**UNIVERSIDADE DE LISBOA**

**FACULDADE DE MEDICINA DE LISBOA**

# Multimodal neuromonitoring in children with severe traumatic brain injury

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**Orientadores**

Prof. Doutor Vitor Augusto Rocha de Oliveira

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Tese especialmente elaborada para obtenção do grau de

Doutor em Medicina, especialidade de Pediatria

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**2021**

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**na reunião de 20 de Outubro de 2020**

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# Preface

I started working in the paediatric intensive care unit of Hospital de Santa Maria in 2008. It was the realization of a dream that began during an intensive care internship in Liverpool two years before.

Hospital de Santa Maria had all the characteristics I was looking for. It had the largest paediatric intensive care unit in Portugal and it was a university-affiliated hospital. Soon after starting my job at the unit I also joined the Faculty of Medicine as an assistant teacher of paediatrics.

The paediatric intensive care unit is the neurotrauma centre in the south of Portugal and traumatic brain injury patients constitute an important part of our work. My interest in neuromonitoring came naturally and very soon I started learning how to perform transcranial Doppler ultrasonography at the Laboratory of Cerebral Ultrasound. This led to the first publication on transcranial Doppler in 2012 about our experience on its use in traumatic brain injury patients.

In 2013, I went to the 3rd Oporto Neurocritical Care Learning Course where I met Celeste Dias and Professor Marek Czosnyka and then the road to my PhD started. I wanted to take neuromonitoring a step further and learning what was being done in adult patients inspired me to perform research in paediatric patients and try to investigate if the same principles would also apply to children. One thing led to another and soon I was in a Brain Physics Laboratory in Addenbrooke's Hospital in Cambridge manufacturing a cable to connect the transcranial Doppler machine to my computer. I realized that I would have to learn much more than medicine if I wanted to do research in this area.

After ten years of research in the area of neuromonitoring I truly believe we have made important progress. The results of this research constitute the basis of this thesis, which have been published in peer reviewed renowned journals. My first original publication as first author on the role of transcranial Doppler

ultrasonography in paediatric emergency and critical care settings has been cited in relevant journals in the field. It was also cited in a recent multidisciplinary expert consensus statement about practice recommendations for transcranial Doppler ultrasonography in critically ill children at paediatric intensive care units.

It is very rewarding to see our work recognized by some of the greatest authorities in neurocritical care. But what truly makes every effort worth is to see how our work positively impacts in the lives of children and families that need our care.

# List of Abbreviations

A
ABP, arterial blood pressure
ABPd, diastolic arterial blood pressure
ABPs, systolic arterial blood pressure
ACA, anterior cerebral artery
ARI, autoregulation index
AUC, area under the curve

B
BP, blood pressure

C
Ca, compliance of the cerebral arterial bed
CaBV, cerebral arterial blood volume
CBF, cerebral blood flow
CBFx, cerebral blood flow index
CFF, continuous flow forward model
CI, confidence interval
CMRO2, cerebral metabolic rate of oxygen
CO2, carbon dioxide
COx, cerebral oximetry index
CPP, cerebral perfusion pressure
CPPopt, optimal cerebral perfusion pressure
CrCP, critical closing pressure
CSF, cerebrospinal fluid
CT, computed tomography
CVR, cerebrovascular resistance

E
ECG, electrocardiogram
ECMO, extracorporeal membrane oxygenation
EEG, electroencephalogram
EtCO2, end-tidal carbon dioxide concentration
EVD, external ventricular drainage

F
FFT, fast Fourier transformation
FV, cerebral blood flow velocity
FVd, diastolic cerebral blood flow velocity
FVm, mean cerebral blood flow velocity
FVs, systolic cerebral blood flow velocity

G
GCS, Glasgow coma scale

H
HbO2, oxyhaemoglobin
HHb, deoxygenated haemoglobin
HR, heart rate

I
ICA, internal carotid artery
ICH, intracranial hypertension

ICP, intracranial pressure
IQR, interquartile range

K KOSCHI, King's Outcome Scale for Childhood Head Injury

L LP, lumbar puncture
LDx, laser Doppler index

M MAP, mean arterial pressure
MCA, middle cerebral artery
MRI, magnetic resonance imaging
Mx, mean flow cerebral autoregulation index based on cerebral perfusion pressure
Mxa, mean flow cerebral autoregulation index based on arterial blood pressure

N NA, not available
nCPP, non-invasive cerebral perfusion pressure
nCPPs, spectral non-invasive cerebral perfusion pressure
nICP, non-invasive intracranial pressure
nICPBB, non-invasive intracranial pressure based on the black box method
nICPFVd, non-invasive intracranial pressure based on the diastolic cerebral blood flow velocity method
nICPCrCP, non-invasive intracranial pressure based on the critical closing pressure method
nICPPI, non-invasive intracranial pressure based on the pulsatility index method
NIRS, near-infrared spectroscopy
NPV, negative predictive value

O ONSD, optic nerve sheath diameter
OR, odds ratio
ORx, oxygen reactivity index

P PaCO2, partial pressure of carbon dioxide
PbtO2, partial pressure of oxygen in brain tissue
PCA, posterior cerebral artery
PE, prediction error
PECO2, pressure of expired carbon dioxide
PFF, pulsatile flow forward model
PI, pulsatility index
PICU, pediatric intensive care unit
PPV, positive predictive value
PRx, pressure reactivity index

R R, correlation coefficient

R2, coefficient of determination
RCSF, resistance to cerebrospinal fluid outflow
RI, transcranial Doppler resistance index
ROC, receiver operating characteristic
rSO2, regional cerebral oxygen saturation

S SAH, subarachnoid haemorrhage
SCA, state of cerebral autoregulation
SD, standard deviation
SDE, standard deviation of the error
Sx, systolic flow cerebral autoregulation index based on cerebral perfusion pressure

T TBI, traumatic brain injury
TCD, transcranial Doppler ultrasonography
THb total hemoglobin

## Summary

Traumatic brain injury (TBI) is a main cause of child morbidity and mortality worldwide. Survivors with severe neurological impairment represent an important burden to families and society.

Modern neurocritical care management focuses on minimizing secondary brain injury and the use of management strategies based on multimodal brain monitoring has a potential to improve patient outcome.

Cerebral autoregulation is an important mechanism allowing cerebral blood flow to stay constant despite fluctuations of cerebral perfusion pressure. It has been shown to be impaired in children with TBI and loss of autoregulation is associated with a poor outcome. There are several techniques that allow continuous calculation of autoregulation indices (and its surrogate - cerebrovascular reactivity) using intracranial pressure, blood flow velocity or cerebral oxygenation and its correlation to arterial blood pressure or cerebral perfusion pressure (CPP).

The aim of this thesis was to study the accuracy of different methods of neuromonitoring, ranging from non-invasive and invasive acquisition of signals involved in cerebral haemodynamics to the study of cerebral autoregulation in children with TBI. The secondary objective was to study the association of autoregulation impairment with clinical outcome.

In the introduction, traumatic brain injury in children and the theoretical principles of neuromonitoring are presented in detail with focus on the parameters used in the studies performed throughout the thesis. The cerebral autoregulation principles are also reviewed.

The main body of the thesis is divided in four sections:

In the first section, I review the role of neurovascular sonography in paediatric traumatic brain injury. Namely, the role of TCD in estimating intracranial pressure and cerebral perfusion pressure; evaluating cerebral autoregulation and continuous monitoring; detecting regional variations on cerebral haemodynamics and in the diagnosis of brain death.

In the second section, I document through several clinical cases the usefulness of TCD for bedside decisions in the paediatric emergency department and in the paediatric intensive care unit. Five patients with different types of acute brain injury are presented. TCD was useful in the identification of intracranial hypertension in traumatic brain injury, hydrocephalus and central nervous system infection; identification of decreased cerebral perfusion pressure in hypovolemic shock and the diagnosis of impending cerebral circulatory arrest in a child with meningococcal septicaemia. I discuss the importance of TCD in each scenario through a revision of relevant literature and with my own experience.

In the third section, I assess TCD as a non-invasive method to estimate cerebral perfusion pressure in children with severe traumatic brain injury. In order to accomplish this objective the feasibility of a novel non-invasive method of cerebral perfusion pressure estimation (nCPP) using a TCD-spectral accounting method in children with severe TBI was tested. There was a good correlation between invasive cerebral perfusion pressure and nCPP and nCPP monitoring with TCD appears to be a feasible method for cerebral perfusion pressure assessment in paediatric TBI. The novel spectral nCPP tested in this study has a decent correlation with invasive CPP and can predict low CPP with excellent accuracy at the 70-mmHg threshold.

In the fourth and final section of this thesis, I present the results of a prospective cohort study performed throughout the four years of the thesis development. All

children admitted to our paediatric intensive care unit with severe TBI were included to study three different methods of monitoring autoregulation: pressure-reactivity index (PRx), transcranial Doppler derived mean flow velocity index (Mx) and near-infrared spectroscopy derived cerebral oximetry index (COx). This is the first study to compare these three different methods of monitoring cerebral autoregulation in a group of children. PRx seems to be the most robust index to access cerebrovascular reactivity in children with TBI. It allows calculation of optimal CPP for the individual patient and has promising prognostic value.

The main conclusions of this thesis are:

- Transcranial Doppler is a useful technique to assist the clinical decisions at the bedside in children with acute brain injury;
- Multimodal neuromonitoring is feasible in paediatric patients with TBI;
- PRx seems to be the most sensitive index for cerebral autoregulation monitoring in children and has prognostic value;
- Non-invasive continuous neuromonitoring is promising but it is still not accurate enough to replace invasive monitoring.

Keywords

Paediatric traumatic brain injury, transcranial Doppler, cerebral autoregulation, multimodal neuromonitoring.

## Resumo

O traumatismo crânio-encefálico (TCE) é uma das principais causas de morbilidade e mortalidade infantil em todo o mundo. Os sobreviventes com sequelas neurológicas graves representam um peso importante para as famílias e para a sociedade.

A atuação dos cuidados neurocríticos modernos visa minimizar a lesão cerebral secundária, pelo que o uso de estratégias de tratamento baseadas na monitorização cerebral multimodal tem potencial para melhorar o prognóstico dos doentes.

A autorregulação cerebral é um mecanismo importante que assegura um fluxo sanguíneo cerebral constante, apesar das flutuações da pressão de perfusão cerebral. Foi demonstrado que pode estar alterado em crianças com TCE ligeiro, moderado ou grave e a perda da autorregulação está associada a um mau prognóstico. Existem várias técnicas que permitem o cálculo contínuo de índices de autorregulação (e seu substituto - reatividade cerebrovascular) usando a pressão intracraniana, a velocidade do fluxo sanguíneo ou oxigenação cerebral e sua correlação com a pressão arterial ou pressão de perfusão cerebral (PPC).

O objetivo desta tese foi estudar a precisão de diferentes métodos de monitorização neurológica; desde a aquisição não invasiva e invasiva de sinais envolvidos na hemodinâmica cerebral até estudos de autorregulação cerebral em crianças com TCE. O objetivo secundário foi correlacionar a perda de autorregulação com o prognóstico.

Na introdução, o traumatismo crânio-encefálico em idade pediátrica e os princípios teóricos da monitorização cerebral são apresentados detalhadamente com foco nos parâmetros utilizados nos estudos realizados ao longo da tese. Os princípios da autorregulação cerebral são também revistos à luz do conhecimento atual.

A estrutura da tese está organizada em quatro secções:

Na primeira secção, revejo o papel da ultrassonografia neurovascular na lesão cerebral traumática pediátrica. Nomeadamente, o papel do DTC na estimativa da pressão intracraniana e da pressão de perfusão cerebral; a sua utilização na avaliação da autorregulação cerebral e monitorização contínua; a capacidade do DTC para detectar variações regionais na hemodinâmica cerebral e a sua importância no diagnóstico de morte cerebral. Nesta secção faz-se uma revisão teórica sobre estes temas utilizando também alguns exemplos da nossa prática clínica. Fica bem patente a versatilidade da técnica do DTC nas suas várias vertentes, o que aliado ao facto de ser uma técnica não invasiva e facilmente disponível à cabeceira do doente a torna particularmente atraente. No entanto, chamo também atenção para algumas limitações da técnica especialmente na monitorização contínua do sinal de Doppler. A gravação de longos períodos de monitorização é extremamente difícil e por vezes impossível. Mesmo com a utilização de suportes para a sonda do DTC é difícil garantir a qualidade do sinal ao longo do tempo. Estão a ser desenvolvidas sondas robotizadas que tentam ultrapassar esta dificuldade, mas os resultados ainda não são fiáveis. Em conclusão, o DTC é útil para avaliar, de forma não invasiva, a existência de hipertensão intracraniana ou diminuição da pressão de perfusão cerebral, para avaliar vários territórios vasculares em patologias regionais e como exame complementar de diagnóstico em casos de morte cerebral. Para monitorização contínua teremos de aguardar mais um pouco pela evolução da tecnologia.

Na segunda secção, documento através da discussão de vários casos clínicos a utilidade do DTC na tomada de decisão no serviço de urgência e na unidade de cuidados intensivos pediátricos. São apresentados cinco doentes com diferentes tipos de lesão cerebral aguda. O DTC mostrou-se útil na identificação de hipertensão intracraniana em doentes com lesão cerebral traumática, hidrocefalia e infeção do sistema nervoso central. Foi também útil na identificação de diminuição da pressão de perfusão cerebral no choque hipovolémico e no diagnóstico de paragem circulatória cerebral iminente em criança com sepsis

meningocócica. Em todos os casos analisados o resultado do DTC foi determinante da atuação clínica, influenciando claramente o tratamento instituído e contribuindo para um melhor prognóstico dos doentes. Discuto a importância do DTC em cada um destes exemplos paradigmáticos através de uma revisão da literatura e da minha própria experiência.

Na terceira secção, avalio o DTC como um método não invasivo para estimar a pressão de perfusão cerebral (PPC) em crianças com TCE grave. Para esse objetivo foi testada a viabilidade de um novo método não invasivo para estimativa de pressão de perfusão cerebral (nPPC) baseado no DTC. Este método utiliza o índice de pulsatilidade espectral, a pressão arterial, a resistência cerebrovascular, a *compliance* das artérias e arteríolas cerebrais e a frequência cardíaca para calcular a nPPC. Foi feita a análise retrospectiva de 69 gravações de DTC de 19 crianças (idade média de 15 anos, variação de 3-16 anos). Verificou-se uma boa correlação entre a PPC e a nPPC (coeficiente de correlação de Spearman: R = 0,67 (p <0,0001), e uma boa correlação média no domínio do tempo (R = 0,55 ± 0,42). A capacidade da nPPC de predizer valores de PPC abaixo de 70 mmHg foi excelente, conforme demonstrado por uma área sob a curva de 0,908 (IC 95% = 0,83-0,98) usando uma análise da curva característica de operação do receptor. A análise de Bland-Altman revelou que a nPPC sobrestimou a PPC em 19,61 mmHg com um amplo IC de 95% de ± 40,4 mmHg. Concluímos que houve uma boa correlação entre a PPC e a nPPC. A monitorização de nPPC com DTC parece ser um método viável para avaliação da pressão de perfusão cerebral no TCE pediátrico. O novo nPPC espectral testado tem uma correlação satisfatória com a PPC invasiva e pode prever PPC baixa com excelente precisão para o limiar de 70 mmHg.

Na quarta e última secção desta tese, apresento os resultados de um estudo de coorte prospectivo realizado ao longo dos quatro anos de desenvolvimento da tese. Todas as crianças internadas na unidade de cuidados intensivos pediátricos do Centro Hospitalar Lisboa Norte com TCE grave foram incluídas para estudar três métodos diferentes de monitorização da autorregulação cerebral: índice de reatividade à pressão (PRx), índice de velocidade de fluxo médio (Mx), derivado

do DTC e índice de oximetria cerebral (COx), derivado de espectroscopia próximo do infravermelho. Este é o primeiro estudo a comparar esses três métodos diferentes de monitorização da autorregulação cerebral em crianças. Foram incluídos no estudo doze doentes, com idades entre 5 meses e 17 anos. Uma análise de regressão empírica da dependência do PRx na pressão de perfusão cerebral (PPC) exibiu a distribuição clássica em forma de U, com valores baixos de PRx (<0,3) refletindo uma autorregulação intacta, para valores de PPC de 50-100 mmHg. A PPC ideal foi de 75-80 mmHg tanto para o PRx como para o COx. Os coeficientes de correlação entre os três índices foram: PRx vs Mx, r = 0,56; P <0,0001; PRx vs COx, r = 0,16; p <0,0001; COx vs Mx, r = 0,15; p = 0,022. O PRx médio com um valor de corte de 0,3 previu corretamente o prognóstico a longo prazo em todos os doentes (p = 0,015). Concluímos que o PRx é o índice mais robusto para avaliar a reatividade cerebrovascular em crianças com TCE. Ele permite o cálculo da PPC ideal para cada doente e tem um valor prognóstico promissor.

As principais conclusões desta tese são:

- O Doppler transcraniano é uma técnica útil para auxiliar nas decisões clínicas à cabeceira do doente com lesão cerebral aguda;
- A monitorização neurológica multimodal é viável em pacientes pediátricos com TCE;
- O PRx parece ser o melhor índice para avaliar a autoregulação cerebral em crianças e tem valor prognóstico;
- A monitorização neurológica contínua não invasiva é promissora, mas ainda não suficientemente precisa para substituir a monitorização neurológica invasiva.

Palavras-chave

Traumatismo crânio-encefálico pediátrico, Doppler transcraniano, autorregulação cerebral, monitorização neurológica multimodal.

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Our family is an intrinsic part of who we are. And I am very fortunate to have a close and united family. I thank my parents for their unconditional love, my

brothers for their true friendship and constructive arguments and Teresa, Duarte, João, Pedro and Tiago for putting up with me and for giving a meaning to my life.

A friend once told me that true friends are the ones that stay beside you in good times. This thesis is also dedicated to my dearest friends: the ones that rejoice with my accomplishments.

# List of Publications

## Publications as first author

1. Abecasis, F., Oliveira, V., Robba, C. & Czosnyka, M. Transcranial Doppler in paediatric emergency and intensive care unit: a case series and literature review. *Child's Nerv Syst* 34, 1465–1470 (2018).

2. Abecasis, F., Cardim, D., Czosnyka, M., Robba, C. & Agrawal, S. Transcranial Doppler as a non-invasive method to estimate cerebral perfusion pressure in children with severe traumatic brain injury. *Child's Nerv Syst* 36, 125–131 (2020).

3. Abecasis, F. "Traumatic Brain Injury - Pediatric" accepted for publication *in* Neurovascular Sonography, currently in print. Editor Springer Nature.

4. Abecasis F., Dias C., Zakrzewska A., Oliveira V., Czosnyka M. Monitoring Cerebrovascular Reactivity In Paediatric Traumatic Brain Injury: Comparison Of Three Methods. *Pediatr Res*. Under review.

## Publications as co-author

1. Vieira, F., Cardoso, K., Abecasis, F. et al. Doppler transcraniano na monitorização do traumatismo craniencefálico grave em pediatria. *Acta Pediátrica Port* 43, 239–245 (2012).

2. Robba, C., Cardim, D., Czosnyka, M., Abecasis, F. et al. Ultrasound non-invasive intracranial pressure assessment in paediatric neurocritical care: a pilot study. *Child's Nerv Syst* 36(1):117-124 (2020).

## Distinctions

The studies and investigations developed as part of this thesis were acknowledged with the following awards and received a scholarship by the non-profit association, ***Associação para as crianças de Santa Maria***:

1. **Jaime Salazar de Sousa award** for the following papers:

    a. Abecasis, F., Oliveira, V., Robba, C. & Czosnyka, M. Transcranial Doppler in paediatric emergency and intensive care unit: a case series and literature review. *Child's Nerv. Syst*. 34, 1465–1470 (2018). (First prize *ex aequo*)

    b. Abecasis, F., Cardim, D., Czosnyka, M., Robba, C. & Agrawal, S. Transcranial Doppler as a non-invasive method to estimate cerebral perfusion pressure in children with severe traumatic brain injury. *Child's Nerv. Syst*. 36, 125–131 (2020). (First prize)

2. **Scholarship for clinical investigation** for the following project:

    a. Doppler transcraniano e medição da bainha do nervo óptico no traumatismo crânio-encefálico moderado a grave em idade Pediátrica (2013)

# Part 1

## Introduction

# Part 1: Introduction

## 1.1. An overview of paediatric traumatic brain injury

Traumatic brain injury (TBI) is the leading cause of trauma-related death and permanent disability in children. Worldwide, it affects more than 3 million children annually (1) and in the United States alone, TBI contributes to the death of more than 1000 children every year (2). In Europe, the overall incidence rate of TBI is estimated to be 262 per 100,000 population, but there is a great heterogeneity in data collection and reporting. The main mechanism of injury is shifting from road traffic accidents to falls, which is mostly explained by the aging of the population. In younger patients and in patients with moderate to severe TBI, road traffic accidents remain the major cause of TBI in most countries (3).

