

DOUTORAMENTO

MEDICINA

**Prognostic value of cardiovascular response in children
with severe brain injury**

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D

2025



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Tese elaborada para obtenção do grau de Doutor em Medicina apresentada à Faculdade de Medicina da Universidade do Porto.

Ao abrigo do Artº4º, §2º do Decreto-Lei nº707/2018, fazem parte desta tese as seguintes publicações:

- 1- Silva, MJ; Antunes, N. The utility of heart rate variability as a prognostic factor in children with traumatic brain injury. *Brain Injury*. 2020 Dec 5;34(13-14):1693-1700. doi: 10.1080/02699052.2020.1836401.
- 2- Silva, MJ; Carneiro, B; Mota, R; Baptista, MJ. Cardiovascular events in children with brain injury: A systematic review. *Int J Cardiol* 2023 Sept 15;387:131132. doi: 10.1016/j.ijcard.2023.131132.
- 3- Silva, MJ; Pinheiro, R; Almeida, R; Cunha, F; Ribeiro, A; Rocha AP; Guimarães, H. Heart Rate Variability in Children Submitted to Surgery. *J Anesth Clin Res* 2016, 7:11. doi: 10.4172/2155-6148.1000688.
- 4- Silva MJ; Gonçalves H; Almeida R; Dias CC; Almeida AI; Rocha AP; Granja C; Baptista MJ; Azevedo I. Cardiovascular responses as predictors of mortality in children with acute brain injury. *Pediatr Res* 2024.
<https://doi.org/10.1038/s41390-024-03679-2>.
- 5- Silva MJ, Gonçalves H, Almeida R, Dias CC, Almeida AI, Rocha AP, Granja C, Baptista MJ, Azevedo I. The role of cardiovascular response as a predictor of neurologic disability in children with brain injury – a pilot study. *European Journal of Paediatric Neurology* 56 (2025): 38-45.
<https://doi.org/10.1016/j.ejpn.2025.04.009>

Foi coautora de outros estudos publicados relacionados com o tema:

- 1- R. Almeida, M. J. Silva; A. P. Rocha, Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients, *Computing in Cardiology 2013*, Zaragoza, Spain, 2013, pp. 61-64.
- 2- A. P. Rocha, R. Almeida, A. Leite, M. J. Silva; M. E. Silva, Long-term HRV in critically ill pediatric patients: Coma versus brain death, *Computing in Cardiology 2014*, Cambridge, MA, USA, 2014, pp. 89-92.
- 3- P. Sousa, R. Almeida, M. J. Silva; A. P. Rocha, Reliability Loss with Sampling Rate Reduction 2015 *Computing in Cardiology 2015*, Nice, France, 2015, pp. 689-692.
- 4- Cardoso, S., Silva, M.J.; Guimarães, H. Autonomic nervous system in newborns: a review based on heart rate variability. *Childs Nerv Syst* **33**, 1053–1063 (2017).

Ao longo da elaboração da presente tese, colaborei ativamente na definição e operacionalização das hipóteses em estudo e dos objetivos a responder em cada um dos artigos, bem como na análise estatística dos dados e interpretação dos resultados. Fui responsável pela redação da versão inicial de todos os manuscritos em que fui primeira autora e participei ativamente na preparação das suas versões finais.

Esta investigação foi realizada no Departamento de Ginecologia-Obstetrícia e Pediatria da Faculdade de Medicina da Universidade do Porto e no Departamento de Matemática da Faculdade de Ciências da Universidade do Porto com a colaboração Departamento de Medicina da Comunidade, Informação e Decisão em Saúde da Faculdade de Medicina da

Universidade do Porto, sob a orientação inicial da Professora Doutora Maria Hercília Ferreira Guimarães Pereira Areias (Faculdade de Medicina da Universidade do Porto) substituída em 2023, por motivos de aposentação, pela Professora Doutora Maria Inês Ferreira Águeda de Azevedo (Faculdade de Medicina da Universidade do Porto), e a coorientação da Professora Doutora Ana Paula de Frias Viegas Proença Rocha (Faculdade de Ciências da Universidade do Porto), da Professora Doutora Maria João Ribeiro Leite Baptista (Faculdade de Medicina da Universidade do Porto) e da Professora Doutora Maria Cristina Granja Teixeira dos Santos (Faculdade de Medicina da Universidade do Porto).

Declaração sobre o uso de tecnologias de Inteligência Artificial generativa e assistida no processo de redação

Durante a preparação deste trabalho, a autora utilizou a ferramenta de Inteligência Artificial Chat GPT com o objetivo de melhorar o inglês e assistir na elaboração da figura 1. Após o uso desta ferramenta, a autora reviu e editou o conteúdo conforme necessário e assume a total responsabilidade pelo conteúdo da publicação.

Agradecimentos

Esta tese só foi possível graças ao apoio e contributo de inúmeras pessoas, a quem deixo a minha mais sincera gratidão. Um projeto de investigação começa com uma ideia simples, que cresce e se desenvolve ao longo de um percurso exigente, até ganhar forma e maturidade. Mas nenhum caminho como este se faz sozinho. Precisa de orientação, apoio e da colaboração de quem partilha os mesmos objetivos e acredita no propósito do trabalho.

Primeiro, quero agradecer profundamente à minha orientadora, Professora Doutora Inês Azevedo. A sua motivação constante, paciência e dedicação foram fundamentais para este projeto. A sua sabedoria, aliada a um incentivo constante e generoso, revelou-se indispensável para a concretização deste trabalho.

Às minhas coorientadoras, Professoras Doutoras Ana Paula Rocha, Maria João Baptista e Cristina Granja, agradeço do fundo do coração. O tempo que me dedicaram, o rigor científico, as discussões que ajudaram a clarificar ideias e o apoio ao longo de todo o processo foram essenciais para o sucesso deste trabalho.

À Professora Doutora Hercília Guimarães, deixo o meu especial agradecimento pela orientação, empenho e generosidade que foram tão importantes no início desta jornada.

Aos colegas e amigos do Serviço de Medicina Intensiva Pediátrica, muito obrigada por partilharem conhecimentos, trabalharem em equipa e estarem ao meu lado nos momentos mais difíceis. O vosso apoio fez toda a diferença.

Ao Dr. Augusto Ribeiro, diretor do Serviço de Medicina Intensiva Pediátrica, agradeço pelas palavras de confiança e incentivo, que foram âncora nos momentos de maior incerteza e me ajudaram a manter firme o propósito de concretizar este trabalho.

À Faculdade de Medicina da Universidade do Porto e ao Programa Doutoral em Medicina, agradeço pelo suporte logístico e académico, que criaram o ambiente ideal para desenvolver esta investigação.

Aos doentes e às suas famílias, que aceitaram participar no estudo mesmo nos momentos mais difíceis, quero deixar um agradecimento muito especial. A vossa generosidade e coragem foram um exemplo de humanidade que guardarei para sempre.

Por último, à minha família, deixo o meu mais profundo e sincero obrigado. Obrigada por acreditarem em mim, pelo vosso amor incondicional e pelo apoio constante, especialmente nos momentos mais complicados. Ao meu pai, pela força e resiliência; à minha mãe, pelo carinho incansável; e, de forma especial, aos meus filhos, João e Sofia, pela compreensão e amor. Dedico este trabalho a vocês, porque é no vosso amor e no sentido que dão à minha vida que encontro a razão para tudo o que faço.

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Abbreviations and acronyms

ABI - acute brain injury

ACh- acetylcholine

ACTH - adrenocorticotrophic hormone

AF - atrial fibrillation

ANS - autonomic nervous system

ApEN - approximate entropy

BI – brain injury

BP – blood pressure

BD – brain death

CI – confidence intervals

CPP - cerebral perfusion pressure

CNS – central nervous system

DBP – diastolic blood pressure

ECG - eletrocardiogram

FFT - Fast Fourier transformation

FMUP – Faculdade de Medicina da Universidade do Porto

ICP – intracranial pressure

ICU – intensive care unit

IQR – interquartile range

LF – low frequency

LF/HF - ratio between the low frequency component and the high frequency component

HF – high frequency

HR – heart rate

HRV – heart rate variability

HRVi – integer heart rate variability

MBP – median blood pressure

MSE – multiscale entropy

NO - nitric oxide

NN – normal to normal

NN50 -number of adjacent NN intervals which differ by at least 50 ms during a 24-h recording

OR – odds ratio

PICU – pediatric intensive care unit

PSNS – parasympathetic nervous system

SBP – systolic blood pressure

SD – standard deviation

TBI – traumatic brain injury

TP – total power

RMSSD – root mean square of successive differences

RR – respiratory rate

SA - sinoatrial

SampEn – sample entropy

SBP – systolic blood pressure

SDANN - standard deviation of average NN intervals

SDNN – standard deviation of NN intervals

SNS – sympathetic nervous system

VLF – very low frequency

Abstract

Introduction

Hemodynamic parameters such as heart rate (HR), blood pressure (BP), and heart rate variability (HRV) have shown potential as predictors of outcomes in severe acute brain injury (ABI). However, their significance and management thresholds remain poorly defined in the pediatric population. HRV represents the oscillations in the intervals between consecutive heartbeats, which reflect the interplay between sympathetic and parasympathetic impulses to the heart. This non-invasive indicator provides valuable insights into autonomic nervous system (ANS) activity. Previous research has suggested HRV as a predictor of mortality regardless of the underlying cause. However, the relationship remains largely qualitative, with no universally accepted measure, limiting its integration into clinical decision-making. Nonlinear HRV indices, although not standardized, provide alternative approaches to traditional HRV measures addressing challenges of data stationarity. Understanding how HRV, measured through both linear and nonlinear methods, can be influenced by stress, pain, and medications, is crucial for determining the role of HRV assessment, alongside with BP and HR, in predicting mortality and medium- to long-term prognosis in children with acquired ABI. These measures can serve as valuable tools, offering additional insights into the patient's condition and guiding appropriate interventions.

Aims

The primary objectives of this thesis was:

1. To evaluate the current state of research on HRV as a prognostic tool in children with ABI (Paper I);
2. To review the role of cardiovascular responses, beyond HRV, in predicting outcomes in children with ABI (paper II);
3. To investigate changes in HRV in healthy children undergoing minor surgery to assess the effects of stress, pain and anesthetic drugs on the ANS (Paper III);
4. To explore the prognostic significance of cardiovascular responses, focusing on HR, BP, and both linear and nonlinear HRV measures, in predicting mortality in children with severe ABI (Paper IV);
5. To explore the prognostic significance of cardiovascular responses, focusing on HR, BP, and both linear and nonlinear HRV measures, in predicting neurologic morbidity in children with severe ABI that survived to PICU discharge (Paper V).

Methods

The objectives of this thesis were achieved through comprehensive literature review and the analysis of data from healthy children submitted to minor surgery and children with severe ABI admitted to the Intensive Care Unit of Centro Hospitalar Universitário São João.

To evaluate the hypothesis that altered ANS regulation could serve as a prognostic factor in pediatric ABI, we performed a comprehensive literature review, synthesizing the available evidence and highlighting the main findings and limitations. In Paper I we identified relevant studies on HRV in children with ABI and for Paper II, we performed a systematic review to investigate the hemodynamic responses of ABI besides HRV in the pediatric population.

For Paper III, we conducted an observational prospective cohort study including a population of healthy children who were scheduled for elective minor surgery at the Pediatric Surgery Department of a tertiary hospital and explored HRV measurements of 10 to 15 minutes periods obtained before and after surgery, using a Holter recorder and the BioSigBrowser® software.

For paper IV we included children under 18 years with severe ABI who survived at least 12 h after PICU admission. In this prospective observational cohort in a tertiary academic PICU we recorded physiological variables, neurological data, laboratory tests results, and medications within 12 h of admission. ECG recordings were automatically annotated using a previously developed and validated wavelet-based system. Linear time-domain analysis included the NN interval mean, the standard deviation of the average NN interval (SDNN) and the square root of the mean squared differences of successive NN intervals (RMSSD). The frequency domain analysis was based on the nonparametric estimation of the spectrum. The following frequency bands were considered: very low frequency (VLF), low frequency (LF) and high frequency (HF). The LF/HF ratio, as well as total power (TP, i.e., all the spectrum area), were also considered. For non-linear analysis, sample entropy (SampEn) was calculated, and additionally, nonlinear indices computed from the *Poincaré* plot, namely SD1 (short-term variability), SD2 (long-term variability) and their ratio SD1/SD2. BP was measured and categorized into percentiles based on age and sex. HR was evaluated and classified as tachycardia or bradycardia according to age-specific criteria. We investigated the utility of cardiovascular responses, including HR, BP, and HRV, in predicting mortality.

For paper V we included children under 18 years with severe ABI who survived to PICU admission and investigated the utility of cardiovascular responses, including HR, BP, and

HRV, as prognostic indicators of neurological morbidity at 3 and 12 months after hospital discharge.

Main findings:

Paper I

We analyzed seven studies on HRV in children with TBI, summarizing the main findings. Patients progressing to brain death (BD) exhibited markedly lower LF/HF ratio, with significant declines within the first few hours of hospitalization. Conversely, higher LF/HF ratios were observed in patients with favorable prognoses.

Paper II

In this systematic review, that included 13 articles, we highlighted that both hypotension and hypertension were associated with worse outcomes. ABI was linked to prolonged QTc intervals and neurogenic stunned cardiomyopathy was frequently observed.

Paper III

In a cohort of 47 healthy children undergoing minor surgery, HRV measurements before and after surgery revealed significant differences in time-domain indices in younger patients and frequency-domain indices in older ones. A decrease in HRV indices up to one-hour post-surgery indicated parasympathetic withdrawal and sympathetic predominance. Sixty minutes after surgery no difference in HRV measures was found and autonomic homeostasis was re-established.

Paper IV

We included 72 children with a median age of 10.7 years, admitted to the ICU with severe ABI; 45 (62.5%) had traumatic brain injury (TBI) and 28 (38.9%) were diagnosed with brain death (BD). The mortality was significantly associated with tachycardia, systolic blood pressure (SBP) and median blood pressure (MBP) below the 5th percentiles, and MBP and diastolic blood pressure (DBP) above the 99th percentiles.

Poincaré SD1/SD2 was an independent predictor of mortality after adjusting for age, sex, and ongoing medications. A *Poincaré* SD1/SD2 ≥ 0.27 added to PRISM III value > 12 significantly increased the ability to predict mortality, although further validation in subsequent studies is necessary for using this cutoff value.

Paper V

Among 31 children with severe ABI that survived to PICU discharge (77.4% male, median age: 11.3 years), favorable outcomes were observed in 51.6% at 3 months and 67.7% at 12 months. Patients with SBP above the 95th percentile in the first 12 hours after admission had significantly better outcomes at both time points. This study suggests that elevated early SBP and HRV indices—particularly LF power measured 12 hours after PICU admission—may serve as independent, non-invasive predictors of long-term neurological outcomes in children with severe ABI. These findings support the role of early autonomic activation as a marker of favorable prognosis and underscore the potential value of incorporating cardiovascular and autonomic monitoring into prognostic models and individualized neuroprotective strategies in pediatric neurocritical care.

Conclusions

Our studies reinforce the relevance of hemodynamic parameters as predictors of outcomes in children with severe ABI. Maintaining a controlled HR and BP within appropriate percentile ranges during the first hours after admission to the PICU is essential for better outcomes. HRV measures, such as the *Poincaré* SD1/SD2 ratio, are robust predictors of mortality and can help identify patients with more favorable prognoses. In addition, parameters like the LF component have shown potential in predicting neurological outcomes among survivors, serving as markers of autonomic integrity and functional recovery.

Resumo

Introdução

Parâmetros hemodinâmicos, como a frequência cardíaca (FC), a pressão arterial (PA) e a variabilidade da frequência cardíaca (VFC), têm demonstrado potencial no prognóstico de doentes com lesão cerebral aguda grave (LCA). No entanto, a sua relevância e os limiares de gestão permanecem pouco definidos na população pediátrica. A VFC representa as oscilações nos intervalos entre batimentos cardíacos consecutivos, refletindo a interação entre os impulsos simpáticos e parassimpáticos para o coração. Este indicador não invasivo oferece informações valiosas sobre a atividade do sistema nervoso autónomo (SNA). Estudos anteriores sugeriram que a VFC pode ser um preditor de mortalidade, independentemente da causa subjacente. Contudo, essa relação continua maioritariamente qualitativa, sem medidas universalmente aceites, o que limita a sua integração na prática clínica. Índices não lineares de VFC, embora não padronizados, fornecem abordagens alternativas às medidas tradicionais de VFC, abordando os desafios da estacionariedade dos dados. Compreender como a VFC, medida através de métodos lineares e não lineares, pode ser influenciada por fatores como stress, dor e medicamentos é crucial para determinar o papel da sua avaliação, juntamente com a PA e a FC, na previsão da mortalidade e do prognóstico neurológico a médio e longo prazo em crianças com LCA adquirida. Estas medidas podem servir como ferramentas valiosas, oferecendo informações adicionais sobre o estado clínico do paciente e orientando intervenções adequadas.

Objetivos

Os principais objetivos desta tese foram:

1. Avaliar o estado atual da investigação sobre a VFC como ferramenta prognóstica em crianças com LCA (Artigo I);
2. Rever o papel das respostas cardiovasculares, para além da VFC, na determinação do prognóstico em crianças com LCA (Artigo II);
3. Investigar alterações na VFC em crianças saudáveis submetidas a cirurgias menores, para avaliar os efeitos do stress, da dor e de medicamentos anestésicos no SNA (Artigo III);
4. Explorar a relevância prognóstica das respostas cardiovasculares, focando na FC, PA e em medidas de VFC lineares e não lineares, na previsão da mortalidade em crianças com LCA grave (Artigo IV);
5. Explorar a relevância prognóstica das respostas cardiovasculares, focando na FC, PA e em medidas de VFC lineares e não lineares, na previsão de morbilidade neurológica em crianças com LCA grave que sobreviveram à alta da UCIP (Artigo V).

Métodos

Os objetivos desta tese foram alcançados através de revisão bibliográfica abrangente e análise de dados de crianças saudáveis submetidas a cirurgia menor e de crianças com LCA grave admitidas na Unidade de Cuidados Intensivos Pediátricos (UCIP) do Centro Hospitalar Universitário São João. Para avaliar a hipótese de que a regulação alterada do SNA poderia servir como fator prognóstico na LCA pediátrica, realizámos uma revisão bibliográfica, sintetizando as evidências disponíveis e destacando os principais achados e limitações. No Artigo I, identificámos estudos relevantes sobre a VFC em crianças com LCA e, no Artigo II, realizámos uma revisão sistemática para investigar as respostas hemodinâmicas na LCA além da VFC na população pediátrica. No Artigo III, conduzimos um estudo prospetivo observacional com uma coorte de crianças saudáveis

submetidas a cirurgias menores no Departamento de Cirurgia Pediátrica de um hospital terciário. Explorámos as medições da VFC em períodos de 10 a 15 minutos antes e após a cirurgia, utilizando um gravador *Holter*® e o software *BioSigBrowser*®. Nos Artigos IV e V, incluímos crianças com menos de 18 anos com LCA grave. No Artigo IV, investigámos as respostas cardiovasculares como preditores de mortalidade em crianças que sobreviveram pelo menos 12 horas após a admissão na UCIP. No Artigo V, explorámos essas respostas como indicadores de morbilidade neurológica a 3 e 12 meses após a alta hospitalar.

Principais Resultados

Artigo I

Foram analisados sete estudos sobre a VFC em crianças com LCA. Os doentes em progressão para morte cerebral apresentaram índices significativamente mais baixos da razão LF/HF, com declínios observados nas primeiras horas de hospitalização. Já os doentes com prognóstico favorável apresentaram razões LF/HF mais altas.

Artigo II

Nesta revisão sistemática, que incluiu 13 artigos, destacámos que tanto a hipotensão como a hipertensão estavam associadas a piores desfechos. A LCA foi frequentemente ligada a intervalos QTc prolongados e a cardiomiopatia neurogénica.

Artigo III

Num total de 47 crianças submetidas a cirurgias menores, as medições da VFC antes e após a cirurgia revelaram diferenças significativas nos índices temporais em crianças

mais novas e nos índices de frequência em crianças mais velhas. Observou-se uma redução nos índices de VFC até uma hora após a cirurgia, indicando retirada parassimpática e predominância simpática. Após 60 minutos, os índices de VFC normalizaram.

Artigo IV

Incluímos 72 crianças (idade mediana: 10,7 anos) com LCA grave. A mortalidade foi associada a taquicardia, PA sistólica (PAS) e média (PAM) abaixo do 5.º percentil, e PA média e diastólica (PAD) acima do 99.º percentil. A medida *Poincaré* SD1/SD2 foi um preditor independente de mortalidade.

Artigo V

Entre 31 crianças sobreviventes, melhores desfechos foram observados em 51,6% aos três meses e 67,7% aos 12 meses. Valores precoces elevados de PAS e de índices de VFC — em particular a potência na banda LF, medida 12 horas após a admissão na UCIP — poderão constituir preditores independentes e não invasivos de prognóstico neurológico a longo prazo em crianças com LCA grave. Estes dados sustentam a ativação autonómica precoce como marcador de prognóstico favorável e reforçam o valor da monitorização cardiovascular e autonómica na estratificação prognóstica e na personalização de estratégias neuroprotetoras em contexto neurocrítico pediátrico.

Conclusões

Os nossos estudos reforçam a importância dos parâmetros hemodinâmicos como preditores de desfechos em crianças com lesão cerebral adquirida grave. A manutenção de uma frequência cardíaca (FC) e pressão arterial (PA) controladas, dentro dos intervalos adequados, nas primeiras horas após a admissão na Unidade de Cuidados Intensivos Pediátricos (UCIP), é crucial para a obtenção de melhores resultados. As medidas da VFC, como a relação SD1/SD2 de *Poincaré*, são preditores sólidos de mortalidade e podem ajudar na identificação de doentes com prognósticos mais favoráveis.

Adicionalmente, parâmetros como o componente LF têm mostrado potencial na previsão de desfechos neurológicos entre os sobreviventes, funcionando como marcadores de integridade autonômica e recuperação funcional.

1. Introduction

“When the heart is affected, it influences the brain, and the condition of the brain, in turn, affects the heart through the pneumo-gastric (vagus) nerve. Thus, during any form of excitement, there is significant mutual interaction and feedback between these two vital organs of the body”

“The Expression of Emotion in Man and Animals!”, Charles Darwin, 1873

1.1 Autonomic Nervous System

The autonomic nervous system (ANS) is part of the peripheral nervous system that acts as a control system regulating various important organs and physiological functions of the body ^{1,2}. It controls the smooth muscles of the internal organs, the cardiovascular system and the secretory function of the glands; comprises sympathetic (SNS) and parasympathetic (PSNS) branches, which differ in their anatomy and function ^{3,4}. The ANS is regulated by reflexes involving sensory input to control centers in the hypothalamus and brainstem, which monitor and regulate many important variables in the body, including heart rate (HR), blood pressure (BP), gastrointestinal peristalsis, glandular secretion, body temperature, hunger, thirst, plasma volume, and plasma osmolarity, while also being influenced by higher brain regions like the limbic system and cerebral cortex ⁵.

The SNS predominates in "fight-or-flight" situations and during exercise, preparing the body for action by increasing blood flow to muscles and triggering responses like tachycardia, hypertension, and bronchodilation. Preganglionic neurons originate in the

thoracic and lumbar spinal cord (T1–L2) and synapse in the sympathetic ganglion chains, enabling widespread effects through a high divergence ratio (1:20). The SNS also directly stimulates the adrenal medulla, releasing hormones into the bloodstream for systemic effects. It plays a unique role in regulating vascular tone and sweating, while also providing innervation to structures in the head, thorax, abdomen, and pelvis ⁵.

The PSNS predominates during rest, promoting energy conservation and regulating functions like digestion and urination. Its preganglionic neurons, originating in the brainstem and sacral spinal cord (S2–S4), have long axons that synapse in terminal ganglia near or within target tissues, resulting in localized effects. The *vagus* nerve (X cranial nerve) carries 75% of parasympathetic fibers, innervating thoracic and abdominal organs, while pelvic nerves serve pelvic viscera. The PSNS has minimal divergence, often with a 1:1 pre-to-postganglionic fiber ratio, ensuring discrete and targeted responses ⁵.

The main autonomic neurotransmitters are acetylcholine (ACh) and norepinephrine. The ACh is released by all preganglionic fibers, parasympathetic postganglionic fibers, and sympathetic fibers to sweat glands, while norepinephrine is primarily released by sympathetic postganglionic fibers. The adrenal medulla, a modified sympathetic ganglion, secretes epinephrine (epinephrine, 80%) and norepinephrine (20%) into the bloodstream, enhancing stress responses. The ACh acts on nicotinic (N-type) and muscarinic (M-type) receptors, while norepinephrine and epinephrine activate adrenergic receptors, including β -receptors, which regulate HR, contractility, and metabolism during sympathetic activation ^{5,6}.

The ANS exerts effects on various organs, including the heart and the eyes. Sympathetic stimulation of the heart increases heart rate, force of contraction, and rate of contraction. In contrast, parasympathetic stimulation decreases heart rate and rate of contraction. In the eye, sympathetic stimulation induces mydriasis by contracting the radial muscle of

the iris, while parasympathetic stimulation causes miosis by contracting the circular muscle of the iris ^{4,5}.

One of the first facts about the two opposing branches of the ANS learned from physiology textbooks is the antagonistic innervation and the balance between the two: more sympathetic activity implies parasympathetic withdrawal and vice versa. It has led to elaborate schemes to quantify the sympathetic/parasympathetic balance, from heart rate variability (HRV) ^{4,5}.

1.2 Autonomic nervous system influence on the cardiovascular system

The ANS continuously alters and regulates HR and its rhythm ⁷. The *vagus* nerve of PSNS innervates the sinoatrial node (SA), atrioventricular (AV) node and myocardium of the heart ⁷. Under normal circumstances, the SA generates heartbeat regulated by the ANS efferent neurons and hormonal control. Pacemaker activity originates from the SA and AV nodes, while cardiac plexuses integrate autonomic and sensory signals. Vagal responses to arterial stretch via the baroreflex are key in sustaining resting HR. Hence, an intricate balanced activity of SNS and PSNS occurs. Because of continuous changes in sympathetic-parasympathetic balance the sinus rhythm exhibits fluctuations around the mean HR and frequent small adjustments in HR are made by cardiovascular control mechanisms ⁸. This leads to fluctuations in HR. The PSNS serves as the primary regulator of HR, maintaining it within a range of 60–100 beats per minute (bpm) at rest. This regulation occurs despite the intrinsic rate of the sinoatrial (SA) node, which is approximately 100 bpm or roughly calculated as $110 - 0.6 \times \text{age}$ ⁹. HR increases during exercise, peaking at $208 - 0.7 \times \text{age}$, with variability influenced by BP (via the baroreflex) and respiration. Beyond its impact on HR, the PSNS reduces contractility in the atrium

and, to a lesser extent, in the ventricles. This effect extends beyond the mere reduction in HR. Additionally, vagal activity slows conduction speed through the AV node as well as in the atria and ventricles ^{10,11}. The SNS controls beat-to-beat arterial BP and regulates blood vessel tone and subsequently blood flow through the organs ¹². SNA increases with BP drops, such as during standing, but in anesthetized conditions, impaired sympathetic drive prevents BP recovery. Cerebral circulation is an exception, maintaining flow via strong autoregulation despite pressure changes ⁴.

1.3 Heart rate variability

“Life is about rhythm. We vibrate, our hearts are pumping blood, we are a rhythm machine, that’s what we are.” - Mickey Hart. With its strategic position, the heart acts not only as the main pump but also as a global coordinator in synchronism with the other body functions. Because of the influence of many factors, the heart does not maintain the exact same rhythm from one heartbeat to the next. It reacts to any stimulus by increasing or decreasing its rhythm so that the body can adapt to any change ¹³. This adaptation is called heart rate variability (HRV) and can also be characterized in terms of amplitude: weak, normal or high. A high HRV is the sign that the heart is healthy since it has more flexibility to react to any stress (physiological or environmental). Alternatively, a reduced HRV is a symptom of health problems and can affect immune functions, self-regulation and psychosocial abilities ¹³. HRV is the variation over time of the period between consecutive heartbeats and it is predominantly dependent on the extrinsic regulation of the HR ³. HRV has gained popularity in the assessment of autonomic activity since the 1970s ¹⁴. To address the lack of standardization and the growing number of HRV measures, a Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology established guidelines in 1996 for measurement, interpretation, and clinical use ¹⁵.

