectively.

Discussion

Kidney hyperfiltration appears to be a frequent finding in critically ill [22], particularly in trauma patients [10]. At present, most ICU's worldwide, still use daily serum creatinine as the endogenous substance to estimate kidney function, due to its high specificity and low cost, in spite of low sensitivity [23]. However, there is an increasing evidence that GFR should be measured daily even in patients with normal kidney function [24]. Until now, the implications of ARC have focused on drug pharmacokinetics and elimination [22, 25–29].

In this paper we documented strong correlation between PRx as a measure of cerebrovascular reactivity, estimated CrCl and outcome in a small group of severe TBI patients. We also searched for the relationship between the consequences of TBI management with CPP manipulation using norepinephrine and hypertonic solutions looking at serum sodium levels and osmolarity. Both procedures were associated with augmented estimated CrCl. Such strong association between PRx and CrCl is rather a logical pathophysiological phenomenon that may be explained on the basis of differential input impedance in the brain and kidney compared with other systemic vascular beds. As clinicians, we understand the relevance of intact autoregulation both for preservation of brain and kidney function. The innovation of our study is balanced on relationship between these two parameters and their effect on outcome. These results may be in accordance with the dual

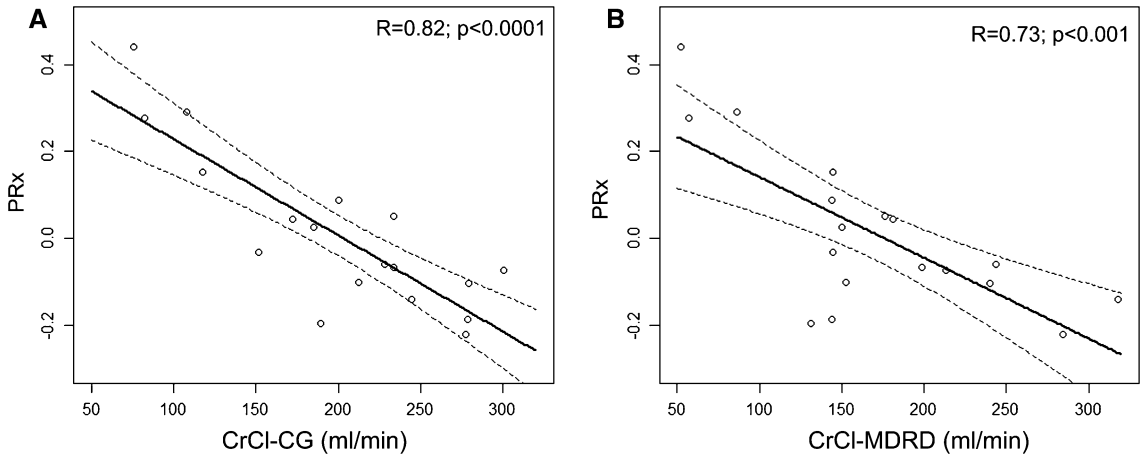

Fig. 2 Mean predicted cerebrovascular pressure reactivity index (PRx) and 95 % confidence interval for different creatinine clearance (CrCl) values, determined by (**A**) the Cockcroft-Gault equation (CrCl-CG) and by (**B**) MDRD modification of diet in renal disease study equation (CrCl-MDRD). Points represent time-averaged observations from the 18 sampled patients during the whole period of intracranial pressure (ICP) monitoring with PRx calculation at the Neurocritical Care Unit

physiological mechanism of renal autoregulation which is based on the myogenic response to pressure and the tubuloglomerular feedback to flow [30]. In fact, renal autoregulation minimizes the impact of changes in ABP on sodium excretion. However, Udy et al. [9] showed that augmented CrCl found in TBI patients receiving active management of CPP persists even after discontinuation of such therapy. Fluid overload and daily protein intake were also considered in this study and revealed no significant difference.