In two recent papers, specific data about TBI in Portugal was analyzed revealing a dramatic decrease in incidence in the last 20 years, particularly in young adults and children (4,5). In the age group < 20 years, mortality due to TBI decreased from 218 cases in the year of 1997 to 32 cases in the year of 2014 (5).

TBI results in two different types of injury. Primary injuries are the direct result of the mechanical forces that are transmitted to the brain and skull at the time of the impact. They can be further divided in diffuse lesions caused by acceleration-deceleration or rotational forces and focal lesions caused by direct contact. Secondary injuries are a result of a complex pathophysiologic cascade of events that reduces cerebral perfusion, oxygen delivery, metabolite delivery and clearance of metabolic toxins of neural tissue that survived the primary insult. These events cause brain oedema, due to vasogenic and cytotoxic oedema, that can lead to intracranial hypertension, further focal ischemic injury, cerebral herniation syndromes and death (6–8).

Modern neurocritical care focuses on the prevention and treatment of secondary injuries. The management strategies to achieve these goals are (9):

- Multimodal brain monitoring
  - Standard neuromonitoring
    - Monitoring of intracranial pressure (ICP)
    - Monitoring of cerebral perfusion pressure (CPP)
    - Neuroimaging
  - Advanced neuromonitoring
    - Brain tissue oxygenation and cerebral oximetry
    - Microdialysis
    - Electrophyiologic assessments
    - Evaluation of cerebral autoregulation
- Monitoring thresholds
  - Raised ICP: >20 mmHg
  - Low CPP: <40-50 mmHg
  - PbtO2: >20 mmHg
  - Microdialysis L/P ratio: >25
  - Microdialysis glucose: >0.7 mmol/L
- Management
  - Hyperosmolar therapy
    - Hypertonic saline (3%) is recommended in patients with intracranial hypertension.
  - Analgesics, sedatives and neuromuscular blocking agents
    - Use sedation and analgesia to temporarily decrease cerebral metabolic rate of oxygen (CMRO2) coupled with the decrease of cerebral blood flow (CBF).
    - Avoid fentanyl or midazolam bolus for ICP crisis.
  - Cerebrospinal fluid (CSF) drainage
    - CSF drainage through an external ventricular drainage is suggested to manage increased ICP.
  - Seizure prophylaxis

- Prophylactic treatment is suggested to reduce the occurrence of early post-traumatic seizures.

- Ventilation therapies
  - If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia is recommended.
  - Prophylactic severe hyperventilation to a $PaCO_2$ less than 30 mmHg in the initial 48 hours after injury is not recommended.
- Temperature control / Hypothermia
  - Moderate (32–33°C) hypothermia is recommended for ICP control.
  - Prophylactic moderate (32–33°C) hypothermia is not recommended over normothermia to improve overall outcomes.
- Barbiturates
  - High-dose barbiturate therapy is suggested in hemodynamically stable patients with refractory intracranial hypertension despite maximal medical and surgical management.
- Decompressive craniectomy
  - Decompressive craniectomy is suggested to treat neurologic deterioration, herniation, or intracranial hypertension refractory to medical management.
- Nutrition
  - Initiation of early enteral nutritional support (within 72 hr from injury) is suggested to decrease mortality and improve outcomes.
- Corticosteroids
  - The use of corticosteroids is not recommended to improve outcome or reduce ICP.

Throughout this thesis I will focus on neuromonitoring for paediatric TBI and although some aspects of treatment strategies are also mentioned they are outside the scope of the research performed.

## 1.2. An overview of neuromonitoring

I investigated the role of several monitoring tools in paediatric TBI. I have also compared different methods of studying cerebral autoregulation and listed the advantages and disadvantages of each method. In this section I will review the theoretical basis for the monitoring parameters studied in this thesis.

### 1.2.1. Intracranial pressure

The Scottish anatomist Alexander Monro first described the concept of ICP in 1783, and his findings were later developed by one of his pupils, the surgeon George Kellie, to what would become known as the Monro-Kellie doctrine. Harvey Cushing, in 1926, formulated the classic explanation of the doctrine: with an intact skull, the volume of the brain, blood, and CSF are constant; an increase in one component will cause a decrease in one or both of the other elements (10).

There are several ways to measure and monitor ICP. The gold standard is still the method described by Nils Lundberg in 1960 and five years later applied continuously for the first time to TBI patients by Lundberg himself. This method consists on a ventricular cannula connected to a transducer that continuously measures the ventricular-fluid pressure. At that time, a standard ink-writing potentiometer recorder amplified the impulses recovered from the transducer (11). This method is still used nowadays and has the unique advantage over all the other methods of allowing treatment of intracranial hypertension by drainage of CSF. Modern ventricular, subdural, or intraparenchymal microtransducers reduce the infection rate and the risk of haemorrhage, but most of them have the potential

disadvantage of not being possible to re-zero the transducers after insertion (12). Non-invasive ICP estimation has been extensively investigated in the last two decades. The most promising techniques are based on transcranial Doppler (TCD) (13) and optic nerve sheath diameter ultrasonography (14), but are still not an alternative for invasive ICP monitoring and are not even considered in the most recent guidelines of the Brain Trauma Foundation (9).

Since the seminal works of Lundberg, monitoring ICP to avoid intracranial hypertension has been one of the main targets in the treatment of patients with TBI. Although there are no randomised controlled trials in children to prove that ICP monitoring improves outcome, there are indirect data that suggest benefit. A marked increase in ICP monitoring in paediatric intensive care units (PICU) and a decrease in mortality from TBI was observed during the last decade of the XX century (15,16). Recently, two large retrospective studies showed a benefit in ICP monitoring in children with TBI (17,18), while another one did not find a difference in functional survival or mortality between monitored and non-monitored children (19). Indirect evidence that ICP monitoring can improve patient care is derived from studies that suggest that improved clinical outcomes are associated with successful control of intracranial hypertension (20,21). The rationale for that is that we cannot control ICP adequately if we do not measure it.

It is difficult to determine the optimal threshold for treatment of raised ICP. Treatment of ICP targeting a threshold of less than 20 mmHg has been suggested for children with TBI and has been used for decades in most centres. This threshold was based largely on adult studies. Several studies in paediatric patients have tried to define the ICP threshold for treatment that would produce the best outcome. Most studies have the bias of using 20 mmHg as the therapeutic target for ICP (22,23). One study included 45 children with TBI and had good results using an ICP target of 15 mmHg for treatment (24). It is generally accepted that an ICP above 20 mmHg sustained for more than 5 minutes should be aggressively treated.

When ICP is monitored continuously it is possible to define different patterns for the mean ICP (25):

- Low and stable ICP (below 20 mmHg)
- High and stable ICP (above 20 mmHg)
- Vasogenic waves - ‘‘B’’ waves and plateau waves
- ICP waves related to changes in arterial pressure and hyperaemic events
- Refractory intracranial hypertension

It is important to mention that ICP is more than a number. In the time domain the ICP waveform presents three peaks P1, P2 and P3 that give information about brain haemodynamics and compliance. In the frequency domain the ICP waveform also has three components corresponding to pulse waveform, respiratory waveform and slow waves. These waveforms carry information that can help in the understanding of cerebrovascular dynamics (25).

ICP monitoring has been used in clinical practice for sixty years and new properties are still being discovered. It is the most used parameter in neuromonitoring.

### 1.2.2. Cerebral perfusion pressure

Cerebral perfusion pressure (CPP) represents the pressure gradient across the cerebral vascular bed driving cerebral blood flow (CBF) and is used as a therapeutic target for brain-injured patients in many intensive care units (26). It is calculated as the difference between mean arterial pressure (MAP) and ICP (CPP = MAP – ICP).

There is considerable controversy in the definition of the CPP threshold for treatment, both in adult and paediatric patients. In adults the lower threshold for CPP depends on the source, but the latest guidelines of the Brain Trauma Foundation recommend a target CPP value between 60 and 70 mmHg to improve

survival and favourable outcomes (27). In children, the only class 2 study on this topic was recently conducted by Allen and colleagues and suggested a goal of CPP above age specific thresholds: above 40 mmHg in children under 6 years-old and above 50 mmHg in children from 6 to 17 years-old (28). Several class 3 studies support these recommendations, although the nature and design of the studies have important limitations (22,29–37). On the contrary, there are also studies that have failed to show a relationship between different CPP thresholds and outcome (23).

The rationale of CPP augmentation is to increase CBF in brain regions that have critically low blood flow. However, an increase in CPP will only lead to an increase in CBF when autoregulation has failed or CPP is below the lower limit of autoregulation (38). A careful management of CPP is extremely important because there is also some evidence that high CPP may actually be deleterious (39).

It is very important to acknowledge that there are no randomized trials of TBI management based in different CPP thresholds and this prevents a conclusion about causality to be made. It is obvious that non-survivors will always have lower CPPs than survivors, considering that death in TBI is due to refractory intracranial hypertension and consequent refractory low CPP. The question is if CPP-oriented treatment protocols are able to improve outcome, yet there is no direct evidence to answer this question.

### 1.2.3. Transcranial Doppler ultrasonography

The Austrian physicist Christian Andreas Doppler first proposed the effect that would be named after him in 1842 in his treatise "*Über das farbige Licht der Doppelsterne und einiger anderer Gestirne des Himmels*" (On the coloured light of the double stars and some other stars of the heavens). Buys Ballot tested the hypothesis for sound waves in 1845. He confirmed that the sound's pitch was higher than the emitted frequency when the sound source approached him, and lower than the emitted frequency when the sound source receded from him (40).

This is the principle used in Doppler equipment. In daily life we can easily testify this phenomenon when an ambulance approaches. The siren will start out higher than its stationary pitch, slide down as it passes, and continue lower than its stationary pitch as it moves away from us.

Transcranial Doppler ultrasonography (TCD) is a non-invasive method of determining the blood flow velocities in the basal cerebral arteries (CBFV). Rune Aaslid was the first to describe this technique in 1982, after experiments in fifty healthy adults. His method is still used nowadays, although the indications for TCD have clearly surpassed the ones he initially suggested: vasospasm after subarachnoid haemorrhage and arterial occlusive disease (41).

The main indications in children are: monitoring patients with sickle cell anaemia for the risk of stroke, monitoring cerebral haemodynamics in patients in intensive care units following TBI or other neurovascular events, as an ancillary test in the diagnosis of brain death and for evaluation of the cerebral vasculature in stroke (42).

Some authors have used it as an indirect and non-invasive method to estimate intracranial pressure (ICP). TCD derived pulsatility index (PI) has been shown to have a decent correlation with cerebral perfusion pressure (CPP) and ICP (43–46), but other reports state that these points are still controversial (47,48). However, current guidelines for treatment of children with TBI do not recommend its use in clinical practice because of the lack of evidence. The Brain Trauma Foundation 2019 guidelines for TBI in children do not even mention TCD, except for a brief citation of the auto-regulatory index that uses the ratio of CPP to flow velocity in the middle cerebral artery to calculate cerebrovascular resistance (9).

Interestingly, a recent survey of 27 centres that provide paediatric neurocritical care services revealed that 93% use TCD. Most commonly, TCD was used in the evaluation and management of patients with intracranial/subarachnoid haemorrhage, arterial ischemic stroke and traumatic brain injury (49). Motivated

by the lack of guidelines and widespread use of TCD around the world, very recently a panel of multidisciplinary experts issued practice recommendations for the use of TCD in critically ill children (50). Although this consensus statement represents an important step in the establishment of TCD as a useful technique in PICU, it lacks important aspects of the TCD evaluation as normative values for the pulsatility index or vasospasm.

A more recent and expanding use of TCD in neurocritical care is evaluation and monitoring of cerebral autoregulation. The first experiments on the use of TCD to access autoregulation date back to the last decade of the XX century, with Aaslid (51) and Diehl (52) setting the principles that led Czosnyka et al. to describe how to use TCD to monitor autoregulation in TBI patients for the first time in 1996. Two indices of autoregulation were described: mean index (Mx) defined as the correlation coefficient between mean flow velocity and CPP and systolic index (Sx) as the correlation coefficient between systolic flow velocity and CPP. They further demonstrated that positive values of Mx and Sx signify severely disturbed cerebrovascular reactivity, which is predictive of a poor outcome (53).

After more than 30 years, one of the major challenges in using TCD signals to evaluate autoregulation is the requirement to record flow velocities for a long period of time. This can be accomplished with probe holders, but the signal can easily be lost with positioning of the patient or spontaneous movement. Children represent an additional challenge because of different head sizes and some holders are difficult to use in small children. More recently, new devices using robotic probes allow for continuous monitoring over extended time periods with good results for at least 4 hours of monitoring (54).

### 1.2.4. Cerebral oximetry

Near-infrared spectroscopy (NIRS) is a method for non-invasive monitoring of cerebral oximetry. The unique ability of light in the near-infrared range (700-1000 nm) to detect the oxygenation state of living tissue was first realized by Jobsis in

1977 (55). Since then, NIRS has evolved as a technique for in vivo and continuous monitoring of cerebral and tissue oximetry.

The skin, scalp, and skull are relatively transparent to near-infrared light, allowing transmission of photons into the brain. These photons undergo attenuation as a result of scattering and absorption by intravascular hemoglobin and intracellular cytochrome aa3. In a given tissue, changes in attenuation can be attributed solely to changes in the concentration of these chromophores (56). NIRS measures changes in concentration of oxyhemoglobin (HbO2), deoxygenated hemoglobin (HHb), and from their sum, changes of total hemoglobin (THb). This way it can also measure the ratio of HbO2/THb, and this is reported as "regional oxygen saturation" (rSO2).

For clarification, it is important to note that unlike pulse oximetry that only measures the pulsatile component of blood (arterial), NIRS provides a global assessment of haemoglobin oxygenation in all vascular compartments (arterial, venous and capillary).

One major limitation of NIRS devices is the inability to provide accurate absolute cerebral oxygenation values. Several studies have compared multiple NIRS devices with disappointing results (57–61). Furthermore the absolute threshold of saturation that results in tissue damage is difficult to be determined (60). In spite of this limitation there is evidence that the correlation between different sensors and devices is good (61). This means that the absolute value should not guide clinical decisions, but the trends and variations overtime can aid the clinicians in monitoring cerebral oxygen saturation and indirectly the cerebral perfusion, allowing continuous information on oxygen supply-versus-demand balance.

Cerebral oximetry with NIRS has been used clinically in many different settings such as cardiac surgery in both adults and children (62–65), neonatology (66), neurology (67), neurosurgery (68), trauma (69) and vascular surgery (70).

Besides measurements of cerebral oxygenation, NIRS has also been used to evaluate and monitor cerebral autoregulation. Brady et al. described this concept for the first time when they presented a novel index of autoregulatory vasoreactivity, the cerebral oximetry index (COx), which is derived from a time-domain analysis that correlates changes in ABP to the output of a NIRS-based monitor of cerebral tissue oxyhaemoglobin saturation (71).

### 1.2.5. Multimodal neuromonitoring and cerebral autoregulation

I have discussed so far individual signals (ABP, ICP, CBFV and rSO2) acquired by different apparatus: arterial and intracranial transducers, TCD and NIRS devices. However a single parameter may not be sufficient to fully understand the complex pathophysiological changes that occur after head injury. Multimodal neuromonitoring refers to the simultaneous use of multiple monitoring devices and the challenge is to correctly interpret and integrate data from these different devices. Modern neurocritical care is rapidly evolving and new technologies will continue to be developed, supported by software programmes that process and integrate the signals from these multiple sources and will aid the clinician in the interpretation of the information provided (72).

One of the advantages of being able to simultaneously record multiple signals is the ability to understand how different signals interact. This is the basis for studying cerebral autoregulation.

Cerebral autoregulation has been known for more than 60 years and refers to the intrinsic mechanism of cerebral arteries reaction that allows cerebral blood flow (CBF) to remain constant despite changes in cerebral perfusion pressure (CPP) within a certain range (73). CBF depends on two factors: the CPP and the cerebrovascular resistance (CVR), so that CBF = CPP / CVR. The CVR changes with constriction and dilation of arterioles in the brain in response to changes in blood pressure. In the healthy brain, autoregulation is effective at a CPP interval from approximately 50 to around 150 mmHg. Outside this range, CBF changes passively

with blood pressure. After TBI, impaired autoregulation can render the brain susceptible to inadequate (ischaemic) or excessive (hyperaemic) CBF (42).

There are several methodologies to measure cerebral autoregulation and they include static and dynamic assessments. There is a good correlation between measures of static and dynamic autoregulation. For all methods the principle is the same: to determine how changes in ABP (or CPP) affect CBF. If CBF remains constant despite changes in ABP it means autoregulation is intact. To be able to determine the state of autoregulation there are some essential requirements:

- A continuous arterial blood pressure monitoring (invasive or non-invasive)
- Direct evaluation of CBF or using its surrogates:
    - Non-invasive (TCD, cerebral oximetry with NIRS)
    - Invasive (ICP, partial pressure of oxygen in brain tissue (PbtO2), Laser Doppler Flow, thermal-diffusion CBF)

Static autoregulation is assessed by analysing changes in CBF in response to an ABP challenge and reflects a steady-state response. For example, a simple test to evaluate autoregulation would be to increase ABP by 10 mmHg with vasopressors while monitoring ICP. After 10-20 min if ICP remains the same or decreases it means intact autoregulation; if ICP increases it means impaired autoregulation (74).

Dynamic autoregulation assessment does not require a challenge, because it analyses changes in CBF in response to spontaneous CPP fluctuations, by using computational techniques. It requires software that is able to record the signals continuously and use a mathematical model to quantify the relationship between ABP and CBF or its surrogates. Depending on the CBF surrogate different indices can be defined and calculated.

Most of these indices use mathematical functions of correlation in the time domain between ABP or CPP and the CBF surrogate. Empirical modelling has also been performed by means of frequency-domain analysis through calculation of the coherence, transfer function, and phase-frequency response between CBFV and ABP (75). More recently, the use of wavelet transforms can give an assessment of autoregulation in both the time and frequency domains simultaneously (76). Frequency domain analysis and wavelet transforms are concepts less intuitive for the clinician when compared to correlations in time domain and a wave physics background is required to fully understand these concepts.

The most common indices of dynamic autoregulation are summarized in the following table:

| **Technique** | **CBF or surrogate** | **Autoregulation index** |
|---|---|---|
| ICP monitor | ICP | PRx- Pressure reactivity index (77) |
| TCD | CBFV | Mx - Mean Index<br>Sx - Systolic Index (53) |
| NIRS | rSO2 | Cox - Cerebral oximetry index (71) |
| Brain tissue oxygenation | PbtO2 | Oxygen reactivity index (ORx) (78) |
| Laser Doppler flowmetry | Regional CBF | LDx - Laser Doppler index (79) |
| Thermal-diffusion flowmetry | Regional CBF | CBFx - Cerebral blood flow index (80) |

The most studied index of autoregulation is the PRx. It is clearly established from studies in adult patients with TBI that positive PRx entails impaired cerebrovascular reactivity to pressure and is a significant and independent predictor of mortality (81–84). In paediatric patients, data are less robust, but smaller cohorts in children with TBI seem to support the concept that deranged autoregulation is associated with worse outcomes (85–88).

Continuous recording of PRx allowed for the determination of the CPP that was associated with the lowest PRx, and by inference the best auto-regulatory status, of a determined patient at a determined time period. The concept of optimal CPP was introduced in 2002 in Cambridge Brain Physics Laboratory and described by Steiner et al. (89).

When investigators put these two facts together - impaired PRx is associated with mortality and it is possible to determine the CPP that is associated with the best PRx in a given patient – they came to the theoretical hypothesis that if CPP is manipulated to remain the nearest to the optimal CPP, patients could have a better outcome. This optimal CPP guided management is currently under investigation and preliminary data are promising, but unfortunately ongoing studies do not include paediatric enrolment (90).

In conclusion, cerebral autoregulation informed by multimodal neuromonitoring is an expanding field of knowledge that has proved to have prognostic implications. Hopefully it will allow a tailored management strategy directed at restoring autoregulation to improve outcome.