1.3.1 Assessment and interpretation of heart rate variability

measurements

Devices such as pulse oximeters, ECG and BP monitors can assess HRV, with ECG being commonly used for this purpose. Accurate measurement requires high-quality data, minimal noise, and sampling rates of 250–500 Hz (minimum 100 Hz with interpolation). HRV signals are non-linear and complex, often requiring manual editing to ensure reliability. Most investigators edit their raw data manually to ensure sufficient quality. R-R is non-linear and non-stationary, a highly complex signal ¹⁶.

The procedure for recording and processing ECG for HRV analysis involves recording the ECG signal, digitizing it using a microcomputer, identifying and editing artifacts in the RR interval data, rejecting irregular RR intervals, and creating NN interval sequences ¹⁷. To quantify HRV, it is essential to identify the NN intervals, which correspond to the intervals between consecutive beats originating from the SA node. HRV analysis requires identifying normal-to-normal (NN) intervals on the ECG while ensuring: 1) a good signal-to-noise ratio, 2) proper classification of beats to distinguish between beats originating in the SA node and ectopic beats, and 3) exclusion of ectopic beats. Only beats originating from the SA node should be considered for HRV analysis ¹⁶. The fact that HRV is based on the NN intervals limits its use to individuals with a sinus rhythm and a limited number of ectopic beats. For the analysis to be reliable, different criteria have been proposed: the number of beats originating in the SA node must be at least 70 % of the total (some authors even demand 99 % of the beats to originate in the SA node). The strictest criteria demands that the recording must not contain more than 10 ectopic beats per hour ¹⁶. These criteria exclude many patients from HRV analysis ¹⁶.

The major methods for analyzing HRV are a): Time domain methods ^{18–20} b): Frequency domain methods ^{21–24} and c): Non-linear ^{25–29} methods. The most common linear and

non-linear HRV measures are summarized in Table 1 and detailed in the following sections.

Table 1. Most common linear and non-linear HRV measures.

Variability analysis	Parameters	Units	Description
Time domain			
Statistical	SDNN	ms	Standard deviation of the NN interval.
	SDANN	ms	Standard deviation of average of NN intervals in 5 min epochs of entire recording.
	RMSSD	ms	Square of the root of the mean of the sum of square differences between adjacent NN intervals.
	SDNN index	ms	Mean of the standard deviations of all NN intervals for all 5 min segments.
	SDSD	ms	Standard deviation of differences between adjacent NN intervals.
	NN50		Number of pairs of adjacent NN intervals differing by more than 50 ms.
	pNN50	%	NN50 count divided by the total number of all NN intervals.
Frequency domain			
Short-term recording (5 min)	Total power (TP)	ms ²	Variance of the NN intervals over the temporal segment.
	VLF	ms ²	Power of very low frequency range (0.0033 Hz–0.04 Hz).
	LF	ms ²	Power of the low frequency range (0.04 Hz–0.15 Hz).
	LF norm	n.u.	Normalized low-frequency power, calculated as $LF / (Total\ Power - VLF) \times 100$
Long-term recording (24h)	HF	ms ²	Power of the high frequency HF in normalized units (0.15 Hz–0.40 Hz).
	HF norm	n.u.	Normalized high-frequency power, calculated as $HF / (Total\ Power - VLF) \times 100$
	LF/HF	n.u.	Low frequency/High frequency ratio.
Non-linear measures			
Poincaré analysis	S	ms	Area of the ellipse, representing total variability.
	SD1	ms	Standard deviation perpendicular to the line of identity in a <i>Poincaré</i> Plot.
	SD2	ms	Standard deviation along the line of identity in a <i>Poincaré</i> Plot.
	SD1/SD2	ms	Ratio of SD1 to SD2.
Entropy analysis	ApEn		Approximate entropy, measures the regularity and complexity associated with a time series.
	SampEn		Sample entropy, measures the regularity and complexity associated with a time series.

Adapted from: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Standards of measurement of HRV guidelines.^{17,30}

The duration of the recordings for HRV analysis is very important and is determined by the nature of the research. Although time-domain parameters can be derived from a short-term investigation, they are more accurately calculated from longer recordings¹⁷. Analysis of HRV have been recommended for both long-term (24 h) and short-term (5 min) studies³¹. Short-term recording is more practical than long-term recording and has been the most used and widely published HRV data along the years³². Short-term HRV

is typically measured over a few minutes (commonly 1 to 5 minutes, though segments of 10 or 20 minutes may also be used ^{33,34}. Middle-term HRV (measurements that span several minutes to a few hours) can give a better overview of HRV under different conditions, such as during different activities or over a part of the day. Long-term HRV (measurements over several hours or even days) can help track overall autonomic health and balance, providing a broader picture of how the HR fluctuates under various life conditions, including sleep, physical activity, and daily stressors ³⁵.

Assessment of heart rate variability by time domain analysis

The time-domain HRV parameter extraction methods comprise the geometrical and statistical methods. The statistical methods provide the parameters derived either explicitly from the RR intervals or indirectly after the alteration in the length of the RR intervals ³⁶.

The time domain analysis provides average values of the variations for different periods of time. The main parameters derived from time domain analysis are the standard deviation of normal-to-normal inter-beat interval (SDNN) and the root mean square of successive RR interval difference (RMSSD). The first parameter is a direct reflection of HRV and presents the overall activity of the ANS, and the second one is associated with the activity of the PSNS ^{17,37,38}.

SDNN is a global index of HRV and is formally the standard deviation of all normal QRS-distances ³⁹. Standard deviation of the average NN intervals (SDANN) is a variant that has been mostly used in critical ill patients over short periods. This index is also called short-term HR volatility is computed for a given patient every 5 min by calculating the standard deviation of all HR samples collected during that time interval ⁴⁰. SDANN is measured and reported in milliseconds (ms), like the SDNN, and provides a “smoothed out” version of SDNN, is less subject to editing error than SDNN because averaging

several hundred NN intervals minimizes the effects of unedited artifacts, missed beats, and ectopic complexity. As such, SDANN is also much less affected by abnormal rhythms⁴¹.

Regarding variables based on interval differences, RMSSD reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HRV (49). And correlates with the non-linear metric *Poincaré* SD1, which reflects short-term HRV. Other short-term interval measures, such as NN50 (the count of successive NN intervals differing by more than 50 ms) and pNN50 (the percentage of NN50 relative to the total NN intervals, typically calculated over a 24-hour recording), are commonly used as indicators of cardiac parasympathetic activity¹⁷.

RMSSD and pNN50 are short-term variables based on interval differences. Twenty-four-hour RMSSD measurements are strongly correlated with pNN50 and HF power (50).

TINN, which stands for “triangular interpolation of NN interval histogram,” and the HRV triangular index, are examples of time-domain geometrical parameters. TINN represents the reference size of the RR interval (or NN interval) histogram when calculated using triangular interpolation. The HRV triangular index is derived from the RR interval histogram by computing the proportion of the entire amount of RRIs to the stature of the RRI histogram⁴².

All time domain HRV estimates are easily calculated. Also, they do not require stationarity in the same manner as most frequency domain and non-linear analyses do. The main limitation of time domain methods is the lack of discrimination between effects of sympathetic and parasympathetic autonomic branches⁴⁸.

Assessment of heart rate variability by frequency domain analysis

Frequency-domain (power spectral density) analysis describes the periodic oscillations of the HR signal, decomposed at standard frequencies ranges ¹⁷, and provides information on the amount of their relative intensity (termed variance of power) in the sinus rhythm of the heart ⁴³. Standard HRV frequency domain measures are listed in Table 2 with brief explanations ⁴⁴.

Table 2. Normal values for frequency-domain variables.

Variable (Unit)	Description	Normal Values
TP (ms ² /Hz)	The total area under the curve in a power spectrum plot. The ms ² /Hz is considered an absolute unit of measure.	3466 ± 1018 ms ² /Hz
ULF (ultra-low frequency)	The peak frequency found in this defined range; obtained from 24-h recordings and may be a graphical representation of direct current (DC).	0.00-0.003 Hz
VLF (very low frequency)	The peak frequency found in this defined range. The physiological significance is unknown but may correspond to thermoregulation. VLF power affected by mathematical algorithms of trend (baseline) removal.	0.003-0.04 Hz
LF (low frequency)	The peak frequency found in this defined range. Both parasympathetic and sympathetic activity influences this component, which may reflect baroreflex mediated modulatory activity.	0.04-0.15
LF power (nu)	Measure represents relative proportional value of LF power to total power, calculated as [LF power/ (total power-VLF power)]x 100. Power in normalized units should be reported in conjunction with absolute units. Normalization minimizes the effect of change in total power dependent on the individual frequency components.	54 ± 4 nu
HF (high frequency)	The peak frequency found in this defined range, which is influenced by both respiratory and parasympathetic activity.	0.15-0.4 Hz
HF power (nu)	Measure represents relative proportional value of HF power to total power, calculated as [HF power/ (total power-VLF power)] x 100.	29 ± 3 nu
LF/HF ratio	Calculated as LF power/ HF power. This controversial measure is considered an assessment of sympathicovagal balance.	1.5 -2.0

Adapted from Schumacher A. Linear and nonlinear approaches to the analysis of R-R interval variability. Biol Res Nurs. 2004 Jan;5(3):211-21. doi: 10.1177/1099800403260619. PMID: 14737922 ⁴⁴.

Frequency domain is based on the relative portion of different frequency areas in the time series. This can be calculated in different ways ⁴⁰. Namely nonparametric and evaluated with the Fast Fourier Transform.

In humans, standard frequency bands have been established, specifically ¹⁷:

- High-frequency band (HF): between 0.15 and 0.4 Hz – modulated by the PSNS and associated to respiratory activity.
- Low-frequency band (LF): between 0.04 and 0.15 Hz – derives from the activity of both the SNS and the PSNS, but since it is the only indicator to

assess the activity of the SNS, it is accepted as a parameter describing it and is thought to reflect the delay in the baroreceptor reflex system.

- Very low-frequency band (VLF): between 0.01 and 0.04 Hz – it is of uncertain origin but has been attributed to a marker of sympathetic activity and associated with the activity of the renin-angiotensin-aldosterone system.
- Ultra-low frequency band (ULF): < 0.017 Hz - dictated by the circadian rhythms but their origin is still unclear and disputable and is only feasible for long-term use.

Total power (TP) is typically measured in milliseconds squared (ms^2) and represents the sum of the power across all frequency bands in the HRV spectrum.

Measurement of both LF power and HF power in normalized units (nu) is obtained by dividing the absolute power of each component by the TP and multiplying by 100. The indices LF (nu), HF (nu) are algebraically dependent and linearly associated, as: $[\text{LF (nu)} + \text{HF (nu)}] = [\text{LF} / (\text{LF} + \text{HF})] + [\text{HF} / (\text{LF} + \text{HF})] = (\text{LF} + \text{HF}) / (\text{LF} + \text{HF}) = 1$. Therefore, each of the indices is predictable from the other: $\text{LF (nu)} = 1 - \text{HF (nu)}$, and $\text{HF (nu)} = 1 - \text{LF (nu)}$ ⁴⁵. According to this linear relationship, it becomes clear that reporting both values is considered as redundant. LF power probably reflects in large parts the baroreflex modulation of heart period in response to spontaneous changes in BP by both vagal and sympathetic efferent mechanisms ⁴⁶. Some earlier research has suggested that when LF is presented as a normalized value, it is interpreted as a measure of pure sympathetic function ^{47–49}. While the normalization process seems methodologically interesting, it is important to point out the paradox associated with the normalized spectral HRV values, which affects the physiological interpretations related to the ANS function ⁵⁰. The Task Force highly recommended that normalized units should always be quoted with the corresponding absolute values to completely describe the distribution of power in the

spectral components ⁴⁵. In a previous meta-analysis on the effects of exercise training on HRV ⁵¹, separate analyses were conducted on frequency-domain HRV indices (absolute values and normalized values were analyzed separately). The result of the HF in absolute values was significant, whereas the result for the same parameter in normalized units was not significant. Moreover, none of the LF (nu), HF (nu), and LF/HF ratio results were significant, confirming the significance dependence between the indices (48). From a physiological perspective, normalized units and absolute values represent different aspects of autonomic regulation.

A frequently used ratio is LF/HF, this variable is feasible for both for short-term and long-term use, it reflects the global sympathicovagal balance and normally is between one and two in resting adults. Despite serious and largely under-appreciated limitations, the LF/HF ratio has gained wide acceptance as a tool to assess cardiovascular autonomic regulation where increases in LF/HF are assumed to reflect a shift to “sympathetic dominance” and decreases in this index correspond to a “parasympathetic dominance”. Therefore, it is vital to provide a critical assessment of the assumptions upon which this concept is based ⁵². The sympathetic influence on HR is mediated by release of epinephrine and norepinephrine, resulting in an accelerating rate of the slow diastolic depolarization and HR, thereby increasing the LF power of HRV. On the other hand, the parasympathetic influence on HR is mediated by release of Ach, decreasing the rate of the slow diastolic depolarization and HR, thereby increasing the HF power of HRV ¹⁷. The hypothesis that LF/HF quantifies sympathicovagal balance depends upon four interrelated assumptions, all whose can be proven to be false. These assumptions are as follows ¹: (1) cardiac sympathetic nerve activity is a major, if not the exclusive, factor responsible for the LF peak of the HR power spectrum; (2) cardiac parasympathetic is exclusively responsible for the HF peak of the heart rate power spectrum; (3) disease or

physiological challenges provoke reciprocal changes in cardiac sympathetic and parasympathetic nerve activity (i.e., increases in cardiac parasympathetic nerve activity a real ways accompanied with corresponding reductions in cardiac sympathetic nerve activity and *vice versa*); and (4) there is a simple linear interaction between the effects of cardiac sympathetic and cardiac parasympathetic nerve activity on HRV. These facts are in direct opposition to the assumptions. The complex nature of LF power, its exceedingly poor relationship to sympathetic nerve activation, and the non-linear (and often non-reciprocal) interactions between sympathetic and parasympathetic nerve activity that are confounded by the mechanical effects of respiration and prevailing HR, make it impossible to delineate the physiological basis for LF/HF with any degree of certainty ⁵². Thus, the LF/HF sympathicovagal balance hypothesis has been disproven the preponderance of evidence confirms that LF/HF data cannot accurately quantify cardiac “sympathicovagal balance” either in health or disease ^{52–55}.

The VLF measurement should be at least 5 and better 10 min minimum and is a major determinant of physical activity and possibly reflects sympathetic activity, though its origin is controversial ⁴⁶. It is not used as often but has been associated to clinical consequences more strongly than LF in some studies ⁵⁶. Decreased VLF is associated with increased inflammatory parameters like C reactive protein (CRP), inter-leucine 6 (IL-6), and white blood cells (WBC) ⁵⁷. Other explanations are as diverse as thermoregulatory processes, the renin–angiotensin system ⁵⁸, hemodynamic feedback delays, mechanical and central neural effects of breathing patterns, a central oscillator, spinal reflexes, and vascular auto rhythmicity ³⁷. The ULF component reflects circadian and neuroendocrine rhythms ⁵⁹. The respiratory component of HRV depends strongly on the breathing volume and its frequency. The HF component decreases markedly as breathing volume decreases. In addition, the power of respiratory peak increases as its frequency decreases. If the

breathing frequency is below 0.15 Hz, it becomes measured not as the HF component but as a part of the LF component ³⁹. The link between the HF component and cardiac parasympathetic activity is due to the association between the magnitude of respiratory sinus arrhythmia and cardiac parasympathetic activity, which requires that the respiratory rate is always maintained in the range of 9-24 beats/min (0.15-0.4 Hz) ⁶⁰.

Assessment of heart rate variability by non-linear methods

HRV could also be assessed by non-linear mathematical analysis. The difference between “linear” and “non-linear” methods is not as clear as it may seem. Frequency-domain analysis is in principle based on predefined patterns. In Fourier transformations the assumed pattern is a sinusoidal wave, and in wavelet analysis a specific wavelet function. Nonlinear methods can start without specifying any pattern simply by looking at the behavior of the sinus node oscillator in a multidimensional phase space, where it turns its rounds in complex trajectories, possibly being thrown of course by a multitude of factors inside and outside the heart (or even the subject) ^{4,40}.

Nonlinear indexes are not standardized ⁶¹ but may be considered as alternatives to other standard HRV measures. Many nonlinear methods based on concepts of chaos, fractality, and complexity have been used in evaluating heart-rate variability to understand cardiovascular dynamics in healthy as well as in pathological conditions ⁶².

Most researchers, have difficulty with using the correct technique, with the correct parameters on the right type of data and interpreting the results accurately. The most applied methods to HRV analysis include the *Poincaré* plot (Pplot), sample entropy (SampEn), and multiscale entropy (MSE) ⁶².

The Pplot is graphed by plotting every RR interval against the prior interval, creating a two-dimensional graphic scatter plot (Figure 1). Pplot analysis allows researchers to visually search for patterns buried within a time series (a sequence of values from

successive measurements). Unlike frequency-domain measurements, Pplot analysis is insensitive to changes in trends in the R–R intervals ⁶³.

The Pplot, also known as a return or delay map, allows assessing the heartbeat dynamics based on a simplified phase-space embedding. The Pplot is a two-dimensional graphic (scatter plot) in which each RR interval (NN interval), $x(i)$, is plotted as a function of the previous RR interval, $x(i - 1)$.

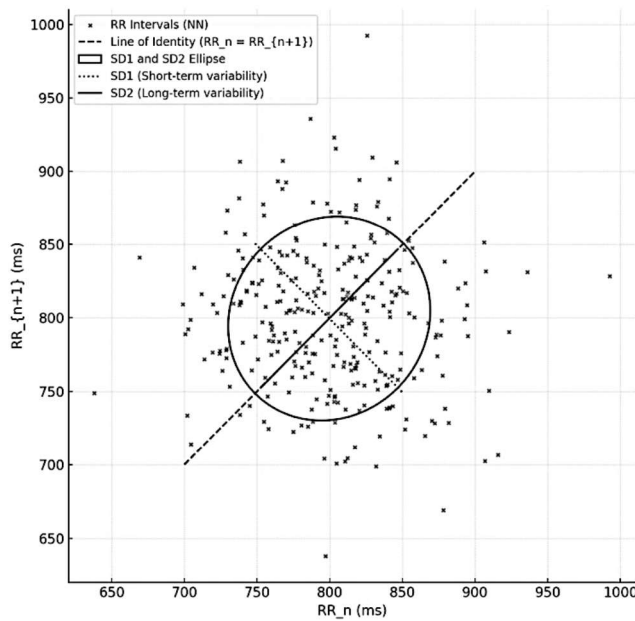
The Pplot analysis is an emerging quantitative-visual technique, whereby the shape of the plot provides summary information on the behavior of the heart ⁶⁴. For a healthy heart, the cloud of points presents a comet shape oriented along the line of identity (Figure 1); the cardiac heart-failure dynamics are characterized by a stretched elliptical-shaped cloud of points also along the line of identity. We can analyze a Pplot by fitting an ellipse to the plotted points. After fitting the ellipse, we can derive three non-linear measurements, S, SD1, and SD2. The area of the ellipse which represents total HRV (S) correlates with baroreflex sensitivity, LF and HF power, and RMSSD ⁶³.

The standard deviation (hence SD) of the distance of each point from the $y = x$ axis (SD1), specifies the ellipse's width. The SD1 measures short-term HRV in *ms* and correlates with baroreflex sensitivity.

The SD1 predicts diastolic BP, HR Max – HR Min, RMSSD, pNN50, SDNN, and power in the LF and HF bands, and TP during 5 min recordings. The standard deviation of each point from the $y = x + \text{average R–R interval}$ (SD2) specifies the ellipse's length.

The SD2 measures short- and long-term HRV in *ms* and correlates with LF power and baroreflex sensitivity ^{65,66}.

Figure 1. Poincaré Plot with SD1 and SD2.



Background: A scatterplot showing RR intervals (NN intervals) on both axes (e.g., RR_n on the x-axis and RR_{n+1} on the y-axis) and a cloud of points demonstrating typical variability in RR intervals. Key features: Line of Identity (45-degree line): A diagonal reference line where $RR_n = RR_{n+1}$; SD1: A line perpendicular to the Line of Identity, representing short-term variability. A standard deviation ellipse highlights the dispersion of points along this axis; SD2: A line along the Line of Identity, representing long-term variability (Figure created with the assistance of Open Artificial Intelligence's ChatGPT).

The ratio of *Poincaré* $SD1/SD2$, which measures the unpredictability of the RR time series, is used to measure autonomic balance when the monitoring period is sufficiently long and there is sympathetic activation. $SD1/SD2$ is correlated with the LF/HF ratio^{66,67}. A few techniques were developed attempting to summarize the plot's geometric appearance quantitatively. The geometrical descriptors, as the ellipse fitting technique, the histogram techniques, and the correlation coefficient, are the most popular in the clinical and HRV literature⁶². The distribution of points along the perpendicular to the line of identity reflects the level of short-term variability measured by SD1^{64,65,68}. On the other hand, the dispersion of points along the line-of-identity is thought to indicate the level of long-term variability and is measured by the standard deviation denoted by SD2

The Pplot is one of the methods most used in the HR field. Henriques et al.⁶² reviewed the most common nonlinear methods applied to HR time series and found that the Pplot has been one of the most used methods in the last years. It is a method easy to compute, it gives a visual display, and its interpretation is understandable by many clinicians.

Measures of entropy are increasingly used to describe the predictability and complexity of biological signals, including HRV⁷⁰.

Approximate entropy (ApEn) and sample entropy (SampEn) are the two most applied methods for biological data analysis⁷¹. The ApEn quantifies the regularity and complexity of a time series, making it suitable for short, noisy datasets without assumptions about system dynamics⁶⁷. In HRV analysis, higher values indicate less predictable RR intervals, while lower values reflect greater regularity⁷². It assesses the recurrence of patterns and the likelihood that similar sequences remain consistent in length⁴⁰.

Sample entropy was developed to address the limitations of ApEn. It quantifies the likelihood of identifying specific patterns in a short time series and is expressed as the negative natural logarithm of this probability⁷³. Diseased systems often have lower SampEn values, but traditional methods like ApEn and SampEn can paradoxically show higher entropy in noisy time series compared to healthy, more complex dynamics. This inconsistency arises because single-scale entropy measures do not capture the intricate temporal fluctuations of healthy physiological systems (70). A multiscale entropy (MSE) approach overcomes this limitation by dividing the original time series into non-overlapping windows, calculating the mean within each window, and generating a new time series for each scale. Entropy measures, such as SampEn, are then calculated across scales, providing a more detailed analysis^{74,75}. The SampEn is less biased and more

reliable than ApEn and can be applied to shorter time series with fewer than 200 data points. Its interpretation is like ApEn but offers greater robustness^{62,76–79}.

Despite their utility, no single method is universally superior. Researchers are encouraged to combine multiple techniques to achieve a more robust interpretation of HRV dynamics³⁹.

Nonlinear analysis methods are generally less sensitive to recording length and artifacts but lack consensus regarding the interpretation of their parameters^{38,80,81}.

Correlation between heart rate variability measurements, their interrelationships, and associations with the autonomic nervous system.

Various time-domain indices show correlations with frequency-domain and non-linear HRV measures, and vice versa, highlighting their interconnected nature.

Table 3 provides an overview of how these different HRV measures align across the time, frequency, and non-linear domains and illustrates their relationships with the ANS^{17,43,46,61,67,82,83}.

Each measure plays a distinct role in evaluating autonomic regulation, offering insights into both parasympathetic and sympathetic activities depending on the specific physiological or clinical context.

Table 3. Summary of the correspondence and interrelations between time-domain, frequency-domain, and non-linear HRV measures ^{17,41,43,46,61,67,82,83}.

Measure	Time-Domain	Frequency-Domain	Non-Linear	ANS Implications
SDNN	Time-domain SDANN (highly correlated)	TP (strong correlation). LF (partial correlation). HF (weak correlation).	<i>Poincaré</i> SD2 (strong correlation).	Reflects overall HRV, both SNS and PSNS influence. Measures of long-term complexity in HR dynamics.
RMSSD	Time-domain pNN50 (highly correlated)	HF (strong correlation). TP (partial correlation).	<i>Poincaré</i> SD1 (equivalent). SampEn/ApEn (strong correlation).	Reflects PSNS (vagal) activity and short-term HRV.
LF	SDNN (partial correlation). pNN50 (weak correlation)	Frequency-domain	<i>Poincaré</i> SD2 (strong correlation). SampEn/ApEn (weak correlation).	Associated with both SNS and PSNS activity. Reflect overall variability, including long-term influences.
HF	RMSSD (strong correlation). pNN50 (strong correlation).	Frequency-domain	<i>Poincaré</i> SD1 (strong correlation). SampEn/ApEn (strong correlation).	Reflects PSNS activity (vagal tone). Reflect variability and adaptability and short-term fractal-like variability modulated by parasympathetic tone.
LF/HF ratio	SDNN (weak correlation). RMSSD (inversely related).	Frequency-domain	<i>Poincaré</i> SD1/SD2 (inversely related). SampEn/ApEn (weak to moderate negative correlation).	A higher ratio suggests SNS dominance. Higher entropy typically reflects greater PSNS modulation, lowering LF/HF.
TP	SDNN (strong correlation). RMSSD (partial correlation).	Frequency-domain	<i>Poincaré</i> SD2 (strong correlation). <i>Poincaré</i> SD1 (partial correlation). SampEn/ApEn (positively associated).	Total HRV; increased TP suggests good autonomic balance and health. Reflecting HRV complexity and adaptability.
<i>Poincaré</i> SD1	RMSSD (equivalent). pNN50 (correlates positively).	HF (strong correlation). TP (partial correlation).	Non-linear measure. SampEn/ApEn (positively associated).	Indicates PSNS activity; higher SD1 correlates with better vagal tone. Reflecting greater variability and healthy autonomic regulation.
<i>Poincaré</i> SD2	SDNN (strong correlation).	LF (strong correlation). TP (partial correlation).	Non-linear measure.	Indicates SNS activity. Reflecting longer-term oscillations influenced by both SNS and PSNS activity.
<i>Poincaré</i> SD1/SD2 ratio	RMSSD/SDNN ratio (conceptually similar). pNN50 (correlates positively).	LF/HF ratio (inversely related).	Non-linear measure. SampEn/ApEn (positively associated).	Reflects the balance between PSNS and SNS activity. Higher SD1/SD2 ratio indicates greater parasympathetic dominance.
SampEn/ApEn	SDNN (positively correlate). RMSSD (moderately correlated).	HF (correlates positively). LF (weak or inconsistent correlations).	Non-linear measure <i>Poincaré</i> SD1/SD2 (positively correlate).	Reflects complexity and regularity of HRV; higher ApEn indicates better autonomic regulation. Higher overall HRV allows for greater complexity. Greater short-term variability often increases irregularity.

1.3.2 Influence of physiological factors on heart rate variability

The factors affecting HRV have been grouped into five categories, such as: 1- Lifestyle factors; 2- Environmental factors; 3- Physiological factors; 4- Pathological factors and 5- non-modifiable factors ^{7,84}.

In this categorization, factors such as age, sex, genetic, chronic health conditions and lifestyle factors (like nutrition, alcohol circadian rhythm, and stress) could affect HRV ^{7,84–86}. Indeed, HRV is being regarded as a health indicator ^{7,84,86}.

Physiological factors like age, gender and ethnicity influence HRV and are depicted in Table 4 ⁴⁰.

Table 4. Effect of physiological factors on HRV.