Although this study was not primarily designed to examine kidney function in the TBI population, the findings obtained from the included cases call attention to a striking association between good cerebrovascular pressure reactivity and kidney hyperfiltration.

The mechanisms behind this phenomenon in this population ask for reflection and further investigation. First, the common effect of CPP management on brain and kidney autoregulation. As Udy et al. [9] and also Albanèse et al. [31] stated during active management of CPP (using norepinephrine and hypertonic solutions) that augmented CrCls are common. Second, brain injury itself associated with loss of autoregulation may contribute to kidney autoregulation impairment [2, 19] and dysfunction leading to a decrease in CrCls, with more susceptibility to develop acute kidney injury. Schiller et al. [32] suggested that "the brain and the kidney present a common and unique way to react to fluctuations in blood pressure and flow due to similar small-resistance vascular beds. …Thus, information about microvascular damage in one organ may provide information about damage in the other organ". Also, Ono et al. [33] monitored brain autoregulation using cerebral oximetry index (COx) with near-infrared spectroscopy and showed that "excursions of mean ABP below the lower limit of CBF autoregulation during cardiopulmonary bypass were independently associated with acute kidney injury". Moreover, a third serum unknown element might be present (cytokines, neurotransmitters, brain and kidney renin-angiotensin systems, vasopressin, autonomic neuronal control) and play an important role in the crosstalk between brain and kidney [3, 11, 34]. In fact, Nongnuch et al. [6] in its paper "Brain-kidney crosstalk" call attention to inflammatory state and increased sympathetic nervous system activity as common pathways between acute kidney injury and acute brain injury. On the other hand, recent findings about autoregulation of cerebral blood flow and nephrectomy [35], and systemic and brain renin-angiotensin systems [36–38] may give some subtle links about biochemical interplay between brain and kidney. Understanding the underlying pathophysiological mechanisms between brain and kidney autoregulation and the practical implications of this relationship remains to be established with further studies. From experimental study [39], we can learn that kidney autoregulation evaluated with NIRS (RVx) is probably more fragile than brain because kidney blood flow becomes pressure passive before cerebral blood flow. Whether this amazingly strong CrCl-PRx association reported in our small series of TBI patients is an epiphenomenon of this observation, remains to be investigated.

Study Limitations and Insights for Future Investigations

Limitations of the present study are related to the small cohort and to the fact that it was not specifically designed to examine GFR. The small number of patients did not allow to consider multivariate analysis, including severity

Table 2 (**A**) Estimates for the crude and adjusted effects of the two calculated values of creatinine clearance (CrCl). CrCl (ml/min) with Cockcroft-Gault formula (CrCl-CG) and modified diet renal disease equation (CrCl-MDRD), outcome at 6 months after hospital discharge (GOS ≥3 as the reference category and classified as *nonfatal status*) and norepinephrine (NE) on the cerebrovascular pressure reactivity index (PRx) for all patients (**B**) Estimates for the crude and adjusted effects of CrCl-CG and CrCl-MDRD and NE on PRx in patients with normal kidney function

(**A**)

Variables for all patients	Crude effects	*p* value	Adjusted effects CrCl-CG model	*p* value	Adjusted effects CrCl-MDRD model	*p* value
Intercept	–	–	0.0880	0.301	−0.0005	0.9941
CrCl-CG	**−0.0015**	<0.0001	**−0.0010**	0.001	–	–
CrCl-MDRD	**−0.0011**	<0.0001	–	–	**−0.0007**	0.015
GOS 6 m	**0.2531**	0.0003	**0.1533**	0.023	**0.1727**	0.014
Norepinephrine	**0.0034**	0.0001	**0.0023**	0.005	**0.0025**	0.003
Sodium	**0.0054**	0.0306	−0.0006	0.802	−0.0005	0.856
Protein Intake	0.0005	0.6098	0.0010	0.291	0.0008	0.394
Water Balance/100[a]	−0.0012	0.3271	−0.0020	0.099	−0.0018	0.126

(**B**)