## 1.3. Aims and hypotheses

### Aims

The aim of this thesis is to study the accuracy of different methods of neuromonitoring, ranging from non-invasive and invasive acquisition of signals involved in cerebral haemodynamics to the study of cerebral autoregulation in children with TBI. The secondary objective is to study the association of autoregulation impairment with clinical outcome.

## Hypotheses

In order to achieve these aims, several hypotheses with increased complexity were formulated and subsequently tested.

### Hypothesis I: Transcranial Doppler is useful in paediatric emergency and critical care settings

This hypothesis was tested through the critical evaluation of several clinical scenarios where TCD was performed in children with acute brain injury, admitted to the paediatric emergency department or the paediatric intensive care unit.

### Hypothesis II: Transcranial Doppler can estimate cerebral perfusion pressure in children with TBI

In many clinical conditions, the assessment of intracranial pressure and cerebral haemodynamics using invasive methods cannot be performed. This part of the thesis focuses on testing a novel non-invasive method for CPP estimation based on cerebral blood flow velocities acquired by TCD in children with severe TBI.

### Hypothesis III: Invasive and non-invasive indices of cerebral autoregulation are feasible and accurate in children with TBI and have prognostic value

To test this hypothesis we performed a prospective cohort study of all children admitted to our pediatric intensive care unit with severe TBI over a four-year period. The primary endpoint was to perform an exploratory study on the measurement properties of three different methods of monitoring cerebrovascular reactivity in children with TBI: pressure-reactivity index (PRx), transcranial Doppler derived mean index (Mx), near-infrared spectroscopy derived cerebral oximetry index (COx). The

secondary endpoint was correlation of impaired autoregulation, as determined by each of the indices studied, with outcome.

# Part 2

# Neurovascular Sonography in Paediatric TBI

# Part 2: Neurovascular Sonography in Paediatric TBI

Adapted from the original book chapter

"Traumatic Brain Injury - Paediatric" accepted for publication in the book Neurovascular Sonography, *in print*. Editor Springer Nature.

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## 2.1. Abstract

Transcranial Doppler ultrasound (TCD) has been used in paediatric traumatic brain injury for more than twenty years. Although there is solid evidence of its utility, many centres don't use it in neurocritical care settings. In this chapter, the role of TCD in paediatric traumatic brain injury will be reviewed. Namely, the role of TCD in estimating intracranial pressure and cerebral perfusion pressure; evaluating cerebral autoregulation and continuous monitoring; detecting regional variations on cerebral haemodynamics and in the diagnosis of brain death. A critical literature review and the author's own experience will hopefully help the reader in a better understanding of this powerful instrument of non-invasive neuromonitoring.

## 2.2. Introduction

Traumatic brain injury (TBI) is the leading cause of trauma-related death and permanent disability in children. Worldwide, it affects more than 3 million children annually (1) and in the United States alone, TBI contributes to the death of more than 1000 children every year (2).

When a child is admitted to the hospital after a moderate or severe TBI, management is targeted at avoiding secondary damage to the injured brain. In order to achieve this goal, maintaining an adequate cerebral blood flow (CBF) is crucial. Guidelines have traditionally used intracranial pressure (ICP) monitoring and treatment of increased ICP as the main objective to improve outcome following TBI. In children, adequate randomized controlled studies to evaluate the role of ICP monitoring and treatment have not been performed and the strength of recommendation of the latest guidelines on ICP monitoring and ICP treatment thresholds is weak (Level III) (9).

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial blood pressure (ABP) and mean ICP, and it is the pressure gradient driving cerebral blood flow. In normal conditions, CBF is autoregulated to maintain an adequate oxygen and glucose delivery to the brain across physiological range of CPP. After TBI, cerebral autoregulation might be impaired and decreases in CPP could lead to cerebral ischemia. Thresholds for adequate CPP in children with TBI have recently been published suggesting that CPP targets should be age-specific: above 40 mmHg in children under 6 years-old and above 50 mmHg in children from 6 to 17 years-old. (28). If CPP is the driving pressure of CBF, it is logical that treatment protocols should focus on CPP, rather then on ICP. CPP by definition can be manipulated by changing ICP or ABP.

Traditionally, an ICP bolt and an arterial line are used to monitor ICP and CPP invasively. In children, invasive ICP-CPP monitoring is reserved for patients in whom the severity of the clinical conditions demand ICP-CPP guided treatment.

Otherwise, the risks associated with invasive neuromonitoring, such as bleeding and infection, may not represent a beneficial intervention. In these cases, non-invasive methods, like transcranial Doppler ultrasonography (TCD), for assessment of these parameters could offer an alternative for treatment or a screening tool to determine the need for invasive monitoring.

## 2.3. Role of transcranial Doppler ultrasonography on Paediatric TBI

### Non-invasive estimate of ICP

One of the most studied roles of TCD in TBI is the ability to estimate or predict ICP non-invasively.

There are two indices commonly used to estimate ICP with TCD:

- Resistance index (Pourcelot) (91):
    - (peak systolic velocity - end diastolic velocity) /peak systolic velocity
- Pulsatility index (Gosling) (92):
    - (peak systolic velocity - end diastolic velocity) /mean velocity

Although the accuracy of TCD to estimate ICP in adult patients with TBI has been studied over the years with relatively good results (13), there is less evidence in children and results are conflicting. Some authors state that transcranial Doppler pulsatility index is not a reliable indicator of intracranial pressure in children with severe traumatic brain injury. The study was conducted based on data from 34 children and 275 examinations (48). A threshold PI of 1 was used to detect ICP 20 mmHg or higher and the sensitivity and specificity was 25% and 88%, respectively. But if the PI threshold was increased to 1.2 the specificity would be 100%. This is in line with our experience that a high PI, in face of a normal arterial pressure and normal pCO2, implies a high ICP. There are also studies with good

results in children (46,93,94). The largest study, included 117 children with severe TBI and PI > 1.31 had a sensitivity of 94% and a specificity of 41% to identify patients with ICP > 20 mmHg. The authors conclude that TCD examination is a safe, reproducible, and reliable method to identified children at increased risk of ICH and decreased CPP after severe TBI, and its use should be encouraged in PICU (94). In our own experience we evaluated 18 children with severe TBI with TCD and invasive ICP. Sixteen patients had ICP values above 20 mmHg, with a mean highest value of 35.7±11.2 mmHg. The first measurement of PI had a mean of 1.12±0.33. There was a significant correlation between the first PI determination and the corresponding ICP value (Pearson correlation coefficient $r=0.755$, $p<0.0001$) (46).

Other studies on mathematical models for continuous non-invasive ICP prediction, using simultaneous measurements of systemic arterial blood pressure and transcranial Doppler flow velocity waveforms, have shown better ability of TCD to estimate and track ICP changes (95–97).

In summary, TCD can accurately predict a raised ICP in paediatric TBI, especially if a higher cut-off value for PI is used. In our clinical practice we use a threshold of 1.4 using the Gosling PI. We have to take into consideration arterial blood pressure and $pCO_2$ as these parameters can change PI and give false negatives, in case of arterial hypertension, and false positives, in case of hypotension or hyperventilation. This non-invasive technique can be extremely useful at admission to help determine the level of care and prioritize actions to take in children who suffered a TBI (98). This is best exemplified by the case of a patient where TCD at admission revealed a very high PI and prompted an emergent surgery instead of invasive ICP monitoring in the PICU (Figure 1).

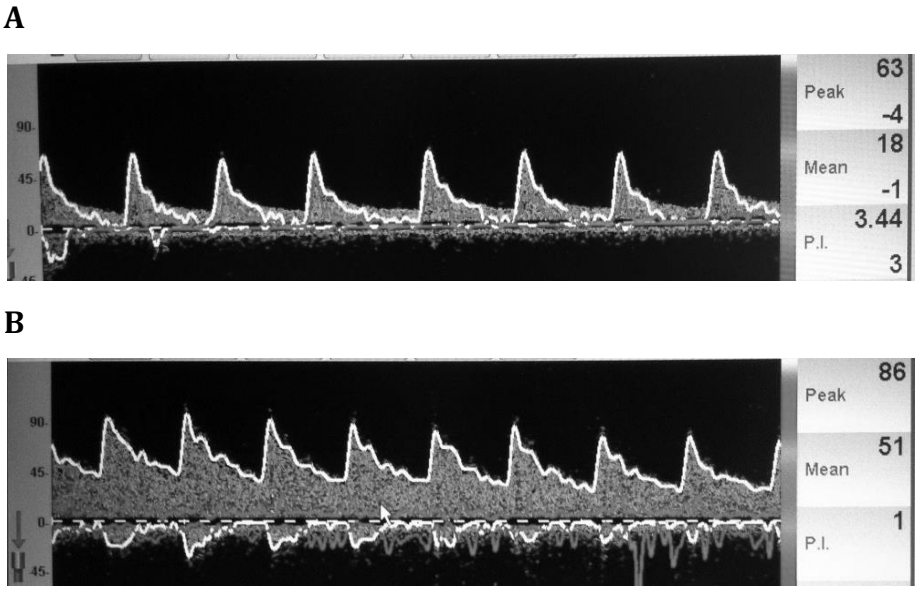


**Figure 1.** TCD examinations in a 17-year-old girl with severe TBI revealing severe compromise of blood flow in the left middle cerebral artery (**A**). After draining a large subdural hematoma, TCD showed normal velocities and PI (**B**).

## Non-invasive estimate of CPP

Among the several non-invasive methods reported for CPP assessment (nCPP) (13,99,100), ultrasound-based alternatives are of special interest since these techniques are low-cost and widely available in the neurocritical care settings. TCD has been one of the most used methods for determination of nCPP in TBI (13). Several studies have tested the feasibility of TCD for these purposes in children (48,94,101). Although Figaji et al. concluded that PI was not a reliable indicator of ICP, they found that the correlation of PI with CPP was much better and significantly related (p=0.001) (48). These data were corroborated in more recent studies that found a sensitivity of 80% of PI to detect a CPP of less than 50 mmHg (94) and in another study where a novel estimator of CPP was calculated using TCD-spectral accounting method that showed a good correlation of nCPP and CPP (Spearman correlation coefficient, R =0.67 ($p < 0.0001$) and the ability of nCPP to predict values of CPP below 70 mmHg was excellent as demonstrated by an area under the curve of 0.91 (95% CI = 0.83–0.98) using a receiver operating curve analysis (101).

It is not a surprise that PI correlates better with CPP than with ICP. It has been elegantly demonstrated by de Riva et al. that PI is not dependent solely on cerebrovascular resistance but it is a product of the interplay between CPP, pulse amplitude of arterial pressure, cerebrovascular resistance and compliance of the cerebral arterial bed as well as the heart rate. Therefore, PI is not an accurate estimator of ICP and it describes CPP in a more accurate manner (47). This is consistent with our practice where we have found cases of paediatric TBI with high PI and normal ICP in patients with low arterial blood pressure (Figure 2) (98).

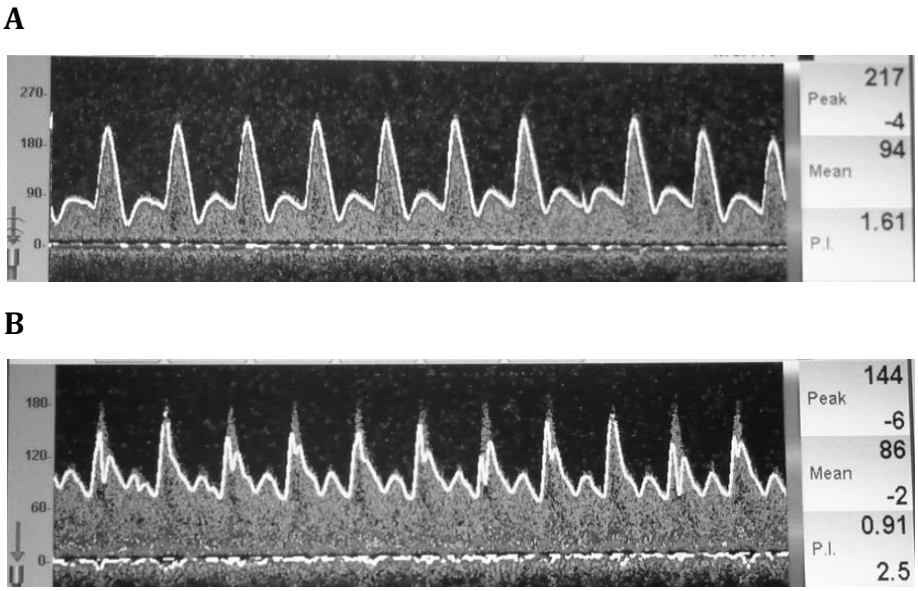


**Figure 2.** TCD of a 16-year-old girl with severe TBI with normal ICP and raised PI due to hypovolemic shock and decreased CPP (**A**). PI and CPP improved after fluid boluses in order to optimize cerebral blood flow (**B**).

## Autoregulation and continuous monitoring of TCD signals

Cerebral autoregulation is a hemodynamic mechanism that allows cerebral blood flow to remain constant with changes of CPP. This is fundamental to protect the brain against inappropriate CBF. If cerebral autoregulation is impaired, CBF becomes dependent on CPP and any changes in arterial blood pressure will reflect

directly on CBF. It has been shown that after a TBI, impaired autoregulation is independently associated with a worse outcome and mortality (78,102,103).

The requirements to measure and monitor dynamic autoregulation over time are:

- Continuous arterial blood pressure monitoring (invasive or non-invasive)
- A surrogate for CBF:
    - Non-invasive (TCD, Near-infrared spectroscopy – NIRS)
    - Invasive (PbtO2, ICP, Laser Doppler Flow)
- A mathematical model to quantificate the relationship between ABP and CBF
    - Time domain analysis (PRx, COx, Mx, LDx, ORx)
    - Frequency domain analysis (coherence, gain of transfer, phase shift)

In the case of TCD, autoregulation monitoring uses the signals of ABP, ICP and cerebral blood flow velocities to calculate indices of autoregulation (53):

- Mx index is the correlation coefficient between mean flow velocity and CPP
- Sx index is the correlation coefficient between systolic flow velocity and CPP

If Mx and Sx are positive it means autoregulation is impaired and this is associated with a bad outcome after TBI. In the example below, we can see a patient with adequate autoregulation and a negative Mx (Figure 3).

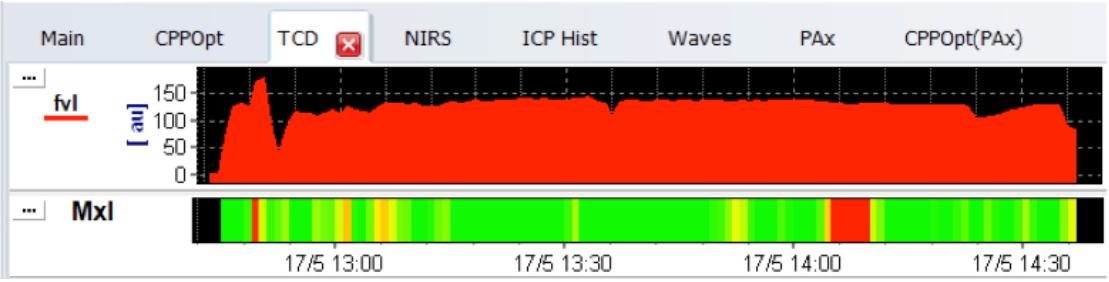


**Figure 3**. Monitoring of blood flow velocity in the left middle cerebral artery for a period of 2h using TCD. Mx is almost always negative (indicated by green colour) reflecting a preserved cerebral autoregulation.

One of the major challenges in using TCD signals to evaluate autoregulation is the necessity to be able to record flow velocities for a long period of time. This can be accomplished with probe holders, but the signal can be lost with positioning of the patient or spontaneous movement. Children represent an additional challenge because of different head sizes and some holders are difficult to use in small children. More recently, new devices using robotic probes allow for continuous monitoring over extended time periods with good results for at least 4 hours of monitoring (54).

In summary, dynamic cerebral autoregulation monitoring can be done non-invasively with TCD but it is difficult to accomplish due to the necessity of long-term acquisition of the TCD signals. New technological advances in this area will make it more usable in clinical practice.

### Detect regional variations on cerebral haemodynamics

One of the challenges in studying the injured brain is that many devices only allow for measurements in one particular area of the brain. This is the case with ICP bolts or PbtO2 probes. TCD has the major advantage of allowing insonation of different territories. This is particular important in pathologies like TBI that can have focal lesions. Although a raised ICP, especially if severe, will ultimately be transmitted

to the whole brain, we have found cases with important asymmetries at an initial phase (Figure 4).

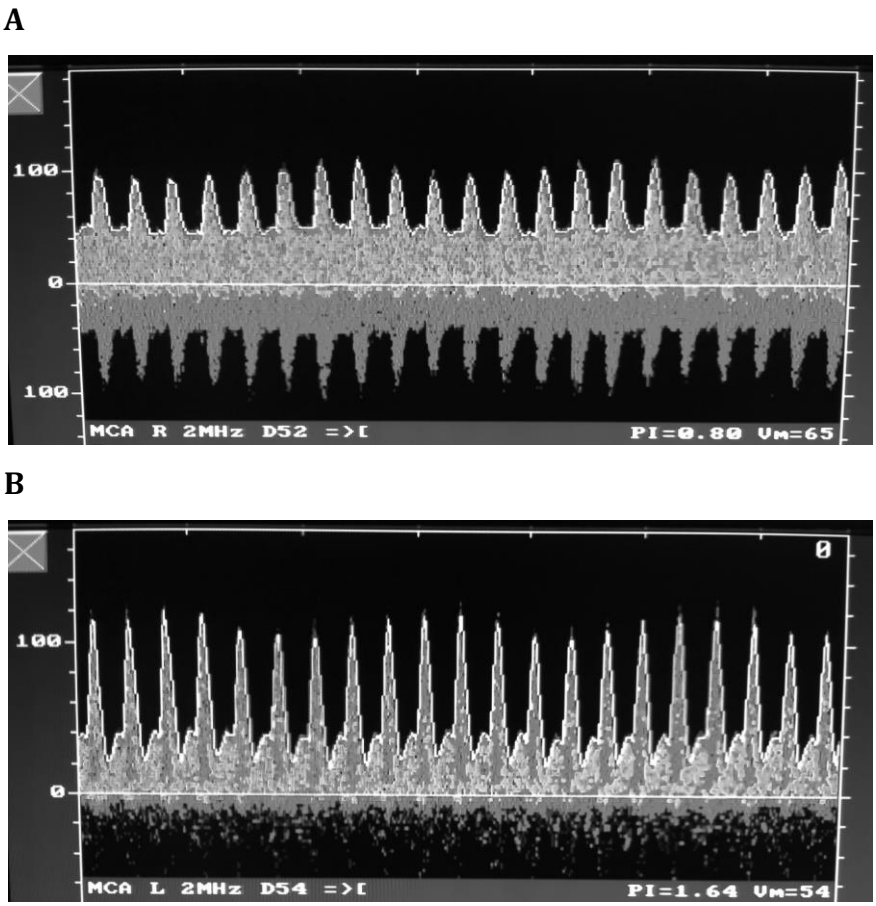


**Figure 4**. TCD at admission of an eight-year-old boy with severe TBI after a road traffic accident. **A**, Right middle cerebral artery with normal flow velocities and PI of 0.80. **B**, Left middle cerebral artery with low diastolic flow velocity and PI of 1.64, compatible with raised ICP/low CPP.

## Diagnosis of brain death

Use of TCD as a tool to aid in the diagnosis of brain death is beyond the scope of this chapter. Nonetheless, TBI is one of the major indications for organ donation and TCD can identify cerebral circulatory arrest and can be extremely useful in determined circumstances. Although TCD is not accepted in all countries for the

diagnosis of brain death, it is commonly used in others. The indications for using an ancillary test of no cerebral blood flow are:

- Impossibility to complete components of the examination or the apnea test
- Uncertainties about the results of the neurological examination
- If a medication effect may be present
- To allow a shorter period of time between the two examinations (in children an interval of 12h is necessary if no ancillary test is used)

In our practice we use TCD in every patient that is considered for organ donation. We find it reassuring for both family members and staff.

## Conclusions

An experienced operator only needs a few minutes to understand if CBF is normal or compromised when performing a TCD. PI is calculated instantaneously and, as previously described, it will be high in cases with decreased CPP. This can be extremely useful for point of care decisions at the bedside in cases of paediatric TBI.

Although TCD can and has been used for cerebral autoregulation monitoring this is more difficult to accomplish in clinical practice and is often performed in investigation settings. New technological advances will make this tool easier to use and help to guide patient management.