Factor	Effect	Reference
Sex	Most parameters are lower in women.	Stein et al. ⁸⁷ and Bonnemeier et al. ⁸⁸
Age	Most HRV parameters decrease with age, except ULF. SDNN, RMSSD, HF, and TP decrease with age, whereas LF/HF increased.	Bigger et al. ⁸⁹ and Stein et al. ⁸⁷ Abhishekh et al. ⁹⁰
Weight	Anorexia nervosa: frequency domain↓. Increased BMI: TP↓. Weight loss >10%: HF↑	Rechlin et al. ⁹¹ , Poirier et al. ⁹² , and Kimura et al. ⁹³
Ethnicity	Lower HRV in Afro Americans compared to Caucasians but did not control social class. Asian children had a higher LF/HF ratio than Caucasian of a same community in Canada.	Choi et al. ⁹⁴ Reed et al. ⁹⁵

Influence of age on heart rate variability

There is general progressive maturation of the ANS after birth as supported by the literature and reported in Table 5. Some authors describe a gradual increase of parasympathetic relative to sympathetic mediation in the first 6–10 years of life followed by a gradual decrease ^{96,97}. There are many studies investigating the relationship between the age of healthy children and HRV in the literature ^{38,98–102}.

Table 5. Influence of age on HRV.

Authors	Characteristics	Main findings
Finley et al. ¹⁰³ , 1987	29 children and young adults in three groups between 5 and 24 years of age. Spectral analysis of the two main frequency bands, HF and LF. 3-min ECG.	LF and HF amplitudes and the LF/HF ratio decreased between 5 and 10 years of age.
Clairambault et al. ¹⁰⁴ , 1992	24 healthy sleeping newborns who were born between 31 and 41 weeks of the conceptional age.	HRV measured by spectral analysis was increased from the premature (31–36 weeks) to the intermediary (37–38 weeks) for both HF and LF, and to the full term (39–41 weeks) of the conceptual age for the LF.
Finley and Nuget et al. ¹⁰¹ , 1995	24-h Holter ECG recording of 61 normal healthy children and young adults (1 month to 24 years of age). Segments of 1-h for the awake state, quiet and active sleep were chosen for the computation of spectral HRV indices.	The power of LF and LF/HF changed significantly with age during both quiet and active sleep whereas HF only changed during quiet sleep. The TP was not related to age irrespective of the sleep or awareness state in this study.
Goto et al. ⁹⁶ , 1997	60 healthy children aged 3–15 years.	Time domain HRV measures showed a significant increase in SDNN in the group 3–9 years old and a decline in children 9–15 years old. For the spectral HRV assessment, 10-min recordings were used—HF and LF increased in children 3–6 years old and then gradually declined in children who were 6–15 years old. The LF/HF ratio increased in the group of 3–6 years old and then no significant differences were observed in older children up to 15 years old.
Massin and von Bernuth et al. ¹⁰⁵ , 1997	24-h ECGs in 210 children aged between 3 days to 14 years old. Time and frequency domain HRV indices.	Age was significantly and positively correlated with all studied HRV parameters.
Umetani et al. ⁹⁹ , 1998	24-h ECGs in a group 260 healthy subjects in a wide range of age between 10 and 99 years old.	HRV (by all measures) decreases with aging. The pattern of HRV decline is measure dependent. These phenomena presumably reflect age- and measure-dependent differences in underlying autonomic or other regulatory mechanisms. Normal aging can lower HRV, as determined by SDNN index, RMSSD and pNN50, to below levels associated with increased risk of mortality, particularly at > 65 years.
Silvetti et al. ¹⁰⁰ , 2001	24-h Holter monitoring of 103 healthy children and adolescents. Subjects were divided into four groups (ages 1–5, 6–10, 11–15, 16–20 years).	With increasing age, there is a progressive and significant decrease in mean RR and increase of SDANN SDNN and pNN50 increased significantly only between the first two age-groups (ages 1–5, 6–10 years).
Galeev et al. ¹⁰⁶ , 2002	5400 cardiac rhythmograms of 5400 healthy schoolchildren between 6- to 16- years	Values of parameters of the HRV (mean NN, SDNN, RMSSD, TF, VLF, HF) increase with age wavelike changing from year to year. Gender differences in mean NN were observed beginning from 9 years of age, in parameters TF, VLF, and LF gender differences were observed beginning from 11 years of age, and in parameters SDNN, RMSSD, and HF, the differences between boys and girls were observed beginning from 12 years of age.

Table 5. Influence of age on HRV (continued).

Authors	Characteristics	Main findings
Rekawek et al. ¹⁰⁷ , 2003	372 healthy subjects aged from 4 to 18 years (mean age 11 years).	Global sympathetic and time domain HRV parameters, such as SDNN and SDANN, increased significantly with age. Parasympathetic parameters, such as RMSSD and pNN50, are not age dependent. LF values increased, and HF values decreased significantly with age.
Lenard et al. ¹⁰⁸ , 2004	Time domain and spectral HRV in 10-min resting ECGs in 137 healthy children and young adults (7 to 22 years old).	SDNN, LF, and HF were significantly larger in the oldest children 15–18 years old compared to the middle group between 11 and 14 years old.
Fukuba et al. ¹⁰⁹ , 2009	136 healthy individuals between 8 and 20 years who were instructed to breathe periodically (0.25 Hz).	No significant correlation between age and neither the parasympathetic (HF/TP) nor sympathetic (LF/HF) indices of the control of HR.
Cysarz et al. ¹¹⁰ , 2015	24-h ECG Holter recordings in 409 healthy children, adolescents and young adults in the age range between one and 22 years.	Age related variation in the SDNN, ULF, VLF, LF, and LF/HF—the value of these parameters was, in general, increasing with age. HF was constant in children up to 13 years old and then slightly declined but in general it was not correlated with age.
Moodithaya et al. ¹¹¹ , 2012	267 healthy volunteers at supine resting condition (126 males) between the age group of 6–55 years [60 children (6–11 years) and 66 adolescents (12–16 years)]. Short-term frequency domain analysis of HRV was analyzed.	The higher relative power of LF and lower ratio of HF/LF from children age group to middle age suggest that ageing is associated with shifting cardiac autonomic tone towards sympathetic dominance. An accelerated decline of HF was observed from adolescent to adult age (20–40 yrs) group and from adult to middle age (41–55 yrs).
Michels et al. ¹¹² , 2013	460 children in the age between 5 and 10 years old. 5-min ECG segments.	Overall, HRV showed wave-like increasing trends, especially in boys, except for LFnu and the LF/HF ratio, which decreased without wave-like patterns. HRV increased until around 6 to 9 years of age, then either decreased or remained stable, with wave-like changes still seen in boys.
Sharma et al. ¹¹³ , 2015	451 volunteer school students in the age between 12 and 17 years old.	No association between age and time and frequency domain parameters of HRV.
Gasior et al. ¹¹⁴ , 2015	346 healthy children in the range 6–13 years old.	No significant correlation between children's age and neither RMSSD nor HF were observed.
Bobkowski et al. ⁹⁸ , 2017	24-h ECGs between 100 healthy girls and boys aged 3–18 years.	HRV parameters derived from the analyses of <i>Poincaré</i> plots and Lomb-Scargle periodograms increase with age.
Shvartz et al. ¹¹⁵ , 2025	5-min ECG of 22468 healthy children ranging 5.5–12.5 years of age. The data were grouped by age and gender.	Total HRV and the activity of the PSNS, increase with age, with a peak increase in their values at 8 and 9 years of age. HR, as well as the activity of the SNS, decreased with age.

Younger people show higher variability and HRV decreases with age. With age HRV decreases ^{35,111,116,117}. Children not only have higher values in the frequency domain parameters but also have stronger response to different stressful stimuli ^{3,118}.

Time domain HRV indices reflecting parasympathetic modulation on sinus node increase with age in children and stabilize after the age of 10 years ¹⁰⁰.

Not all HRV indices that contribute to total HRV show such a significant relationship in all age ranges. Neither HF nor *Poincaré* SD1 alter significantly with age. This observation is partially like some other studies who reported that two measures of short-term variability, i.e., pNN50 and RMSSD (which is the rescaled SD1 and thus identical in interpretation with it) were only partially related to age—these are correlated with age only for children up to 10 years old—later, this relationship is no longer significant ^{100,107,110,114}. The control of the cardiac ANS seems already to be compatible with that in adulthood before approximately 10 years ¹⁰⁹. Although both HF and RMSSD (or SD1) come from different methods, in general they describe similar physiological phenomena of short-term or high frequency HRV ^{17,83,119,120} and according to the previous reports we may conclude that the association between age and the measures of fast oscillations influences on HRV are either weakly or not at all correlated with the age of healthy children.

Influence of sex on heart rate variability

The sympathetic and parasympathetic performance of ANS varies in male and female, which results in the sex-based difference in HRV, and this variation is said to begin during adolescence ¹²¹ and decrease by the age of 50 ^{7,85}. However, as showed in Table 6, data about the influence of sex in HRV parameters are contradictory.

Some authors indicate that females have significantly lower LF nu and higher HF nu in the adolescent and adult groups, while the ratios are almost similar in the extremes of age—children and postmenopausal women—emphasizing the important role of female sex hormones in cardiac autonomic modulation. This supports the hypothesis that lower sympathetic activity in females compared to males may contribute to their reduced risk

of cardiovascular disease, with estrogen potentially acting as a protective factor through direct or indirect effects on the electrical properties of the sinus node or chronic developmental differences in sinus node function ^{111,122}. However, other authors report that boys exhibit significantly higher HRV, while some present the opposite findings, and others reveal no association between HRV and the sex of children (Table 6).

Table 6. Influence of sex on HRV.

Authors	Characteristics	Main findings
Goto et al. ⁹⁶ , 1997	25 healthy boys and 35 healthy girls between 3 to 15 years old.	No significant differences by sex in any of the studied HRV indices.
Umetani et al. ⁹⁹ , 1998	24-h HRV of 260 healthy subjects (10 to 99 years old; 112 males, 148 females). 30 children up to 19 years old. For the analysis of sex effects, these children were combined with adults up to 29 years old.	HRV was significantly lower in “young” (10 to 29 years old) female subjects than in age-matched male subjects. Sex differences subsequently decreased and then disappeared with aging. All HRV parameters were lower in women under 30 years of age, but this difference diminished with age and disappeared entirely after the age of 50.
Silveti et al. ¹⁰⁰ , 2001	24-h ambulatory Holter monitoring of 103 (46 females) healthy children and adolescents.	Males showed SDNN and SDANN values significantly higher than females while for RMSSD, pNN50 there were no significant differences between sexes.
Galeev et al. ¹⁰⁶ , 2002	Cardiac rhythmograms of 5400 healthy schoolchildren between 6- to 16- years	SDNN was significantly higher in boys from 12 to 14 years old children. TP was significantly higher in boys in the age interval 11–15 years old, VLF was larger in boys in the age 13–15 years but lower for 12 years old. Sex differences in LF and HF were present for children in the age between 15 years but in changing patterns, (these parameters were higher in boys, then in girls, and then again in boys). LF/HF was larger in boys than in girls between 12 and 15 years old. No differences between 16-year-old boys and girls in all HRV parameters of were found.
Fukuba et al. ¹⁰⁹ , 2009	48 boys between 8 and 14 years old and 88 girls between 8 and 20 years old who were asked to breathe periodically at a rate of 15 breaths/min. 3-min ECGs.	No sex differences were found in HF, TP and LF/HF.
Cysarz et al. ¹¹⁰ , 2011	24-h ECG Holter recordings in 409 healthy (220 female) children, adolescents and young adults in the age range between one and 22 years.	SDNN and all spectral measures of HRV were significantly lower in girls and young women than in boys and young men.
Moodithaya et al. ¹¹¹ , 2012	267 healthy volunteers at supine resting condition (126 males) between the age group of 6–55 years [60 children (6-11 years) and 66 adolescents (12-16 years)]. Short-term frequency domain analysis of HRV was analyzed.	HF nu and HF/LF were significantly higher and LF nu was lower in female in the adolescents and young adult age (20-40 years) groups.

Table 6. Influence of sex on HRV (continued).

Authors	Characteristics	Main findings
Michels et al. ¹¹² , 2013	460 children in the age between 5 and 10 years old. 5-min ECG segments.	Mean RR interval, SDNN, RMSSD, pNN50, the powers of VLF, LF, and HF were significantly larger in boys than in girls, but there was no significant difference in any of the relative measures of spectral HRV indices (LF/HF, LF nu, HF nu).
Seppälä et al. ¹²³ , 2014	465 mainly prepubertal children with 6 to 8 years of age. Resting ECGs of 1- and 5-min duration.	No significant difference was found between girls and boys in the studied HRV parameters (mean RR, SDNN, RMSSD, pNN50, HRV triangular index, TINN, LF peak, HF peak, LF power, HF power, LF/HF, <i>Poincaré</i> SD1, <i>Poincaré</i> SD2, <i>Poincaré</i> SD1/SD2, SampEn, DFA a1, DFA a2, D2).
Gasior et al. ¹¹⁴ , 2015	Resting ECG in 158 boys and 173 girls in age between 6 and 13 years old and selected 5-min segments.	Boys presented significantly higher HRV values (SDNN, RMSSD, pNN50, TP, LF, and HF) but lower HR. However, in the linear multiple regression analysis adjusted for sex, all HRV parameters were significantly related to HR but not sex of the children. This suggests that if there are any sex differences in HRV in children they are rather an effect of HR than the sex itself.
Koenig and Thayer ¹²⁴ , 2016	Meta-analysis looking into influence of gender on HRV, 63 612 participants (31 970 females) were studied.	Females had a significantly lower mean RR interval, SDNN, TP, LF power, LF/HF ratio but higher HF power.
Jarrin et al. ¹²⁵ , 2015	1,036 children (481 boys and 555 girls) with 9 to 11 years old.	Boys had significantly higher values of time and spectral HRV parameters except for LF/HF which appeared to be lower. However, the analysis of mean values of these parameters and their standard deviations shows that the differences in the means were rather small.
Bobkowski et al. ¹²⁶ , 2017	24-h ECGs between 100 healthy girls and boys aged 3-18 years.	No differences in HRV parameters (neither from the spectral analysis by Lomb-Scargle method nor <i>Poincaré</i> plots). No influence of the interaction between age and children's gender on the studied HRV parameters.
Shvartz et al. ¹¹⁵ , 2025	5-min ECG of 22468 healthy children ranging 5.5–12.5 years of age. The data were grouped by age and gender.	Parameters characterizing the activity of the peripheral nervous system were significantly higher in boys than in girls across all age groups.

Studies such as Jarrin et al.¹²⁵ and Galeev et al.¹²⁷ raise a question whether all statistically significant differences are clinically relevant? Whether, in fact, the small differences in the values of HRV measures are statistically different because of the mass effect, i.e., large sample sizes influencing p-value¹²⁸.

1.3.3 Heart rate variability in various diseases

Many studies found that pathological conditions (such as inflammation and infection) decrease the HRV ^{129,130}.

Badke and colleagues ¹³¹ present data to further support the notion that intrinsic physiologic variability is also an important part of life. Using data from two observational cohorts of critically ill children from a single institution, the authors demonstrated that lower median age-normalized HRV in the 12-hour period prior to biomarker collection was associated with higher levels of the pro-inflammatory cytokines IL-6, IL-8, and CRP. Although there was not an association with the earlier, more hyperacute cytokines IL-1 β or tumor necrosis factor (TNF)- α , the correlation of HRV with IL-6 persisted after adjusting for illness severity using PRISM-III and the correlation with CRP persisted after adjusting for both PRISM-III and age ^{131,132}.

The HRV is reduced in myocardial infarction (MI) ^{133–135}, myocardial dysfunction ¹³⁶ usually in congestive heart-failure ¹³⁷, post-cardiac transplant ¹³⁸, depression ^{139,140}, ^{141,142}, fetal distress ¹⁴³, hypertension ¹⁴⁴, diabetic neuropathy ¹⁴⁵, autonomic dysfunction (anxiety, asthma) ^{139,140}, tetraplegia ¹⁴⁶, sepsis ¹⁴⁷, liver cirrhosis ¹⁴⁸ in relation to premature babies and sudden infant death syndrome (SIDS) ^{139,140}, and all cause-mortality ^{149,150}. HRV assessment after myocardial infarction is one of the first and most widely used applications of the method. It could provide important information about sympathetic predominance and impaired vagal control on the heart after myocardial infarction, which are strong predictors of survival, and the risk of rhythm and conductive disorders associated with sudden cardiac death ¹⁵¹. Low HRV can be found in patients with severe coronary artery disease and congestive heart failure ^{152–154}. Several lines of evidence indicate that low HRV may be associated with increased cardiovascular disease-related morbidity and mortality. Decreased HRV has been found to be a potent predictor

of cardiac mortality after acute myocardial infarction, independent of ventricular function, ventricular ectopic activity, heart rate, and other previously identified prognostic indicators ^{155–158}. Bigger et al⁵⁹ found that power spectral measures of HRV were predictors of all-cause, cardiac, and arrhythmic mortality and sudden death ¹¹⁸. HRV occurs inversely to clinical severity and prognosis. The difficulty of introducing ANS monitoring in the daily practice of intensive care units is due to the limitation of its use as a prognostic tool and, above all, to the difficulties involved in continuous and dynamic monitoring and in the interpretation and applicability of its results. Successful implementation depends on HRV monitoring going from a prognostic tool to a real-time monitoring instrument to be useful in therapeutic guidance; for example, as a guide for fluid therapy through analysis of the HF component and for treatment with vasoactive amines through analysis of the LF/HF ratio ¹⁵⁹.

1.3.4 Influence of drugs on heart rate variability

Different drugs might influence HRV parameters, but often the evidence is conflicting. Beta blockers are mentioned most frequently ^{17,40}, but in most studies, individuals taking beta blockers are excluded, analyzed separately or included into the statistical model.

Interestingly, drugs that would be expected to have profound effects on the ANS such as catecholamines have also been shown to have variable effects on HRV ¹⁶⁰. A systematic review reported three studies that did not show any association between HRV parameters and vasopressor requirement or administration of exogenous catecholamines ¹⁶¹. Despite no finding of an association, the authors highlighted that most of studies failed to report the administration of cardiovascular drugs, vasopressors or catecholamines and had limited ability to draw any conclusions regarding the potential effects on HRV ^{38,161}.

An overview of some drugs and its effects on HRV is given in Table 7 ⁴⁰.

Table 7. Effects of some drugs on HRV.

Drugs	Effect	Reference
Catecholamines	No association between HRV parameters and vasopressor requirement or administration of exogenous catecholamines. Infusion of noradrenaline and adrenaline did not induce changes in frequency-domain values of short-term HRV. Adrenaline and high plasma concentrations of noradrenaline were accompanied by low HRV.	Karmali et al. ¹⁶¹ Rajendra et al. ³⁸ Tulen et al. ¹⁶² Breuer et al. ¹⁶³ Kienze et al. ¹⁶⁴
Anesthesiological Drugs		
Fentanyl	No effects on frequency-domain variables were detected. It decreased absolute TP and LF, not HF. No effect on normalized measurements of LF, HF, and LF/HF ratio. 1 ug/kg decreases LF nu without increases of HF nu, in addition to decrease of TP.	Galletly et al. ¹⁶⁵ Riznyk et al. ¹⁶⁶
Midazolam	Slight depression of HF and LF and unchanged LF/HF ratio. Depression of HF in deep-sedated ICU patients.	Vettorello et al. ¹⁶⁷ Michaloudis et al. ¹⁶⁸ Unoki et al. ¹⁶⁹
Propofol	Decreased LF, MF, and HF, LF to a lesser extent than the latter two. Decreased TP and HF and increased LF/HF ratio.	Galletly et al. ¹⁶⁵ Howell et al. ¹⁷⁰
Thiopental	Absolute TP and HF decreased. Decreased TP and HF and increased LF/HF ratio. Absolute TP, HF, and LF decreased. LF nu increased, and HF nu decreased. Increase of LF/HF ratio.	Riznyk et al. ¹⁶⁶ Howell et al. ¹⁷⁰ Riznyk et al. ¹⁶⁶
Proton-Pump Inhibitors	Use of esomeprazole did not induce changes in HRV.	Yi et al. ¹⁷¹
Spirolactone	Increased time-domain parameters of HRV. Reduced HRV in diabetic patients (RMSSD, LF, and HF).	MacFadyen et al. ¹⁷² Davies et al. ¹⁷³

Most agents used for induction of anesthesia, with the exceptions of ketamine and etomidate, result in a decrease in HRV¹⁷⁴. Kanaya et al.¹⁷⁵ studied thirty patients randomly allocated into the propofol or sevoflurane for induction of anesthesia. The depth of hypnosis was monitored by the Bispectral Index (BIS). They found that induction of anesthesia with propofol decrease BP, entropy, and HF in a BIS-dependent manner, indicating that propofol reduces cardiac parasympathetic tone depending on the depth of hypnosis. Conversely, sevoflurane did not show the BIS-dependent decreases in heart rate, blood pressure, HF, and entropy, indicating that sevoflurane has little or no effect on cardiac parasympathetic tone.

1.3.5 Heart rate variability in intensive care

It is very common to see autonomic dysfunction in ICU patients with a severe brain injury, systemic infection, organ failure, neurological illness (e.g., Guillain–Barré syndrome), cardiovascular disease (myocardial infarction) and more. Research indicates that HRV can be used as a biomarker to assist a physician in the ICU in making clinical decisions ³⁹. Bento et al.¹⁵⁹ and Karmali et al.¹⁶¹ conducted systematic reviews examining the use of ANS monitoring as a prognostic tool in adult intensive care units (ICUs), with a focus on HRV. They concluded that HRV is inversely correlated with clinical severity and prognosis in ICU patients, regardless of their underlying pathology. Specific findings are summarized in Table 8 ¹⁵⁹.

Table 8. Characteristics of the selected studies of ANS monitoring as a prognostic tool in adult intensive care units.

Author	Characteristics	Evaluated outcomes	Results
Winchell et al. ¹⁷⁶ , 1996	Prospective cohort study. General ICU population. N = 742	Mortality	The relative risk of death in patients with low HRV was 7.4, with an increased HF/LF ratio of 4.55.
Winchell et al. ¹⁷⁷ , 1997	Retrospective cohort study. Patients with severe head trauma. N = 80	In-hospital mortality and probability of discharge home. CPP and ICP.	Low HRV was associated with increased mortality, patients with a predominance of SNS activity and with a low HF/LF ratio had improved survival.
Yien et al. ¹⁷⁸ , 1997	Prospective cohort study. General population admitted for noncardiac causes. N = 52.	Mortality	Deceased patients had decreased VLF and LF power.
Haji-Michael et al. ¹⁷⁹ , 2000	Prospective cohort study. Neurosurgical patients. N = 29	3-month outcome	Patients who died had decreased HRV, LF/HF ratio and baroreflex sensitivity.
Rapenne et al. ¹⁸⁰ , 2001	Prospective cohort study. Severe head trauma. N = 20.	Brain death. Neurological recovery.	On the first post-trauma day, an increase in the parasympathetic tone (RMSSD and TP) may be associated with imminent brain death.
Grogan et al. ¹⁸¹ , 2004	Retrospective cohort study. Trauma patients admitted to the ICU. N = 923.	ICU mortality.	Patients with loss of heart rate volatility during the first 24 hours of hospitalization have a higher probability of death.
Gujjar et al. ¹⁸² , 2004	Prospective cohort study. Acute stroke. N = 25	ICU mortality	LFn was an independent predictor of survival, with a regression coefficient of -6.73 and an OR of 0.002.
Papaioannou et al. ¹⁸³ , 2006	Prospective cohort study. General ICU population. N = 53	ICU mortality	The minimum ApEn value correlated with mortality ($r = 0.41$; $p = 0.01$)

Table 8. Characteristics of the selected studies of ANS monitoring as a prognostic tool in adult intensive care units (continued).

Author	Characteristics	Evaluated outcomes	Results
Mowery et al. ¹⁸⁴ , 2008	Retrospective cohort study. Patients with head trauma and ICP monitoring. N = 145.	High ICP and mortality.	There is a relationship between percentage of ICP rise and cardiac decoupling with mortality.
Norris et al. ¹⁸⁵ , 2008	Retrospective cohort study. Trauma patients admitted to the ICU. N = 285.	In-hospital mortality.	There was a decrease in HRV in deceased patients.
Papaoiannou et al. ¹⁸⁶ , 2008	Prospective cohort study. Head trauma. N = 20.	Neurological dysfunction and ICU mortality.	Reduced HRV, baroreflex sensitivity and sustained LF/HF ratio reduction were associated with increased mortality.
Schmidt et al. ¹⁸⁷ , 2008	Prospective cohort study. Multiple organ dysfunction syndrome (MODS). N = 90.	Analysis of survival at 180 and 365 days.	Natural logarithm of VLF with a cutoff point of 3.9 was a strong predictor of 28-day and 2-month mortality in patients with MODS.
Riordan et al. ¹⁸⁸ , 2009	Retrospective cohort study. Multiple trauma patients admitted to the ICU. N = 2 178.	Risk of death in the subgroups based on trauma location and mechanism and on probability of survival.	Decreased multiscale entropy; was significantly associated with increased mortality, being an independent factor of probability of survival in the multivariate analysis, with OR 0.87 - 0.94.
Kahraman et al. ¹⁸⁹ , 2010	Prospective cohort study. Patients admitted to the ICU with head trauma and ICP monitoring. N = 25.	Capacity to predict ICP, cerebral hypoperfusion, in-hospital mortality or functional outcome.	Integer HRV can predict in-hospital mortality, with a sensitivity of 67% and a specificity of 91-100%.
Kasaoka et al. ¹⁹⁰ , 2010	Prospective cohort study. Patients admitted to the ICU with systemic inflammatory response syndrome. N = 10.	To trial a real-time HRV measurement and analysis system.	LF, HF and LF/HF higher in patients spontaneously breathing compared to mechanical ventilation.
Pfeifer et al. ¹⁹¹ , 2011	Prospective cohort study. Patients admitted to the ICU after cardiac arrest, subjected to therapeutic hypothermia. N = 18.	28-day mortality.	There was a more pronounced reduction in HRV immediately after the rewarming phase in patients who died compared with survivors (SDNN 10.9 versus 40.2, Shannon entropy 2.2 versus 3.7).
Chen et al. ¹⁹² , 2012	Case-control study with patients with sepsis and out of hospital cardiac arrest. N = 210.	Compare HRV between post-resuscitation cardiac arrest patients and patients with severe sepsis.	No significant differences in HRV indices. Low LF, LF nu, LF/HF associated with mortality.
Gomez Duque et al. ¹⁹³ , 2012	Prospective cohort study. Patients admitted to the ICU with sepsis. N = 100.	Investigate the incidence of cardiovascular adverse events in patients with sepsis.	Deceased patients demonstrated lower SDNN than survivors.
Brown et al. ¹⁹⁴ , 2013	Prospective cohort study. Patients admitted to the ICU with sepsis. N = 48.	Assess if HRV can predict vasopressor dependence at 24 hours.	Traditional HRV indices not associated with vasopressor requirement after controlling for HR.
Green et al. ¹⁹⁵ , 2013	Prospective cohort study. Patients admitted to the ICU with MODS. N = 33.	Association of HRV and illness severity in MODS.	Low LF nu and LF/HF associated with increased MODS.
Bradley et al. ¹⁹⁶ , 2013	Prospective cohort study. Patients admitted to the ICU with mixed etiology. N = 33.	Impact of sedation and sedation interruptions on HRV.	SDNN, RMSSD and HF all increased during sedation interruption (more pronounced in less unwell patients).
Hammash et al. ¹⁹⁷ , 2015	Prospective cohort study. Patients in the ICU that started weaning. N = 35.	Relationship between HRV and incidence of dysrhythmias during weaning.	LF was higher during spontaneous breathing than during controlled mechanical ventilation.
Nagaraj et al. ¹⁹⁸ , 2016	Retrospective analysis case series not specified. N = 40.	Assess if sedation levels can be classified by HRV algorithms.	Algorithms using composite measures of HRV may discriminate between levels of sedation in ICU patients.

Patients admitted to ICUs are permanently monitored for temperature, oxygen saturation, respiration, urinary output and ECG. These parameters are most of the time only monitored while setting alarm ranges, to trigger the corresponding alarm for any deviation from the normal range. However, many of these variables are controlled by the ANS, which can be affected by several pathological processes and/or drugs. The overall accuracy of HRV to predict outcome within the ICU may simplify workflow and enable prompt response to any clinical status change, while all these parameters can be automatically extracted from raw physiological signals that are already routinely monitored ¹⁹⁹. Multiple studies performed on trauma patients confirmed a correlation between low HRV and short-term poor prognosis ^{200–202}.