Variables for patients with normal kidney function	Crude effects	*p* value	Adjusted effects CrCl-CG model	*p* value	Adjusted effects CrCl-MDRD model	*p* value
Intercept	–	–	**0.1658**	0.032	0.0779	0.230
CrCl-CG	**−0.0012**	0.0001	**−0.0011**	0.001	–	–
CrCl-MDRD	**−0.0009**	0.0017	–	–	**−0.0008**	0.006
Norepinephrine	**0.0012**	0.0028	**0.0010**	0.010	**0.0011**	0.008

Panel **A** Crude and adjusted effects of sodium, protein intake, and water balance are also presented: sodium was the only variable showing a significant crude effect ($p = 0.03$); all adjusted effects failed to be statistically significant. Obtained 95 % confidence intervals for the correlation parameter and residual standard error of the adjusted models were (0.2616, 0.5460) and (0.2208, 0.2794) for the CrCl-CG model and (0.3016, 0.5706) and (0.2255, 0.2865) for the CrCl-MDRD model, respectively

Panel **B** Obtained 95% confidence intervals for the correlation structure parameter and residual standard error of the adjusted models were (0.2606, 0.5384) and (0.2148, 0.2729) for the CrCl-CG model and (0.3016, 0.5669) and (0.2197, 0.2806) for the CrCl-MDRD model, respectively