# Part 3

# TCD in Paediatric Emergency and Intensive Care Unit

# Part 3: TCD in Paediatric Emergency and Intensive Care Unit

Adapted from the original paper

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## 3.1. Abstract

**Purpose:** Transcranial Doppler (TCD) has been used for more than 30 years in clinical practice. Although adult intensive care is relatively well covered, paediatric cases are still underrepresented. We intend to review a series of paediatric cases where TCD was determinant in clinical decisions and a literature review on this topic.

**Methods:** We describe cases with different pathologies where TCD had an important role in clinical management of the patients. We discuss TCD utility and potential role both in the emergency department and the intensive care unit.

**Results:** Five patients with different neurologic insults are presented. TCD was useful in the identification of intracranial hypertension in traumatic brain injury, hydrocephalus and central nervous system infection; identification of decreased cerebral perfusion pressure in hypovolemic shock and the diagnosis of impending cerebral circulatory arrest in a child with meningococcal septicaemia. We discuss how TCD can be used in emergency and intensive care settings, reviewing relevant literature and our own experience.

**Conclusions:** Non-invasive testing using TCD can aid clinical decisions. More widespread use of this technique will allow for better care of children with neurologic insults.

## 3.2. Introduction

Since its introduction in 1982, many authors have used transcranial Doppler (TCD) to assess cerebral blood flow velocities (41). This technique is well established in cases of vasospasm after subarachnoid haemorrhage, arterial stenosis or occlusion, and for the diagnosis of brain death (104). More recently, some authors have used it as an indirect and non-invasive method to estimate intracranial pressure (ICP). TCD derived pulsatility index (PI) has been shown to have a decent correlation with cerebral perfusion pressure (CPP), ICP, and outcome in patients with severe head injury (43–46), but other reports state that these points are still controversial (47,48). Nevertheless, with TCD it is possible to estimate the severity of cerebral hemodynamic disturbance after traumatic brain injury (TBI) at admission in order to establish prognosis and help deciding the level of care to be provided. However, current guidelines for treatment of these patients do not recommend its use in clinical practice because of the lack of

evidence. The Brain Trauma Foundation 2012 guidelines for TBI in children stated that more studies are needed to determine the optimal monitoring of these patients. It specifically included TCD as one of the techniques that should be considered (105), but surprisingly the new 2019 guidelines do not even mention TCD (9). However, the feasibility of this technique is limited in the paediatric population because of the paucity of studies in children with TBI (48,93,94,106,107).

With this case series and literature review we intend to give further support to the use of TCD in children with TBI and other diseases where cerebral blood flow could be compromised.

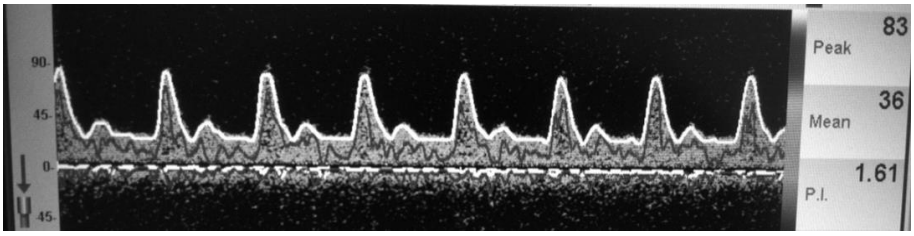
All images were acquired and recorded with RIMED® Digi-Lite, using a 2 MHz pulsed wave probe.

## 3.3. Case reports

**Case 1**

A seventeen year-old boy with known hydrocephalus and a ventriculoperitoneal shunt presented to the emergency department with headache. He had been diagnosed with migraine by the paediatric neurologist, but the headache persisted despite medical treatment. Ophthalmological examination and CT scan were inconclusive and the neurosurgeon asked for a TCD. Pulsatility index (PI) was increased (1.6), blood pressure was normal (123/66 mmHg) and the TCD waveform suggested intracranial hypertension. The decision to operate was based on this result and after reviewing the ventriculoperitoneal shunt the PI normalized (figure 1; table 1) and headache improved.

**A**




**B**

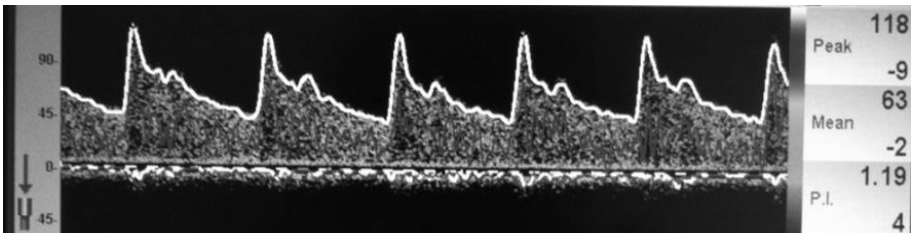



**Figure 1.** TCD of a 17 year-old boy with hydrocephalus and inconclusive CT scan that was operated based on an increased pulsatility index (PI) of 1.61 (**A**). After reviewing the ventricular shunt the PI normalized (**B**).

**Table 1**. Numeric values of TCD parameters, arterial blood pressure (ABP) and non-invasive cerebral perfusion pressure (nCPP). Values in columns show reading before and after intervention.

| Case | FVs (cm/s) | | FVm (cm/s) | | FVd (cm/s) | | PI | | ABP (mmHg) | | nCPP (mmHg) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 94 | 118 | 36 | 64 | 7 | 37 | 1.6 | 1.1 | 123/66 | 119/55 | 31 | 58 |
| **2** | 63 | 86 | 18 | 51 | -4 | 34 | 3.6 | 1 | 168/96 | 63/51 | N/A | 50 |
| **3** | 217 | 144 | 94 | 86 | 33 | 57 | 1.6 | 0.9 | 85/44 | 129/70 | 34 | 74 |
| **4** | 104 | - | 14 | - | -31 | - | 7.3 | - | 154/102 | - | N/A | - |
| **5** | 82 | 118 | 36 | 65 | 13 | 39 | 1.9 | 1.2 | 100/68 | 95/55 | 40 | 54 |

FVs – Flow velocity systolic; FVm – Flow velocity mean; FVd – Flow velocity dyastolic; PI – Pulsatility Index. FVd was calculated using the formula FVd = (3*Vm-Vs)/2). nCPP = MAP x FVd/FVm +14.

**Case 2**

A seventeen year-old girl was transferred from a district hospital with severe TBI after a road traffic accident. A computed tomography (CT) scan at the referring hospital showed a subdural hematoma on the left side. At admission in the emergency department she was sedated and ventilated (PaCO2 = 39.5 mmHg), with high arterial blood pressure (168/96 mmHg) and an urgent TCD was performed revealing severely compromised blood flow in the left middle cerebral artery (Mean flow= 18 cm/s, diastolic flow= 10 cm/s, PI= 3.6). The initial plan of monitoring ICP in the PICU was changed and she was immediately transferred to the operating room. After draining a large intracranial hematoma, TCD showed normal velocities and PI (figure 2; table 1).

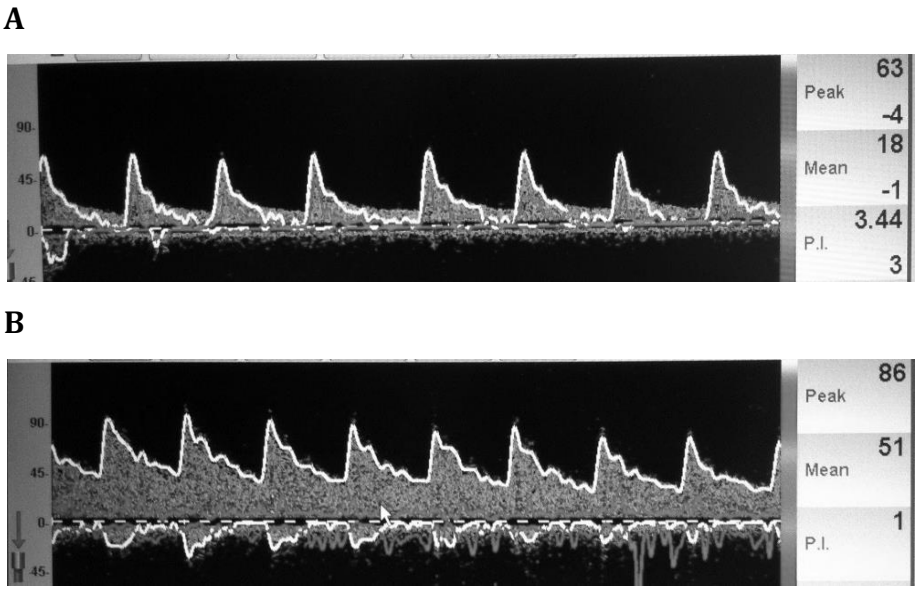
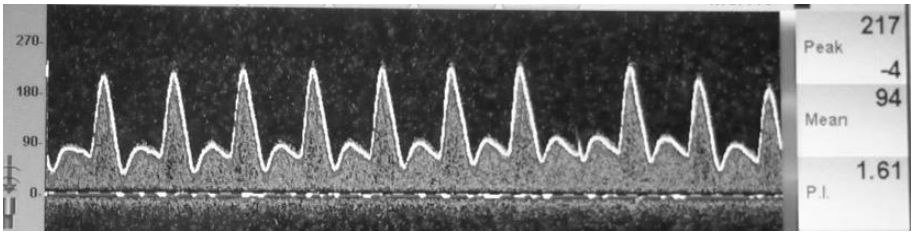



**Figure 2**. TCD examinations in a 17 year-old girl with severe TBI revealing severe compromise of blood flow in the left middle cerebral artery (**A**). After draining a large subdural haematoma, TCD showed normal velocities and PI (**B**).

**Case 3**

A sixteen year-old girl suffered a TBI and extensive abrasion lesions after falling from a horse and being dragged for several minutes. An ICP bolt was inserted and invasive monitoring revealed an ICP of 8 mmHg. Nonetheless, a TCD was performed and PI was increased (1.6) (figure 3; table 1). Blood pressure was low (85/44 mmHg) due to hypovolemic shock and PI was high, reflecting decreased cerebral perfusion pressure. Measured CPP (ABP-ICP) was 51 mmHg. On this case, TCD results prompted treatment with fluid boluses in order to increase blood pressure and optimize cerebral blood flow. After restoring normovolaemia, blood pressure normalized and so did the flow velocities and PI, that decreased to 0.9 (table 1).

**A**




**B**

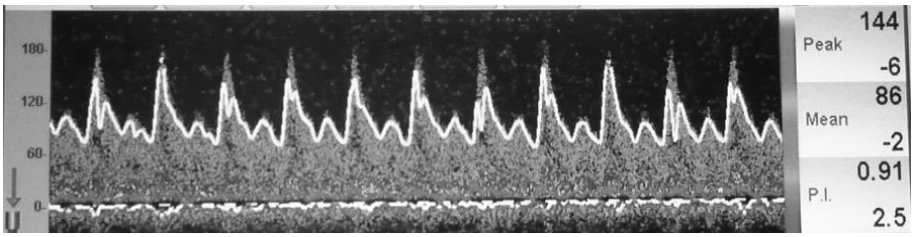



**Figure 3**. TCD of a 16 year-old girl with severe TBI with normal ICP and raised PI due to hypovolemic shock and decreased cerebral perfusion pressure (**A**). After fluid boluses in order to optimize cerebral blood flow PI improved (**B**)

**Case 4**

An eleven year-old boy was admitted to the paediatric intensive care unit (PICU) with severe meningococcal septicaemia. After 48h of intensive treatment with fluid boluses, inotropes, steroids, blood transfusions and extensive fasciotomies of the lower limbs, he had a sudden neurologic deterioration with dilated pupils, absence of spontaneous respiratory trigger and no reaction to external stimuli. An urgent TCD confirmed very high PI (7.3) with arterial hypertension (154/102 mmHg), compatible with severe intracranial hypertension and severe compromise to cerebral blood flow with no diastolic flow (figure 4). CT scan of the brain confirmed severe cerebral oedema and the patient eventually died.

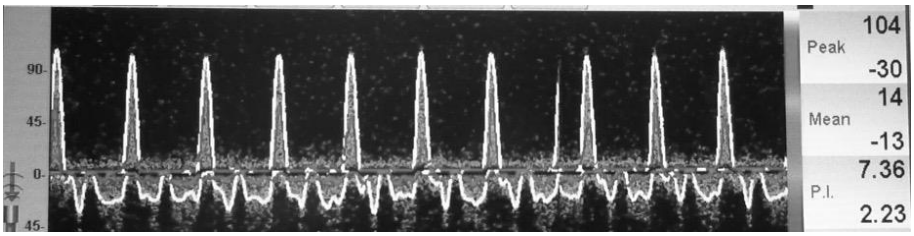



**Figure 4**. TCD of an 11 year-old boy with meningococcal septicaemia that had neurologic deterioration 48h after admission, showing severe compromise to cerebral blood flow with no diastolic flow. Computed tomography of the brain confirmed severe cerebral oedema.

**Case 5**

A 4-month-old infant was admitted to the infectious diseases ward with pneumococcal meningitis and a subdural empyema. The neurosurgeons were reluctant to operate on such a small child due to lack of clear indications for drainage in this age group. The child was awake and showed signs of irritability, but was otherwise stable. As she was not improving a TCD was performed and the decision to drain the empyema was based on a raised PI (1.9) with mild arterial

hypertension (100/68 mmHg) and normocapnia, which was interpreted as a sign of raised ICP. After drainage TCD was repeated and the PI was normal (figure 5; table 1).

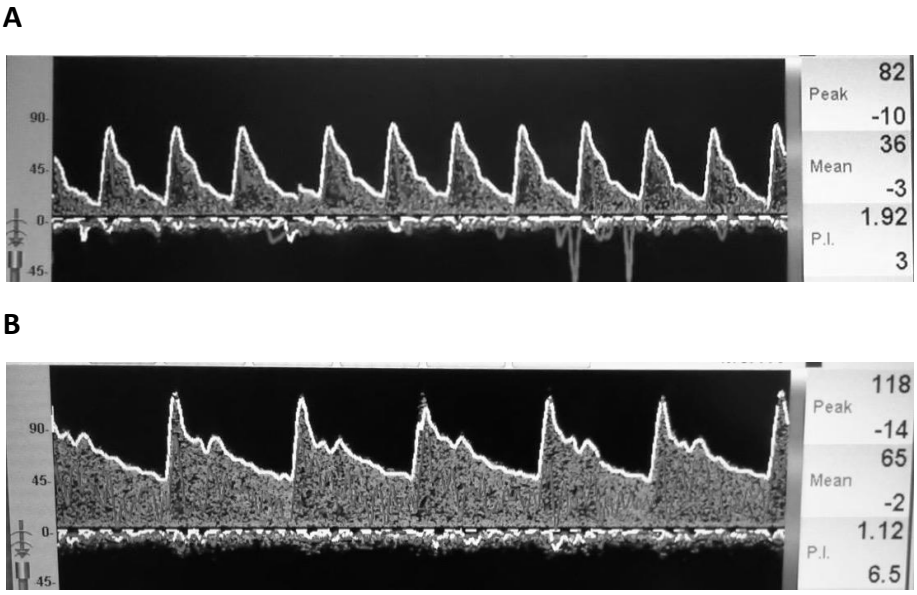



**Figure 5**. TCD of a 4-month-old infant with bacterial meningitis and subdural empyema. Decision to drain the empyema was based in a raised PI on the TCD, which was interpreted as a sign of raised ICP (**A**). After surgery PI was normal (**B**).

## 3.4. Discussion

Evaluating cerebral blood flow is essential in many disease processes. TCD is a non-invasive, bedside, technique that allows direct measurement of blood flow velocities in intracranial arteries. Assuming the diameter of the insonated artery is constant, changes in the Doppler acquired flow velocities reflect changes in cerebral blood flow through that artery.

Measuring blood flow velocities allows us to calculate indices based on systolic, mean and diastolic flow velocities. One of those is the Gosling pulsatility index (PI) that is calculated from the relationship between systolic and diastolic flow

velocities divided by the mean flow velocity (92). PI has been extensively used as an estimate of ICP in adults, but its use in children is still limited. A recent review study has only found 3 papers between 2005 and 2015 addressing this particular interaction in children (107). Although it has been largely interpreted as a measure of cerebral vascular resistance (CVR), it has been suggested that PI is a complex function of various hemodynamic factors and not only of CVR (47). First of all it is an inverse function of cerebral perfusion pressure (CPP), so, it increases both with low MAP or raised ICP. It also increases with low PaCO2, as hypocapnia raises CVR. As our case 3 shows, PI can be increased even in face of normal ICP. In this case it reflects CPP better than ICP and even if in most cases ICP and CPP will be inversely related we must take arterial blood pressure into account in order to correctly interpret PI. In our opinion PI is a good measure of CPP and the higher the PI the lower the CPP. These has been previously demonstrated by others (45,48,94). Some authors use a formula to estimate CPP based on mean arterial pressure and flow velocities. Czosnyka et al. have suggested the formula: 'MAP x FVd/FVm +14' to estimate CPP (108). This formula has since been used and validated by others (109,110). In clinical practice, being able to estimate CPP is extremely important because ultimately what matters to the patient is assuring adequate perfusion of the brain tissue.

In neurocritical care, TCD has been used in many different settings including TBI, subarachnoid haemorrhage, stroke, hydrocephalus, brain tumours, sickle cell disease, brain death, cardiac shunts, carotid surgery, central nervous system infection, liver failure, preeclampsia and sepsis (111).

In this paper we focus on its use in the paediatric emergency department and intensive care unit. It is a valuable tool to assess cerebral blood flow in these settings. A qualified doctor or technician can quickly evaluate the patient providing it has a good acoustic window. Fortunately, most paediatric patients do. This means that in a few minutes, with the proper equipment and expertise, one can tell how compromised is perfusion to the brain.

If used judiciously in the emergency department it can help to make quick decisions in cases where it is not obvious what the best approach would be. It has been shown to effectively predict which patients with no severe brain lesions on CT after mild to moderate traumatic brain injury were at risk for secondary neurologic deterioration (112). Others have demonstrated an association with poor outcome, if the TCD performed in children with moderate to severe head injury at admission in the emergency department showed an end-diastolic velocity less than 25 cm/s and a PI more than 1.31 (113). We have also used it many times to decide if children with hydrocephalus, presenting to the emergency room with clinical symptoms of raised ICP, need revision of their shunt or if they can be managed conservatively. In every case where TCD was suggestive of raised ICP this was confirmed by the neurosurgeon during surgery.

Traumatic brain injury is definitely one of the major indications for using TCD in the PICU, but we have also used it successfully in many other scenarios like hydrocephalus, shock, brain death, central nervous system infections and stroke. In the case of an acute ischemic stroke it is possible to document the occlusion of the affected vessel and in selected cases monitor reperfusion while treating with intravenous thrombolysis (114). We have done it successfully in a 14 year-old boy with an acute ischemic stroke. The treatment was performed under transcranial Doppler ultrasound monitoring, and recanalization of the left middle cerebral artery was documented during the first 5 minutes of r-TPA perfusion (115). We have also used it in patients during extracorporeal membrane oxygenation (ECMO). These patients are not easy to move and a bedside test is of utmost importance. In these cases we have to take into consideration the nonpulsatile flow of the ECMO system, particularly in patients with veno-arterial ECMO. Nonetheless, it could be determinant in cases of suspected stroke that unfortunately is one of the risks of the patients submitted to this technique of extracorporeal circulation. Others have also studied the role of TCD in ECMO patients, although there are no studies in children (116,117).

Another well established role for TCD is diagnosis and monitoring of vasospasm after subarachnoid haemorrhage (SAH). The study from Lindegaard et al. showed that there was a clear inverse relationship between the MCA diameter and MCA flow velocity (118). He also established the limit of a mean flow velocity above 140 cm/s to define a significant vasospasm. At this velocity the diameter of the MCA reduces to one half of its original diameter, decreasing from 3 to 1.5 mm. Many authors have validated these results and assessing vasospasm after SAH is probably the most common indication for TCD in neurocritical care (119–121). Nonetheless, results should be interpreted cautiously because intermediate velocities – mean flow velocity in MCA 120-200 cm/s – may not have a good correlation with angiographic findings (122). In our unit we monitor every child with SAH with alternate day TCD and daily if there is vasospasm, although there are no normative values for children with SAH. We use the reference values for adults and the Lindegaard ratio to exclude hyperaemia in selected cases.