HRV measurement was also demonstrated to be effective during ventilatory weaning ^{203,204}, acute stroke ²⁰⁵, delirium prediction ^{206,207}, and pain management ^{208,209}. In 2017 in a multicenter randomized trial of 70 ICU patients, Nagaraj et al. studied the possibility of a customized algorithm based on HRV measure to manage patient sedation ²¹⁰. They modified HRV measurement according to sedation level, thus establishing a new framework for patient sedation management to limit the harmful effect of a deep sedation. When considering the available variables for HRV analysis, several characteristics may be extracted, either in the temporal, frequency or fractal domain. While simpler to compute than other parameters, the temporal domain characteristics of the cardiac rhythm do not necessarily indicate whether a change in HRV had been caused by the sympathetic or the para-sympathetic system. Frequency domain analyses seem to be better equipped than temporal domain to discriminate the individual contribution of the sympathetic/parasympathetic systems, as they manifest themselves in two non-overlapping frequency bands (LF, HF), and considering these arguments, the LF/HF ratio has gained a wide acceptance as a tool to assess cardiovascular autonomic regulation.

However, the LF peak of the heart rate power spectrum which is often assumed to have a dominant sympathetic component (the HF peak reflecting the cardiac parasympathetic nerve activity), is complex to evaluate as it may at least be modified by various stimulus and medications ^{211–213}.

It is also established that increases in respiratory frequency reduce the amplitude of heart rate oscillations ²¹⁴ while increases in tidal ^{214,215} or static lung volume ²¹⁶ provoke increases in the R–R interval variability; the influence of mechanical ventilation within the ICU may therefore have a major influence on HRV variation in such environment. Considering such frequently under-appreciated limitations, HRV frequency domain evaluation may rather reflect a complex and not easily discernible mix of sympathetic, parasympathetic, but also the impact of other unidentified factors ⁵². Despite all these limitation, lower LF/HF ratios on admission were significantly associated to a lesser outcome within adult ICU population.

The VLF peak is a third part of the frequency spectrum that has been less evaluated, but that seems to be associated to prognosis in various pathologies, such as during congestive heart failure ²¹⁷. Considering that the R-R intervals are non-linear, it is also needed to measure it using non-linear methods. In other ways, nonlinear methods are used to observe regularity, predictability, and complexity in the time series while considering the impact of several interventions and the influence pathological processes.

The concept of complexity is different from variability, but no consensus definition of what complexity includes do exist. It is often used to characterize the behavior of a non-linear system that contains many parts that interact with other in highly different ways; two signals can have the same degree of variability (i.e., same variance and coefficient of variation), but different complexity properties. Complexity may be approached by the means of entropy measurements or by the *Poincaré* plot analysis. No single measure is

sufficient to capture the properties of the most complex signals; instead, an ensemble of measures is required to probe signals of interest for different attributes.

Critically ill patients' care and decision-making is complex, involving interpretation of many variables and comparative evaluation of various therapy options. Many critical care indices are not captured automatically, and relevant data are thus difficult to evaluate, especially while considering human factors like vigilance in a constraint environment, varying expertise of the attending physicians, and the constant need to deal with a high-level of uncertainty under time-constraints. The lack of standardization for the different methods of HRV measurements in the critical care setting may also require specific attention, thus requiring adequate parameters selections that would consider either technical consideration, but also patients' complexity and the potential impact of several pathological processes and therapeutic interventions as mentioned earlier¹⁹⁹. Bodenes et al.¹⁹⁹ recorded plethysmogram (PPG) tracings from 540 consecutive adult patients at 75 Hz using a standard monitoring system for a 2-hour period during the first 24 hours following ICU admission. They observed that lower LF/HF ratios, *Poincaré* SD2/SD1 ratios, and Shannon entropy values at admission were associated with higher ICU mortality.

In multivariate analysis, LF/HF and Shannon entropy were independently correlated with mortality. The team employed a machine learning model utilizing a k-Nearest Neighbors algorithm and developed a simple decision tree based on the three most significant predictors: SDNN, Shannon entropy, and the *Poincaré* SD2/SD1 ratio. They concluded that HRV measured upon admission can predict ICU and Day-28 outcomes, regardless of the admission diagnosis, treatment, or need for mechanical ventilation.

1.3.6 Blood pressure and heart rate variability

There are three major systems involved in the regulation of BP, the ANS, the renal system, and the endocrine system ^{218,219}. The SNS regulates arterial BP by functionally influencing the vasculature, kidney, and heart. Indeed, altered sympathetic function is firmly established in the development, maintenance, and pathophysiology of numerous cardiovascular diseases including hypertension ^{220,221}. Sympathetic hyperactivity in human hypertension has been revealed through elevated NE spillover, increased muscle sympathetic nerve activity via microneurography, surgical sympathectomy, and greater depressor responses to acute ganglionic blockade. Notably, some antihypertensive pharmacotherapies lower BP by targeting the SNS ^{221,222}. Recent advances regarding the role of the SNS in hypertension have focused on brain pathways or associated signaling mechanisms that increase or decrease BP ²²³. Population-based studies have reported reduced HRV in patients with long-term arterial hypertension, despite treatment with antihypertensive drugs. In the ARIC study ¹⁴⁴, decreased HRV was observed in the hypertensive population, and even in normotensive population low HRV predicted hypertension after a follow-up of nine years. Pal et al. ²²⁴ suggested that spectral analysis of HRV, performed through regular screening from early stages of life, could be used as a predictive tool for autonomic dysfunction. This is based on the observation of ANS imbalance, characterized by increased sympathetic activity and reduced vagal activity, in individuals with risk factors for essential hypertension who later develop the condition. Mussalo et al. ²²⁵ showed that the severity of essential hypertension was related to the severity of impairment of cardiac autonomic control measured by time and frequency domain analysis of HRV. HRV is strongly decreased in patients with arterial hypertension induced left ventricle hypertrophy, which can be explained by the impaired baroreflex sensitivity in this pathological condition ^{53,151}. Hypertension is reported to be associated

with SNS overactivity ^{226,227} . During a 9% decrease in arterial pressure obtained with intravenous (IV) nitroglycerin, there was a marked increase in LF, because of reflex sympathetic activation ²²⁸. Normotensive subjects with family history of hypertension have greater sympathetic activity and early parasympathetic attenuation ^{229–231}. In recent years, many researchers have studied the feasibility of an HRV analysis as a marker for hypertension detection (Table 9) ³⁶.

Table 9. Selected recent articles on an HRV analysis for hypertension detection.

Author, Year	HRV methods use	Inferences
Ni et al. ²³² , 2018	Time-domain and frequency-domain methods, entropy features	The study proposed a method that can distinguish hypertensive patients from healthy controls with 93.33% accuracy when tested on 24 hypertensive patients and 24 healthy controls.
Lan et al. ²³³ , 2018	Time-domain and frequency-domain method.	HRV analysis can predict hypertension at an early stage. SDNN has the best predictive power.
Martinez et al. ²³⁴ , 2018	Non-linear methods	The study indicated that hypertensive and diabetic subjects exhibited reduced SD1 (calculated using <i>Poincaré</i> plot) and Shannon entropy than non-hypertensive diabetic patients.
Poddar et al. ²³⁵ , 2019	Time-domain, frequency-domain, and non-linear methods	The study proposed an SVM classifier that could achieve a classification accuracy of 96.67% for the healthy volunteers and hypertension and coronary artery disease classes.

1.3.7 Heart rate and heart rate variability

HR significantly impacts HRV in pediatric population and turns out to be the strongest determinant of all standard HRV indices ^{114,236}. HRV varies with HR, however, HR accounts for less than 30% of the variance ²³⁷. Different approaches to analyzing HRV signals may exhibit varying behaviors when applied to individuals with differences in HR ³⁶.

- Time-Domain Analysis: In subjects with tachycardia, shorter RR intervals can result in reduced variability between consecutive intervals, potentially affecting time-domain measures such as the SDNN and RMSSD. In subjects with bradycardia, longer RR intervals might lead to increased variability, potentially influencing the same time-domain measures. Geometric methods,

like the triangular index, might be sensitive to the distribution of RR intervals, which can differ in tachycardia and bradycardia. They might need normalization or transformation to account for such differences ³⁶.

- Frequency-Domain Analysis: In subjects with tachycardia, the faster HR can lead to HF power dominating the spectrum potentially obscuring the interpretation of LF and HF components. In subjects with bradycardia, the opposite might occur, making frequency-domain interpretation more straightforward.
- Non-linear Analysis: Non-linear HRV analysis methods, such as *Poincaré* plots and fractal analyses, might be affected by the irregularity of the HR in tachycardia and the extended RR intervals in bradycardia. These methods might need adjustments or specific considerations for accurate interpretation.

There is some contradictory data about the relation between HR and HRV. Some authors found a significant inverse correlation between HRV measures and HR itself ^{133,238}. While others ²³⁹ concluded that there is no relation between these parameters. HR dependence of the HRV was augmented by a sympatholytic drug and depressed by a high dose of atropine ²³⁸. This result corresponds well with that of La Rovere et al. ²⁴⁰ who found a high correlation between the mean RR and the RMSSD, which is strictly related to vagal activity. It seems that the vagal influences determine not only the HR itself, but also the extent of the inverse correlation of the HRV and HR. In contrast with this, sympathetic innervation may depress this relation ²³⁸. Some authors concluded that depressed HRV observed in tachycardiac patients with sympathetic overactivity originates primarily from the autonomic imbalance itself rather than the accelerated HR ²³⁸. This effect is known as cycle length dependence ^{241,242}. The lower the HR, the greater the HRV ²⁴³. Different authors have noted that HRV indices are highly dependent on

values of the HR and that the relationships between them are nonlinear, possibly introducing limitations for the use of HRV indices if not appropriately corrected ^{236,243}. Rather than being a pure marker of cardiac ANS activity, HRV is primarily dependent on HR, with HRV increasing when the R-R interval increases (when HR slows) and decreasing when the R-R interval decreases (when HR quickens) ²⁴⁴. HRV is a nonlinear measure of HR and, therefore, the higher morbidity and mortality associated with a decrease in HRV is likely to be the result of the concurrent increase in HR. Different mathematical corrections have been proposed, but there remain several concerns about their utility, justifications for their use, and doubts about the effect of the removal on the corrected values ^{236,244,245}. Sacha et al. ^{246–251} have noted the nonlinear relationship between HR and HRV, and its effects on the inferences derived from investigations of non-corrected procedures to eliminate the bias. These authors also proposed and assessed the effects of mathematical correcting methods ^{247,248,250–252} that were also applied and analyzed by other authors in different investigations ^{253–256}. The correcting procedures proposed by Sacha et al. consisted of the multiplication or division of HRV indices by the mean RR average, or by the mean RR index to the powers from two to 16. Tsuji et al ^{150,257} studied HRV (SDNN) in 736 human subjects enrolled in the Framingham study, finding that HRV was correlated with the HR. However, they ²⁵⁷ showed that age was an independent factor determining HRV, with HRV being lower in older subjects for a given HR. They were able to separate age from HR, because of the large number of subjects investigated. If it is assumed that HRV is primarily the result of fluctuations in ANS activity in the conscious human, the study of Tsuji et al suggests a decrease in ANS activity with age ²⁵⁷. Studies concerning HRV should rigorously and openly correct for differences in HR before drawing conclusions ²⁴⁴. When HRV is not HR corrected, there is a sharp increase between birth and adolescence ^{100,258}. However, this increase is

connected to HR, which is strongly age-dependent in the young ²⁵⁹. After HR correction, SDNNc and RMSSDc decrease continuously from birth to adolescence, and further into higher ages. Gasior et al.¹¹⁴ studied 346 healthy children aged 6–13 and found that normalized HRV (adjusted for HR) decreases with age, accompanied by a reduction in average HR (longer R-R intervals). Despite this, standard HRV (unadjusted for HR) remains constant across ages. Younger children with higher HR exhibit greater normalized HRV, while older children with lower HR show reduced normalized HRV. They concluded that HR significantly influences HRV and is the strongest independent determinant of standard HRV indices. Normalizing HRV reveals its decline with age, alongside reduced HR. Van den Berg et al. ¹⁰², studied 13,943 ECGs of cardiovascular healthy participants with ages ranged from 11 days to 91 years. Normal limits have been established for HR corrected SDNN and RMSSD, derived from 10-s ECGs, using a consistent and automatic methodology for all ages and both sexes. HR correction formulas were derived using an exponential model and analyzed two time-domain HRV markers: the corrected standard deviation of the normal-to-normal RR intervals (SDNNc) and corrected root mean square of successive RR-interval differences (RMSSDc). There was a considerable age effect. For both SDNNc and RMSSDc, the median and the lower limit of normal decreased steadily from birth until old age. The upper limit of normal decreased until the age of 60 but increased markedly after that age. Their coverage of the pediatric population allows age-specific comparisons of HRV of the pediatric ECGs, from birth to puberty, independent of the rapid change in HR in this period of life. The marked difference between the corrected and uncorrected HRV markers in infancy and adolescence can be explained by the strong age-dependence of HR in children. The lower the age, the higher the average HR, and thus the larger the difference between corrected and uncorrected HRV markers. Since average HR in middle-aged and elderly people are

constant (65–70 beats per minute), the correction factor in the correction formulas is also constant (e.g., for SDNN 1.12 for 65 bpm and 1.25 for 70 bpm). As a result, the corrected values for these age groups, on average, differ from the uncorrected by a small, constant factor. When HRV is not HR corrected, there is a sharp increase between birth and adolescence^{100,102,258}. However, this increase is connected to HR, which is strongly age-dependent in the young²⁵⁹. After HR correction, SDNNc and RMSSDc decrease continuously from birth to adolescence, and further into higher ages. Using these normal values, both researchers^{102,114} and clinicians have a tool to decide upon cut-off values of HRV. HR and HRV are influenced by a variety of modifiable and non-modifiable factors (Table 10), including uncontrollable physiological factors, diseases, lifestyle choices, and external influences, independent of acute stress²⁶⁰.

Table 10. Factors influencing HR and HRV²⁶¹.

Influencing factor	Effect on HR	Effect on HRV
Non-influenceable physiological factors		
Age	HR normally decrease with increase in age ²⁶² .	HRV increases sharply in the first year of life, then increases until the age of 15 ²⁶³ , is highest in young adulthood and falls non-linearly with age ^{99,262–274} .
Circadian rhythm/time of the day	The HR follows a circadian rhythm, with a fall of HR at night ²⁷⁵ .	The HR follows a circadian rhythm, but the HRV is decreased at night due to the predominance of the parasympathetic activity and reduced during the day because of the predominance of the sympathetic activity ²⁷⁶ .
Genetic		HRV appears to vary between members of different ethnic backgrounds ²⁷⁷ .
Biological sex	The HR is normally higher in women than in men ²⁷⁸ .	Most of the studies showed a higher parasympathetic activity in women as compared to men ^{278–284} , which however showed a narrower difference after the age of 50 ^{264,274,285} . Some of the studies showed a higher baseline sympathetic activity in women ^{99,265,286,287} .
Diseases		
Cardiovascular diseases	Cardiac insufficiency leads to a raised HR ²⁸⁸ and unrestricted maximum HR. In patients with previous myocardial infarction, the activation of the sympathetic nervous system often leads to an increase in the HR, which is important for the prognosis ^{289–292} .	Cardiac insufficiency generally leads to a reduction in the HRV ^{288,293,294} . With hypertension, HRV is usually reduced ^{100,295} .
Metabolic disorders	Diabetes mellitus is often associated with increased sympathetic activity and hence a raised HR ²⁹⁶ .	The HRV is often reduced in patients with diabetes mellitus ^{257,297–300} , however, a correlation between the value of the HRV and the duration of the diabetes exists especially in cases of badly controlled diabetes ³⁰¹ . A metabolic syndrome often leads to a reduction of the HRV ^{301–307} , this is particularly evident in women ³⁰⁸ .
Pain	Pain usually rises HR.	In chronic pain, HRV is usually reduced ³⁰⁹ .

Table 10. Factors influencing HR and HRV (continued).

Influencing factor	Effect on HR	Effect on HRV
Influenceable lifestyle factors		
Body fat/body weight	Increased body mass index (BMI) generally leads to a raised HR ³¹⁰ , which can be partly explained by the stimulating effect of leptin on central sympathetic neurons ^{311,312} .	Increased body mass index (BMI) and increased mass of body fat often cause a fall in the HRV ³¹³ .
Stress/mental tension	Stress (mental, workplace related) generally leads to an increase in the HR ^{314–317} .	Stress (mental, workplace related) generally leads to decreased parasympathetic activity and thus to a reduction in the HRV ^{315,317–321} .
External factors		
Breathing	During inspiration there is a short-term increase in HR, during expiration there is a short-term decrease in HR ^{322,323} . This is essentially due to pulmonary afferents from stretch receptors and interactions from central respiratory neurons to the circulatory center in the medulla oblongata.	The effects of respiration on HRV are reflected in the form of respiratory sinus arrhythmia (RSA) and is seen in the HF band. Overall, the HRV parameter, RMSSD, does not seem to be affected by respiration ³²⁴ . For the rest of the parameters, the present state of knowledge is not conclusive ^{325,326} .
Cold, low temperatures	In men, low ambient temperatures usually lead to a decrease in HR both at rest and during exercise, while in women there is no decrease in HR, but rather a slight increase in HR ³²⁷ .	Only few studies about the effects of low temperatures on HRV are currently available: a reduction in the sympathetic activity and thus a raised HRV has been observed ³²⁸ , while long-term exposure to cold, including in winter months or occupational exposure to cold, no influence on HRV could be shown ^{328–330} .
Heat, high temperatures	High environmental temperatures lead to an increase in the HR caused on the one hand by direct temperature effects on the sinoatrial node and on the other hand by the increase in sympathetic activity because of the activation of warm receptors ^{331,332} .	High environmental temperatures lead to an increase in the sympathetic activity and a reduced HRV ^{330,333} .
Hypoxia		Hypobaric hypoxia usually leads to short-term sympathetic activation and long-term to a reduction in HRV ^{334,335} .
Noise	Noise often causes a rise in the HR, caused by activation of sympathetic nerves ³³⁶ .	Only few studies that give information about the effects of noise on HRV are available; HRV appears to fall in the presence of noise ^{337–340} .
Pharmacological drugs	Pharmacological drugs can have an increasing or decreasing effect on HR ¹⁷ .	Pharmacological drugs can have an increasing or decreasing effect on HRV ¹⁷ .

Adapted from Sammito et al. Guideline for the application of heart rate and heart rate variability in occupational medicine and occupational health science. *J Occup Med Toxicol* 19, 15 (2024) ²⁶¹

1.3.8 Brain injury, autonomic nervous system and cardiovascular system

Brain injury can be divided into two major causes: traumatic and non-traumatic. Whilst a traumatic brain injury (TBI) is one of the major morbidity and mortality causes in children worldwide ³⁴¹, non-traumatic brain injury (NTBI), which includes insults such as anoxia, vascular causes, brain tumors, central nervous system infections, toxic effects of substances and metabolic encephalopathies, can lead to negative and long-lasting consequences, particularly in the pediatric population, since they are in a critical period of neurodevelopment ³⁴². Traumatic brain injury, which is associated with autonomic

dysfunction and corresponds to 40% of deaths in American children under 1 year of age¹⁰¹, is the main cause of traumatic death^{343,344}. Despite the vast experience and research in this field, the determinants of its occurrence in children are still not well defined. While BI is an important killer of our youth, survival is often accompanied with permanent neurological sequelae resulting in substantial impact to the survivors and their families. It is, therefore, essential to prognosticate BI accurately to mitigate secondary brain injury and optimize outcomes³⁴⁵. Despite early and aggressive management, there remain times when survival is unlikely. Accurate prediction of outcomes in pediatric BI patients is needed to guide clinicians towards aggressive interventions and/or end-of-life discussions. Although previous attempts to develop accurate prognostic models for BI have been insufficient, several variables associated with poor outcome in pediatric BI have been identified including lower initial Glasgow Coma Scale (GCS) score^{346–348}, lower motor GCS^{349–353} absent or sluggish pupillary response^{348–350,352–355} hypotension^{348–350,356}, hyperglycemia^{357,358} coagulopathy^{359–361} hyponatremia³⁴⁸ basal skull fracture^{351,353}, subarachnoid hemorrhage^{350,355}, cerebral edema^{351,362} ischemia^{350,351,353} midline shift³⁵⁵ blood transfusion³⁴⁹, and early onset of central diabetes insipidus^{348,350,362}. All these outcome variables were determined with conventional statistical methods, and therefore, are rarely informative on the individual level. Indeed, the methodologies utilized limit their use in personalized medicine and the ability of health care providers to prognosticate on individual patients.

The development of a novel clinical outcome prediction tool requires a more advanced mathematical methodology that can integrate many complex and non-linear data points to generate an accurate outcome prediction model that is highly discriminative and that can be utilized with confidence for outcome prognostication of individual patients³⁴⁴.

In 2019, the Third Edition of the Brain Trauma Foundation (BTF) guidelines for hospital care for severe pediatric traumatic brain injury (pTBI) was published ³⁶³. Intracranial pressure (ICP) control was considered an outcome along with mortality. The authors, while acknowledging that any conclusive demonstration that ICP-targeted therapy would improve long-term outcome is lacking, recommend the inclusion of this outcome by virtue of the high-quality evidence stemming from studies having ICP control as primary endpoint. A high variability in locally used treatment protocols, particularly for topics with limited evidence (e.g., ICP control) has been reported by both American and European TBI centers ³⁶³. Thus, both stood as an integral part of TBI management despite the lack of evidence with all centers unanimously reporting the use of an ICP threshold of 20 mmHg ³⁶⁴.

Nevertheless, three new class III retrospective observational studies were added to the evidence base for this topic. Apparently divergent recommendations were made on the approach to temperature control depending on the considered outcome—either ICP control or overall outcome. Prophylactic mild hypothermia—as a first-tier therapy for all severe TBI cases is not recommended, while hypothermia has support as an option for second tier use in the setting of refractory intracranial hypertension. This approach highlights how effects of therapies on both ICP and long-term outcome can help guide provision of care in TBI patients ³⁶⁵. Critical gaps in knowledge of pathophysiological differences between children and adults concerning TBI outcomes, the paucity of pediatric trials and the uncertain extrapolation of adult data to pediatrics demand collaborative research. As prognostic models for TBI remain in their infancy, greater emphasis should be placed on identifying reliable and predictive scores to monitor both the historical outcome, that is, mortality and functional (assessed by GOS-E-Peds score) and cognitive outcome. BI can induce catecholamine mediated and inflammatory responses leading to neurogenic

stunned cardiomyopathy (NSC), characterized by left ventricular dysfunction, the development of both hypertension and hypotension, arrhythmias, ischemia-like ECG changes and, even the mild increase in serum biomarkers of cardiac injury ³⁶⁶. These abnormalities are usually reversible and caused by an “autonomic storm”, secondary to a local excessive release of norepinephrine from the sympathetic nerve terminals in the myocardium, resulting in severe changes in the patient's hemodynamics ³⁶⁷. While neurogenic cardiovascular dysfunction has been associated with a higher morbidity and mortality ³⁶⁸, little is still known about which hemodynamic parameters can predict poor outcome, its significance and no management thresholds have been well established in the pediatric population. Changes in HR and arterial BP variability have been seen in BD patients, compared with vegetative and normal patients and with themselves before BD ³⁶⁹. Table 11 summarizes some key studies exploring the relationship between HRV and BI outcomes, including mortality, neurological recovery, and autonomic dysfunction. The findings highlight the prognostic potential of HRV in various clinical contexts, ranging from severe TBI to BD, and emphasize its utility in predicting outcomes and guiding clinical decisions.

Table 11. Key Studies on HRV in Brain Injury and Mortality.

Authors	Characteristics	Main findings
Adults		
Lowensohn et al. ³⁷⁰ , 1977	Ten patients with acute neurological deficits. HR characteristics reflect the central nervous system's condition, like patterns seen in fetuses.	Normal HR cyclic changes were diminished with severe BI. HRV decreased rapidly as ICP rose, and the recovery rate of variability indicated neuronal function, even after pressure normalization. HRV may reflect the central nervous system's functional state in this context.
Rapenne et al. ³⁷¹ , 2001	20 patients with severe BI. They compared HRV in patients who progressed to BD with survivors; as well as HRV in survivors with good recovery (GCS $\geq$ 10) to HRV in those with worsened neurologic state.	During the awaking period, global HRV and the parasympathetic tone were significantly lower in the worsened neurologic state group. These findings suggest that HRV may be a helpful predictor of imminent BD and a useful adjunct for predicting outcome of patients with severe head injury.
Conci et al ³⁷² , 2001	Assessed HRV in 11 patients before and one hour after brain death (BD).	They observed a significant shift in pulse interval power toward lower frequencies and an overall reduction in spectral power, likely due to the loss of cardiovascular brainstem activity. These findings suggest that HRV spectral analysis, along with baroreflex sensitivity and BP variability, could help confirm BD diagnosis.

Table 11. Key Studies on HRV in Brain Injury and Mortality (continue).

Authors	Characteristics	Main findings
Adults		
Meglic et al. ³⁷³ , 2001	Assessed HRV by power spectra analysis in 14 patients with acute brainstem stroke.	Transient dysfunction of ANS was found in patients with acute medullary stroke (n=6) in contrast to those with non-medullary (n=8) brainstem stroke.
Baillard et al. ³⁷⁴ , 2002	Evaluated HRV continuously during the time of BD.	They showed that an improved method of HRV analysis immediately identified the loss in the spectral power of HR occurring during transition to BD. This approach may be used to confirm the cessation of brainstem function in clinical practice.
Papainannou et al. ¹⁸⁶ , 2008)	20 ABI patients treated in the PICU. Relate longitudinally over time HR and BP variability and baroreflex sensitivity with the severity of neurologic dysfunction and outcome.	In acute BI patients, low variability, low baroreflex sensitivity, and sustained decrease in LF/HF of HR signals are linked with a high mortality rate.
Vakilian et al. ³⁶⁹ , 2011	14 BD patients with clinical signs of imminent BD and 15 comatose patients.	HRV and RR-interval analysis appeared as an early finding for the diagnosis of brainstem death in comparison to comatose patients with normal brainstem function. QT dispersion had not significant in this regard.
Ryan et al. ³⁷⁵ (2011)	218 adult patients with severe ABI.patients.	Decreased VLF is an independent predictor of mortality and morbidity in hemodynamically stable trauma patients. Other time and other frequency domain variables correlated with some, but not all, outcomes. All were heavily influenced by factors that alter autonomic function, especially patient age.
Machado-Ferrer et al. ³⁷⁶ , 2013	Assessed ANS in coma by HRV in sixteen comatose patients and 22 normal subjects with comparable ages and sex.	They found a notable reduction of HRV in the subgroup with GCS = 3. Absolute power for the whole frequency spectrum decreased whenever GCS scores were lower. A significant decrement was found for absolute power of the VLF and LF bands in the subgroup of GCS = 3, and although it was lower for the HF band in these patients, those changes were not statistically significantly different. The LF/HF ratio and the Shannon' s entropy indices were significantly reduced in the subgroup with GCS = 3.
Sykora et al. ³⁷⁷ , 2016	262 patients with a median age of 36 years with TBI.	Autonomic impairment, as measured by HRV and baroreflex sensitivity, is significantly associated with increased mortality after TBI. These effects, though partially interlinked, seem to be independent of age, trauma severity, intracranial pressure, or autoregulatory status, and thus represent a discrete phenomenon in the pathophysiology of traumatic brain injury.
Pediatric		
Goldstein et al. ³⁷⁸ , 1998	14 pediatric patients with severe ABI.	Severity of neurological injury, outcome, and survival are inversely associated with the degree of cardiovascular variability and baroreceptor sensitivity. BD results in near-zero levels of variability in cardiovascular signals and baroreceptor sensitivity.
Biswas et al. ³⁷⁹ , 2000	15 severe TBI children and four control subjects.	ICP of >30 mm Hg or a CPP of <40 mm Hg may be associated with marked autonomic dysfunction and poor outcome. HRV power spectral analysis may be a useful adjunct in determining the severity of neurologic insult and the prognosis for recovery in children. The LF/HF ratio may be helpful not only in identifying those patients who will progress to BD but also in predicting which patients will have favorable outcomes.
Martin et al. ³⁸⁰ , 2022	15 children underwent continuous monitoring of ECG over 7 days post TBI. HRV analysis was performed retrospectively. Outcome of children 6 months post TBI was assessed using the Glasgow Outcome Scale – Extended Pediatric (GOS-E Peds).	Altered HRV is associated with unfavorable neurological outcome and in-hospital adverse events. Larger prospective studies are needed to confirm these findings and to explore if HRV offers reliable and clinically useful prediction data that may help clinical decision making.