[a] Water balance was divided by 100 only for scaling purposes

Significant values are presented in bold

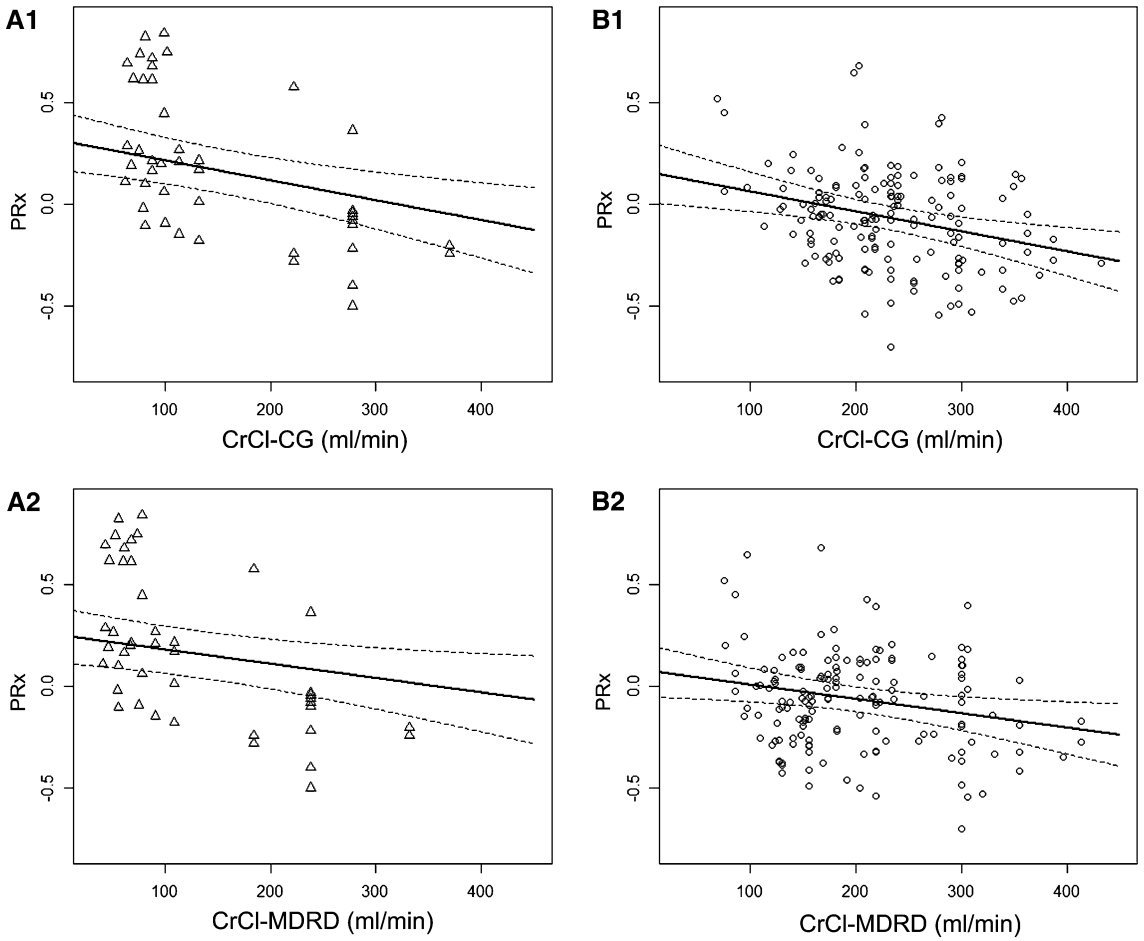

Fig. 3 Expected behavior for the pressure reactivity index (PRx) and 95 % confidence interval for the mean prediction, according to creatinine clearance (CrCl) estimates determined by the Cockcroft-Gault equation (CrCl-CG) and by the MDRD modification of diet in renal disease study equation (CrCl-MDRD), for different outcomes and for a norepinephrine (NE) dose fixed at its sample mean value (31.4 mg/day). Outcome was defined with Glasgow outcome score (GOS) at 6 months after hospital discharge (**A1** and **A2**—GOS <3 and **B1** and **B2**—GOS ≥ 3). The models estimated PRx to have very similar mean decreases (0.010 for CrCl-CG and 0.007 for CrCl-MDRD, respectively) for each increase of 10 ml/min in CrCl. The expected PRx value for GOS <3 was 0.1533 (resp. 0.1727) greater than the expected PRx for GOS ≥ 3 ($p = 0.024$; resp. $p = 0.015$). The points represent the observed values

of TBI, or concomitant systemic injuries. To counteract limitations of under- and overestimation of the real value of CrCl, we used two (Cockcroft and MDRD) of the recommended equations by the National Kidney Foundation [40].

For the near future, we are preparing a more detailed and adjusted study to confirm these results. Further investigations are necessary to evaluate the exact importance and the clinical implications of these findings in the management of TBI patients.

Conclusion

Better cerebral autoregulation evaluated with cerebrovascular PRx is statistically, significantly associated with ARC observed in TBI patients and also better outcome.

Acknowledgments The software for brain monitoring ICM + (www.neurosurg.cam.ac.uk/imcplus) is licensed by the University of Cambridge (Cambridge Enterprise). Peter Smielewski and Marek Czosnyka have financial interests in a part of the licensing fee. Rita Gaio and Óscar Felgueiras were partially funded by the European Regional Development Fund through the program COMPETE and by the Portuguese Government through the FCT—Fundação para a Ciência e a Tecnologia under the project PEst-C/MAT/UI0144/2013. Joseph Donnelly is supported by a Woolf Fisher Scholarship.

Conflict of interest All other authors declare that they have no conflict of interest

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CONCLUSIONS

CONCLUSIONS

The scientific contribution of this thesis takes the form of the six published papers presented in the publication section which basically highlight the importance of multimodal brain monitoring and cerebral autoregulation assessment at bedside in patients after TBI.

Dedicated Neurocritical Care Unit progressed from primary control of intracranial pressure and maintenance of cerebral perfusion pressure to a multidimensional approach of neuronal rescue and protection with high complexity and fast dynamic evolution.

The management of severe acute neurological patients is a constant medical challenge based on clinical evaluation, laboratory findings, imaging studies and continuous multimodal brain monitoring. The data collected by the several systemic and brain monitors with the help of advanced statistical and mathematical tools are now being applied providing clinicians better understanding of the pathophysiological events and helping to define individual patient-specific therapeutic targets. Neurocritical care bioinformatics may help neurointensivists to accomplish the challenge of healing the brain and rescuing lives.