In our study we present paradigmatic cases where TCD aided clinical management. We selected these cases because they are examples of daily conditions that require an understanding of cerebral hemodynamics to guide therapy. These cases include frequent causes of intracranial hypertension like traumatic brain injury, hydrocephalus and central nervous system infection; we also describe a case of decreased cerebral perfusion pressure in hypovolemic shock to draw attention to the fact that PI can be increased with normal ICP if CPP is compromised due to low arterial blood pressure; finally we also give an example of a common application of TCD in diagnosing impending cerebral circulatory arrest or even complete circulatory arrest where it can aid in the establishment of brain death. This is particularly useful in cases where the clinical criteria of brainstem death cannot be applied on their own, for example is sedative substances are in circulation.

TCD is not a replacement for other established techniques of neuromonitoring, but should be included in the multimodal monitoring as a useful tool to estimate cerebral blood flow. TCD is inexpensive, non-invasive, real-time, harmless, easy to

perform with the correct training and can be done in almost all environments without having to move the patient. It can be repeated as needed, but continuous monitoring for more than 30-60 minutes is still challenging. New technologies are currently being developed and tested that will probably allow continuous monitoring to be feasible in the near future.

## 3.5. Conclusions

This case series demonstrates how TCD, a non-invasive, bedside monitoring tool, can be used in different settings and aid clinical decisions. We believe that more widespread use of this inexpensive technique would allow a better care of children with neurologic insults and that it truly constitutes a 'stethoscope for brain'.

# Part 4

## TCD as a non-invasive method to estimate CPP

# Part 4: TCD as a non-invasive method to estimate CPP

## Adapted from the original paper

Abecasis, F., Cardim, D., Czosnyka, M., Robba, C. & Agrawal, S. Transcranial Doppler as a non-invasive method to estimate cerebral perfusion pressure in children with severe traumatic brain injury. *Child's Nerv Syst* 36, 125–131 (2020).

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## 4.1. Abstract

**Introduction:** Cerebral perfusion pressure (CPP) is one of the most important parameters in preventing ischemic brain insults. Guidelines have used CPP values to guide treatment of traumatic brain injury (TBI) for many years. We tested the feasibility of a novel non-invasive method for CPP estimation (nCPP) in children with severe TBI.

**Methods:** Retrospective analysis of prospectively monitored paediatric TBI patients with invasive intracranial pressure (ICP) monitoring, arterial blood pressure and Transcranial Doppler (TCD) studies performed daily. A novel estimator of CPP (nCPP) was calculated using TCD-spectral accounting method. We analysed the correlation coefficient and correlation in time domain between CPP and nCPP, prediction ability of nCPP to detect low CPP, and the confidence intervals for CPP prediction (95% CI).

**Results:** We retrospectively analysed 69 TCD recordings from 19 children (median age 15 years, range 3-16 years). There was a good correlation between CPP and nCPP (Spearman correlation coefficient: R=0.67 ($p<0.0001$), and a good mean correlation in time domain (R=0.55±0.42). The ability of nCPP to predict values of CPP below 70 mmHg was excellent as demonstrated by an area under the curve of 0.908 (95% CI = 0.83-0.98) using a receiver operating curve analysis. Bland-Altman analysis revealed that nCPP overestimated CPP by 19.61 mmHg with a wide 95% CI of ±40.4 mmHg.

**Conclusions:** nCPP monitoring with TCD appears to be a feasible method for CPP assessment in paediatric TBI. The novel spectral CPP tested in this study has a decent correlation with invasive CPP and can predict low CPP with excellent accuracy at the 70-mmHg threshold.

## 4.2. Introduction

Maintaining an adequate cerebral blood flow (CBF) after a traumatic brain injury (TBI) is one of the most important goals to avoid secondary damage to the injured brain. Guidelines have traditionally used intracranial pressure (ICP) monitoring and treatment of increased ICP as the main objective to improve outcome following TBI (123). Although this is a standard of care in developed countries, a recent randomized study failed to show a difference in outcome when patients with TBI were randomly assigned to invasive ICP monitoring vs clinical and radiological assessment (124). In children, evidence is even less robust and adequate randomized controlled studies to evaluate the role of ICP monitoring and treatment, have not been performed. There is evidence that sustained ICP >20 mmHg is associated with poor outcome, but there is no data to support an absolute ICP target in children with TBI (105).

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial pressure (ABP) and mean ICP, and it is the pressure gradient driving cerebral blood to flow. In normal conditions, CBF is autoregulated to maintain an adequate oxygen and glucose delivery to the brain across physiological range of CPP. After TBI, cerebral autoregulation might be impaired and decreases in CPP could lead to cerebral ischemia. Thresholds for adequate CPP in children with TBI have recently been published suggesting that CPP targets should be age-specific (28). This report, from Allen and colleagues, describes a new method to establish a goal of CPP above specified thresholds (above 40 mmHg in children under 6 years-old and above 50 mmHg in children from 6 to 17 years-old).

If CPP is the driving force of CBF, it is logical that treatment protocols should focus on CPP, first of all and then on ICP. CPP can be manipulated by changing ICP or ABP. Both strategies can be used depending on the clinical situation, but ultimately the goal should be to maintain an adequate CBF by maintaining adequate CPP and avoiding intracranial hypertension.

In children, invasive ICP-CPP monitoring is reserved for patients in whom the severity of the clinical conditions demand ICP-CPP guided treatment. Otherwise, the risks associated with invasive neuromonitoring, such as bleeding and infection (105), may not represent a beneficial intervention.

In such cases, non-invasive methods for assessment of these parameters could offer an alternative for treatment or a screening tool to determine the need for invasive monitoring. Among the several non-invasive methods reported for CPP assessments (nCPP) (13,99,100), ultrasound-based alternatives are of special interest since these techniques are low-cost and widely available in the neurocritical care settings. Transcranial Doppler ultrasonography (TCD) has been one of the most used methods for nCPP in TBI (13). Several studies have tested the feasibility of TCD for these purposes in children (48,94). There are contrasting results on the application of the TCD-derived pulsatility index for predicting cerebral hypoperfusion. Nevertheless, other studies on mathematical models for continuous non-invasive ICP prediction using simultaneous measurements of systemic arterial blood pressure and transcranial Doppler flow velocity waveforms have shown better ability of TCD to estimate and track ICP changes (95–97).

The aim of our study is to test the feasibility and accuracy of a novel TCD-based method for nCPP assessment in children with TBI to estimate CPP absolute values and changes of CPP over time.

## 4.3. Methods

### Patients

We retrospectively studied digital recordings of MCA flow velocity, ICP and arterial blood pressure from paediatric TBI patients admitted to Addenbrooke's Hospital, Cambridge, UK and recruited prospectively between 1992 and 2009 to a

project aimed at daily assessment of cerebral autoregulation in children with severe TBI. All patients presenting with severe (admission Glasgow Coma Score (GCS) <9) or moderate (admission GCS <13) traumatic brain injury (TBI), with secondary neurological deterioration requiring intubation and mechanical ventilation, were eligible for inclusion in this study. All patients were sedated and paralysed as per relevant time-matching local guidelines for management of TBI in children.

TBI data collection was approved by the Institutional Review Board (REC 97/290, 1997). For patients recruited before 1997, The Neurosciences Users' Committee allowed TCD examinations for the assessment of TBI patients. Further use of the anonymised data was allowed as a part of clinical audits.

### Monitoring and data analysis

ABP was measured directly from the radial artery calibrated at the level of the heart (Baxter Health Care Corp., CardioVascular Group). ICP was monitored continuously using a microtransducer placed in the brain parenchyma (MicroSensors ICP Transducer; Codman and Shurtleff, Inc.). CPP was calculated as the difference between the mean ABP and ICP.

Arterial cerebral blood flow velocity ($CBFV_a$) was obtained bilaterally from the left and right middle cerebral arteries (MCA) by using a TCD ultrasonography system (DWL Multidop X4, DWL Elektronische Systeme GmbH), with the probe held in place during the entire recording using a head frame provided by the TCD device manufacturer. Mean $CBFV_a$ was calculated as the average between left and right $CBFV_a$.

Raw signals were digitized using an analog–digital converter (DT 2814, Marlborough, California, United States of America) sampled at a frequency of 100 Hz and recorded with ICM+® (Cambridge Enterprise, https://icmplus.neurosurg.cam.ac.uk/). The recorded signals were subjected to manual artefacts removal and analysed with ICM+®. All parameters were

calculated and averaged. All calculations were performed over a 10 s long-sliding window.

### Statistical analysis

The analysis of the data was conducted with R Studio software (R version 3.4.1). Multiple recordings were considered as independent events. Data were tested for normal distribution using the Shapiro-Wilk test and are presented as median and interquartile range. All parameters assessed were non-parametric in nature.
To assess the performance of the proposed method, the correlation between CPP and the nCPP were verified using the Spearman correlation coefficient (R, with the level of significance set at 0.05), as well as the correlation coefficient in the time domain during monitoring period.

The Bland-Altman method was used to determine the agreement between absolute values of invasive CPP and nCPP, with the respective bias and 95% confidence intervals (CI) for CPP prediction.

The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was performed to determine the ability of nCPP to detect low CPP. Different low CPP thresholds of 50, 60 and 70 mmHg were tested, according to Allen et al.'s established age-specific CPP thresholds for TBI patients (28). The prediction ability is considered reasonable when the AUC is higher than 0.7, strong when the AUC exceeds 0.8 and excellent when the AUC exceeds 0.9 (125).

### Non-invasive CPP calculation

Formula was created using arithmetics described previously (47):

$$nCPP = \frac{a1}{sPI} \times \sqrt{(CVR \cdot C_a)^2 \cdot HR^2 \cdot (2\pi)^2 + 1}(mmHg)$$

Where a1 represents the pulse amplitude of the first harmonic of the ABP waveform, sPI denotes the spectral pulsatility index; CVR, cerebrovascular

resistance; $C_a$, compliance of arteries and arterioles; HR, heart rate (expressed in Hz).

## 4.4. Detailed description of the spectral model development and formula

A common approach to model the cerebral vasculature is to compartmentalize the different regions of the brain and mechanistically capture their interactions through a mathematical model. A model of CBF and cerebrospinal fluid (CSF) dynamics has been proposed by Ursino and Lodi (126,127), which captures the dynamics in the arterial, capillary, venous and CSF circulation. This model has been modified later by Czosnyka et al. (128), which incorporates realistic values for known components including cerebrovascular resistance, intracranial and arterial compliance, and CSF outflow resistance. The electrical equivalence of this model is presented in Figure 1.

The input circuit of the model may be presented in a simplified way as a resistance-capacitance circuit. A parallel arrangement of ohmic resistance (CVR) and conductive resistance ($1/j\omega \cdot C_a$) adds to a total impedance:

***Equation 1***

$$Z(j\omega) = \frac{\frac{CVR}{j\omega \cdot C_a}}{CVR + \frac{1}{j\omega \cdot C_a}} = \frac{CVR}{j\omega \cdot CVR \cdot C_a + 1}$$

Where $\omega$ symbolizes circular frequency ($\omega = 2\pi \cdot frequency$); $CVR$ represents cerebrovascular resistance; $C_a$, compliance of arteries and arterioles. Units are given in mmHg/(cm$^3$/s).

The modulus of impedance can be expressed as:

***Equation 2***

$$|Z(\omega)| = \frac{CVR}{\sqrt{(CVR.C_a.\omega)^2 + 1}}$$

For a constant flow ($\omega=0$), the modulus of impedance becomes:

***Equation 2a***

$$|Z(0)| = CVR = \frac{CPP}{CBFV_a}$$

*CPP* denotes mean cerebral perfusion pressure (in mmHg); CB$FV_a$, mean blood flow velocity in the MCA (in cm/s). In equation (2a), we assume that the drive for MCA blood flow is CPP.

Considering pulse waves ($\omega_{HR}$ = *frequency of heart rate* (HR)), the modulus equals the ratio*:*

***Equation 2b***

$$|Z(\omega_{HR})| = \frac{a1}{f1}$$

Where *a1*, represents the pulse amplitude of the first harmonic of the ABP waveform; *f1*, the pulse amplitude of the first harmonic of the FV waveform. The pulse amplitude of first harmonics is determined with fast Fourier transformation (FFT). We presume that the pulse amplitude of ICP is much lower than of ABP (usually it is – 20 to 30 times, with exception of cases with very large ICP pulse amplitude – like plateau waves of ICP or cases of extremely diminished pressure-volume compensatory reserve).

Considering **(2)** for heart rate ($\omega= 2\pi \cdot HR$), and substituting CVR and Z($\omega_{HR}$) by **(2a)** and **(2b)**, it results in:

***Equation 3***

$$CPP = \frac{a1}{sPI} \times \sqrt{(CVR \cdot C_a)^2 \cdot HR^2 \cdot (2\pi)^2 + 1}(mmHg)$$

Where:

$$sPI = \frac{f1}{CBFV_a}$$

*sPI* denotes the spectral pulsatility index. *HR* is expressed in Hz.

Equation **(3)** presents the non-invasive estimator of CPP that can be evaluated on the heart beat-by-beat basis. CVR and $C_a$ used in equation **(3)** can be estimated using mathematical transformations of TCD and ABP pulse waveforms measurements based on a model of cerebral arterial blood volume changes (see below for details).

### *Pulsatile changes in cerebral blood volume*

The amount of arterial blood supplied to the cerebral space by the vascular system during a cardiac cycle is partially compensated by simultaneous outflow of blood through the venous system. Both the arterial inflow ($CBF_a$) and venous outflow ($CBF_v$) of cerebral blood have a pulsatile character, but their pulse waveform shapes are phase-shifted resulting in detectable cerebral blood volume (CBV) changes during a heartbeat.

The methodology and concept behind the monitoring of CBV with TCD were derived from early works of Avezaat and Eijndhoven, who used electromagnetic flowmetry on the exposed common carotid artery in dogs (129). They studied similarities between the pulsatile blood flow and ICP pulse waveform. Transcranial Doppler flowmetry non-invasively allows a similar calculation of CBV, the difference being that TCD does not measure the volume of blood inflow but the arterial blood inflow velocity. However, CBV can be mathematically approximated using TCD. The change of cerebral blood volume over one cardiac cycle can be formulated as an integral of the subtraction between the arterial inflow and the venous outflow. This approximation model assumes that the cross-sectional area of the large cerebral arteries remains constant.

The interaction between pulsatile changes in $CBF_a$ and $CBF_v$ determines the transient, time dependent change in cerebral blood volume ($\Delta CBV$) and can be described by the following equation (130):

***Equation 4***

$$\Delta CBV(t) = \int_{t_0}^{t} \left(CBF_a(s) - CBF_v(s)\right) ds$$

where $t_0$ is the beginning of single cardiac cycle and $ds$ is the variable of integration.

With TCD, the venous outflow velocity can be monitored continuously with Doppler ultrasound, but an input velocity cannot be easily related to an output velocity because they will have different vessel diameters and represent flow in different distributions of the vascular tree. Thus, two models of approximation of $\Delta CBV$ are worth consideration:

**Continuous flow forward model (CFF):** we presume that venous outflow, being far less pulsatile (131) may be substituted by the mean value of arterial CBF. This leads to the formula:

***Equation 5***

$$\Delta C_a BV_{CFF}(t) = \int_{t_0}^{t} (CBF_a(s) - meanCBF_a) ds$$

Where $C_aBV$ represents cerebral arterial blood volume. Units are given in $cm^3$.

**Pulsatile flow forward model (PFF):** in this approach, the pulsatile arterial blood inflow inflating and deflating cerebral arteries during each cardiac cycle is modelled as the difference between CBF(t) and cerebral blood flow forward from big arteries to small resistive arterioles:

***Equation 6***

$$\Delta C_a BV_{PFF}(t) = \int_{t_0}^{t} \left( CBF_a(s) - \frac{ABP(s)}{CVR} \right) ds$$

Where CVR is defined as follows:

$$CVR = \frac{ABP}{CBFV_a} (mmHg/(cm/s))$$

Formulas **(5)** and **(6)** will yield values of CBV per unit of cross-sectional area of the insonated vessel. Assuming that the cross-sectional area remains constant, $CBFV_a$ can substitute $CBF_a$ in **(5)** and **(6)**.

Obtained from the presented calculations, both virtual signals $CaBV_{CFF}$ and $CaBV_{PFF}$ have a pulsatile component. However, the shape of the $CaBV_{PFF}$ waveform is different, and its amplitude is lower than $CaBV_{CFF}$ (pulse amplitudes of first harmonic of $CaBV_{CFF}$ and $CaBV_{PFF}$ for the heart frequency are denoted further as $C1_{CFF}$ and $C1_{PFF}$) – see Figure 2.

Then arterial compliances are defined, accordingly:

***Equation 7***

$$C_{aCFF} = {C1_{CFF}}/{a1}$$

***Equation 8***

$$C_{aPFF} = {C1_{PFF}}/{a1}$$

Where $C1_{CFF}$ and $C1_{PFF}$ were determined using FFT as the pulse amplitudes of the first harmonics of $CaBV_{CFF}$ and $CaBV_{PFF}$ and ABP pulse waveforms.

Both compliances have units (cm/mm Hg), i.e., these values are expressed as a value of arterial compliance per unit of cross sectional area of the insonated vessel.

$CVR$ used in formula **(3)** can be estimated in two ways:

***Equation 9***

$$CVR_1 = \frac{ABP}{CBFV_a}$$

***Equation 10***

$$CVR_2 = a1/f1$$

$CVR_2$ is an equivalent of the so-called 'resistance area product' (132), and is usually lower than $CVR_1$, but its advantage relies on immunity to inaccuracies related to not zeroing the blood pressure transducer for arterial cerebral circulation and the absence of time delays between ABP and $CBFV_a$ given these parameters are calculated in the frequency domain.

Any combination of $CVR \cdot C_a$ (four combinations altogether): $CVR_1 \cdot C_{aPFF}$, $CVR_2 \cdot C_{aPFF}$, $CVR_1 \cdot C_{aCFF}$, $CVR_2 \cdot C_{aCFF}$ may result in four nCPP estimators. A nCPP estimator

composed of an average of values from these four estimators was further used to analyse clinical data. Given the spectral nature of this estimator, we named it as spectral nCPP.

While estimators using CFF model are not affected by time delays between any signals, estimators using PFF are: ABP is measured from the radial artery distant from the brain, and therefore is delayed in comparison to MCA flow velocity signal. This assumption is made from preliminary findings that the delay may range from a median ± interquartile range (IQR) of 10±15 ms (based on unpublished analysis of 53 healthy volunteers, a population presented and described elsewhere [29], in which the time delay between ABP and $CBFV_a$ was determined using a cross-correlation algorithm) (Figure 2) and may be different between individuals and may vary in time. To compensate for this time delay, estimators of *C1* can be calculated in the spectral domain. This considers that the Fourier transform of the integral of the time function *f(t)* is equal to its Fourier transform divided by $j\omega$. For the frequency of heart rate, this will be $j\omega_{HR}$. Under the assumption that the phase shift between the first harmonic of *ABP(t)* and $CBFV_a(t)$ signals is small (median ± IQR: 13.12±3.59 degrees after adjustment for time delays resulting from the distance between the site of ABP measurement and the middle cerebral artery – based on unpublished analysis of the aforementioned population of healthy volunteers), the frequency domain estimators of *C1* can be expressed as:

***Equation 11***

$$C1_{CFF} = \frac{f1}{\omega_{HR}}$$

***Equation 12***

$$C1_{PFF} = \frac{(f1 - a1/CVR)}{\omega_{HR}}$$

The latter assumption rises from the spectral analysis basis that requires signals to be time invariant.