Table 11. Key Studies on HRV in Brain Injury and Mortality (continue).

Authors	Characteristics	Main findings
Systematic reviews		
Florez-Perdomo et al. ³⁸¹ , 2021	Systematic review and meta-analysis (PubMed, SCOPUS, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE) to determine the utility of HRV in predicting mortality in moderate to severe TBI.	Five articles comparing 542 patients were included. Predicted high mortality based on odds ratio for variables LF/HF ratio, HF peak, and TP. However, the statistical analysis was weakened owing to the high level of heterogeneity in the included studies. Further research is needed to generate high-quality recommendations regarding HRV as a predictor of mortality after TBI.
Hart et al. ³⁸² , 2023	Systematic review and metanalysis on the effect of use of beta blockers in patients with TBI on mortality and functional outcome.	The use of beta blockers is associated with an overall decrease in in-hospital mortality and higher rate of good functional outcome. Beta-blockers, significantly influence HRV by modulating ANS activity. These agents primarily reduce SNS activity while enhancing PSNS tone, leading to increased HRV in most cases.
Talbert et al. ³⁸³ , 2024	Systematic review of the relationship between TBI and disruptions in HRV.	89 papers met the inclusion criteria. TBI of any severity is associated with decreased HRV. Decreased HRV following TBI predicts mortality beyond age; HRV disturbances may persist following mild TBI. Overall, current literature suggests HRV is decreased following TBI and may be a good indicator of physiological change and predictor of important outcomes including mortality and symptom improvement.

Children with ABI often present ANS dysfunctions that produce alterations on the cardiac parameters³⁸⁴. Hemodynamic parameters like HR and BP can predict poor outcome in severe ABI, but its significance and management thresholds have not been well established in the pediatric population^{384,385}. Contrary to the adult literature, pediatric patients with severe TBI and hypertension on presentation do not appear to have worsened outcomes compared to those who are normotensive. However, a trend toward increased mortality did exist at extremes of age adjusted hypertension. Research has established that a diminished HRV is a predictor of death irrespective of the cause but, despite the potential of HRV as a useful tool in the management of critically ill patients, is yet to be used routinely in clinical decision making^{200,201,379,386,387}.

2. Research questions and aims

The main objectives of this investigation were:

1. To examine the current state of research on the value of HRV as a prognostic tool in children with brain injury.
2. To review the current state of cardiovascular events, beyond HRV, in predicting outcomes for children with brain injuries.
3. To examine changes in HRV in healthy children undergoing minor surgery to assess the influence of anesthetic drugs and stress on the ANS.
4. To investigate the prognostic significance of cardiovascular responses in children with severe brain injury, with a focus on HR, BP, and both linear and non-linear measures of HRV as predictors of mortality.
5. To investigate the prognostic significance of cardiovascular responses in children with severe brain injury, with a focus on HR, BP, and both linear and non-linear measures of HRV as predictors of neurologic morbidity at three and 12 months.

3. Publications

3.1 Paper I

The utility of heart rate variability as a prognostic factor in children with traumatic brain injury.

Silva, MJ; Antunes, N.

Brain Injury. 2020 Dec 5;34(13-14):1693-1700.

doi: 10.1080/02699052.2020.1836401.

<https://pubmed.ncbi.nlm.nih.gov/33190529/>



The utility of heart rate variability as a prognostic factor in children with traumatic brain injury

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ABSTRACT

Objective: This study aimed to do a literature review to prove the hypothesis that a change in autonomic nervous system regulation, more precisely a decrease in heart rate variability (HRV), is associated with a worse outcome and could be used as a prognostic factor in children with TBI.

Methods: Databases (Pubmed, World of Science and Scopus) studies were conducted from 1996 to 2017, considering HRV in children with TBI. Seven studies were analyzed.

Results: Patients that became brain dead had a markedly lower LF/HF ratio, with a significant decrease after the first few hours of hospitalization. Patients with a more favorable prognosis had significantly higher LF/HF ratios.

Discussion: The HRV can be useful when determining the severity of neurological damage and a prognostic factor in the evaluation of its recovery. However, to assess the true value of HRV monitoring in children with TBI, a prospective study with identified thresholds for HRV, comparison to the standard methods of assessment and predictions should be made blinded to outcome at admission and then through the clinical course including the post-acute phase of rehabilitation. In the absence of this, any recommendation for its use as a prognostic tool may be premature.

ARTICLE HISTORY

Received 6 November 2019

Revised 26 August 2020

Accepted 9 October 2020

KEYWORDS

Autonomic dysfun; child;
head trauma; prognosis

Introduction

Heart rate variability (HRV) is defined as the variation over time of the interval between consecutive heartbeats. It reflects the heart's ability to adapt and respond to changing circumstances by detecting and responding to unpredictable stimuli. It serves as an indicator of autonomous activity in the regulation of circulation. It is also considered as the method of analysis of the autonomic nervous system (ANS) activity. Changes in HRV have been associated with several pathological conditions. HRV measurements can be grouped in time domain, frequency domain and non-linear measurements. HRV derives from the difference in duration of intervals between two consecutive beats, called R-R intervals, and is measured in milliseconds. These intervals are obtained on the ECG: the QRS complexes correspond to heartbeats, and R-R¹ and R-R² are intervals between beats.

Many frequency bands have been defined in humans, namely, high-frequency band (HF): between 0.15 and 0.4 Hz – modulated by the parasympathetic nervous system and generated by respiratory, low-frequency band (LF): between 0.04 and 0.15 Hz – derives from the activity of the sympathetic system and is thought to reflect the delay in the baroreceptor reflex system and very low-frequency band (VLF): between 0.01 and 0.04 Hz – it is of uncertain origin but has been attributed to a marker of sympathetic activity (1).

As the heart rate (HR) is a nonstationary signal, its variability (especially a reduction) may indicate the existence or eminence of current disease: the reduction of the HRV is associated with increased mortality. HRV is widely used to

efficiently monitor the human body, more precisely in the evaluation of ANS, through its sympathetic and parasympathetic components. Therefore, it has become a relevant non-invasive clinical tool (2). Traumatic brain injury (TBI), which is associated with autonomic dysfunction and corresponds to 40% of deaths in American children under 1 year of age (3), is the main cause of traumatic death (4). Despite the vast experience and research in this field, the determinants of its occurrence in children are still not well defined.

TBI may result in dysautonomia (dysfunction of ANS), which is a condition characterized by marked paroxysmal changes in blood pressure, HR, respiratory rate, temperature and sweating (5). Dysautonomia affects a small sub-group of survivors who have suffered severe TBI.

The authors did a literature review focusing on HRV to prove the hypothesis that significant changes in the regulation of the ANS, more precisely a decrease in HRV, are associated with a lower probability of survival and a higher rate of mortality and morbidity.

Methods

A systematic research of the literature was made in January 2018, based on three databases (Pubmed, World of Science and Scopus) with the keywords: (heart rate variability) and (children) and (head trauma) and (pediatric patients) and (dysautonomia). Two hundred and twenty-one articles from

Table 1. Selected time-domain measures of HRV (1).

Variable	Units	Description	Interpretation
SDNN	ms	Standard deviation of all RR intervals	Estimates overall HRV.
SDANN	ms	Standard deviation of the average of RR intervals in all 5 min segments of entire recording	Estimates long-term components of HRV.
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent RR intervals	Estimates short-term components of HRV.

ms – milliseconds

Table 2. Selected frequency domain measures of HRV (1).

Variable	Units	Description	Frequency range	Interpretation
HF	ms ²	Power in high frequency range	0.15 a 0.40 Hz	Heart rate changes related to the respiratory cycle (respiratory sinus arrhythmia). They are typically modulated by the parasympathetic.
LF	ms ²	Power in low frequency range	0.04 a 0.15 Hz	Modulated by both sympathetic and parasympathetic, with sympathetic predominance in some specific situations, and reflecting the oscillations of the baroreceptor system.
VLF	ms ²	Power in very low frequency range	≤0.04 Hz	Dependent on thermoregulatory mechanisms and the renin-angiotensin system, whose regulation is also effected by sympathetic and parasympathetic.
LF/HF	ms ²	Ratio LF/HF		It provides useful information on balance between the sympathetic and parasympathetic systems.
TP	ms ²	Total power: variance of all NN intervals	Approximately ≤ 0.04 Hz	It provides useful information on balance between the sympathetic and parasympathetic systems.

ms² – milliseconds², Hz – Hertz

Pubmed, 102 from the Web of Science and 2 from the Scopus database were found.

The abstracts were analyzed according to the following criteria: articles from 1996 to 2017, human studies in pediatric age (1 month to 18 years), without congenital diseases or comorbidities, of empirical investigations (excluding meta-analyses, review articles and reports of single cases), using time and frequency domain methods as HRV evaluation according to the Task Force guidelines (1) and available in full text in Portuguese or English.

Seven articles fulfilled the inclusion criteria. Integral texts of articles with matching predefined criteria were screened. Data extraction records were performed for each of the seven selected articles. The aim, study format, author and year, characteristics of participants, parameters used to measure HRV (time domain and frequency), experimental conditions and key ideas were extracted.

Results

According to the Task Force of the European Society of Cardiology and the North American Society for Rhythm and Electrophysiology (1) and several studies (6–15) the authors used the time and frequency domains to determine the utility of HRV as a prognostic factor in children with TBI. The results are summarized in Tables 1 and 2. The data extracted from the selected articles are summarized in Table 3.

Except for Su et al. (11) who did not specify how many children with TBI are included, in the remaining six eligible articles, the sample size was variable, between four and 114 children, but the total number of children with TBI ranged from four to 25. Only children included in the study by Kim et al. (12) were studied after an average of 535 days post-TBI. In the remaining studies, the data included were collected in the acute phase even during the first 24 hours on admission or the date of discharge from pediatric intensive care (PICU).

The authors verified that there was a variation between the low frequency (LF) and high frequency (HF) values in the analyzed studies when compared with those suggested by the Task Force (Table 2). The HF band starts at the value at which the LF band ends: 0.15 Hz (Table 3). Five studies excluded the very low-frequency band (VLF), starting the LF band between 0.01 and 0.04 Hz and those that included the VLF band, used the value 0.01 Hz to start it (Table 3).

According to Biswas et al. (6) children with TBI who progressed to brain death had a very low LF/HF ratio ($p < .001$), with a significant decrease in the first 4 hours of hospitalization. Patients with better prognosis had higher LF/HF ratio.

Goldstein et al. (7) found significant correlations between survival and mean HR ($p = .004$) and LF ($p = .009$). In other words, the severity of the neurological injury, prognosis and survival were inversely related to the degree of cardiovascular variability. Brain death occurred at very low values of HRV (near zero). In addition, the cardiovascular and autonomic systems were proportionally decoupled at various levels during acute brain injury. Thus, monitoring the degree of decoupling in these systems allows a better understanding of neuroautonomic and cardiovascular interactions during acute brain injury.

Goldstein and colleagues (8) also found a negative correlation between the minimum value of LF ($p < .001$), HF ($p < .001$) and LF/HF ($p = .007$), recorded during hospitalization. At discharge from PICU, the prognostic showed a negative correlation between the minimum value of LF ($p < .001$), HF ($p < .001$) and LF/HF ($p = .008$), in other words, low values of HRV demonstrated a greater severity of the illness and a worse prognosis.

According to Goldstein et al. (9), maximal values of LF ($p < .001$), and minimum values of HF ($p < .001$) demonstrated a higher probability of survival, suggesting that HRV may prove to be a sensitive and specific method useful in determining the severity of the neurological injury in children who suffered brain injury.

Almeida et al. (10) concluded that the group of patients with brain death presented reduced HRV in all frequency bands ($p < 10^{-16}$).

Table 3. HRV in children with TBI.

Authors (year)	Aim design	Participants	HRV measurement	Experimental conditions	Key findings
Goldstein B et al. (9)	To study sequential changes in HRV in patients with acute brain injury and correlate it with the severity of neurologic dysfunction and patient outcome.	42 children, 5 were excluded. 37 children (13 males/24 females) with brain injury (injury occurring within 24 h of hospital admission). 25 children had TBI. Data were obtained within the first 24 h of admission to the Strong Children's Critical Care Center between August 1990 and March 1992.	ECG using monitors 78213 C e 78212D, Hewlett-Packard, Waltham, MA. Sampling rate: 1 kHz. Duration of recording: 256secs. FD: VLF (0.01 to 0.04 Hz), MLF (0.04 to 0.07 Hz), LF (0.01 to 0.15) and HF (0.15 to 0.50 Hz).	Inclusion criteria: GCS $\leq$ 12 or the need for frequent (every 1 hour) nursing assessment of the patient's neurologic status. Exclusion criteria: Prolonged cardiopulmonary arrest with severe hypoxemic cardiac damage and/or cardiac dysrhythmias. Data were obtained within 24 hours of admission and on days 2,3,7 and weekly thereafter until hospital discharge or death. 10 who received low-dose dopamine ($<5 \mu\text{g/kg/min}$) or epinephrine ($<0.1 \mu\text{g/kg/min}$) were included in the study.	Significant association between LF and severity of neurologic dysfunction ($p < .001$) and patient outcome ($p = .05$). Maximum values for LF ($p < .001$) and minimum value HF ($p = .001$), predicted an increased likelihood of survival.
Goldstein B et al. (7)	Uncoupling of the autonomic and cardiovascular systems in acute brain injury.	24 children with brain injury (10 males/14 females). Data were obtained within the first 24 h of admission to the pediatric ICU between September 1994 and March 1997. Aged from 0.2 to 17.5 years (mean = 5.9 ± 5.1 years) 5 children had TBI.	HRView software (Boston Medical Technologies, Boston, MA). Sampling rate: 1 kHz. Duration of recording: 600secs. 128 secs time series that was artifact free was chosen for analysis by one author. FD: LF (0.01 to 0.15 Hz).	Included pathologies: anoxic/ischemic injury, multiple trauma, head trauma, central nervous system infection and intracranial hemorrhage. There were 17 survivors and 7 non-survivors, 3 of which were diagnosed as brain dead.	Neurological injury and survival was associated with LF (0.01–0.15 Hz). Brain death patients showed decreased LF ($p = .03$) compared with non-brain-dead patients. The more severe the neurological injury, the worse the prognosis and the lower the HRV.
Goldstein B et al. (8)	To determine if decomplexification of heart rate dynamics occurs in critically ill and injures pediatric patients.	135 consecutive pediatric ICU admissions. 21 children were excluded. 13 children had TBI.	ECG using monitors 78213 C, Hewlett-Packard, Palo Alto, CA. Sampling rate: 1 kHz. Duration of recording: 256secs. A 128 secs segment was selected for determination of heart rate power spectra and analyzed. FD: LF (0.01 to 0.15 Hz), HF (0.15 to 2.0 Hz) and LF/HF ratio.	HRV was compared with a previously validated measure of severity of illness – Pediatric Risk of Mortality (PRISM) and with validated measures of outcome from pediatric intensive care – Pediatric Overall Performance Category (POPC) e Pediatric Cerebral Performance Category (PCPC). Exclusion criteria: patients who were not physically in the ICU at the time of study; were off electrocardiographic monitoring; had a high cervical cord tumor; had cardiac dysrhythmias at the time of ECG recording or were receiving anticholinergic medications or other drugs that may have significantly impaired analysis of HRV. All patients were studied in the supine position.	The lower the HRV, the greater the severity of illness (LF $p = .001$ e HF $p = .004$). The lower the HRV, the worse the outcome (LF $p = .002$ e HF $p = .011$). LF or sympathetic modulation of HRV, showed a consistently higher degree of correlation with PRISM, POPC and PCPC scores than did HF suggesting that sympathetic modulation of heart rate may be a more sensitive measure of severity of illness and outcome than parasympathetic activity.

(Continued)

Table 3. (Continued).

Authors (year)	Aim design	Participants	HRV measurement	Experimental conditions	Key findings
Biswas A et al. (6)	To evaluate HRV by power spectral analysis and outcomes in children with acute traumatic head injury.	15 children (10 male/5 female) with TBI occurring within 8 hrs. of hospital admission. Data collected from April 1997 to June 1998 in Pediatric Intensive Care Unit (ICU) in a level II trauma center. Age between: 7 months to 12 years.	Semi-automated system (Fukuda-Denshi and DMS 300: Total Disclosure Analyzer, Diagnostic Monitoring Software, Santa Ana, CA). This system received the electrocardiogram (ECG) signal from bedside monitors in real-time and sampled the ECG signal at 128 Hz. Duration of recording: 1 hour. RR intervals: 5 min. – series of 256 points. FD: LF (0.04 to 0.15 Hz) and HF (0.15 to 0.40 Hz) and LF/HF ratio.	Relationship between intracranial pressure, cerebral perfusion pressure and HRV in children with TBI was studied. Inclusion criteria: TBI occurring within 8 hrs. of hospital admission, Glasgow Coma Scale (GCS) ≤ 8 and placement of an intracranial pressure monitor. Exclusion criteria: Recent cardiopulmonary arrest, β -adrenergic receptor antagonist and/or atropine use within the previous 24 hrs., history of preexisting neurologic injury or disease, moderate dose of infusions of catecholamine, sepsis or suspicion of significant infection, and history of heart disease or other pathology associated with abnormal HRV.	There was a significant decrease in the LF/HF ratio when the intracranial pressure was > 30 mmHg ($p < .001$) or the cerebral perfusion was < 40 mmHg ($p < .001$). Children with a GCS score of 3–4 had a lower LF/HF ratio compared with those who had a GCS score of 5–8 ($p < .005$). Patients who progressed to brain death had a markedly lower LF/HF ratio ($p < .001$). Patients with more favorable outcomes had significantly higher LF/HF ratios.
Su C et al. (11)	To investigate the autonomic function in patients with brain damage of various extents.	121 patients 31 subjects were excluded. 90 patients (67 males/23 females) aged from 4 to 84 years (mean 45 years). Patients were divided in 5 groups according with GCS. There were children in I, II, IV and V group.	Precordial ECG. Sampling rate: 256 kHz. Duration of recording: 5 minutes. FD: LF (0.04 to 0.15 Hz) and HF (0.15 to 0.40 Hz) and LF/HF ratio.	Exclusion criteria: without available consent; with diabetic neuropathy; cardiac arrhythmia and other cardiovascular or neurological disease and patients with long term use of drugs such as hypnotics, autonomic stimulants or suppressants that may affect the heart rate. Control group: 17 volunteers aged from 18 to 42 years. Patients were divided into 5 groups according with GCS: group I – mild head concussion used as control and group V – brain-stem death.	The LF, HF and LF/HF in group I were essentially similar to those in the normal subjects. LF and HF decreased from group I to IV. All parameters were nearly absent in group V.
Almeida R et al. (10)	Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients.	16 children with acute brain injury. These data were integrated of a larger database (45 cases) collected between 2006 and 2011. Only children within 11 and 14 years were included. 8 children had TBI (7 survived and 1 was brain death confirmed).	ECG Holter recordings. FD: VLF (< 0.04 Hz), LF (0.04 to 0.15) and HF (0.15 to 0.40 Hz).		As expected brain death group presented reduced HRV in all frequency bands, with high significance ($p < 10^{-16}$).

(Continued)

Table 3. (Continued).

Authors (year)	Aim design	Participants	HRV measurement	Experimental conditions	Key findings
Kim S et al. (12)	To find evidence of autonomic imbalance and present the HRV parameters that reflect the severity of paroxysmal sympathetic hyperactivity in children with acquired brain injury.	13 children (8 males/5 females) with acute brain injury who were admitted from October 2013 to January 2016. 4 children had TBI.	SA-6000 device (Medicore Co., Seoul, Korea). Duration of recording: 5 minutes. TD: SDNN and rmSSD. FD: LF (0.04 to 0.15), HF (0.15 to 0.40 Hz) and LF/HF ratio.	13 age- and sex-matched patients with cerebral palsy were selected as the control group. Test were conducted in a noise-free environment after 30 minutes of rest, in a relaxed supine position. In order to avoid the influence of circadian changes in the HRV results, data was collected between 1:00 PM and 3:00 PM in every patient. The room temperature during data collection was 24–26°C. Exclusion criteria: history of cardiac disease; diabetes or other peripheral neurological impairment; patients taking cardiovascular medications and sepsis or suspicion of significant infection.	There was a statistically significant increase in the mean heart rate of the acute brain injury group compared to the control group ($p = .0119$). According to the time domain analysis, the rmSSD was significantly different between the two groups ($p = .0240$). All indices of the frequency domain analysis demonstrated a statistically significant difference between the two groups. The LF and HF decreased in the acute brain injury group compared to the control group. Only the LF / HF ratio increased in the acute brain injury group compared to the control ($p = .0018$ and $p = .0018$, respectively).

LF – low frequency; VLF – very low frequency; MLF – mid-low frequency; HF – high frequency; secs – seconds; FD – frequency domain; TD – time domain

Su et al. (11) proved that a percentage increase in the LF band and in the LF/HF with the decrease in HF indicated a greater power on the part of the sympathetic nervous system and attenuated parasympathetic. These changes were related to the severity of damage to the brainstem. It was also observed that in brain death, LF and HF presented very low values, concluding that HRV may be a useful tool in the evaluation of ANS functions in patients with various levels of brain injury.

Kim et al. (12) found that a significant increase in LF ($p = .0119$) patients with acute brain injury indicated a high sympathetic excitatory activity since LF had a sympathetic predominance. However, HF had a parasympathetic modulation. The significantly decreased values observed in the group of patients with acute brain injury (ABI) suggested a decreased parasympathetic activity. The significant increase in the LF/HF ratio of the group of patients with acquired brain injury infers a greater power on the part of their sympathetic nervous system ($p = .0018$). In the time domain, SDNN, which reflects every cyclic aspect that was related to the variability during the recording period, was decreased in ABI group ($p = .0134$); rmSSD, which represents the parasympathetic regulation of the heart, was significantly different between the two groups ($p = .0240$). In summary, according to this study, the group with acute brain injury had a sympathetic predominance when compared to the control group.

Discussion

The main result of this study is that HRV can be useful when determining the severity of neurological damage and a prognostic factor in the evaluation of its recovery. It was found that the more severe the neurological injury, the worse

the prognosis and the lower the HRV. This suggests that as HRV is commonly used to efficiently monitor the human body in the evaluation of ANS, through its sympathetic and parasympathetic components, it is a relevant noninvasive clinical tool (2). Short-term variations in HR are observed at all ages and are an important sign of normal homeostatic mechanisms of the cardiovascular system. The degree of HRV provides information about how the nervous system interferes with HR and heart responsiveness. In addition, disorders of the central and peripheral nervous system have effects on HRV. Furthermore, all normal cyclic changes in HR are attenuated in the presence of severe brain damage (13).

Our interest in the present study was to explore HRV changes and to investigate their relationship in the prognosis of children with TBI. Even though not much has been published about this matter, in the analyzed studies, HRV was markedly depressed in children who progressed to brain death after TBI.

In addition, LF/HF ratio was significantly reduced in brain-dead children. The low LF/HF ratio was evident in all brain-dead and non-surviving patients, while in the control group there was a progressive increase in all measured variables. However, it is hypothesized that these conclusions are biased in relation to the importance of each variable, due to the small sample size of each study. For this reason, the authors think that a similar study with a larger and more homogenous group could have a significant value in HRV as a predictive element, rather than simply associated, with mortality.

There are several relevant limitations to this review. The lack of standardization of the Task Force guidelines for the pediatric population. The standard values described may not apply to children with the result that different authors used different frequency bands. Furthermore, the implementation of a standard method to collect and analyze HRV would

contribute to more reliable findings. This and the fact that most studies included mostly adults and only a small number of children made it difficult to establish a comparison about the importance of HRV and its role in the prognosis of children with TBI. Hence, the importance of setting appropriate guidelines for the pediatric age as well as a cutoff to define the prognosis of children with TBI on admission. On the other hand, the fact that all available studies are limited by very small numbers of children with TBI (4–25 per study) limited the results of the studies. Nonetheless, it seems well established that LF/HF ratio may be helpful not only in identifying those patients who will progress to brain death but also in predicting which patients will have favorable outcomes but there are no clear cut-off values of decreased of the single parameters or increase of LF/HF ratio.

The authors did not consider no specific threshold for HRV above or below which a prediction can be made of prognosis. There are several clinical variables that have an association with outcome (higher or lower levels of any test may be associated with bad outcome) but these are general associations. There is no generalizable threshold that can be used as a guide for individual patients. It is still uncertain the real value of such monitoring method for the early identification of prognostically worse cases. To know that it is necessary to make a comparison to the standard methods of assessment of the injury severity, e.g., initial Glasgow Coma Scale, presence of fixed dilated pupils, initial intra-cranial pressure and cranial perfusion pressure monitoring or loss of cerebrovascular autoregulation in the first 24 hours.

The association of HRV and brain death may or may not have clinical utility. As a diagnostic tool, it is important to determine its utility by testing it against known brainstem death criteria to see if it is independent of the existing ability to predict the progression to brain death.

As we can see in the results of our study, in the acute phase, reduced HRV power in children with TBI is positively associated with injury severity and a worse outcome, however, in the post-acute phase of rehabilitation these variables are very little documented.

King et al. (14) were the first to demonstrate abnormalities in HRV of patients with TBI during the post-acute recovery phase. They studied seven adult patients at a mean of 4 months post-injury and found changes in HRV with lower SDNN, LF, HF and total power values in survivors of severe TBI when compared to controls.

One pediatric HRV study of 12 boys post severe TBI reported a significantly lower RMSSD of the HRV at rest and decreased time-domain values during exercise only in TBI children (15). Another similar study (16) was performed in ten children 3–5 years post-severe TBI and also found a decreased HRV at rest and in response to exercise. Both studies found a cardiac autonomic system less efficient at rest and less adaptive to exercise and activity in children post-severe TBI compared to controls.

In the same way, Baguley et al. (17), studied 16 adult patients with TBI and found reduced SDNN and total LF power compared to controls at a mean of 2.6 months post-injury. They divided the TBI group into two subgroups, with and without dysautonomia, and found that patients with

dysautonomia had more severe injuries and worse rehabilitation outcomes with lower LF power, greater LF/HF ratio and prolonged uncoupling of HR and HRV parameters compared to non-dysautonomic patients. These HRV abnormalities were maintained for a mean of 14 months post-injury. On the other hand, Keren et al. (18) found a tendency to normalize HRV changes during the first 3 months after TBI, suggesting recovery of the ANS.

More studies are needed to document how long changes in the ANS are maintained after TBI, it will probably depend on several factors. However, this information may have important implications for the management of these patients in the medium to long term.

Dysautonomia, also known as autonomic dysfunction syndrome or paroxysmal sympathetic hyperactivity (PHS), is a syndrome that affects a subset of severe BI survivors and is characterized by changes in HR, respiratory rate (RR), systolic and diastolic blood pressure, temperature, sweating and muscle tone increase (19–21). The prevalence of PHS in children after severe TBI has varied between 6% and 38% although these values are thought to be underestimated (22–26).

Kim et al. (12) studied 13 children with acquired brain injury (four with TBI) and found a decline of the RMSSD, LF, HF, normalized LF/HF and significant incline of the normalized LF, LF/HF ratio in these patients demonstrating that they have higher sympathetic excitatory activity and more dominant sympathetic power than parasympathetic power compared to control group. They also diagnosed five patients with PHS and found that they had significantly lower values of the SDNN and TP compared to non-PHS group indicating a less variable nature of the HR during environmental change.

Children with PHS have greater PICU length of stay and worse functional and cognitive outcomes with a long-term course in rehabilitation indicating that new strategies for rehabilitation and patient follow-up are needed to improve outcome (22–24,26,27).