"Traumatic Brain Injury in Portugal is changing"

Hypothesis 1: Hospital health care resource utilization due to adult traumatic brain injury in the last decade in Portugal is changing but TBI still remains an important health problem.

TBI in Portugal is still an important public health problem but its population characteristics and health resource utilization has evolved in the last decades. Retrospective analysis of the Portuguese DRG-database since 2000 to 2010 showed a clear decrease in total number of hospital admissions of adult patients with TBI as primary diagnosis. Mean age is increasing but male preponderance is maintained, except in the age group above 80 years-old. External causes of TBI have changed over the study period with arise in falls and a reduction in traffic accidents. There seems to be an increase in TBI severity and accordingly an increase of hospital length of stay. As severity of TBI patients admitted to hospital increases, so does the availability of intensive care and surgical resources, allowing treatment of patients in a more differentiated environment. Nevertheless, mortality did not decline and is still very high.

"ICP is more than a number"

Hypothesis 2: During spontaneous cerebrovascular phenomena such as plateau waves of intracranial pressure specific changes in cerebral hemodynamic indices occur.

Acute intracranial hypertension is an important cause of secondary lesion in neurocritical care patients that should be avoided. At bedside we need to understand and if possible anticipate this phenomenon, with the aim of reducing its negative impact on brain oxygenation and cerebral blood flow. The ICP analysis of pulsatile waveform and time pattern combined with multimodal brain monitoring may provide important information not only about cerebral perfusion and autoregulation reserve but also about cerebral hemodynamics combined with cerebral oxygenation.

The crisis associated with high ICP in TBI patients depends on multiple intrinsic and extrinsic factors frequently interdependent. During our clinical research we featured the influence on cerebrovascular reactivity of ICP peaks and response to intracranial hypertension management.

Plateau waves were frequent phenomena in TBI patients with preserved autoregulation but decreased volume–pressure compensatory reserve. At the top of the plateau wave, we showed both significant decrease of CPP and increase of mean ICP pulse amplitude. CBF and CVR decreased and brain oxygenation decreased significantly to values below 20 mmHg. Cerebrovascular reactivity indices (PRx, PAx and ORxs) change reflected impairment of autoregulation during the crest of the wave. Moreover the data showed that the power of the vasodilatory cascade and consequently the magnitude of plateau wave were associated with lower PRx and higher oxygenation parameters. Plateau waves are not benign phenomena and, at the lower limit of autoregulation, there is a risk of zero flow due to the collapse of brain vessels. So, accurate identification and understanding of plateau waves, may help the adequate management of acute TBI at bedside.

"Hypertonic saline is a powerful tool for intracranial hypertension"

Hypothesis 3: Management of intracranial hypertension with hypertonic saline can be monitored and explained with multimodal brain monitoring.

An analysis of the temporal profile of brain monitoring parameters response to repeated bolus of 20% hypertonic saline during intracranial hypertension showed a significant improvement of cerebral hemodynamics (CBF and CVR) and cerebrovascular reactivity (PRx and CBFx).

Recovery of CBF appeared almost ten minutes before the normalization of ICP, though no significant changes in brain oxygenation were identified. We stress cerebrovascular and hemodynamic properties of hypertonic saline as a relevant clinical observation.

"Optimal CPP: are we ready for it?"

Hypothesis 4: Optimal CPP management is possible to be conducted prospectively at bedside using pressure reactivity index analysis, and shows a potential to improve outcome following TBI.