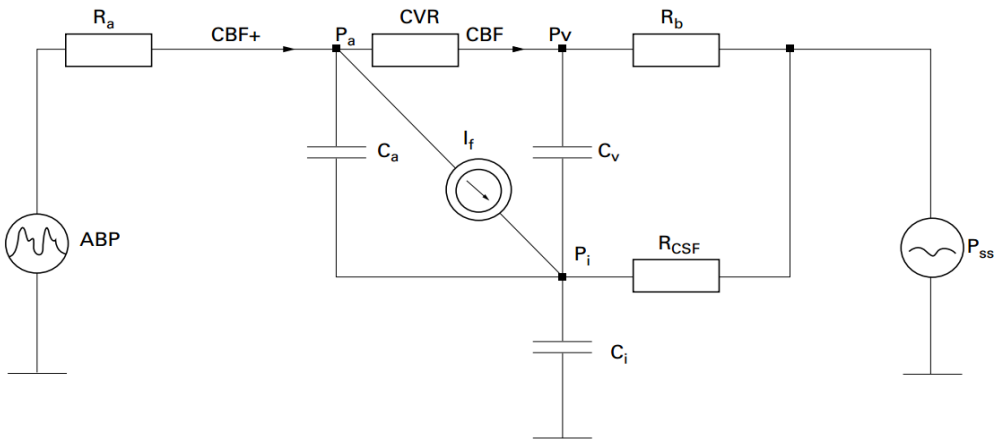


**Figure 1.** Electrical equivalence of a model of cerebral blood flow and cerebrospinal fluid dynamics. The CBF pathway starts with the arterial blood inflow to the brain through the resistance of large intracranial arteries (Ra), with arterial blood pressure (ABP) as the input pressure from the carotid and basilar arteries. From there, arterial blood passes at high pressure (Pa), through the small cerebral arteries. These vessels act as a storage system for pulsatile blood volume, which is modelled by the compliance Ca. Forward flow through the cerebrovascular resistance (CVR) vessels is modulated by the cerebral autoregulation. The capillary and venous blood flow and storage are lumped together and modelled by the compliance of Cv at pressure Pv. Finally, venous blood flows out through the bridging veins represented by the Starling resistor Rb to the sagittal sinus at pressure Pss. The CSF pathway encompasses formation of CSF (with a rate of If), storage in the distensible fluid structures formed by the ventricles, basal cisterns and spinal sac (with compliance of Ci), and finally reabsorption through the arachnoid granulations to the sagittal sinus with the resistance to outflow being denoted as RCSF. Both CBF and CSF pathways take place inside the rigid skull with an intracranial pressure being depicted here as Pi. Extracted from Czosnyka et al. (128).

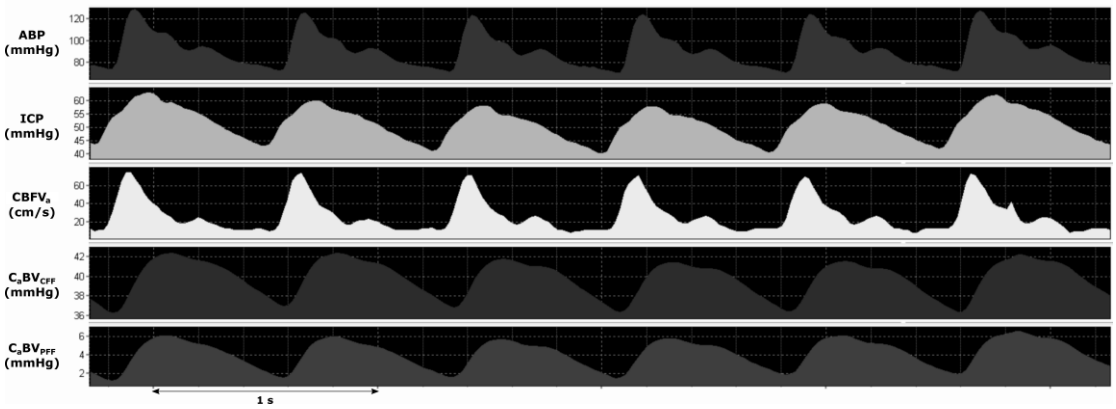


**Figure 2.** Example of signals of arterial blood pressure (ABP), intracranial pressure (ICP), cerebral blood flow velocity ($CBFV_a$) and estimators of pulsatile arterial blood volume calculated using constant flow forward ($C_aBV_{CFF}$) and pulsatile flow forward ($C_aBV_{PFF}$) methods. In this example, we can observe that the pulse amplitude of $C_aBV_{CFF}$ is greater than $C_aBV_{PFF}$. Given the distance between the sites of ABP and $CBFV_a$ measurements, the time delay between these signals is assumed as 10±15 ms (median ± IQR), based on a preliminary study with healthy volunteers and calculated using a cross-correlation algorithm implemented on ICM+ software (unpublished analysis). This population of healthy individuals (N=53, not age-matched to the TBI populations analysed in our study) has been presented and described thoroughly elsewhere (133).

## 4.5. Results

Nineteen patients were included in the study. Their median age was 15 years (interquartile range (IQR): 13-16; range 3-16 years; 63% males). We analysed 69 TCD recordings from these patients and all other variables collected simultaneously during that period.

In Table 1, we present the median (IQR) values of the neurophysiologic variables analysed. The percentage of measurements presenting low CPP at the threshold ≤50 mmHg was 10% (N=7), at ≤60 mmHg was 28% (N=19), at ≤70 mmHg was 52% (N=36). The median initial GCS score was 6.5 (IQR: 5-7; range 3–9).

**Table 1.** Median (IQR) values of the neurophysiologic variables analysed.

| Parameter | Median (IQR) |
|---|---|
| **ABP** | 88.03 (99.81-78.97) |
| **ICP** | 18.70 (25.68-13.38) |
| **CPP** | 68.97 (81.71-58.29) |
| **FV** | 64.73 (77.67-52.82) |
| **nCPP** | 80.05 (103.99-70.81) |

ABP - arterial blood pressure (mmHg); ICP – intracranial pressure (mmHg); CPP – cerebral perfusion pressure (mmHg); FV – flow velocity (cm/s); nCPP – spectral non-invasive cerebral perfusion pressure (mmHg).

There was a good correlation between nCPP and invasive CPP (R=0.67 [p<0.0001]) (Figure 3). The averaged correlation in the time domain between CPP and nCPP was R=0.55±0.42 (95% CI: 0.45-0.65).

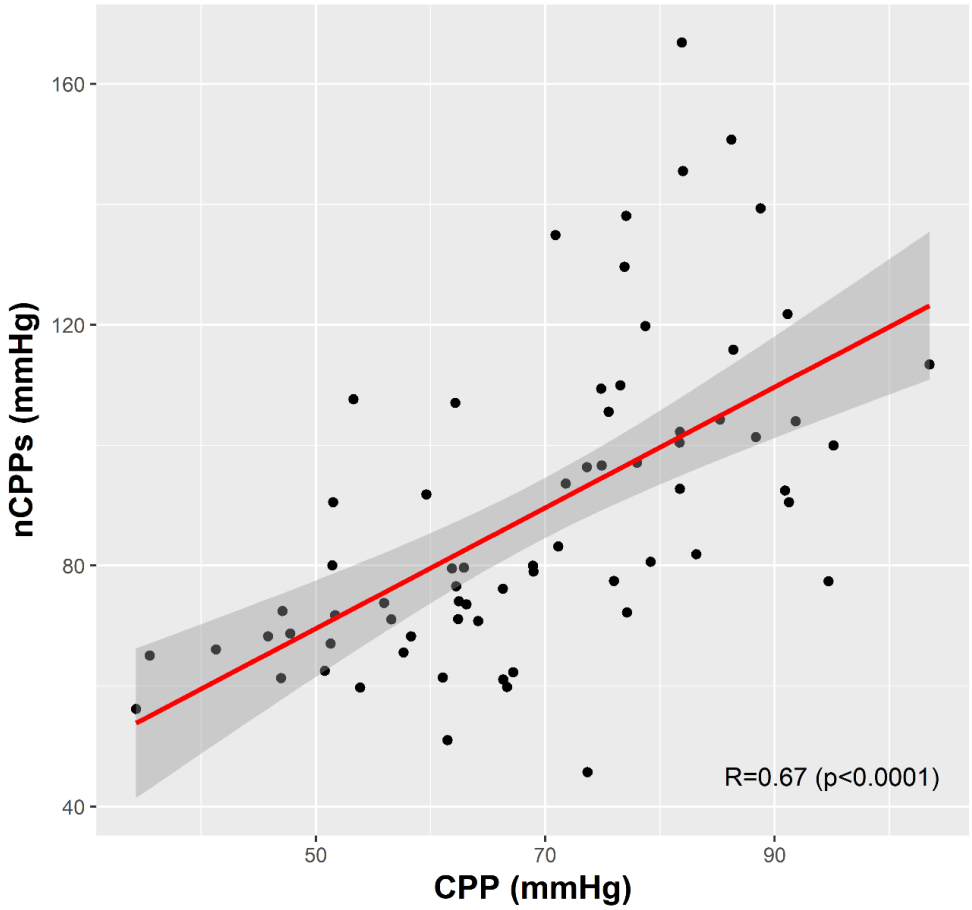


**Figure 3.** Spearman Correlation coefficient. nCPP vs CPP: R = 0.67 (P<0.0001). N = 69 recordings (19 patients).

There were three cases where the correlation in time domain was almost perfect (R>0.97) (Figure 4). The accuracy of the method obtained with Bland-Altman analysis revealed not only a wide 95% CIs for prediction of ± 40.4 mmHg but also a negative bias of -19.61 (Figure 5), meaning that nCPP overestimated true CPP by about 20 mmHg.

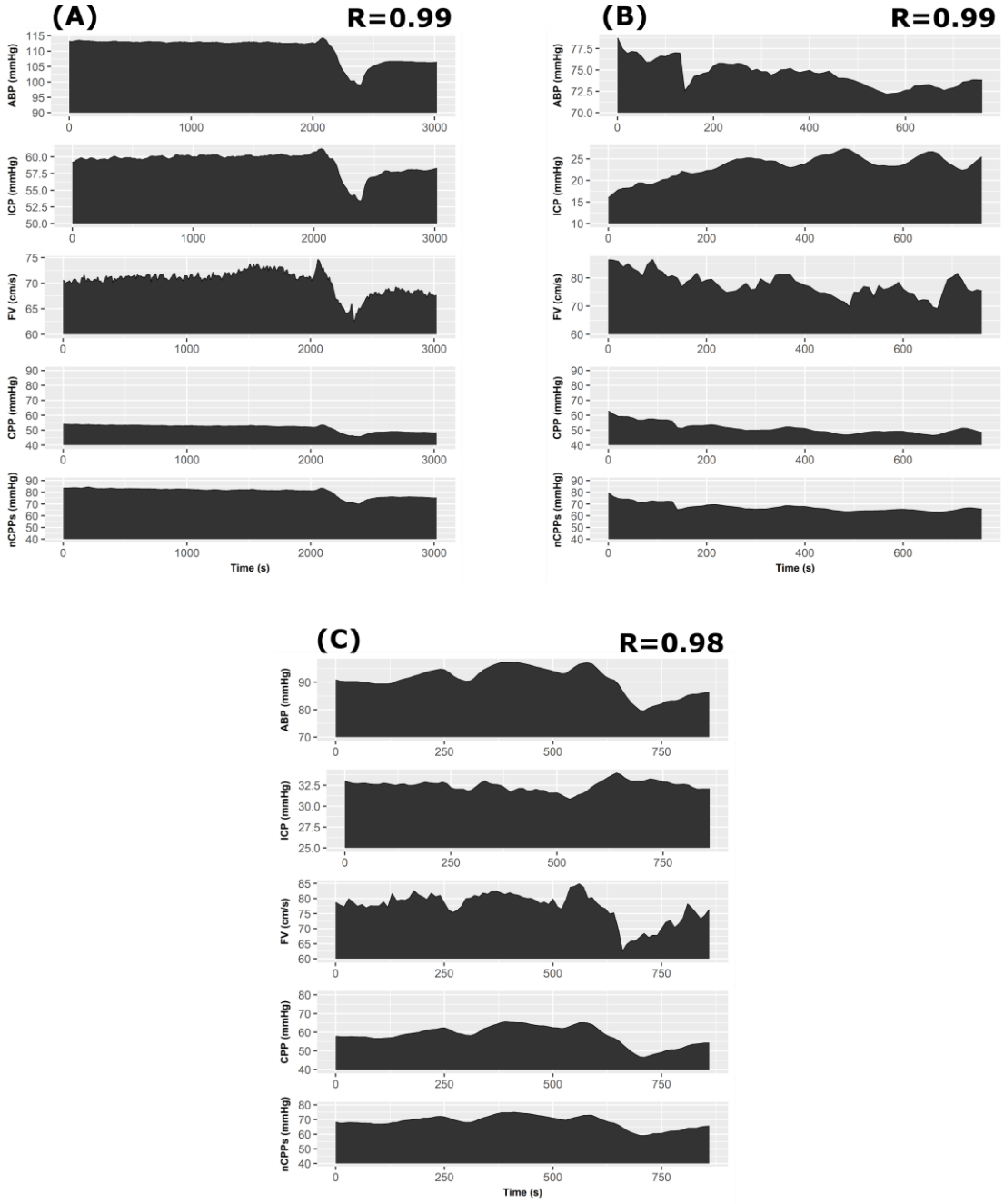


**Figure 4**. A-C Correlations in time domain of nCPP to CPP in three cases with almost perfect correlation. ABP, arterial blood pressure; ICP, intracranial pressure; FV, cerebral blood flow velocity; CPP, invasive cerebral perfusion pressure; nCPP, spectral non-invasive cerebral perfusion pressure.

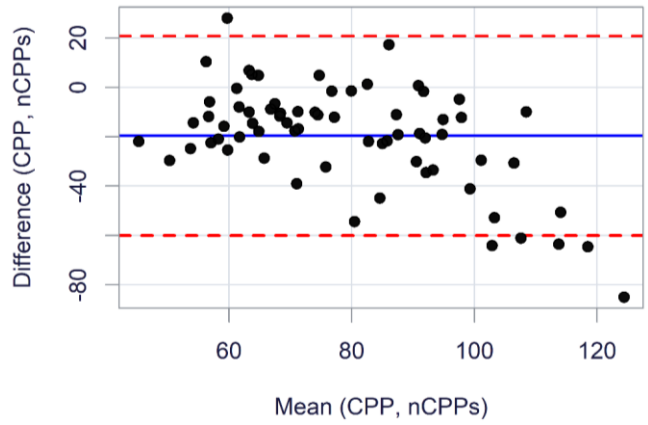


**Figure 5.** Bland-Altman analysis. Bias (mean difference): -19.61 mmHg. 95% CI for prediction: ±40.40 mmHg.

The ability of nCPP to predict CPP ≤70 mmHg was excellent, presenting an AUC=0.91 (95% CI: 0.83-0.99). The optimal cut-off values for prediction of a CPP < 70 mmHg was a nCPP of 73.95 mmHg. The sensitivity and specificity and positive and negative predictive powers for this threshold were 0.46 and 0.97 and 0.94 and 0.63 respectively (Figure 6). This means that a nCPP < 74 mmHg very likely predicts a CPP < 70 mmHg.

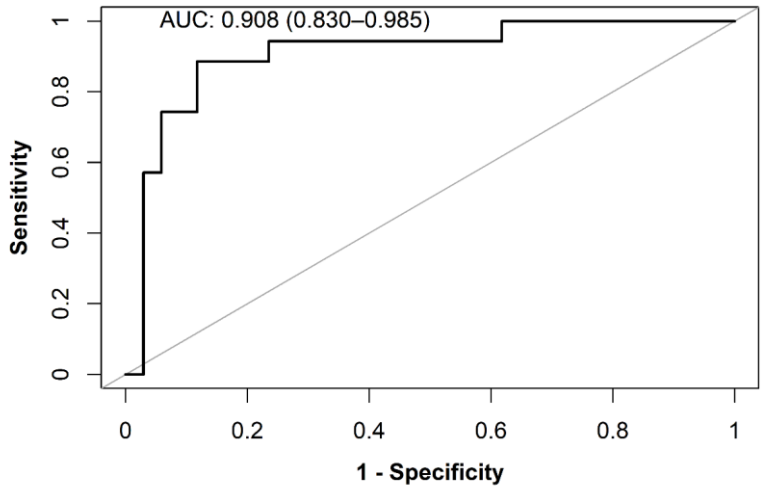


**Figure 6.** ROC curve analysis. AUC for CPP <70 mmHg: 0.908 (95% CI = 0.83-0.98); Best threshold: 73.947 (0.800-0.789); Sensitivity: 0.46; Specificity: 0.97; Positive predictive value: 0.94; Negative predictive value: 0.63.

The ability of nCPP to predict at the thresholds of 60 and 50 mmHg was also good (AUC=0.80 and AUC=0.86 respectively), but there were only five episodes with nCPP <60 mmHg (Table 2).

**Table 2.** Area under de Receiver Operating Characteristic Curve (AUC) for different cerebral perfusion pressure (CPP) thresholds

| CPP Threshold (mmHg) | AUC (95%CI) |
|---|---|
| **70** | 0.91 (0.83-0.99) |
| **60** | 0.80 (0.69-0.91) |
| **50** | 0.86 (0.77-0.95) |

## 4.6. Discussion

This is, to our knowledge, the first study to evaluate the accuracy of TCD in estimating CPP in a cohort of children with severe TBI. We have demonstrated that it can predict CPP values below 70 mmHg and that it also has a good correlation in time domain. This means that TCD-based nCPP allows for monitoring of the patients' CPP over time and detect improvement or deterioration. It can also aid in assessing response to treatment or other interventions.

The threshold of 70 mmHg for CPP is much higher than the current guidelines recommendations for children. Nonetheless, some of our patients were treated before current guidelines were issued and a higher CPP was targeted. We tested three different thresholds of nCPP: 50, 60 and 70 mmHg. They all had a good agreement with CPP, but the performance of our new model was best at the higher threshold. This does not necessarily have a clinical implication and that was not the aim of this study. There are recent studies about cerebral autoregulation and

optimal CPP in children with TBI suggesting that higher CPP targets could be linked to better outcomes (134), but more data are needed to define the best strategy and CPP goals in the treatment of paediatric TBI.

Unfortunately, our results also demonstrate that currently the accuracy of this method to estimate absolute CPP values is not good enough to be applied in the clinical practice and to substitute invasive measurement of CPP, since nCPP values overestimated CPP values by about 20 mmHg. We believe that more data are needed to test this technique and to make the model more accurate. With larger sample sizes it could be possible to improve the model taking into account this difference and adding a correction factor to the formula.

Nonetheless, for clinical decisions, measuring the absolute value of nCPP is not the only thing that matters; its trend and how it changes in response to treatment or insults seems equally important. With our study of correlations in time domain we prove that this can be done and in some cases with excellent results (Figure 4).

Another objective of our study was to test the prediction ability of nCPP to detect low CPP. For a threshold of 70 mmHg results were excellent with an AUC of 0.91. This test was very specific (97%) and with very high positive predictive value (94%). Although the values of the AUC for thresholds of 60 and 50 mmHg were also good, and are clinically more relevant to the situation of children below the age of 13 years, we cannot generalize the results because of the low number of episodes with nCPP <60 mmHg. As this is a retrospective data from a historical cohort, the target CPP limits used were higher than used in current guidelines to manage TBI in children, it is difficult to extrapolate these results to present day CPP targets. We do however prove feasibility of the equation to predict nCPP in this small cohort of children with TBI. Further work is required to see if nCPP predictions would be still applicable to lower CPP in the range of 40-60 mmHg to match the current thresholds used clinically.

Impaired autoregulation is associated with a poor prognosis, and observational data suggests that optimal neurologic outcome and survival are associated with optimal perfusion pressure both in paediatric and adult population (135,136).

Thresholds of ICP and CPP are not clear and might be dependent on the autoregulatory state of the patients (137). However, no randomized, controlled, interventional data are available to assess autoregulation monitoring after paediatric traumatic brain injury.

Non-invasive assessment of CPP and therefore of ICP have been more widely studied in the adult population using TCD (138). In a series of twenty-five consecutive patients with head injury non-invasive CPP was calculated as "ABPx$FV_d$/$FV_m$+14" ($FV_d$, $FV_m$ diastolic and mean $CBFV_a$, respectively) and compared with invasive CPP. The absolute difference between direct CPP and nCPP was less than 10 mmHg in 89% of measurements and less than 13 mmHg in 92% of measurements. The 95% confidence range for predictors was no wider than ±12 mmHg (109).

In order to use nCPP in clinical practice the values must be calculated in real-time analysis. This can be done with ICM+ software. As shown in the time domain analysis examples (Figure 6) one can detect changes in CPP by following the trends of nCPP. This is particularly valuable in patients without invasive ICP monitoring. There are two potential groups of patients who could benefit from non-invasive CPP monitoring; patients with a contraindication to invasive ICP monitoring (like coagulopathy or scalp infection) and patients without a clear indication for invasive monitoring who could potentially benefit from it (moderate TBI with potential to deteriorate, patients with TBI and confounders that prevent adequate neurological assessment like alcohol or drugs intake or previous neurological lesions). Another reason to use nCPP would be centres without neurosurgery specialists or expertise in invasive ICP monitoring.

Our study has some limitations. There was a low number of episodes with CPP below 60 mmHg in this cohort. Treatment protocols used in these patients focused on maintaining an appropriate CPP and episodes of low CPP were aggressively treated. The number of TCD recordings was adequate, but the total number of patients is small so that no speculations regarding lower CPP thresholds used currently in children can be made.

According to data from the Centres for Disease Control and Prevention (https://www.cdc.gov/traumaticbraininjury/data/rates_hosp_byage.html) TBI in children is steadily decreasing over the years. A multicentre project would allow collection of more robust data and generalization of the model proposed in the current study.