The ANS dysfunction, commonly assessed by HRV, is a major factor in the symptomatology in TBI and may occur because of neurogenic causes such as a large catecholamine release and inflammatory response after injury (28). This sequelae of increased sympathetic or reduced vagal activity may produce arrhythmias, ischemia, arterial hypertension, myocardial infarction or sudden cardiac death (28,29). The pathophysiology of HRV changes can be interpreted in several ways. In the acute setting Goldstein et al. (7) suggested that the cardiovascular system and ANS are uncoupled following TBI and that the more severe the injury, the greater the uncoupling would be. Baguley et al. (17), on the other hand, found an ongoing reduction of HRV components in patients with dysautonomia regardless of GCS, and suggests that this uncoupling continues for dysautonomic subjects in the post-acute setting arising from damage extending rostrally from the brainstem into the hypothalamus or above resulting in an incomplete breakdown of communication between supraspinal and spinal ANS drivers and inhibitors. However, in addition to the decoupling between cerebral autonomic control and the cardiovascular system, we also have to take into account the role of catecholamine elevation as a contributing factor to these changes. Clifton et al. (30) studied 48 patients with head

injuries (including about 10 children and adolescents) and found that patients with head injury and without systemic trauma usually had an elevated plasma norepinephrine (NE) when their GCS was below 10. Elevations of plasma NE correlated with elevations of blood pressure, pulse rate and temperature. The plasma NE level reflects the amount of sympathetic nervous release of this neurotransmission translating a high activity of the sympathetic nervous system in these patients which can have deleterious effects on the cardiovascular system (30,31).

During paroxysm, patients have increased metabolic expenditure which would reduce total spectral power as a result of high sympathetic drive (17). However, changes in HRV were found in patients with dysautonomia during a post-acute and non-paroxysmal phase and independently of HR, supporting the disconnection theory (17). Further studies are needed to assess the role of catecholamine and its potentially damaging effects on stress response to injury, especially in children with TBI.

Patients with TBI have reduced life expectancy depending on age, sex and severity of disability ('31–34). Hilz et al. (35) studied cardiovascular-autonomic dysregulation after mild traumatic brain injury (mTBI) in 20 adults 5–43 months post-injury and found impaired autonomic modulation in the post-mTBI group what can probably contribute to cardiovascular events and fatalities. Wilson and colleagues (36) compiled a series of studies concerning adults with traumatic brain injury that included follow-up of 5 years or more after injury and concluded that there are multiple lines of evidence suggesting that TBI may be chronic, evolving, and lifelong disorder with an altered risk not only for various neurological pathologies but also systemic pathologies, with associated increased morbidity and mortality, extending for many decades in survivors of TBI. Strauss et al. (37) studied the long-term mortality risk and life expectancy after TBI in 946 children and adolescents and found that inactivity in lower functioning TBI survivors plays a role in late mortality with a high correlation between mobility and mortality. Accordingly, it is pertinent to consider children after TBI as a risk population justifying tighter control, such as routine cardiovascular screening, and lifestyle interventions as keys in secondary prevention and mortality reduction.

TBI can result in a broad signs and symptoms that include physical, emotional and cognitive disturbances that can lead to headaches, dizziness, nausea, concentration deficits, slowed mental processing, memory impairment, irritability, gait disturbance and fatigue (28,38). ANS dysfunction has been found as a major factor in the symptomatology during the acute and sub-acute phase post TBI and is a marker for anxiety, post-traumatic stress, depression, schizophrenia and panic disorder (28,38,39).

A prospective study must be done, with identified thresholds for HRV and comparison to the standard methods of assessment, and predictions should be made blinded to the outcome at admission and then regularly through the clinical course to recommend HRV monitoring as a prognostic tool in children with TBI. Further prospective studies to understand the long-term effects of TBI on the autonomous nervous system and the usefulness of HRV in the post-acute rehabilitation phase in children with and without PHS as a prognostic factor

for cardiovascular risk, psychiatric disorders or other potential effects are also needed.

Conclusions

In summary, according to the eligible studies, the analysis of HRV in children with severe brain lesions caused by TBI and the prognosis of their recovery is inversely associated with HRV, with cerebral death levels of almost zero variability. The frequency domain is used more frequently and the LF reflected the activity of the sympathetic component. The evidence indicated that during severe brain injury, the cardiovascular and autonomic systems are proportionally decoupled at various levels in relation to the degree of neurological injury, and their monitoring may lead to a better understanding of neuroautonomic interactions. Patients who after brain injury evolved to brain death had a markedly lower LF/HF ratio ($p < .001$) with a significant decrease after the first hours of hospitalization. Patients with a more favorable prognosis had significantly higher LF/HF ratios. Thus, the LF/HF ratio may be useful in identifying patients who will progress to brain death, as well as in the prognosis of those who will recover favorably. But these are general associations and to assess the true value of HRV monitoring in children with TBI, a prospective study must be done, with identified thresholds for HRV, comparison to the standard methods of assessment and predictions should be made blinded to the outcome at admission and then regularly through the clinical course. In the absence of this, any recommendation for its use as a prognostic tool may be premature.

Declaration of interest

The authors report no declarations of interest.

References

1. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. standards of measurement, physiological interpretation and clinical use. *Euro Heart J.* 1996;17:354–81. doi:10.1093/oxford-journals.eurheartj.a014868.
2. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Bio Eng Comput.* 2006;44:1031–51. doi:10.1007/s11517-006-0119-0.
3. Finley JP, Nugent ST, Hellenbrand W. Heart rate variability in infants, children and young adults. *J Auton Nerv Syst.* 1995;51:103–08. doi:10.1016/0165-1838(94)00117-3.
4. Massimo SS, Fabrizio D, Ragonese P. Heart rate variability in healthy children and adolescents is partially related to age and gender. *Int J Cardiol.* 2001;81:169–74. doi:10.1016/S0167-5273(01)00537-X.
5. Ryan ML, Thorson CM, Otero C, Vu T, Proctor KG. Clinical applications of heart rate variability in the triage and assessment of traumatically injured patients. *Anesthesiol Res Pract.* 2011;2:416–590.
6. Biswas A, Scott W, Sommerauer J, Luckett PM. Heart rate variability after acute traumatic brain injury in children. *Crit Care Med.* 2000;12:3907–12. doi:10.1097/00003246-200012000-00030.
7. Goldstein B, Toweill D, Lai S, Sonnenthal K, Kimberly B. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. *J Physiol.* 1998;44:1287–92.

8. Goldstein B, Fiser D, Kelly MM, Mickelsen D, Ruttiman U, Pollack MM. Decomplexification in critical illness and injury: relationship between heart rate variability, severity of illness and outcome. *Crit Care Med.* 1998;26:352–57.[doi:10.1097/00003246-199802000-00040](#).
9. Goldstein B, Kempinski M, DeKing D, Cox C, DeLong DJ, Kelly MM, Woolf PD. Autonomic control of heart rate after brain injury in children. *Crit Care Med.* 1996;24:234–40.[doi:10.1097/00003246-199602000-00009](#).
10. Almeida R, Silva MJ, Rocha A. Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients. *Comput Cardiol* (2010). 2013;40:61–64.
11. Su CF, Kuo TB, Kuo JS, Lai HY, Chen HI. Sympathetic and parasympathetic activities evaluated by heart-rate variability in head injury of various severities. *Clin Neurophysiol.* 2005;116:1273–79.[doi:10.1016/j.clinph.2005.01.010](#).
12. Kim SW, Jeon HR, Kim JY, Kim Y. Heart rate variability among children with acquired brain injury. *Ann Rehabil Med.* 2017;41(6):951–60.[doi:10.5535/arm.2017.41.6.951](#).
13. Lowensohn I, Weiss M, Hon H. Heart-rate variability in brain-damaged adults. *Lancet.* 1997;1:626–28.
14. King ML, Lichtman SW, Seliger G, Ehert FAS, Steinberg JS. Heart-rate Variability in Chronic Traumatic Brain Injury. *Brain Inj.* 1997;11:445–53.
15. Katz-Leurer M, Rotem H, Keren O, Meyer S. Heart rate and heart rate variability at rest and during exercise in boys who suffered a severe traumatic brain injury and typically-developed controls. *Brain Inj.* 2010;24:110–14.[doi:10.3109/02699050903508234](#).
16. Katz-Leurer M, Rotem H, Shofer M, Meyer S. Pediatric cardio-autonomic response to variable effort after severe traumatic brain injury. *Brain Inj.* 2016;30:1239–42.[doi:10.1080/02699052.2016.1179343](#).
17. Baguley IJ, Heriseanu RE, Felmingham KL, Cameron ID. Dysautonomia and heart rate variability following severe traumatic brain injury. *Brain Inj.* 2006 April;20(4):437–44. [doi:10.1080/02699050600664715](#).
18. Keren O, Yupaton S, Radai MM, Elad-Yarum R, Faraggi D, Abboud S, Ring H, Groswasser Z. Heart rate variability (HRV) of patients with traumatic brain injury (TBI) during post-insult sub-acute period. *Brain Inj.* 2005 August;19(8):605–11. [doi:10.1080/02699050400024946](#).
19. Baguley IJ, Nichols JL, Felmingham CJ, Gurka JA, Wade LD. Dysautonomia after traumatic brain injury. A forgotten syndrome? *J Neurol Neurosurg Psychiatry.* 1999;67:39–43. [doi:10.1136/jnnp.67.1.39](#).
20. Pozzi M, Locatelli F, Galbiati S, Radice S, Clementi E, Strazzer S. Clinical scales for paroxysmal sympathetic hyperactivity in pediatric patients. *J Neurotrauma.* 2014;31:1897–98.[doi:10.1089/neu.2014.3540](#).
21. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT for the consensus working group: paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. *J Neurotrauma.* 2014;31:1515–20.[doi:10.1089/neu.2013.3301](#).
22. Pozzi M, Conti V, Locatelli F, Galbiati S, Radice S, Citerio G, Clementi E, Strazzer S: paroxysmal sympathetic hyperactivity in pediatric rehabilitation: clinical factors and acute pharmacological management. *J Head Trauma Rehabil.* 2015;30:357–63. [doi:10.1097/HTR.0000000000000084](#).
23. Alofisan TO, Algarni YA, Alharfi IM, Miller MR, Stewart TC, Fraser DD, Tijssen JA. Paroxysmal sympathetic hyperactivity after severe traumatic brain injury in children: prevalence, risk factors and outcome. *Pediatr Crit Care Med.* 2019 March;Vol 20(3):252–58.[doi:10.1097/PCC.0000000000001811](#).
24. Krach LE, Kriel RL, Morris WF, Warhol BL, Luxenberg MG. Central autonomic dysfunction following acquired brain injury in children. *Neurohabil Neural Repair.* 1997;11:41–45.[doi:10.1177/154596839701100107](#).
25. Krach LE, Kriel RL, Morris WF, Wharlor BL, Luxenberg MG. Central autonomic dysfunction following acquired brain injury in children. *J Neurol Rehabil.* 1997;11:4–5.
26. Kirk KA, Shoykhet M, Jeong JH, Tyler-Kabara EC, Hendersson MJ, Bell MJ, Fink EL. Dysautonomia after pediatric brain injury. *Dev Med Child Neurol.* 2012 August;54(8):759–64.[doi:10.1111/j.1469-8749.2012.04322.x](#).
27. Rodriguez N, Meléndez M. Disfunción autonómica en el niño con traumatismo craneoencefálico. *Rev Neurol.* 2006;43(3):143–46. [doi:10.33588/rn.4303.2004453](#).
28. Esterov D, Greenwald BD. Autonomic dysfunction after mild traumatic brain injury. *Brain Sci.* 2017;7:100.[doi:10.3390/brainsci7080100](#).
29. Lim HB, Smith M. Systemic complications after head injury: A clinical review. *Anaesthesia.* 2007;62:474–82.[doi:10.1111/j.1365-2044.2007.04998.x](#).
30. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. *Neurosurgery.* 1998;8:No1.
31. Baguley IJ, Slewa-Younan S, Lazarus R, Green A. Long-term mortality trends in patients with traumatic brain injury. *Brain Inj.* 2000;14:505–12.[doi:10.1080/026990500120420](#).
32. Brooks JC, Shavelle RM, Strauss DJ, Hammond FM, Harrison-Felix CL. Long-term survival after traumatic brain injury, part II: life expectancy. *Arch Phys Med Rehabil.* 2015;96:1000–05. [doi:10.1016/j.apmr.2015.02.002](#).
33. McMillan TM, Weir CJ, Wainman-Lefley J. Mortality and morbidity 15 years after hospital admission with mild head injury: a prospective case-controlled population study. *J Neurol Neurosurg Psychiatry.* 2014;85:1214–20.[doi:10.1136/jnnp-2013-307279](#).
34. Zygun D, Kortbeek JB, Fick GH, Laupland KB, Doig CJ. Non-neurologic organ dysfunction in severe traumatic brain injury. *Crit Care Med.* 2005;33:654–60.[doi:10.1097/01.CCM.0000155911.01844.54](#).
35. Hilz MJ, DeFina PA, Andres S, Koehn J, Lang CJ, Pauli E, Flanagan SR, Schwab S, Marthol H. Frequency analysis unveils cardiac autonomic dysfunction after mild traumatic brain injury. *J Neurotrauma.* 2011;28:1727–38.[doi:10.1089/neu.2010.1497](#).
36. Wilson L, Stewart W, Dams-O'Connor K, Diaz-Arrastia R, Hortone L, Menon DK, Polinder S. The chronic evolving neurological consequences of traumatic brain injury. *Lancet Neurol.* 2017;16:813–25.[doi:10.1016/S1474-4422\(17\)30279-X](#).
37. Strauss DJ, Shavelle RM, Anderson TW. Long term survival of children and adolescents after traumatic brain injury. *Arch Phys Med Rehabil.* 1998;79:1095–100.[doi:10.1016/S0003-9993\(98\)90177-0](#).
38. Pertab JL, Merkley TL, Cramond AJ, Paxton H, Wu T. Concussion and the autonomic nervous system: an introduction to the field and the results of a systematic review. *NeuroRehabilitation.* 2018;42(4):397–427.
39. Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: A systematic review and meta-analysis. *J Psychiatry Neurosci.* 2016;41:89–104.[doi:10.1503/jpn.140217](#).

3.2 Paper II

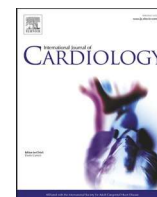
Cardiovascular events in children with brain injury: A systematic review.

Silva, MJ; Carneiro, B; Mota, R; Baptista, MJ.

International Journal of Cardiolology. 2023 Sept 15:387:131132.

Doi: [10.1016/j.ijcard.2023.131132](https://doi.org/10.1016/j.ijcard.2023.131132)

<https://www.sciencedirect.com/science/article/pii/S0167527323009397?via%3Dihub>



Cardiovascular events in children with brain injury: A systematic review

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ARTICLE INFO

Keywords:

Pediatrics
Brain injury
Myocardial injury
Blood pressure
Arrhythmias

ABSTRACT

Background: Brain injury is a leading cause of morbidity and mortality in the pediatric population. Neurogenic stunned cardiomyopathy is a complication associated with several neurological conditions that can lead to worse outcomes. It presents as alterations in blood pressure, cardiac rhythm disturbances and the increase in cardiac injury biomarkers. This systematic review aims to assess the hemodynamic consequences of brain injury in the pediatric population to identify better management strategies and improve outcomes.

Methods: An electronic literature search was performed in Pubmed, Scopus and WebOfScience, up until October 3rd, 2022. The selected articles underwent quality assessment using the National Heart, Lung and Blood Institute tools for cohort and case-control studies.

Results: This systematic review includes thirteen articles on the effects of brain injury in arterial pressure, rhythm disturbances and biomarkers of myocardial injury. These studies showed the following key results: both hypotension and hypertension are associated with worse outcomes; brain injury could be related to longer QTc intervals; neurogenic stunned cardiomyopathy was a common found after brain injury.

Conclusion: This is the first systematic review to report cardiovascular abnormalities arising from brain injury in children. An early arterial pressure, electrocardiographic and echocardiographic evaluation, as well as the measure of serum biomarkers for myocardial injury, can be critical in identifying poor prognostic factors. Further research is required to understand the implications of our findings in clinical practice.

1. Introduction

Brain injury can be divided into two major causes: traumatic and non-traumatic. Whilst a traumatic brain injury (TBI) is one of the major morbidity and mortality causes in children worldwide [1], non-traumatic brain injury (nTBI), which includes insults such as anoxia, vascular causes, brain tumors, central nervous system infections, toxic effects of substances and metabolic encephalopathies, can lead to negative and long-lasting consequences, particularly in the pediatric population, since they are in a critical period of neurodevelopment [2].

The theory of a possible linkage between our brain and heart function has already been hypothesized for decades, being the Cushing reflex a famous example of this crosstalk [3,4]. This relationship is an intricate one, with not much being studied in the pediatric population.

What we know is that brain injury can induce catecholamine mediated and inflammatory responses leading to neurogenic stunned cardiomyopathy (NSC), characterized by left ventricular dysfunction, the development of both hypertension and hypotension, arrhythmias,

ischemia-like electrocardiographic (ECG) changes and, even the mild increase in serum biomarkers of cardiac injury [5]. These abnormalities are usually reversible and caused by an “autonomic storm”, secondary to a local excessive release of norepinephrine from the sympathetic nerve terminals in the myocardium, resulting in severe changes in the patient's hemodynamics [6]. While neurogenic cardiovascular dysfunction has been associated with a higher morbidity and mortality [7], little is still known about which hemodynamic parameters can predict poor outcome, its significance and no management thresholds have been well established in the pediatric population.

As far as we are aware, this is the first systematic review focusing on the systemic hemodynamic consequences after brain injury, designed in the pediatric population. Our aim is then to collect and report the clinical evidence regarding abnormalities in the systemic hemodynamics, the presence of electrocardiographic changes, arrhythmias, and the elevation of markers of cardiovascular damage, arising from brain injury, in the pediatric population, in order to set a path to determine management goals and achieve better outcomes.

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<https://doi.org/10.1016/j.ijcard.2023.131132>

Received 27 March 2023; Received in revised form 14 June 2023; Accepted 20 June 2023

Available online 22 June 2023

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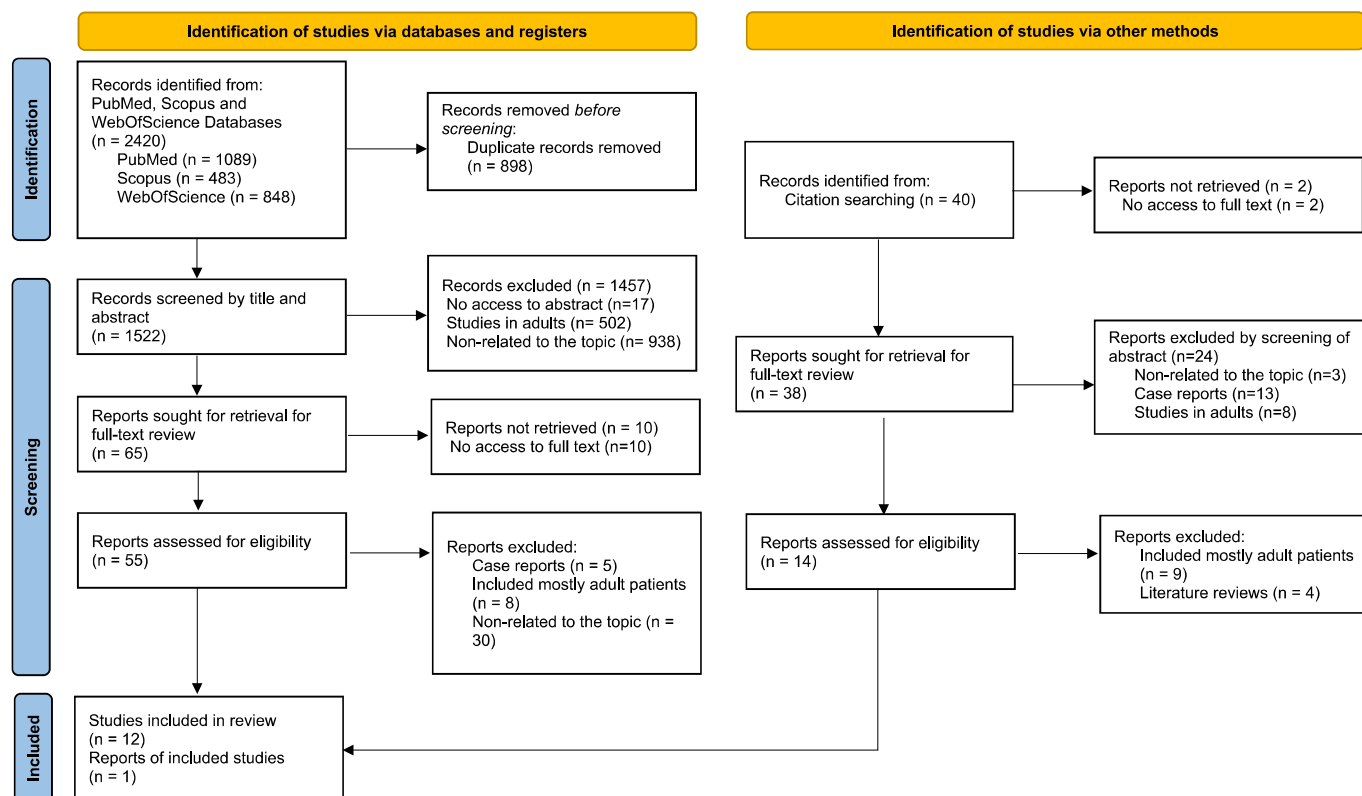


Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

2. Methods

2.1. Search strategy and study selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews (PRISMA) recommendations. An electronic literature search was performed in PubMed, Scopus and WebOfScience databases, in order to identify clinical studies relevant to the topic of cardiovascular changes in children after brain injury, up until the 3rd of October of 2022.

For search purposes, the coming terms were applied: “children”, “pediatrics”, “child” or “adolescent” and “brain injury” combined with one of the following “arrhythmias”, “tachycardia”, “bradycardia”, “arterial pressure”, “hypertension” or “hypotension”, with no restriction regarding date of publication or language of the study (Supplementary Material 1).

Based on the search strategy applied, two investigators independently extracted data, which was subsequently compared. Any doubtful situation was decided by a consensus or by a third investigator. After data extraction, on a first phase, two investigators independently screened and assessed titles and abstracts, with the purpose of excluding duplicates and the ones which were clearly not related to the topic. If it was not yet clear if the study met the premise of our research, on a second phase, the investigators would then retrieve the full text of the study and analyze it, according to its clinical relevance and characteristics. On a third phase, the references of the selected studies were evaluated in order to find additional relevant studies. Disagreements were decided by a consensus or by a third investigator.

2.2. Inclusion and exclusion criteria

In order to be eligible to this systematic review, the studies were selected taking into account the following criteria: (i) – peer-reviewed original observational articles, involving prospective or retrospective

data collection, (ii) – the population of the study should be children (<18 years old), (iii) – the participants should not have other more significant organ injuries that could explain better the cardiovascular changes, (iv) – the studies should focus on cardiovascular abnormalities arising from brain injury, (v) – access to the full-text publication was required. Studies which included mostly adults or neonates, animal models, intervention studies, patients with pre-existing cardiovascular disease such as cardiomyopathies, retracted studies, review articles and case reports were excluded from this review, as well as articles that did not mention hemodynamic irregularities following a brain insult. No articles were excluded based on the language they were written in or publication date.

2.3. Data extraction and quality assessment

A data extraction form was created to capture all pertinent information. Following is a list of the extracted data: publication details (author, country and publication year), study design, population details (number of participants, age, cause and severity of the brain injury), which and when hemodynamic parameters were evaluated (heart rate, blood pressure, the presence of cardiac rhythm disturbances or markers myocardial injury), relevant results and main conclusions. Selected full articles underwent thorough evaluation and quality assessment, using the National Heart, Lung and Blood Institute (NIH) tools for quality assessment of cohort and case-control studies (available at <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>), (Supplementary Tables 1 and 2). To evaluate the risk of bias of the studies, two separate investigators answered several questions with Yes/No/Other (Cannot Determine (CN), Not Reported (NR) or Not Applicable (NA)). Afterwards, studies were graded as of “good”, “fair” and “poor” quality by reaching a consensus between the two investigators.

3. Results

3.1. Study characteristics

Overall, the database search retrieved a total of 2420 studies, of which 1522 had their titles and abstracts scrutinized after eliminating the double publications. In this first evaluation, 1440 studies were considered not appropriate, by either focusing on adults or not being related to the main aspects of this review, and we could not have access to 17 abstracts. The remaining 65 studies were sought for retrieval with 10 articles not being retrieved due to lack of access to full text; 55 articles were then submitted to a full-text analysis, which excluded 43 studies: 5 case-reports, 8 whose study subjects were either adults or children above the age of 16 years old and adults and 30 which didn't measure the variants we wanted to include in this review. The selected 12 articles consisted of 10 retrospective cohort studies [8–17], 1 prospective cohort study [18] and 1 case-control study [19]. From these, 1 retrospective cohort study [20] was retrieved from their references, making it a total of 13 studies included in this systematic review (Fig. 1). Articles were published between 1985 and 2022 and conducted in USA, UK, Singapore, Turkey, Iraq and Afghanistan.

3.2. Brain injury and arterial blood pressure

Ten studies assessed the effect of brain injury in arterial blood pressure. Coates BM, et al. demonstrated that, while in older children hypotension might be defined as it is in adults (Systolic Blood Pressure (SBP) < 90 mmHg), in younger children the classic definition might overestimate its incidence following brain injury, with SBP < 5th percentile for age being a better definition of hypotension and a better representation of poor outcome [8]. Regarding the correlation between outcomes and the timing of hypotension, Young AMH, et al. states that the development of hypotension (Mean Arterial Pressure (MAP) < 70 mmHg) in a pre-hospital setting is associated with higher intracranial pressure (ICP) during the first 3 days of monitoring, in comparison to those who didn't develop pre-hospital hypotension ($p = 0.01$) [9]. This could be explained by an early hypoxic insult, triggering an acute response culminating in cerebral edema, a rise in ICP and poor outcome [9]. These findings are in accordance to those of Coates BM, et al. which state that the development of hypotension, either in the field or in the emergency department, is associated with poor discharge outcome, with a Glasgow Outcome Scale (GOS) < 4, and field hypotension was associated with a longer stay in the Pediatric Intensive Care Unit (PICU) and in the Hospital [8]. Samant UB, et al. took a step further and limited this early hypotension effect to the first 6 h following severe TBI ($p = 0.006$), where the risk of poor discharge outcome (GOS < 4) peaks at hour 6 (89% of hypotensive children with GOS < 4), while hypotension from hour 7 to 72 did not increase the risk any further ($p = 0.67$) [10].

Focusing on the role of hypotension, Yao SHW, et al. confirmed that patients with SBP < 5th percentile had the greatest percentage of in-hospital mortality ($p < 0.001$), with half of the hypotensive patients dying [11]. Even though it turned out to be not statistically significant in the adjusted analysis ($p = 0.148$), in the univariate analysis the presence of concomitant diastolic hypotension had a higher predictive value for worse discharge outcome than systolic hypotension alone ($p < 0.001$) [11]. This trend in neurological outcomes and mortality could suggest a role for the establishment of diastolic blood pressure (DBP) and MAP targets in management of pediatric TBI patients [11]. Erickson's findings support this last theory by demonstrating that children with a single measure of MAP < 10th percentile in the first 12 h after admission to the PICU had worse outcomes and highest rates of in-hospital mortality, in comparison to children with MAP between the 50th and the 94th percentile [12]. Besides that, his study states that the association between blood pressure parameters and outcome is stronger when considering MAP, over SBP, and that different targets should be established for the best possible treatment, with MAP ideally above the 10th

percentile and SBP above the 5th percentile [12].

Suttipongkaset and Vavilala share similar views, both emphasizing that better outcomes occurred when patients presented with SBP > 75th percentile, with no further improvements from this threshold [13] in children below the age of 15 years old, with an increase in mortality being noticed in children from 15 to 17 years old when SBP > 95th percentile [14]. In both studies, the most cases of in-hospital mortality occurred when SBP < 75th percentile, particularly when below the 5th percentile [14], even when SBP > 90 mmHg [13].