The goal of 'real-time' continuous cerebral autoregulation monitoring is to enable the early detection of potentially harmful events before they cause irreversible damage. "Optimal CPP" can be calculated at bedside retrospectively, based on continuous evaluation of PRx. A prospective pilot study was designed to evaluate the primary results and to investigate the applicability of an algorithm of CPPopt-guided therapy in severe TBI patients. In our hospital the CPPopt could be detected in around 60% of ICP monitoring time. The median fraction of time spent with impaired cerebrovascular pressure reactivity (% of time PRx >0.25) was greater in patients with adverse outcome (GOS≤2). We also demonstrated that this group of patients presented significant larger discrepancy (> 10 mmHg) between real CPP and CPPopt. This finding stresses the importance (but also urges confirmation with multicentre randomized controlled trial) of guiding TBI treatment using autoregulation indices in clinical practice.

As a secondary aim we assessed the agreement between CPPopt (PRx) and offline calculations of CPPopt estimates based on ORxs, COx and CBFx indices. Real CPP averaged over the whole monitoring period significantly correlated with CPPopt. Comparison of the 4 methods of calculating CPPopt revealed that the lowest bias (-0.1 mmHg) was obtained with COx-CPPopt using non-invasive NIRS.

"Cerebral-systemic links and brain-kidney crosstalk"

Hypothesis 5: Disturbance of cerebral autoregulation is associated with systemic pathophysiology especially with kidney function.

Immediately after traumatic injury to the brain an abrupt neurometabolic cascade triggers an energy crisis. Changes in cerebral blood flow (hypo- and hyperperfusion), impairment of cerebrovascular autoregulation, cerebral metabolic dysfunction and inadequate cerebral oxygenation are followed by systemic inflammatory response syndrome with hemodynamic, respiratory, renal, metabolic and water-electrolyte imbalance consequences.

Univariate regression analysis between mean PRx and creatinine clearance showed a strong negative and very significant association.

In fact, cerebrovascular autoregulation and kidney function are frequently impaired in patients with TBI and conversely, increased glomerular filtration rate with augmented renal clearance and polyuria are also frequently observed in this group of patients. Importantly, our finding suggests that better cerebral autoregulation evaluated with cerebrovascular pressure reactivity index (PRx) is statistical significantly associated with augmented renal clearance observed in TBI patients and also with better outcome.

In conclusion, despite limited sample of patients, the harvested data provide an ample evidence that multimodal brain monitoring with continuous evaluation of cerebral autoregulation at bedside is a significant contributor to optimize management of TBI patients and has a potential to improve outcome after traumatic brain injury.

DIRECTION OF FUTURE RESEARCH

DIRECTION OF FUTURE RESEARCH

PATHOPHYSIOLOGY PERSPECTIVES

We have a lack of solid data on the cellular mechanisms of autoregulation impairment after traumatic brain injury and its relationship with different subtypes of lesions. Further investigation dedicated to target the pathophysiological processes of traumatic dysautoregulation and discovery of new molecular pathways may lead to the development of new therapeutic drugs to restore autoregulation and improve outcome.

Our knowledge of the complex mechanisms that interplay between normal brain and kidney function or after traumatic brain injury is still very incomplete. Inflammatory state, increased sympathetic nervous system activity and systemic and brain renin-angiotensin systems may be common pathways between acute brain injury and acute kidney injury. Understanding the underlying pathophysiological mechanisms between brain and kidney autoregulation and the practical implications of this relationship remains to be established with further studies.

CLINICAL PERSPECTIVES

Cerebral pressure-volume-flow-time relationship analysis at bedside is still very incipient and urges for new monitoring tools to help daily clinical practice.

Retrospective analysis of CPPopt-guided therapy showed improvement of outcome after diverse acute brain lesions. Our prospective pilot study, though with a small number of patients, also showed that management at averaged real CPP close to CPPopt seem to provide better outcome. Nevertheless, this concept has never been tested prospectively in a randomized controlled manner. It was recently announced that a protocol for a multicentre prospective feasibility study for autoregulation CPP-oriented management is being discussed.

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“Quando você quer alguma coisa, todo o Universo conspira para que você realize o seu desejo.”
“When you really want something all the universe conspires in helping you to achieve it.”
in “O Alquimista”, Paulo Coelho