## 4.7. Conclusions

Non-invasive CPP monitoring with TCD appears to be a feasible method for CPP assessment in paediatric patients with TBI. The novel spectral CPP tested in this study has a decent correlation with invasive CPP and can predict low CPP with excellent accuracy at the 70 mmHg threshold.

Further work is required to test the non-invasive CPP predictions using this equation for CPP thresholds below 70 mmHg.

# Part 5

# Monitoring Cerebrovascular Reactivity in Paediatric TBI

# Part 5: Monitoring Cerebrovascular Reactivity in Paediatric TBI

### Adapted from the original paper

Abecasis F, Dias C, Zakrzewska A, Oliveira V, Czosnyka M. Monitoring Cerebrovascular Reactivity In Paediatric Traumatic Brain Injury: Comparison Of Three Methods. *Pediatr Res*. Under review.

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## 5.1. Impact Statement

- This is the first study to compare three different methods of monitoring cerebral autoregulation in children.
- PRx seems to be the most robust index to access cerebrovascular reactivity in children with TBI.

- PRx allows calculation of optimal CPP for the individual patient and has promising prognostic value.

## 5.2. Abstract

Background: Autoregulation of cerebral blood flow is impaired after traumatic brain injury (TBI).

Methods: Prospective cohort study of all children admitted to the paediatric intensive care unit at a university-affiliated hospital with severe TBI over a four-year period to study three different methods of monitoring autoregulation: pressure-reactivity index (PRx), transcranial Doppler derived mean flow velocity index (Mx), near-infrared spectroscopy derived cerebral oximetry index (COx).

Results: Twelve patients were included in the study, aged 5 months to 17 years old. An empirical regression analysing dependence of PRx on cerebral perfusion pressure (CPP) displayed the classic U-shaped distribution, with low PRx values (<0.3) reflecting intact auto-regulation, within the CPP range of 50-100 mmHg. The optimal CPP was 75-80 mmHg for PRx and COx. The correlation coefficients between the three indices were: PRx vs Mx, r = 0.56; P<0.0001; PRx vs COx, r = 0.16; p<0.0001; COx vs Mx, r = 0.15; p=0.022. The mean PRx with a cutoff value of 0.3 predicted correctly long-term outcome (p=0.015).

Conclusion: PRx seems to be the most robust index to access cerebrovascular reactivity in children with TBI. It allows calculation of optimal CPP for the individual patient and has promising prognostic value.

## 5.3. Introduction

Traumatic brain injury is a main cause of child morbidity and mortality worldwide (1,2). Survivors with severe neurological impairment represent an important burden to families and society.

All human trials assessing the use of pharmacological neuroprotection after TBI failed to show unequivocal clinical efficacy (139). Modern neurocritical care management focus on minimizing secondary brain injury. The use of management strategies based on multimodal brain monitoring have a potential to improve patient outcome (140).

Autoregulation of cerebral blood flow (CBF) is an important mechanism allowing CBF to stay constant despite fluctuations of cerebral perfusion pressure. It has been shown to be impaired in children with mild, moderate or severe TBI (141) and loss of autoregulation is associated with a poor outcome (85). There are several techniques that allow continuous monitoring of indices of autoregulation (and its surrogate - cerebrovascular reactivity) comparing intracranial pressure (ICP), blood flow velocity or cerebral oximetry to arterial blood pressure (ABP) or cerebral perfusion pressure (CPP). These indices could help to identify patients at risk of losing CBF control and aid developing tailored therapies. It has yet to be determined if autoregulation can be always effectively restored, how it can be done, and if restoring autoregulation improves outcome. Nonetheless, data from pilot studies in adult patients with TBI point in that direction (142) and a multicentre Phase II trial for using an autoregulation based protocol is underway: CPPOpt Guided Therapy - Assessment of Target Effectiveness (COGITATE) (90).

The most thoroughly studied index of cerebrovascular reactivity is the pressure reactivity index (PRx). It was first described in the late nineties (77) and has been evaluated both clinically and experimentally since then. PRx is calculated as the correlation coefficient between slow waves (0.005 to 0.05Hz) of ABP and ICP. In several studies it is consistently associated with outcome both in adult

(78,136,143) and paediatric (85,87,144) TBI. When plotted against CPP it shows a U-shaped curve that allows the determination of the CPP that corresponds to the lowest PRx and so to the best state of autoregulation. This has been termed "optimal CPP" (89).

Transcranial Doppler (TCD) derived mean index (Mx) can also be used to evaluate cerebrovascular pressure reactivity (53). Mx is the correlation between mean blood flow velocity measured by TCD and CPP. Mx has also been shown to reflect cerebral autoregulation and to correlate with outcome in patients with TBI (145). The disadvantage of Mx is its intermittent nature. It may be monitored only if ultrasound probes are focused on middle cerebral arteries, which in the busy environment of neurocritical care units remains problematic.

Near-infrared spectroscopy (NIRS) is a non-invasive technique based on the transmission and absorption of near-infrared light (700 – 1000 nm) as it passes through tissue. It is a non-invasive method of assessing cerebral hemodynamic and metabolic parameters (140). It is used clinically during neonatal cardiac surgery to guide regional perfusion to the brain (146) and it has also been proposed as a method to measure cerebral autoregulation using the cerebral oximetry index (COx) (71). NIRS derived COx has been validated to represent changes in CBF in several animal studies (147,148) and has been used in clinical practice.

We performed an exploratory study on the measurement properties of these three different methods of monitoring cerebrovascular reactivity in children with TBI: pressure-reactivity index (PRx), TCD derived mean index (Mx), near-infrared spectroscopy derived cerebral oximetry index (COx). Such a comparison has never been conducted in paediatric patients.

## 5.4. Methods

We performed a prospective cohort study of all children (>28 days and <18 years) admitted to the paediatric intensive care unit (PICU) at a university-affiliated hospital with severe TBI during the study period (4 years). Exclusion criteria included patients with previous severe neurological impairment.

**Ethical approval and informed consent**

The Ethical Committee of the Lisbon Academic Medical Centre has approved this study and an informed consent was obtained from parents or next of kin at the time of admission and from the children older than 14 years old when they recovered if they were able to understand and give consent. All performed procedures were part of the standard care for severe TBI in the PICU.

**Data collected from all patients:**

Gender and age; type and time of trauma; severity of TBI - Glasgow coma score (GCS) at the scene of the accident); neurological examination at admission and discharge from PICU; computed tomography scan and magnetic resonance imaging results; King's Outcome Scale for Childhood Head Injury (KOSCHI) (149) applied at discharge from the PICU, 3, 6, 12 months since admission.

**Data acquisition, storage and analysis:**

To determine systolic, end-diastolic and mean arterial blood flow velocities (CBFV) in intracranial arteries, the main investigator (FA) performed TCD using a Digi-lite equipment with a 2-MHz PW probe, using classical transtemporal windows. The probe was held in place by a helmet or an elastic bandage in younger children and a continuous recording for periods of one to two hours were obtained. In offline analysis the 45 minutes with the best signal of each recording were analysed.

Invasive arterial blood pressure was recorded continuously with the transducer at the level of the right atrium, as usually practiced in paediatric critical care. Children are treated with the head of the bed elevated 20-30 degrees, so values of CPP are at least 5-10 mmHg higher than the values that would be obtained if the arterial line transducer was at the level of the external ear canal.

A parenchymal probe was used to monitor ICP. If an external ventricular drainage (EVD) catheter was used for monitoring ICP, we only analysed data from the periods when the EVD was closed to avoid cerebrovascular reactivity evaluation limitations related to an open EVD.

Cerebral oximetry with NIRS was performed continuously using the Covidien, INVOS™ 5100C Cerebral/Somatic Oximeter to measure cerebral regional oxygen saturation (rSO2). Two sensors were used to measure right and left cerebral oxygen saturation.

All signals (ICP, ABP, CBFV, rSO2, End-tidal CO2, ECG) were recorded and analysed digitally using ICM+ software (Cambridge Enterprise, Ltd.).

**Optimal CPP calculation**

Optimal CPP was calculated through CPP-PRx and CPP-COx error bar chart analysis as described previously (136). Using ICM+ software, optimal CPP was determined for each patient using data from all the recording period and calculating the CPP that corresponded to the lowest PRx value.

**Comparing different cerebrovascular reactivity measurements:**

Three different indices of cerebrovascular reactivity were compared (PRx, Mx, COx). The indices were calculated automatically with real time analysis using ICM+ by the following process: a moving Pearson correlation coefficient was calculated between ICP and MAP (for PRx), CBFV and CPP (for Mx), rSO2 and MAP (for COx), using 30 consecutive 10-sec moving average windows (i.e., 5 min of data), updated every minute. The mean value of both sides of COx was used for

comparison. Statistical analysis was performed using Pearson's and Spearman correlation coefficients and Bland Altman plots with IBM® SPSS® statistics version 24. Data from all patients were combined and cross-correlation analysis was performed.

**Outcome evaluation and correlation with autoregulation**

Although small number of studied patients invalidated formal analysis of outcome, we intended to compare if there was any trend between autoregulation indices and outcome. Autoregulation was dichotomized for statistical analysis in preserved or disturbed (a cut-off value of 0.3 was set (71,150)) and compared to outcome evaluated with KOSCHI and also dichotomized in bad outcome (1, 2, 3a and 3b) or good outcome (4a, 4b, 5a and 5b). Chi-square and exact Fisher tests were used.

## 5.5. Results

Thirteen patients fulfilled the entry criteria during the recruitment period. One patient was excluded because he already had signs of brain death when the recording of data started. Nonetheless, this patient had a PRx value always above 0.3.

Twelve patients were included in the final analysis. No patients were lost during the study period but it was not possible to perform TCD in all patients due to technical issues, like wounds in the head that prevented the use of the helmet to hold the probes.

Table 1 shows patient demographics and outcome of all patients included in the study. There were 8 boys and 4 girls, aged 5 months to 17 years. All patients suffered a road traffic accident. The last two patients were not comatose immediately after the accident, but deteriorated later meeting the criteria of severe TBI.

**Table 1.** Patient Demographics and Outcome

| Patient | Age (years) | Mechanism of Injury (vehicle) | GCS at site | Optimal CPP (mmHg) | KOSCHI at discharge | Long-term outcome |
|---|---|---|---|---|---|---|
| 1 | 9 | Pedestrian | 5 | 80 | 2 | Good |
| 2 | 10 | Pedestrian | 9 | 66 | 4b | Good |
| 3 | 17 | Motorcycle | 8 | 47 | 3b | Good |
| 4 | 16 | Motorcycle | 6 | 70 | 3a | Good |
| 5 | 10 | Pedestrian | 7 | 52 | 5a | Good |
| 6 | 13 | Bicycle | 7 | 68 | 3a | Good |
| 7 | 13 | Motorcycle | 7 | 70 | 2 | Bad |
| 8 | 14 | Bicycle | 8 | 57 | 4b | Good |
| 9 | 11 | Car | 4 | NA[a] | 1 | Bad |
| 10 | 9 | Pedestrian | 4 | 72 | 3a | Good |
| 11 | 13 | Pedestrian | 14 | 66 | 4a | Good |
| 12 | 0 (5 months) | Car | 14 | 78 | 3b | Good |

[a] Not applicable - An optimal CPP could not be calculated due to a persistently increased PRx (>0.3).

GCS, Glasgow Coma Score; CPP, Cerebral perfusion pressure; KOSCHI, King's Outcome Scale for Childhood Head Injury.

**Relationship between PRx versus CPP and COx versus CPP**

The results of the empirical regression analysis with data from all patients analysing dependence of PRx and COx on CPP are shown on Figure 1. The PRx versus CPP plot displays the classic U-shaped distribution, with low PRx values (<0.3), reflecting intact auto-regulation, within the CPP range of 50-100 mmHg. Outside of these two limits of CPP, PRx subsequently trends toward higher values indicating impaired autoregulation. The CPP that corresponds to the lower value of PRx or COx and theoretically to the best state of autoregulation (optimal CPP) is 75-80 mmHg for both indices.

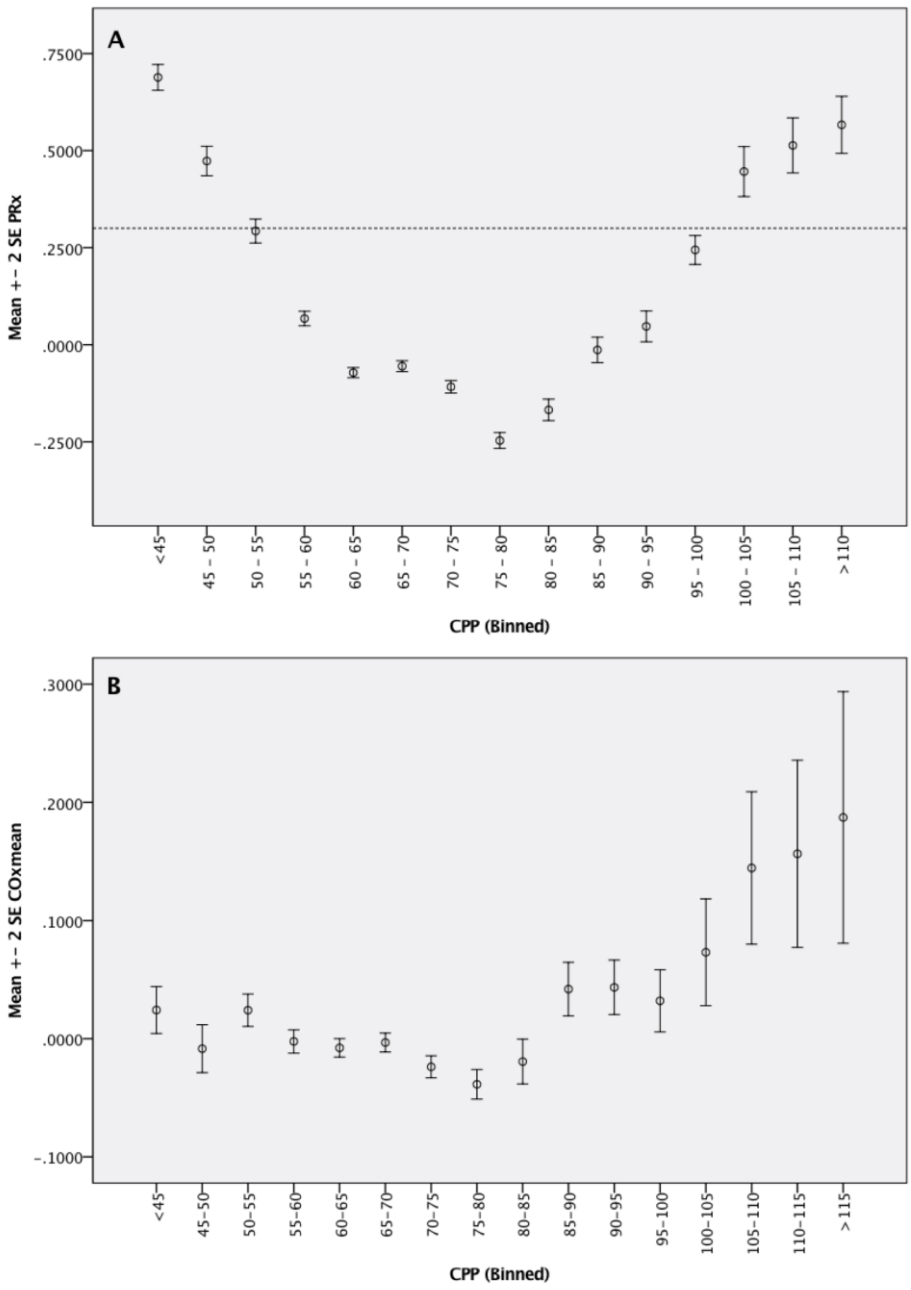


**Figure 1**. Pressure reactivity index (PRx) (**A**) and near-infrared spectroscopy derived cerebral oximetry index (COx) (**B**) plotted against cerebral perfusion pressure (CPP). CPP was binned in 5 mmHg intervals and the mean of PRx or COx ± 2 standard errors was calculated for each interval. The dashed line represents the PRx 0.3 cutoff for impaired autoregulation. 19,414 data points (12 patients).

Optimal CPP was also calculated individually for all patients using PRx as described in methods. The results are displayed in table 1. For patient number 9 it was not possible to calculate optimal CPP because PRx values were persistently positive until the death of the patient. Optimal CPP varied between 47 and 80 mmHg. In Figure 2 we show an example of a patient with an optimal CPP of 67.6 mmHg calculated by this method.

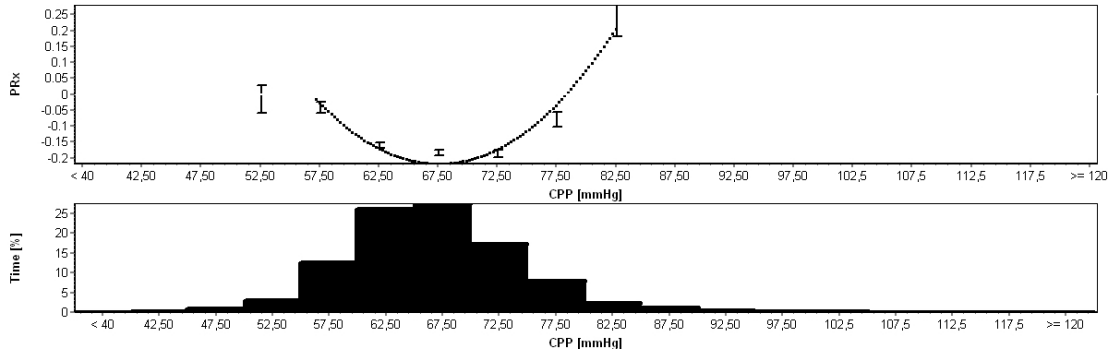


**Figure 2.** Determination of the optimal cerebral perfusion pressure (CPP) in patient number 6. CPP opt = 67.6 mmHg; corresponding to a pressure reactivity index (PRx) of -0.22.

## Comparing different cerebrovascular reactivity indices

In Figure 3 we show an example of a time-interval monitoring with a very good correlation between PRx and Mx (r=0.82) and a good correlation between COx and Mx (r=0.53) and COx and PRX (r=0.57).

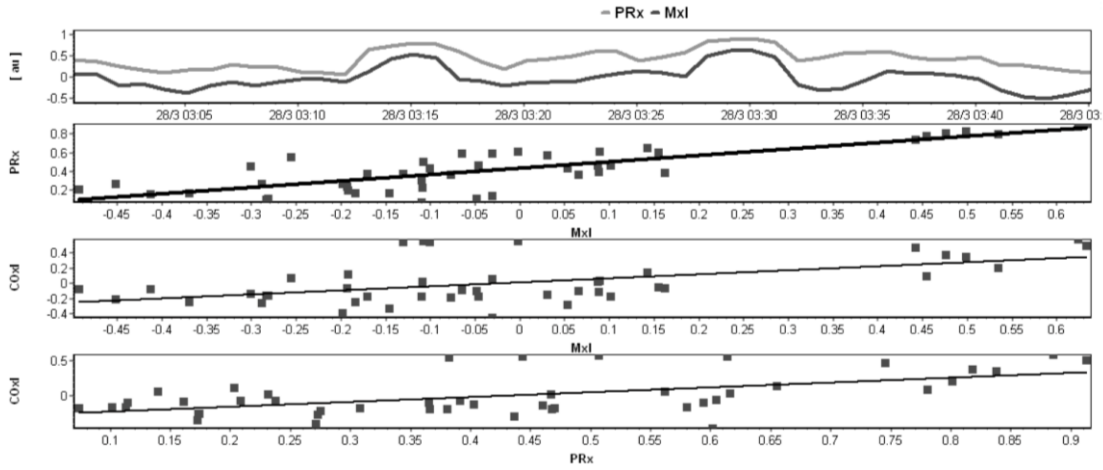


**Figure 3**. An example of a time-interval monitoring over a 45 minute period of recording showing the correlation between the three indices of cerebrovascular reactivity: pressure reactivity index (PRx), near-infrared spectroscopy derived cerebral oximetry index (COx) and transcranial Doppler derived mean flow velocity index (Mx). Correlation coefficients: PRx vs Mx 0.82; COx vs Mx 0.53; COx vs PRx 0.57.