In contrast to Yao's study, in which the majority of hypertensive patients survived with a good neurologic outcome [11], Johnson's findings report that in-hospital mortality has a U-shape curve distribution, with both hypotensive ($p = 0.01$) and hypertensive patients with SBP > 99th percentile ($p < 0.01$) having the highest 24 h in-hospital mortality [15]. However, once deaths in the first 24 h were excluded, there was no longer a statistically relevant association between any blood pressure category and mortality [15]. An older study by Kanter used the measure "excess blood pressure – BPe", expressed in torr, defined as peak blood pressure in 6 h intervals minus the SBP at the 95th percentile for age, in comatose children after acute brain injury [16]. His findings are in accordance to Johnson's work, showing a drastic difference in poor outcome between children whose BPe never exceeded 20 Torr (13%) versus children whose BPe exceeded 20 Torr (56%) ($p = 0.0316$) and the longer the period of hypertension, the worse the prognosis (74% vs 26%, $p = 0.0026$) [16]. Freeman's study, even though it found no difference in mortality between normotensive and hypertensive TBI patients (13.3% vs 13.3%, $p = 1.0$), supporting Suttipongkaset's findings, did observe a trend towards increase mortality, even if not statistically significant, when comparing mortality in the 95th (15.8%) and 99th percentile groups (14.1%) to mortality in the 90th percentile group (6.7%) [17], which is more in concordance to Johnson's study. Additionally, it reported a relevant difference when the outcome was the need for neurosurgical intervention, with the SBP > 99th percentile group needing intervention 59.2% of the time, the SBP > 95th percentile group 26.3% of the time and SBP > 90th percentile group 46.7% ($p = 0.036$) [17].

3.3. Brain injury and cardiac rhythm disturbances

Data regarding the effect of brain injury in heart rhythms and electrocardiographic changes was provided in two studies. According to Ozdemir D., et al., patients with severe head trauma presented with longer QTc intervals and a larger QTc dispersion, in comparison to their control counterparts ($p = 0.013$ and $p = 0.002$, respectively) [19], which is in accordance with Plymale J., which stated that children diagnosed with brain death had a longer QTc interval (452 ms) versus an average QTc duration in healthy children (399 ms) [20]. Besides that, children with severe head trauma were more commonly admitted with electrolyte disturbances, namely low serum calcium, potassium and magnesium levels [19], which are known to be connected to cardiac arrhythmias due to a longer QTc interval, causing sudden cardiac death. An inverse correlation was then found between Glasgow Coma Scale (GCS) score and serum calcium levels, and to a lesser degree, serum potassium levels and the previously described ECG alterations [19]. Plymale J., et al. validates these findings by identifying hypokalemia ($p = 0.006$) and the male sex ($p = 0.003$) as independent risk factors for QTc prolongation in a multivariate analysis [20]. It has also been hypothesized that more severe brain injuries, such as a purely ischemic brain injury, may be associated with more pronounced QTc prolongations [20].

Some mechanisms have been considered for the development of cerebrogenic arrhythmias leading to sudden death, such as the development of a heterogeneous myocardial repolarization, an uncoupling between the autonomic and the cardiovascular system and a sympathetic stimulation leading to electrocardiographic changes [20].

3.4. Brain injury and biomarkers of myocardial injury

One study evaluated the prevalence and mechanisms of myocardial injury by measuring plasma troponin levels in children hospitalized for TBI [18]. 57.9% of children with isolated TBI had at least one cardiac troponin I (cTnI) level of >0.4 ng/mL between hospital day 1–10, with it occurring regardless of age, sex, severity of TBI and types of computerized tomography (CT) scan lesions, and 100% of all elevated cTnI levels were registered within the first 6 days after admission. One patient with elevated cTnI and isolated TBI underwent echocardiographic evaluation which showed an ejection fraction of 41% and mild ventricular akinesis, compatible with NSC.

Age-adjusted admission tachycardia was identified as a risk factor for myocardial injury after TBI (AUC 0.82, $p < 0.001$), with it being seen in 72.7% of children with isolated TBI and elevated cTnI levels, which suggests it might be the most common presentation of myocardial injury.

The high incidence of myocardial injury in patients with isolated TBI, and its association with tachycardia, suggests a neurogenic cause due to high levels of circulating catecholamines, which mainly occurs in the first 6 days after hospital admission.

3.5. Risk of bias

Quality assessment of the selected studies was done by using the NIH tools for cohort and case-control studies. Eleven of the selected studies are retrospective in nature [8–17,20], which can be a source of information bias, since they mostly rely on recorded data, making it impossible to control all potential confounders. Another possible source of information bias are some studies focusing on the effects of arterial blood pressure, as the investigators were unable to determine the exact method of blood pressure measurement [10–12,15,17]. Only two studies justified sample size and calculated study power [10,17], with most of the studies being single centered and identifying their small sample of participants as potential threats to internal and external validity [8–14,17,20]. Finally, the lack of blinding in all but two studies [19,20] presents a potential risk of bias, undermining the validity and reliability of the results.

4. Discussion

To the best of our knowledge, this is the first systematic review that summarizes current clinical research on the impact of brain injury in the systemic hemodynamics, in the pediatric population. The key findings are the following: (i) a SBP measure below the 5th percentile for age and sex, particularly in the first 6 h following a TBI, is associated with worse discharge outcomes; (ii) hypertension, even though it may have a protective role at a later stage after brain injury, it could be associated with higher mortality in the first hours; (iii) brain injury could be a potential cause of longer QTc intervals, which correlates to cardiac arrhythmias; (iv) NSC was a common found after brain injury, perceived as a rise in serum troponin levels; (v) age-adjusted tachycardia at the time of admission might be the most common presentation of NSC.

Neurogenic stunned cardiomyopathy, a cardiac dysfunction syndrome neurologically mediated, has been associated with multiple conditions, such as subarachnoid and intracerebral hemorrhages, seizures and TBI [3]. The most accepted theory for its pathophysiology is the “catecholamine hypothesis”, a sympathetic discharge and an increase in local catecholamines that can cause the opening of calcium channels, leading to vigorous cardiac muscle contractions and, if persistent, to myofibrillar degeneration, reperfusion damage, cardiac cell death and contraction band necrosis [21]. The main manifestations include left ventricular dysfunction, arrhythmias, hypertension, hypotension, elevation of biomarkers of myocardial damage and ECG changes, with high morbidity and mortality [4,5,21]. There have been some studies stating the beneficial effect of beta-blockers in acute TBI

[22], but no data is available in the pediatric population.

Studies have reported NSC after TBI in adults, with an incidence of cardiac dysfunction of around 20–25% and abnormal echocardiographic examination in 22.3% of patients [23]. Additionally, an increase in serum troponin and creatine phosphokinase-MB (CK-MB) levels within two weeks after hospital admission should alert physicians for cardiac dysfunction [23]. Krishnamoorthy's findings are in line with what was previously stated, with the incidence of early systolic dysfunction increasing alongside the severity of the TBI, in both children and adults, and a younger age and a lower GCS score on admission presenting as risk factors [24]. Children following brain injury should be submitted to an echocardiographic evaluation to rule out cardiac dysfunction, according to how common this clinical entity is in the adult population, associated with a limited number of pediatric case-reports [25,26].

Hasanin, besides reporting abnormal echocardiography, hypotension and cardiac injury in severe TBI patients, adds to the conversation by analyzing ECG changes, present in a majority of patients, from abnormal QTc intervals, to tachyarrhythmia and sinus bradycardia [27]. Krishnamoorthy also reported prolonged QTc intervals in almost half of TBI admitted patients and that both repolarization abnormalities and tachycardia were associated with cardiac dysfunction in isolated TBI patients [28]. A prolonged QTc interval was also found in children after severe head trauma [19] or diagnosed with brain death [20], which might suggest a crucial role of an electrocardiographic assessment to predict prognosis and prevent a possibly fatal arrhythmia. Beyond that, Hasanin introduced the neurogenic cardiac injury score (NCIS) calculated by taking into account the presence of cardiac dysfunction, cardiac injury and hypotension, reflecting the patient's hemodynamic status and presenting as a likely useful tool in the pediatric population. In this study, both myocardial dysfunction and a NCIS score > 1 were associated with higher mortality [27]. Myocardial injury is also a common encounter in children, with cTnI levels rising mostly in the first 6 days after TBI and tachycardia being the most common clinical presentation [18]. As so, the evaluation of cTnI levels in cases of tachycardia might alert clinicians for myocardial injury before the permanent establishment of cardiac dysfunction [18].

Hypotension is a common finding following TBI and studies in adults have suggested that it might occur due to an acute systolic cardiac dysfunction [24]. It is also a marker of worse prognosis and higher mortality, as it translates into decreased cerebral blood flow and brain ischemia [14,29]. While in adults it might be easier to set a target, as mortality increases as SBP decreases below 120 mmHg [29], in the pediatric population all efforts should be put into trying to raise the SBP > 5 th percentile for sex and age, particularly in the first 6 h, as this period represents a time-sensitive window for therapeutic intervention [8,10,11]. Erickson also emphasizes the importance of monitoring MAP in children after severe TBI, since it's an essential factor in predicting cerebral perfusion pressure (CPP), alongside ICP and, as so, the use of MAP could be of more advantage than solely SBP when ICP monitoring is not common or not possible [12]. In these cases, MAP > 10 th percentile for sex and age appeared to be the target associated with a better prognosis [12].

On the other end of the spectrum, while not yet clear in pediatrics, it appears hypertension could also be a predictor of higher morbidity and mortality. Zafar described the relation between blood pressure and mortality, in adults following moderate to severe TBI, as bimodal, with mortality increasing both when SBP was below 120 mmHg and when above 140 mmHg [29], similarly to an older study by Butcher [30]. One possible interpretation is that hypertension generates excessive flow through the breakdown of the blood-brain barrier, causing hemorrhage, hyperperfusion injury, infarction and vasogenic edema, due to a failure of the vascular autoregulation in the injured brain [29]. In pediatrics, this issue has not yet been vastly studied, with published mixed results. While most studies did not report worse prognosis when SBP was higher at admission [11,13,14], Johnson described a U-shaped curve between mortality and admission SBP [15], Kanter stated that hypertension was a

Table 1

Description of the included articles in the systematic review.

Author, Year and Country	Study Design	Age	Participants	Brain injury cause and severity	CV parameters evaluated	Relevant statistical results	Main conclusions	Notes on inclusion/exclusion criteria and management of bias
Yao SHW, et al. (2022), Singapore	Retrospective cohort	<18y	152	Isolated moderate to severe TBI	HR, SBP, DBP, MAP on arrival to ED	HR ($p = 0.484$) was not predictive of less favorable outcome (GOS 3–8 and in-hospital mortality). Systolic hypotension alone was independently predictive of less favorable outcome – worse long-term neurological function ($p = 0.015$), while diastolic hypotension ($p = 0.148$) and MAP hypotension ($p = 0.148$) were not.	(i) Concomitant MAP and DBP ≤ 5 th percentile was more associated with poor outcomes than SBP alone, in a univariate analysis, but were insignificant in a multivariate analysis. (ii) Initial age-adjusted hypotension is associated with poor outcomes.	Patients were included if they had a CT scan confirming cranial injuries, a traumatic injury with a head AIS ≥ 3 and an AIS < 3 in all other organs. None of the patients had prehospital advanced airway interventions performed, resuscitation drugs or fluid resuscitation prior to arrival to ED. The multivariate analysis was adjusted for age, mechanism of injury and initial GCS < 8 . Severe TBI was defined as having an admission GCS ≤ 8 and a head AIS > 3 . Patients with head AIS of 6 and non-head AIS > 2 were excluded. Results were adjusted for age, sex, GCS score, ISS, and need for mechanical ventilation but not MAP on admission, ICP, blood gas data, glucose, temperature and coagulation.
Suttipongkaset P, et al. (2018), USA	Retrospective cohort	<18y	10,473	Isolated severe TBI	Subgroup analysis of SBP at admission by age	Compared with SBP in the 75th–94th percentile, there was an increase in in-hospital mortality in all groups with lower SBP (< 5 th [RR 3.2]; 5th – 24th percentile [RR 2.3]; 25th – 74th percentile [RR 1.4]).	Admission SBP < 75 th percentile was associated with in-hospital mortality.	Severe TBI was defined as GCS ≤ 8 at admission. If patients had SBP < 5 th percentile for age on presentation, received CPR prior to or at admission or if GCS > 8 on arrival, they were excluded. The need for neurosurgical intervention was defined as placement of an intracranial pressure monitoring device, decompressive craniectomy, evacuation of intracranial hemorrhage, or any other surgical intervention.
Freeman AD, et al. (2020), USA	Retrospective cohort	<18y	150	Severe TBI	SBP at admission	When comparing normotensives with hypertensives, they had similar outcomes, with a mortality rate of 13.3% in both groups. When the outcome was need for neurosurgery, the 99th percentile group required intervention 59.2% of the time, 95th group 26.3%, and 90th group 46.7% ($p = 0.036$). There was also a trend towards increased mortality in the 95th and 99th percentile groups (15.8% and 14.1%), versus the 90th percentile	(i) Hypertension on initial presentation is not associated with morbidity or mortality when compared to normotension. (ii) Above the 95th percentile of SBP there was a trend towards increased mortality.	

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Table 1 (continued)

Author, Year and Country	Study Design	Age	Participants	Brain injury cause and severity	CV parameters evaluated	Relevant statistical results	Main conclusions	Notes on inclusion/exclusion criteria and management of bias
Erickson SL, et al. (2021), USA	Retrospective cohort	<18y	166	Severe TBI	SBP and MAP during the first 12 h after PICU admission	group (6.7%) but not statistically significant. Poor discharge outcome (in-hospital death or transfer to nursing or long-term care facilities) most commonly occurred in children with MAP in the <5th (42.9%) and 5-9th percentile (40%), and the lowest proportion of poor discharge outcome occurred in children with MAP in the 50th–94th percentile (4.8%). SBP was associated with poor discharge outcome when SBP <5th percentile.	(i) MAP <10th percentile in the first 12 h after PICU admission was associated with poor discharge outcome. (ii) MAP percentile was more strongly associated with outcome when compared to the lowest SBP percentile in the first 12 h. (iii) Thresholds of <10.2 percentile for MAP and < 6.7 percentile for SBP provided the greatest sensitivity and specificity for poor outcome.	Patients were included if they had confirmation of intracranial hemorrhage on head CT and GCS <9 at any point during their PICU stay, who survived the first 12 h after PICU admission. Analyses were adjusted for head AIS, non-head AIS, and vasoactive medication use.
Johnson MA, et al. (2018), Iraq and Afghanistan	Retrospective cohort	<18y	740	Isolated or predominantly severe TBI	SBP upon ED arrival	Hypotension and severe hypertension were associated with increased 24-h mortality ($p = 0.01$ and $p < 0.01$) but once early deaths were removed, there were no longer differences in mortality according to arrival SBP categories.	(i) Both hypotension and SBP > 99th percentile were associated with 24-h mortality. (ii) Neither hypotension nor severe hypertension were associated with in-hospital mortality after accounting for early deaths.	Patients were considered to have a severe isolated TBI if their AIS of head, neck, and cervical spine was ≥ 3 and all remaining AIS scores were < 3. Patients with a non-traumatic injury mechanism, primary thermal injuries, absent pulse or missing BP records were excluded. Multivariable analysis included the following variables: age, gender, AIS-head, ISS, arrival O2 saturation, arrival SBP, intubation, volume of blood product transfused, neurosurgical interventions, days on ventilator, PICU stay, total hospital days, death in the first 24 h and in-hospital mortality.
Lele AV, et al. (2020), USA	Prospective cohort	<18y	28	Mild to severe TBI	cTnI levels in the first 10 days of hospital stay and HR, SBP and echocardiography evaluation within 24 h of plasma cTnI sampling.	The prevalence of elevated cTnI (>0.4 ng/mL), which showed no significant differences by age group, sex, severity of TBI, and types of CT lesions, was 57.9% in isolated TBI. 100% of all	(i) Myocardial injury with elevation of cTnI occurs mostly in the 6 days following brain injury. (ii) Age adjusted tachycardia is a risk factor for myocardial injury. (iii) Elevated troponins might be	Patients with evidence of TBI in CT scan of the head, that were hospitalized in the PICU, were included. Pregnant minors, patients with ongoing CPR or with brain death were excluded.

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Table 1 (continued)

Author, Year and Country	Study Design	Age	Participants	Brain injury cause and severity	CV parameters evaluated	Relevant statistical results	Main conclusions	Notes on inclusion/exclusion criteria and management of bias
Ozdemir D, et al. (2005), Turkey	Case-control	<18y	92 (49 control subjects – children with no or mild TBI; and 43 case subjects – children with severe TBI)	Severe TBI	QTc interval at admission	elevated cTnI levels occurred within the first 6 days of admission. Age-adjusted tachycardia was seen in 72.7% of patients with isolated TBI who had high levels of cTnI ($p < 0.001$). A prolonged QTc interval (>440 ms) was more frequently found in case subjects (37%) than in control subjects (6%). The levels of calcium, potassium and magnesium at admission were significantly lower in the patients with severe head trauma ($p = 0.001$, $p = 0.019$, $p = 0.027$, respectively).	associated with cardiac-cerebral-renal dysfunction. (i) Children with severe head trauma were more associated with prolonged QTc and QTc dispersion values than the control subjects. (ii) Children with severe head trauma had more electrolyte abnormalities (hypocalcemia, hypokalemia) than children with no or only mild head trauma.	Cases were defined as patients with severe head trauma with a GCS ≤ 12 and controls were children with no or mild head injury after blunt head trauma (GCS 14–15) and a normal CT scan. The patients were excluded if they had cardiac or endocrine diseases, renal failure, previous neurological or intracranial injury, if they were taking any drugs that affected QT interval or if they had received a diuretic or were receiving adrenergic agents prior to the blood sampling and ECG.
Samant UB, et al. (2008), USA	Retrospective cohort	<18y	146	Severe TBI	Time of hypotension (SBP <5 th percentile for sex and gender) through the first 72 h after TBI.	The risk of poor discharge outcome (GOS < 4) was higher with hypotension, specially in the first 6 h following injury (RR 2.0, 95% IC 1.3–3.3) vs hypotension occurring from hour 7 to 72 after the head trauma (RR 1.2).	(i) The relationship between hypotension and poor discharge outcome peaked at hour 6 and, beyond that, the risk of poor outcome did not increase. (ii) Hourly assessment of SBP in the first 6 h can be a reliable predictor of discharge outcomes.	Severe TBI was defined as head AIS ≥ 3. Children who died or were extubated in the ED, who had GCS ≥ 9 at admission of PICU, or who were admitted >72 h after injury were excluded. Results were adjusted for head AIS.
Coates BM, et al. (2005), USA	Retrospective cohort	<14y	93	Severe TBI	Definition of hypotension and time of hypotension in the ED, field and PICU.	SBP < 5th percentile for age, when compared to SBP < 90 mmHg, was a better predictor of poor outcome (hospital length of stay OR 18.8 vs OR 14.0). 28% children who developed hypotension either in the field or in the ED presented with hypotension in the PICU, whilst new-onset PICU hypotension only	Early hypotension (defined by SBP < 5th percentile) was a better predictor of poor outcome (discharge GOS < 4 or discharge to a skilled nursing facility or death) than late hypotension or the definition of hypotension as SBP < 90 mmHg.	Severe TBI was defined as head AIS ≥ 3. Children who died, were extubated in the ED or had PICU admission GCS ≥ 9 were excluded. Results were adjusted for the following potential confounders: age, gender, hypoxia, hypocapnia, hypercapnia, hyperglycemia, hyperthermia in the

(continued on next page)

Table 1 (continued)

Author, Year and Country	Study Design	Age	Participants	Brain injury cause and severity	CV parameters evaluated	Relevant statistical results	Main conclusions	Notes on inclusion/exclusion criteria and management of bias
Vavilala MS, et al. (2003), USA	Retrospective cohort	<14y	172	Severe TBI	SBP on arrival to the ED	occurred in 9% of patients. The greatest number of good outcomes (GOS 4–5) occurred once SBP > 75th percentile, with no further improvement in outcome after that. Children with SBP > 90 mmHg but lower than the 75th percentile had a higher risk of poor outcome (GOS < 4) (OR 3.5) and death (OR 4.6). Children with pre-hospital hypotension had a higher mean ICP over the first 3 days of monitoring (p = 0.01).	The odds for a good outcome increased once SBP > 75th percentile. Even if the SBP > 90 mmHg but below the 75th percentile, children had a 4-time greater risk of a poor outcome.	ED or PICU, ISS and extracranial AIS. Patients were included if they had an ED GCS < 9, diffuse intracranial injury diagnosed by CT scan of the head and isolated TBI, defined as AIS for other injuries < 2. Results were adjusted for hypothermia, intentional injury, age and gender but not coagulopathy or ICP.
Young AMH, et al. (2018), UK	Retrospective cohort	6 m–15y	39	TBI (severity not mentioned)	Pre-hospital hypotension (MAP < 70 mmHg)		Pre-hospital hypotension should alert physician for higher risk of complications regarding ICP control.	Patients were included if they had a clinical need for ICP monitoring.
Plymale J, et al. (2010), USA	Retrospective cohort	<18	37	Brain death by anoxic brain injury, trauma subarachnoid injury or any other cause	QTc interval closer in time to admission	A multivariate analysis showed that lower potassium levels (p = 0.006) and male sex (p = 0.003) were associated with longer QTc intervals.	(i) Previously healthy children admitted with a diagnosis of brain death had a prolonged QTc interval vs average QTc in healthy children. (ii) The more severe the brain injury, the longer the QTc.	Patients with severe pre-existing conditions or comorbidities and those receiving medications known to prolong QTc were excluded. Univariate linear regression models were used to evaluate for correlation between QTc and electrolytes, pH, temperature, sex, brain injury type, and ventricular function. Significant independent variables were entered into a multivariate regression model predicting QTc duration.
Kanter RK, et al. (1985), USA	Retrospective cohort	6w–14y	42	Comatose patients (GCS < 7) with reye's syndrome, TBI, brain anoxia or central nervous system infections	Hypertension (BPe, expressed in torr, defined as peak blood pressure in 6 h intervals minus the SBP at the 95th percentile for age) during PICU stay, every 6 h	Only 13% of the infants whose BPe never exceeded 20 Torr had a poor result, compared to 56% of the children whose maximal excess blood pressure surpassed 20 Torr (p = 0.0316). When hypertension persisted after PICU discharge, the outcomes were poorer in 74% of cases, while when BP was normalized	(i) hypertension is a common severe finding in children after brain injury. (ii) systemic hypertension, with SBP > 20 Torr over the 95th percentile can identify the patients at risk of permanent neurologic disability and death.	Patients who died from circulatory failure were excluded. A good outcome was defined as normal or moderate deficit not interfering with independent life function and a poor outcome was defined as a severe deficit that would interfere with independent life function or death.

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Table 1 (continued)

Author, Year and Country	Study Design	Age	Participants	Brain injury cause and severity	CV parameters evaluated	Relevant statistical results	Main conclusions	Notes on inclusion/exclusion criteria and management of bias
						before PICU discharge, the outcomes were worse in only 26% of cases ($p = 0.0026$).		

TBI - Traumatic Brain Injury; HR - Heart Rate; BP - Blood Pressure; BPe - Excess Blood Pressure; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure; MAP - Mean Arterial Pressure; cTnI - Cardiac Troponin I; ECG - Electrocardiogram; ICP - Intracranial Pressure; ED- Emergency Department; PICU - Pediatric Intensive Care Unit; CT - computerized tomography; CPR - cardiopulmonary resuscitation; AIS - Abbreviated Injury Scale; GCS - Glasgow Coma Scale; ISS - Injury Severity Score; GOS - Glasgow Outcome Scale; RR- Relative Risk; OR - Odds Ratio.

common and fatal finding in children after brain injury, predicting permanent neurological damage and death [16], and, finally, Freeman revealed a higher need of neurosurgical intervention as SBP rose and a trend towards increased mortality [17]. While this hypertensive response after TBI may arise from an excess of circulating catecholamines, it could also reflect the children's capacity to preserve, even in early shock, stable blood pressure and vascular tone [15]. After TBI, changes in cerebral perfusion are assumed to occur over a certain length of time: firstly, there is a period of hypoperfusion, with ischemic levels of cerebral perfusion, followed by a phase of hyperemia, increasing ICP and, finally, a phase of recurrent ischemia with vasospasm [31]. While it may seem that early hypertensive episodes could be neuroprotective, by boosting cerebral perfusion pressure, it may also play a role in destabilizing developing clots, increasing edema and ICP [15].

The development of larger prospective studies in children following TBI is of crucial importance, as to increase the available literature and, consequently, drawing more conclusions when comparing the pediatric and adult populations.

4.1. Limitations

There are some limitations in the present systematic review. Firstly, relying almost only on retrospective studies can be problematic as they are more prone to biases and may not provide as strong evidence as prospective studies. Secondly, the studies included mainly focused on TBI, neglecting the other possible causes of brain injury in the pediatric population, making it difficult to extrapolate our conclusions based in traumatic causes to others. Thirdly, the studies lacked homogeneity concerning the definition of the population under evaluation, using different scales and cutoffs to determine severity (Table 1). Finally, some of the studies did not exclude, or include in their adjusted analysis, variables that could potentially influence the exposure in question (Supplementary Tables 1 and 2).

5. Conclusions

This is the first systematic review to report cardiovascular abnormalities arising from brain injury, hypothesizing their pathophysiological mechanisms and possible role as prognostic factors. Hypotension turned out to be a common finding in children after brain injury, associated with worse prognosis. Even though the relationship between hypertension and outcome still requires further investigation, we can infer that there seems to be a trend towards increased mortality as arterial blood pressure rises. As so, efforts should be focused on keeping the SBP between the 5th and the 95th percentiles for age and sex. Besides that, early aberrant ECG alterations appear to be a common finding in patients after brain injury, which is why an early electrocardiographic assessment can be of crucial importance, as to prevent future arrhythmias. Lastly, although only a few studies have focused on the incidence of cardiac dysfunction following brain injury in the pediatric population,

taking into account how common it is in adults and how it can be used to prevent permanent cardiac damage, an echocardiographic evaluation, as well as the measure of serum biomarkers for myocardial injury, should be established. Future larger studies are required to validate our findings and lay foundation for a better clinical practice with improved treatment strategies.

Funding

This research did not receive a specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author statement

This statement is to certify that all authors have seen and approved the revision of the manuscript being resubmitted.

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the resubmission.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2023.131132>.

References

- [1] A.M. Rubiano, et al., Global neurotrauma research challenges and opportunities, *Nature* 527 (7578) (2015) S193–S197.
- [2] V. Chan, et al., Children and youth with non-traumatic brain injury: a population based perspective, *BMC Neurol.* 16 (2016) 110.
- [3] J.G. Ripoll, J.L. Blackshear, J.L. Díaz-Gómez, Acute cardiac complications in critical brain disease, *Neurol. Clin.* 35 (4) (2017) 761–783.
- [4] V. Krishnamoorthy, et al., Cardiac dysfunction after neurologic injury: what do we know and where are we going? *Chest* 149 (5) (2016) 1325–1331.
- [5] T. Gregory, M. Smith, Cardiovascular complications of brain injury, *Contin. Educ. Anaesth. Critic. Care Pain* 12 (2) (2011) 67–71.
- [6] G. Tavazzi, et al., Are neurogenic stress cardiomyopathy and Takotsubo different syndromes with common pathways? Etiopathological insights on dysfunctional hearts, *JACC Heart Fail* 5 (12) (2017) 940–942.
- [7] Z. Chen, et al., Brain-heart interaction: cardiac complications after stroke, *Circ. Res.* 121 (4) (2017) 451–468.
- [8] B.M. Coates, et al., Influence of definition and location of hypotension on outcome following severe pediatric traumatic brain injury, *Crit. Care Med.* 33 (11) (2005) 2645–2650.
- [9] A.M.H. Young, et al., Pre-hospital predictors of impaired ICP trends in continuous monitoring of paediatric traumatic brain injury patients, in: *Acta Neurochirurgica, Supplementum*, 2018, pp. 7–10.