The correlation between the different indices of cerebrovascular reactivity and the respective Bland-Altman plots are displayed in Figure 4. For comparison between PRx and Mx we analysed 494 data points from 6 patients; for comparison between COx and Mx, 229 data points from 6 patients and for comparison between PRx and COx, 19,414 data points from 12 patients. The best correlation found was between PRx and Mx ($r=0.56$;$p<0.0001$), followed by PRx and COx ($r=0.16$; $p<0.0001$) and then by COx and Mx ($r=0.15$; $p=0.022$). The Bland-Altman plots show that the agreement between the three indices is poor and the 95% confidence interval (CI) for prediction is very large for all the comparisons made. In the case of PRx and COx, even though the correlation is not good, the agreement between the two measures greatly improves for extreme values (<-0.5 and >0.5), as illustrated by the losange shape of the respective Bland-Altman plot.

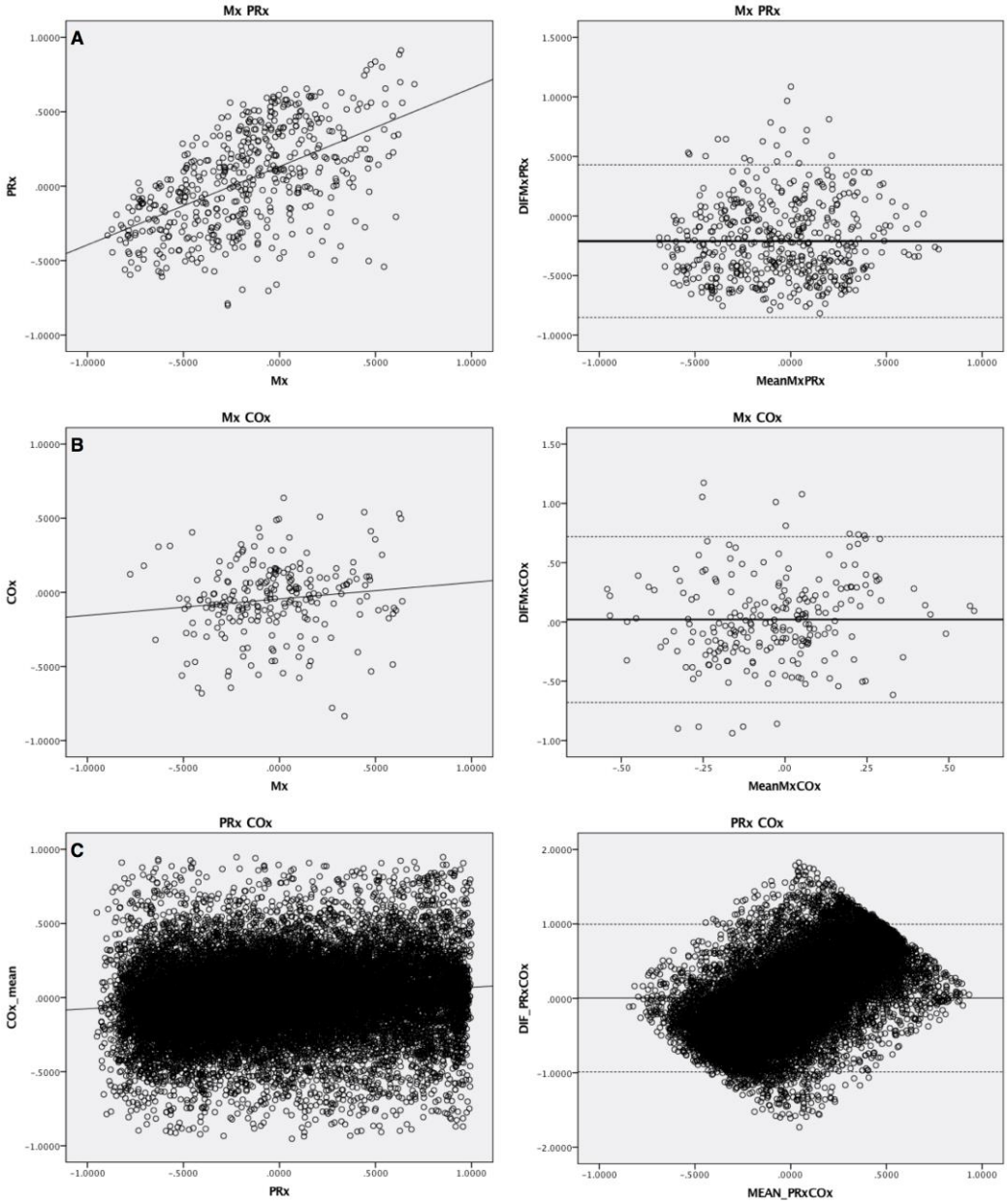


**Figure 4**. (**A**) Correlation between PRx and Mx, Spearman's rank correlation coefficient = 0.56; P<0.0001 and Bland-Altman plot PRx vs Mx, Bias (Mean difference) -0.21; 95% CI for prediction, ± 1.28; (**B**) correlation between Cox and Mx, Spearman's rank correlation coefficient = 0.15; p=0.022 and Bland-Altman plot COx vs Mx, Bias (Mean difference): 0.02; 95% CI for prediction, ± 1.40; (**C**) correlation between PRx and COx, Spearman's rank correlation coefficient = 0.16; p<0.0001 and Bland-Altman plot PRx vs COx, Bias (Mean difference): 0.004; 95% CI for prediction, ± 1.98.

### Outcome implications

PRx was the only cerebrovascular reactivity index that significantly correlated with outcome. When the mean PRx of the entire period of monitoring was used to determine long-term outcome it was correct in all patients ($p=0.015$). Two patients had a mean PRx > 0.3 and had a bad long-term outcome and 10 patients had a mean PRx < 0.3 and had a good long-term outcome. Even when the mean PRx of the first 24 hours of monitoring was used it was still able to discriminate between good or bad outcome ($p=0.045$). There were three patients with a mean PRx > 0.3 in the first 24h and two of them had a bad outcome and one had a good long-term outcome. All patients with a mean PRx < 0.3 in the first 24 hours had a good long-term outcome.

## 5.6. Discussion

This prospective cohort study aimed to compare three different indices of cerebrovascular reactivity in children with severe TBI. To our knowledge, this is the first study to compare PRx, COx and Mx in one group of children.

One of the main objectives for studying cerebral autoregulation is to guarantee that we treat patients within the limits of autoregulation. If cerebral perfusion pressure drops below the lower limit of autoregulation the CBF will dramatically decrease as has been shown by Lassen more than 60 years ago (73).

Our results set the limits of autoregulation between a CPP of 50 and 100 mmHg, when analysing PRx versus CPP. The lower limit of 50 mmHg is higher than the limit of 40 mmHg recommended for children with TBI in the last guidelines of the Brain Trauma Foundation (9). For younger children (<2 years old) a minimum CPP of 45 mmHg has been proposed (22). In a recent paper that included more than 2000 patients and 317 children, age specific targets for CPP were defined. It was recommended that the goal for CPP for children 0-5 years old should be 40 mmHg and for 6-17 years old should be 50 mmHg (28). This is in accordance with our results since all children, except one infant, included in our study were more than 6 years old. We believe that for older children and adolescents a limit of 50 mmHg of CPP is more appropriate and closer to the optimal CPP in most patients. In fact, only one patient had an optimal CPP of less than 50 mmHg.

When comparing the properties of the three indices studied, we found that the PRx appears to measure cerebrovascular reactivity with the best accuracy as exemplified by the classic U-shaped curve when data from all patients were combined (Figure 1). This is in agreement with previous studies (85,136,142) and suggests that PRx is the most powerful index of autoregulation. The correlation between the three indices was significant, but not good. There are periods when all indices have a good or very good correlation as shown in Figure 3, but this is

not consistent over time. COx and Mx may be useful for offline analysis, but their use for guiding clinical decisions needs further studies and validation.

In terms of helping in the determination of prognosis, PRx was the only index associated with outcome. Even though our population was limited to twelve patients, PRx was able to predict outcome correctly in all patients. There are three studies in children with TBI that came to a similar conclusion (85,87,144) reinforcing PRx as an accurate predictor of outcome in these patients. This is clinically very significant because it can help the physician at the bedside when only limited neurological evaluation is usually possible in heavily sedated or comatose patients. It has yet to be demonstrated by a randomized controlled trial that a treatment protocol oriented at restoring autoregulation through the manipulation of CPP improves outcome. But all available evidence and logics suggest it does. If this were confirmed in children with TBI, PRx would become not just a way to determine outcome but a tool to change the outcome.

The current study main limitation is the number of patients. Fortunately, in recent years we have observed a dramatic decrease in children with severe TBI admitted to our PICU. Although no patients were lost during the study period the total number of participants was low. Nonetheless, many hours of recording for each patient allowed the collection of more than 20,000 data points to be analysed. We acknowledge that the conclusions have to be cautious, but we still believe that this pilot study helps to a better understanding of how these indices can be used in children.

In table 2 the main characteristics of the three indices of cerebrovascular reactivity studied are summarized.

**Table 2.** Main characteristics of the three indices of cerebrovascular reactivity

| Cerebrovascular reactivity index | Variables | Technology | Advantages | Disadvantages |
|---|---|---|---|---|
| **PRx** | MAP<br>ICP | ICP monitor | Continuous<br>Allows calculation of optimal CPP<br>Good correlation with outcome<br>Calculated based on ICP monitoring which is a widely available standard clinical procedure in all centers treating children with TBI | Invasive<br>Not possible with external ventricular drainage (open) |
| **COx** | MAP<br>$rSO_2$ | NIRS | Non-invasive<br>Continuous<br>Potential calculation of optimal CPP | Poor correlation with PRx<br>Poor correlation with outcome.<br>Disturbed with artifacts (e.g. intracranial bleeding) |
| **Mx** | CPP<br>CBFV | TCD | Potentially non-invasive (If MAP is used instead of CPP) | Not continuous (30-60 min is feasible)<br>Technically difficult<br>User dependent<br>Artifacts (e.g. probe displacement) |

PRx, pressure-reactivity index; COx, near-infrared spectroscopy derived cerebral oximetry index; Mx, transcranial Doppler derived mean flow velocity index; MAP, mean arterial pressure; ICP, intracranial pressure; $rSO_2$, cerebral regional oxygen saturation; CPP, cerebral perfusion pressure; CBFV, cerebral blood flow velocity; NIRS, near-infrared spectroscopy; TCD, transcranial Doppler; TBI, traumatic brain injury.

## 5.7. Conclusions

PRx seems to be the most robust index to access cerebrovascular reactivity in children with TBI. It allows calculation of optimal CPP for the individual patient and has prognostic value. Non-invasive indices of cerebrovascular reactivity like COx and Mx are less accurate and may need further validation, before being used clinically.

# Part 6

# Discussion, Conclusions and future directions

# Part 6: Discussion, Conclusions and future directions

In this last part, I will make a systematic discussion about the results of our research, related to each of the three hypothesis formulated. Finally, I will summarize the main conclusions and point future directions of investigation on this topic.

## 6.1. The role of neurovascular sonography in paediatric TBI

TCD is a powerful technique with multiple roles in the evaluation and management of patients in neurocritical care. On this part of the thesis I undertook a critical appraisal on the role of TCD in paediatric patients with TBI based on my own experience and literature review.

The main roles of TCD in paediatric TBI can be summarized in the following manner:

### Non-invasive estimate of ICP

TCD can accurately predict a raised ICP after paediatric TBI, especially if a higher cut-off value for PI is used. In our clinical practice we use a threshold of 1.4 using the Gosling PI. Arterial blood pressure and pCO2 have to be taken into consideration as these parameters can change PI. There can be false negatives, in case of arterial hypertension, and false positives, in case of hypotension or hyperventilation. It can be extremely useful at admission to help determine the level of care and prioritize actions to take in children who suffered a TBI.

### Non-invasive estimate of CPP

Among the several non-invasive methods reported for CPP assessment, TCD has been one of the most used for determination of nCPP in TBI. It is not a surprise that PI correlates better with CPP than with ICP, because PI is not dependent solely on cerebrovascular resistance but it is a product of the interplay between CPP, pulse amplitude of arterial pressure, cerebrovascular resistance and compliance of the cerebral arterial bed as well as the heart rate. Therefore, PI is not an accurate estimator of ICP and it describes CPP in a more accurate manner.

### Autoregulation and continuous monitoring of TCD signals

In the case of TCD, autoregulation monitoring uses the signals of ABP, ICP and cerebral blood flow velocities to calculate indices of autoregulation:

- Mx index is the correlation coefficient between mean flow velocity and CPP
- Sx index is the correlation coefficient between systolic flow velocity and CPP

If Mx and Sx are positive it means autoregulation is impaired and this is associated with a bad outcome after TBI.

Dynamic cerebral autoregulation monitoring can be done non-invasively with TCD but one of the major challenges is the necessity to be able to record flow velocities for a long period of time. This can be accomplished with probe holders, but the signal can be lost with positioning of the patient or spontaneous movement. Children represent an additional challenge because of different head sizes and some holders are difficult to use in small children. New devices using robotic probes allow for continuous monitoring over extended time periods and will make it more usable in clinical.

### Detect regional variations on cerebral haemodynamics

One of the challenges in studying the injured brain is that many devices only allow for measurements in one particular area of the brain. This is the case with ICP bolts or PbtO2 probes. TCD has the major advantage of allowing insonation of different territories. This is particular important in pathologies like TBI that can have focal lesions. Although a raised ICP, especially if severe, will ultimately be transmitted to the whole brain, there can be important asymmetries at an initial phase.

### Diagnosis of brain death

Paediatric TBI is one of the major causes for organ donation and the identification of cerebral circulatory arrest with TCD can be very helpful to clinicians. Although TCD is not accepted in all countries for the diagnosis of brain death, it is commonly used in others. It is indicated to use an ancillary test of no cerebral blood flow when the clinical examination cannot be completed or there are drugs that could affect the results. In our practice we use TCD in every patient that is considered for organ donation. We find it reassuring for both family members and staff.

## 6.2. TCD is useful in paediatric emergency and critical care settings

I have demonstrated through several paradigmatic examples that TCD can aid clinical management. I selected different examples of common conditions that require an understanding of cerebral haemodynamics to guide therapy. In all cases presented TCD was crucial in determining the course of action to be taken. Based on our experience, I find TCD to be especially useful in the following circumstances in the emergency department and paediatric critical care units:

- Conditions presenting with intracranial hypertension
    - Traumatic brain injury
    - Hydrocephalus
    - Central nervous system infections

- Conditions presenting with decreased cerebral perfusion pressure
    - Hypovolemic shock
    - Septic shock

- In the diagnosis of impending or complete cerebral circulatory arrest
    - Establishment of brain death

TCD is not a replacement for other established techniques of neuromonitoring, but should be included in multimodal neuromonitoring as a useful tool to estimate cerebral blood flow. TCD is inexpensive, non-invasive, real-time, harmless, and easy to perform with the correct training and can be done in almost all environments without having to move the patient. It can be repeated as needed, but continuous monitoring for more than 30-60 minutes is still challenging.

I believe that more widespread use of this inexpensive technique would allow a better care of children with neurologic insults and that it truly represents a non-invasive window to cerebral blood flow.

## 6.3. TCD can estimate cerebral perfusion pressure in children with TBI

In many clinical conditions, the assessment of intracranial pressure and cerebral haemodynamics using invasive methods cannot be performed. Based on the results of the study we performed in children with TBI, we have demonstrated that a novel non-invasive spectral CPP can accurately predict CPP values below 70 mmHg and that it also has a good correlation in time domain. This means that TCD-based nCPP allows for monitoring CPP over time and detect improvement or deterioration. It can also aid in assessing response to treatment or other interventions.

Unfortunately, our results also demonstrated that currently the accuracy of this method to estimate absolute CPP values is not good enough to be applied in the clinical practice and to substitute invasive measurement of CPP. Nonetheless, for clinical decisions, measuring the absolute value of nCPP is not the only thing that matters; its trend and how it changes in response to treatment or insults seems equally important. With our study of correlations in time domain we prove that this can be done and in some cases with excellent results.

## 6.4. Cerebral autoregulation monitoring and prognostic implications

To test the hypothesis that invasive and non-invasive indices of cerebral autoregulation are feasible and accurate in children with TBI and have prognostic value, we performed a prospective cohort study of all children admitted to our pediatric intensive care unit with severe TBI over a four-year period. We aimed to compare three different indices of cerebrovascular reactivity, PRx, COx and Mx, in children with severe TBI.

Our results set the limits of autoregulation between a CPP of 50 and 100 mmHg, when analysing PRx versus CPP. The lower limit of 50 mmHg is higher than the

limit of 40 mmHg recommended for children with TBI in the last guidelines of the Brain Trauma Foundation. Based on our data we believe that for older children and adolescents a limit of 50 mmHg of CPP is more appropriate and closer to the optimal CPP in most patients. In fact, only one patient had an optimal CPP of less than 50 mmHg.

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PRx was the only index associated with outcome. Even though our population was limited to twelve patients, PRx was able to predict outcome correctly in all patients. This is clinically very significant because it can help the physician at the bedside when only limited neurological evaluation is usually possible in heavily sedated or comatose patients. It has yet to be demonstrated by a randomized controlled trial that a treatment protocol oriented at restoring autoregulation through the manipulation of CPP improves outcome. But all available evidence and conceptual framework suggest it does. If this were confirmed in children with TBI, PRx would become not just a way to determine outcome but also a tool to change the outcome.

## 6.5. Conclusions

The main conclusions of this thesis are:

- Transcranial Doppler is a useful technique for aiding clinical decisions at the bedside in children with acute brain injury;
- Multimodal neuromonitoring is feasible in paediatric patients with TBI;
- PRx seems to be the most sensitive index of cerebral autoregulation in children and has prognostic value;
- Non-invasive continuous neuromonitoring is promising but it is still not accurate enough to replace invasive monitoring.

## 6.6. Implications for practice and future directions

The results of this research led to original conclusions and some of them can be immediately applied to clinical settings.

The use of TCD in the emergency department and in the intensive care unit is becoming part of the usual management of patients with acute brain injury. Other specialities, like neurosurgery, increasingly ask for TCD examinations and many times support their decision on the results of this exam. It is rewarding to watch the growing confidence in our work, sustained in solid results that are usually confirmed in the operating room or in the clinical course of the patients.

Multimodal neuromonitoring is currently applied to all patients admitted in our unit with severe TBI. It has become a reality as a consequence of our research work. Concepts like cerebral autoregulation and optimal CPP are becoming more

familiar in our daily practice and I believe that in the future the management of TBI will be driven by autoregulation optimization.

Future investigation will focus on the improvement of non-invasive methods of neuromonitoring. New technologies and algorithms will probably increase the accuracy of these methods that are still not accurate enough to replace invasive methods as shown in our research.

Another topic for future research will be the organization of randomized trials to test management protocols oriented to restore autoregulation. Unfortunately, there are no studies with paediatric enrolment at the time of this writing. Data from adult patients is very promising and hopefully a multicentre study that includes children will take place in the future and I will definitely want to take part of that study.

# Final remarks

## Connecting the dots

I decided to become a doctor when I was 5 years old. Beside the obvious influence of my father being a doctor, I believe the main reason for my choice was to be able to help people. And what a better way to help than when they most need it? Since that day I have never wanted to be anything else but a doctor.

Choosing to be a paediatrician came much later. It was a surprise to many, including some of my closest relatives and friends. But it fulfilled all my goals: to be able to help people when they most need it, to have a speciality that covers different aspects of medicine, to maintain a global vision of the patients.

I see myself as a clinician that has an interest in teaching and investigation. Throughout my professional life I have embraced these other aspects of Medicine with full commitment. I believe teaching is an integral part of being a doctor. I was fortunate to have great masters that taught me what you cannot learn from books. And I try to return their teachings by passing them on to my students, residents, nurses and colleagues.

A doctor is also an investigator. That is part of our daily activity. We ask questions and try to find answers. The spirit to investigate and increase our knowledge is always there. May it be to find a diagnosis for a patient or to perform a clinical trial. A PhD project is taking investigation to the next level, by pushing the boundaries to increase the global knowledge on a specific field.

Another aspect of my life that has always been present is sports. Volleyball was my whole life sport, but unfortunately I had to quit playing due to a shoulder injury. I turned to running. I started for fun and never stopped running. Last year

I completed my first marathon. The marathon, like the PhD, is by definition a one-person project. Nonetheless, to be able to run a marathon you have to commit to hard training, but also find friends that will help you out during practice and even on race day. This is also true for a PhD project where I learned to value friendship and collaboration. There were times of great joy and sharing but also difficult times and even lonely ones. It is said that what matters is the journey and not the destiny. And beyond any doubt the journey is definitely an incredible part of the project. But there are no words to describe the happiness and feeling of accomplishment when I crossed that finish line after running 42,195 Km. I hope that I can have the same feeling when I complete this journey.

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