- [10] U.B. Samant, et al., Time of hypotension and discharge outcome in children with severe traumatic brain injury, *J. Neurotrauma* 25 (5) (2008) 495–502.
- [11] S.H.W. Yao, et al., Associations of initial haemodynamic profiles and neurological outcomes in children with traumatic brain injury: a secondary analysis, *Emerg. Med. J.* 39 (7) (2022) 527–533.
- [12] S.L. Erickson, et al., Mean arterial pressure and discharge outcomes in severe pediatric traumatic brain injury, *Neurocrit. Care.* 34 (3) (2021) 1017–1025.
- [13] M.S. Vavilala, et al., Blood pressure and outcome after severe pediatric traumatic brain injury, *J. Trauma* 55 (6) (2003) 1039–1044.
- [14] P. Suttipongkaset, et al., Blood pressure thresholds and mortality in pediatric traumatic brain injury, *Pediatrics* 142 (2) (2018).
- [15] M.A. Johnson, et al., Severely elevated blood pressure and early mortality in children with traumatic brain injuries: the neglected end of the spectrum, *West. J. Emerg. Med.* 19 (3) (2018) 452–459.
- [16] R.K. Kanter, J.B. Carroll, E.M. Post, Association of Arterial Hypertension with poor outcome in children with acute brain injury, *Clin. Pediatr.* 24 (6) (1985) 320–323.
- [17] A.D. Freeman, et al., Does hypertension at initial presentation adversely affect outcomes in pediatric traumatic brain injury? *J. Pediatr. Surg.* 55 (4) (2020) 702–706.
- [18] A.V. Lele, et al., Cardiac-cerebral-renal associations in pediatric traumatic brain injury: preliminary findings, *J. Clin. Neurosci.* 76 (2020) 126–133.
- [19] D. Ozdemir, et al., QTc dispersion in children with severe head trauma, *Pediatr. Emerg. Care* 21 (10) (2005) 658–661.
- [20] J. Plymale, et al., Corrected QT interval in children with brain death, *Pediatr. Cardiol.* 31 (7) (2010) 1064–1069.
- [21] A. Grunsfeld, J.J. Fletcher, B.R. Nathan, Cardiopulmonary complications of brain injury, *Curr. Neurol. Neurosci. Rep.* 5 (6) (2005) 488–493.
- [22] A.S. Alali, et al., Beta blockers for acute traumatic brain injury: a systematic review and meta-analysis, *Neurocrit. Care.* 20 (3) (2014) 514–523.
- [23] S. Prathep, et al., Preliminary report on cardiac dysfunction after isolated traumatic brain injury, *Crit. Care Med.* 42 (1) (2014) 142–147.
- [24] V. Krishnamoorthy, et al., Early systolic dysfunction following traumatic brain injury: a cohort study, *Crit. Care Med.* 45 (6) (2017) 1028–1036.
- [25] M. Piastra, et al., Pulseless ventricular tachycardia and ventricular fibrillation complicating severe traumatic brain injury in pediatrics, *Minerva Anesthesiol.* 85 (12) (2019) 1226–1227.
- [26] F. Ruggieri, M.R. Calvi, L. Beretta, A dangerous Cushing response in a Child: neurogenic heart damage, *Am. J. Emerg. Med.* (2014) 32(4).
- [27] A. Hasanin, et al., Incidence and outcome of cardiac injury in patients with severe head trauma, *Scand. J. Trauma Resusc. Emerg. Med.* 24 (2016) 58.
- [28] V. Krishnamoorthy, et al., Association between electrocardiographic findings and cardiac dysfunction in adult isolated traumatic brain injury, *Indian J. Crit. Care Med.* 18 (9) (2014) 570–574.
- [29] S.N. Zafar, et al., Presenting blood pressure in traumatic brain injury: a bimodal distribution of death, *J. Trauma* 71 (5) (2011) 1179–1184.
- [30] I. Butcher, et al., Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study, *J. Neurotrauma* 24 (2) (2007) 294–302.
- [31] N.A. Martin, et al., Characterization of cerebral hemodynamic phases following severe head trauma: hypoperfusion, hyperemia, and vasospasm, *J. Neurosurg.* 87 (1) (1997) 9–19.

3.3 Paper III

Heart Rate Variability in Children Submitted to Surgery

Silva, MJ; Pinheiro, R; Almeida, R; Cunha, F; Ribeiro, A; Rocha AP; Guimarães, H.

Journal of Anesthesia & Clinical Research. 2016, 7:11.

Doi:10.4172/2155-6148.1000688

<https://www.longdom.org/open-access/heart-rate-variability-in-children-submitted-to-surgery-2155-6148-1000688.pdf>

Heart Rate Variability in Children Submitted to Surgery

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Received date: September 17, 2016; Accepted date: November 22, 2016; Published date: November 29, 2016

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Abstract

Objective: Heart Rate Variability (HRV) is known to reflect the sympathetic/parasympathetic interaction on several physiological and pathological conditions such as the cardiac activity responsiveness to physiological and environmental stimuli. Therefore, it has been widely used to assess nervous autonomic fluctuations and their influence on sinus node. Studies on children have demonstrated the correlation between HRV and different parameters like age, gender, physical activity and autonomic diseases whereas little evidence exists of the effects of surgery and residual anesthetic drugs on HRV. The aim of this study was to define the possible role of minor surgery in HRV in healthy children.

Design: Observational prospective cohort study.

Setting: Pediatric Surgery Department of a tertiary, university-affiliated hospital.

Patients: 47 healthy children who were scheduled for elective minor surgery.

Measurements and main results: HRV measurements of 10 to 15 minutes were obtained before and after surgery, using a Holter recorder and the BioSigBrowser[®] software. Results showed significant differences in HRV time domain indices before and after surgery in younger patients and in frequency domain in the older ones. They also demonstrated decreased HRV indices until one hour after being submitted to surgery in both time domain and LF parameters, reflecting a parasympathetic withdrawal and sympathetic predominance. Differences were also found when analyzing other variables such as anesthetic drugs.

Conclusion: This study demonstrated that surgery has impact on Autonomic Nervous System function in healthy children but, independently of anesthetic drugs, type of surgery, age and existence of pain 60 minutes after surgery no difference in HRV measures was found and autonomic homeostasis was re-established. However, further investigation in this area is required in order to a better support of the role of HRV monitoring on early prognosis prediction and risk stratification in the surgical context.

Keywords: Heart rate variability; Autonomic nervous system; Children; Surgery; Anesthesia; Healthy

Introduction

Heart Rate Variability (HRV), defined as the variation of the interval between consecutive R peaks of the electrical heart beat signal obtained through the electrocardiogram (ECG) reflects the heart's capacity to respond to physiological and environmental stimuli [1,2]. Heart Rate Variability is widely accepted as a valuable tool to investigate the sympathetic and parasympathetic contribution to regulation of heart rate rhythm. Variations in heart rate may be

evaluated by a number of methods (Task Force, 1996). Time and frequency domain measures, determined by either the heart rate or the intervals between successive normal complexes, are a widely used tool in the investigation of autonomic cardiovascular control.

Three main spectral components are distinguished and usually differentiated in the spectral profile (Task Force, 1996): (a) the high frequency (HF) band (0.15 to 0.40 Hz); (b) the low frequency (LF) band (0.04 to 0.15 Hz); and (c) the very low frequency (VLF) band (<0.04 Hz). Evidence suggested that HRV was a tool to understand the interplay between the sympathetic and parasympathetic nervous system on the regulation of cardiac activity and on assessing cardiac

health [3,5], so it was used as a marker of nervous autonomic modulation of sinus node [4], providing an insight into several conditions and enhancing risk stratification [2,5].

Reyes del Paso et al. [6], made a critically review of the state of research challenging the suitability of the LF component of HRV as an index of cardiac sympathetic control and the LF/HF ratio as an index of sympathovagal balance. They concluded that all HRV components predominantly relate to vagal control. However, it does not imply that they provide the same information about autonomic regulation. Each HRV component provides information about different physiological control mechanisms. HF oscillations relate to respiratory influences what reflect effects of respiration on heart rate (HR), also referred to as respiratory sinus arrhythmia (RSA). LF oscillations provide information about blood pressure control mechanisms such as the modulation of vasomotor tone including the so-called 0.1 Hz fluctuation. VLF power is related to kidney functioning and thermoregulation, meaning that HRV also gives information about sympathetic mechanisms (e.g., vasomotor tone fluctuations, rennin-angiotensin system) which manifest resonant phenomena through cholinergic oscillations in the sinus node [6].

Healthy children have higher ranges of normal respiratory rate and heart rate when compared to adults, which can interfere with Autonomic Nervous System (ANS) analysis [7,8]. Some authors suggest different ranges for heart rate and respiratory rate cited in international paediatric guidelines [8]. Since children can breathe at higher rates than 24 cpm we also calculated HF_n corresponding to frequencies higher than 0.15 Hz (defined later) and can include all high rates of breathing.

Factors known to influence HRV indices includes age, gender, and physical activity [1] or non-physiological conditions, such as smoking, alcohol and drugs [3,5].

The main objective of the ANS is the maintenance of cardiovascular, respiratory, metabolic and thermal homeostasis, representing the primary defense against any internal or external factor jeopardizing systemic homeostasis [5]. The measurement of HRV from the ECG is a bedside, non-invasive and easy to perform method, which, by reflecting the balance of the ANS regulation of heart rate, detects the presence of ANS dysfunction [5].

In children, several studies have shown reduced or delayed cardio-vagal development in different pathologies such as diabetes mellitus [6-8], respiratory distress syndrome of the new-born [9-11], brain death [12] and sudden infant death syndrome [13,14]. There is also evidence of low HRV in functional pain conditions, anxiety and emotional disorders, which may indicate HRV as a potent biomarker of general stress and health [15-18].

Concerning the post-operative period, it is known, in adults, the correlation between ANS dysfunction and life-threatening complications after surgery [19-21]. The effect of anesthetics per se also affects ANS function. The ANS dysfunction represents a serious source of anesthetic risk affecting the outcome of patients undergoing surgery [5].

The aim of this study was to define the possible role of surgery in HRV in healthy children by HRV assessment both before and after minor surgery (76.7% correction of phimosis and/or inguinal, umbilical or abdominal wall hernia), accounting for several of its dimensions, namely, drugs involved, pain, airway access and surgical stress [5].

Methods

Study design

This observational prospective cohort study included a convenience cohort population of children who were scheduled for elective minor surgery at the Pediatric Surgery Department of a tertiary hospital, Sao Joao Hospital Center in Oporto, between September and November of 2015.

The study was conducted according to the Declaration of Helsinki and the Ethics Committee approved the project protocol. Written informed consent was obtained from the parents.

Sample

Participants included 47 subjects: 35 aged between 4 to 6 years (10 females and 25 males) and 12 aged between 14 to 16 years. Only healthy children, defined as children without any known congenital or chronic disease were enrolled in the study. Subjects under daily medication were also excluded.

Study measurement

HRV was assessed by high resolution 12 lead ECG acquired with a Holter H12+ Mortara recorder, exported using SuperECG propriety software from Mortara Rangoni, Italy and the BioSigBrowser software (BSB) [22,23]. Measurements of 15 minutes (min) were tentatively obtained at two different moments: the first before surgery, with the child seated in 45 degrees chair in the preoperative holding area and the second in the post-anesthesia care unit, with the subject still lying on the bed at 30 degrees. Both environments were dark and quiet. The time elapsed from the end of the anesthesia until the second HRV measurement was also registered.

Other study variables

Other variables were assessed as possible determinants, including physical activity [measured in hours per week (hours/week)] and Body Mass Index (BMI), calculated using the formula weight (Kg)/[height (m)] [2]. The percentiles of BMI were defined according to the growth charts developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion 2000 [21].

Pain after surgery was quantified in younger children according to a pain numeric rating scale (NRS) and in the older ones a visual analog scales (VAS).

Respiratory Rate (RespR) before and after surgery was collected. Heart Rate (HR) in beats per minute (bpm) and Systolic Blood Pressure (SBP) in mmHg before and after surgery were also collected and the difference between the pre and post-surgical values were calculated.

Information regarding the type of anesthesia and drugs used during the procedure was obtained from the anesthetic report.

In order to compare the differences between age and gender, the sample was divided into three groups: group A (n=10) including girls from 4 to 6 years old (yo), group B (n=25) including boys from 4 to 6 yo and group C (n=12) corresponding to male adolescents aged between 14 and 16 yo.

Data analysis

The graphical interface BSB [25] was used to perform the automatic ECG annotation and beat-to-beat series extraction. Namely, a multiscale wavelet-based ECG annotator previously developed and validated [26] was applied to obtain single lead (SL) based annotations and multilead based peak annotations obtained as the median mark of the 8 SL annotators for R peak from leads I, III, V1-V6. The interval RR(n) related to the nth beat is defined as the time from (n-1)th to the nth beat measured between consecutive R multilead based annotated R peaks.

The graphical interface BSB [22] was also used to obtain both “time domain” and “frequency domains” HRV measures following the standards defined by Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [2].

Series were then divided in short segments of a fixed duration of 5 min.

Each segment of analysis was detrended using the approach proposed by Tarvainen [28]. Series were assumed to be equally sampled at the local mean heart rate, as this has been shown acceptable for spectral analysis for frequencies far from Nyquist frequency [29].

HRV “time domain” local measures [2] were obtained over each available 5-min segment and includes “% HRM”: mean heart rate (beats/min); “% SDNN”: standard deviation of normal-to-normal (NN) intervals (milliseconds-ms); “% RMSSD”: square root of the mean squared differences of successive NN intervals (ms) and “pNN50”: the NN50 count divided by the total number of all NN intervals (%).

“Frequency domain” techniques, using a fast Fourier transform method applied to 5-min recording allow to estimate a spectrum in which two major bands of frequency assess ANS activity: low frequency (LF) band, from 0.04 to 0.15 Hz, is the expression of

baroreceptor-mediated regulation and is mainly due to the contribution of sympathetic discharge; high frequency (HF) band, from 0.15 to 1.4 Hz, reflects the modulation of vagus nerve discharge caused by respiration [2]. We calculate also HFn+ (>0.15 Hz) since small children breathe faster and the window spanning of HF-HRV from 0.15 to 0.4 Hz could not be appropriate. This was calculated by the formula $HFn \pm (TP-VLF-LF)/TP$.

Welch method in 64 points windows, with 50% overlap and 512 points for fast Fourier transform estimation was used over each segment. Non parametric (np) measures were taken as the power in each standard band (LF_np, HF_np), measured as the area under the spectra. LFn_np and HFn_np are power measures respectively at LF and HF bands, normalized by power in the band above 0.04 Hz, which is TP_np-VLF_np. Autonomic balance (B_np) was obtained as LF_np/HF_np and reflects the sympathovagal balance [5]. These measures were taken in normalized units.

Statistical analysis

Descriptive statistics are reported as frequencies for categorical variables and median (iIQR) or (minimum-maximum) for continuous variables. Patient and clinical characteristics were compared using Chi-square test or Fisher's exact test, as appropriate, for the categorical variables and Wilcoxon rank sum test or Kruskal Wallis test for continuous variables. All data were analyzed using SPSS ver. 22 (SPSS, Chicago, IL, USA). A P-value less than 0.05 were considered statistically significant.

Results

Characterization of each group relative to the parameters evaluated, including age, weight, BMI, physical activity, surgery duration and pre and post-surgical HR, respiratory rate (RespR) and systolic blood pressure (SBP) is shown at Table 1.

Group (n)	Age (yo)	Weight (kg)	BMI (kg/m ²)	Physical Activity (hours/week)	SBP (mmHg)		Surgery Duration (min)	Respiratory Rate (cpm)		Heart Rate (bpm)	
					Before Surgery	After Surgery		Before Surgery	After Surgery	Before Surgery	After Surgery
A (10)	5 (4-6)	20 (18-28)	15 (13.6-16.8)	2 (0-3)	99 (86-112)	102.5 (90-111)	36.5 (23-56)	19.5 (17-28)	18 (15-25)	94 (76-109)	100.5 (83-127)
B (25)	5 (4-6)	20 (11-34)	15 (11-29.9)	1 (0-3)	98.5 (86-120)	104 (84-123)	29 (18-103)	20 (16-26)	19.5 (13-23)	88.5 (61-110)	91 (72-113)
C (12)	15 (14-16)	64.5 (44-104)	20.9 (16.3-32.1)	4.5 (2-10)	124 (100-142)	126 (105-137)	29 (12-130)	18.5 (14-23)	17 (13-24)	75 (61-108)	71.5 (51-101)
Total (47)	6 (4-16)	21 (11-104)	15.8 (11-32.1)	2 (0-10)	104 (86-142)	106 (84-137)	29 (12-130)	19 (14-28)	18 (13-25)	88 (61-110)	88.5 (51-127)

Values are expressed as median (minimum-maximum)

Table 1: Description of the sample and assessed variables.

When analyzing the nature of the surgeries, 76.7% of patients had phimosis and/or hernia correction (inguinal, umbilical and abdominal wall), three patients (11.6%) had winged ear correction, three (7.0%) cutaneous lesion extraction and two (4.7%) excision of sacroccygeal cyst.

Participants BMI was categorized according to CDC Growth Charts into percentile<5 (n=5; 10.6%), percentile 5 to percentile 85 (n=34; 72.3%) and percentile>85 (n=8; 17%).

Physical activity was divided in three groups: less than 2 hours/week (n=32; 68.1%), 2 to 5 hours/week (n=10; 21.3%) and more than 5 hours/week (n=5; 10.6%).

When studying the influence of physical activity, three groups were formed: children who practiced less than 2 hours/week (n=32; 68.1%), children who practiced from 2 to 5 hours/week (n=10; 21.3%) and children who practiced more than 5 hours/week (n=5; 10.6%).

They were also divided according to surgery duration into three groups: those whose surgery lasted less than 30 min (n=26; 55.3%), those surgeries lasted from 30 to 60 min (n=17; 36.2%) and those whose surgery lasted more than 60 min (n=4; 8.5%). The median time of surgery duration in minutes was 29 ranging from 12 to 130 minutes and with IQR of 26 and 40 minutes.

Concerning the effect of time between surgery and the second measurement of HRV and in order to simplify the analysis, participants were divided in three groups: those whose measurement was performed in less than 30 min (n=15; 31.9%) after surgery, those in which it was performed from 30 to 60 min after surgery (n=23; 48.9%) and those whose measurement was taken more than 60 min after surgery (n=9; 19.1%). The median time between registration and surgery in minutes was 43 (22-57) minutes ranging from 7 to 115 minutes.

Pain after surgery was reported only in 17 (36.2%) cases with a similar distribution between groups A, B and C.

With regard to the anesthesia, all of the participants from A and B group were submitted to induction with sevoflurane, ten of them were also submitted to fentanyl (eight from A group and two from B group) and none of them were submitted to propofol. In C group, sevoflurane was used to induce anesthesia in nine cases, associated to fentanyl in eight of them and to propofol in six. Three cases were submitted to intravenous induction with propofol and, in one of them, in association to fentanyl. In summary, sevoflurane was used in 44 subjects, propofol in nine and fentanyl in seventeen.

The values of HRV parameters comparing the different groups (A, B or C) before and after surgery are expressed in Table 2. Group A (girls from 4 to 6 yo) and group B (boys from 4 to 6 yo) presented significant lower values of HRV in the time domain measures after the surgery while no difference was found in spectral components except for Group B that showed a significant decrease of HFn+. On the other hand, group C (boys from 14 to 16 yo) showed a decrease in HF component, non-significant in HFn but significant in HFn+, and an increase in LFn values after surgery and, consequently, in balance (B). Furthermore, no significant differences were found in the time domain measures. Globally, significant differences were found for HRV decrease in the time domain measures and HFn+ component and an increase in LF component.

Group (n)	Measure	Before surgery	After surgery	Difference (before-after)	P (Wilcoxon test)
A (10)	SDNN	57.6 (48.6-70.8)	42.3 (24.3-54.5)	25.2 (-0.1-30.2)	0.037*
	RMSSD	40.0 (19.6-60.8)	20.1 (11.6-32.2)	22.5 (2.6-39.0)	0.013*
	pNN50	11.4 (2.5-19.4)	2.4 (0.2-10.2)	10.8 (-0.3-15.3)	0.028*
	LFn	1.7 (1.4-3.5)	1.9 (1.5-3.1)	0.2 (-0.3-1.4)	0.553
	HFn	38.6 (24.8-50.5)	37.9 (24.7-64.7)	-0.1 (-5.9-7.9)	0.959
	B(LF/HF)	0.07 (0-0.1)	0.1 (0.0-0.1)	0.0 (-0.07-0.06)	0.914
	HF+	0.98 (0.97-0.99)	0.98 (0.97-0.99)	-0.001 (-0.01-0.01)	0.646
B (25)	SDNN	66.6 (58.6-85.2)	52.9 (40.4-84.6)	14.9 (-2.3-27.4)	0.028*
	RMSSD	56.2 (41.3-71.3)	29.3 (16.9-71.8)	18.2 (7.6-42.8)	0.011*
	pNN50	22.2 (16.1-34.3)	5.6 (0.9-27.5)	13.1 (1.2-23.7)	0.004*
	LFn	1.7 (1.4-2.3)	1.9 (1.3-3.9)	-0.2 (-1.3-0.3)	0.072
	HFn	30.9 (24.4-40.9)	37.9 (28.5-48.1)	-1.8 (-18.7-5.3)	0.166
	B(LF/HF)	0.1 (0.04-0.10)	0.1 (0.0-0.1)	0.0 (0.0-0.0)	0.221
	HF+	0.98 (0.97-0.99)	0.97 (0.96-0.99)	0.005 (-0.002-0.15)	0.026*
C (12)	SDNN	76.4 (52.3-93.2)	65.7 (44.5-98.3)	-4.6 (-22.5-21.6)	0.638
	RMSSD	43.7 (18.5-69.7)	22.1 (16.4-78.9)	2.9 (-42.8-24.6)	0.875
	pNN50	17.6 (2.4-42.3)	3.3 (0.9-36.7)	3.1 (-7.6-13.8)	0.583
	LFn	6.2 (3.9-9.8)	8.9 (5.6-26.2)	-4.1 (-14.7-0.2)	0.023*
	HFn	61.8 (42.2-70.7)	59.8 (52.4-63.9)	1.9 (-14.2-14.2)	1

	B(LF/HF)	0.1 (0.1-0.19)	0.2 (0.1-0.4)	-0.07 (-0.3-0.0)	0.017*
	HF+	0.93 (0.89-0.96)	0.90 (0.78-0.96)	0.03 (0.004-0.15)	0.028*
All	SDNN	66.6 (55.4-80.8)	53.6 (39.6-78.1)	9.4(-5.5-28.5)	0.021*
	RMSSD	48.6 (35.7-70.7)	23.4 (15.9-50.6)	17.7 (-3.6-36.7)	0.003*
	pNN50	18.9 (10.1-32.8)	3.9 (0.9-25.3)	42.2 (-1.1-18.7)	0.00*
	LFn	2.1 (1.6-5.0)	2.8 (1.6-5.0)	6.3 (-2.4-0.3)	0.024*
	HFn	39.1 (26.2-50.5)	43.2 (31.2-62.2)	61.5 (-16.8-7.8)	0.288
	B(LF/HF)	0.1 (0.05-0.1)	0.10 (0.0-0.1)	0.1 (-0.05-0.0)	0.272
	HF+	0.98 (0.95-0.99)	0.97 (0.94-0.98)	0.06 (-0.002-0.02)	0.005*
Values are expressed as median (IQR-interquartile range); *Significant difference between measures before and after surgery (p<0.05)					

Table 2: HRV parameters by age and gender.

No significant difference was found on HRV measures when comparing them by BMI percentile.

With respect to physical activity influence on HRV parameters before and after surgery, statistically significant decreases were found in the time domain measures in children who practiced less than 2 hours/week (SDNN: 63.3 (53.4-76.8) versus 51.2 (40.6-73.9), p=0.02; RMSSD: 48.6 (36.6-65.8) versus 23.4 (15.2-48.9), p=0.003; pNN50: 19.4 (10.2-32.5) versus 3.7 (0.8-21.4), p=0.002). No other significant findings related to physical activity were observed.

Comparing the groups by the surgery duration significant differences were observed between pre and post-surgical HRV values only in the group in which it lasted from 30 to 60 min and in time domain parameters, with decreased values in SDNN [62.9 (54.3-70.2) versus 36.1 (26.9-53.6), p=0.002], RMSSD [46.3 (27.3-62.0) versus 17.1 (12.5-20.1), p=0.001] and pNN50 [14.8 (6.3-20.6) versus 0.58 (0.3-2.4), p=0.001]. No differences were found in the frequency domain parameters in any of the groups.

When analyzing the effect of the time occurred since the end of the surgery until the measurement of HRV (Figure 1), a statistically significant reduction in RMSSD [43.3 (19.7-52.1) versus 19.2 (12.7-32.1), p=0.003] and pNN50 [12.6 (2.5-26.4) versus 7.2 (1.9-12.2), p=0.005] was observed in those patients whose HRV measurement was taken in less than 30 min after surgery. Those whose measurement was taken between 30 to 60 min after surgery presented a statistically

significant decrease in pNN50 [28.7 (14.7-38.8) versus 8.4 (1.3-28.8), p=0.036] and LF [29.9 (23.8-39.4) versus 3.2 (1.6-5.3), p=0.013]. Beyond these, no other significant differences were found in the other HRV measures related to time after surgery.

The patients who have reported pain after surgery (Figure 2) showed a significant decrease in all time domain indices [SDNN: 63.3 (51.1-83.1) versus 48.7 (38.3-60.1), p=0.031; RMSSD: 44.1 (29.6-74.4) versus 19.2 (15.2-33.6), p=0.011; pNN50: 20.7 (6.3-36.4) versus 2.1 (0.5-11.9), p=0.002] while in those with no reported pain only pNN50 was significantly reduced [18.5 (12.9-32.5) versus 6.6 (0.9-28.5), p=0.043].

Analysis of propofol and fentanyl influence on HRV is presented in Table 3. Most of the patients (93.6%) were submitted to sevoflurane (only 3 were not) so the results of HRV parameters on sevoflurano are very similar to the general population posted on Table 2. In the group in which propofol was used there was only significant differences in LFn component, in balance (B) and in HFn+. Nevertheless, time domain parameters revealed to be significantly different among those cases in which propofol were not used during anesthesia. All patients that were submitted to propofol were from C group, they presented lower values of HR before and after surgery than the others were not submitted to propofol and HR lowered after surgery. SBP was lower in the patients who did propofol also.

	Measure	Before surgery	After surgery	p (Wilcoxon test)
Propofol (n)	HR	76 (68-106)	71 (60-88)	0.032*
	SBP	127 (119-133)	129 (122-135)	0.889
	RespR	19 (15-21)	17 (16-20)	0.669
	SDNN	67.9 (49.7-102.9)	59.8 (38.7-109.1)	0.767
	RMSSD	44.1 (12.9-66.8)	18.1 (15.6-73.8)	0.953
	pNN50	17.3 (0.5-41.6)	1.5 (0.6-31.2)	0.953
	LFn	7.4 (4.5-10.7)	12.2 (8.0-29.5)	0.038*
Yes (9)				

		HF _n	66.4 (43.3-70.1)	60.6 (47.3-64.2)	0.953
		B (LF/HF)	0.1 (0.1-0.2)	0.2 (0.2-0.6)	0.027*
		HF _n +	0.92 (0.89-0.95)	0.87 (0.74-0.92)	0.038*
	No (38)	HR	96 (91-102)	99 (89-109)	0.049*
		SBP	100 (93-108)	104 (97-107)	0.081
		RespR	20 (18-22)	19 (17-22)	0.050*
		SDNN	65.3 (56.1-79.9)	51.2 (39.4-78.8)	0.007*
		RMSSD	50.9 (36.9-71.0)	25.2 (16.3-52.1)	0.001*
		pNN50	19.4 (12.0-32.8)	4.4 (0.9-25.6)	0.001*
		LF _n	1.8 (1.5-3.6)	2.01 (1.6-3.9)	0.177
		HF _n	33.7 (24.8-47.8)	39.6 (28.4-59.4)	0.252
		B (LF/HF)	0.1 (0.04-0.1)	0.1 (0.0-0.1)	0.573
		HF _n +	0.98 (0.91-0.99)	0.97 (0.96-0.98)	0.064
Fentanyl	Yes (17)	HR	87 (77-105)	87 (72-100)	0.489
		SBP	112 (99-124)	109 (104-121)	0.571
		RespR	19 (18-21)	19 (17-22)	0.073
		SDNN	63.2 (50.9-79.1)	53.3 (32.1-75.9)	0.218
		RMSSD	41.9 (22.7-53.4)	20.5 (15.4-33.9)	0.033*
		pNN50	13.9 (3.9-30.2)	2.9 (0.5-12.5)	0.011*
		LF _n	3.5 (1.7-6.2)	4.5 (2.1-10.2)	0.025*
		HF _n	46.4 (30.6-64.1)	57.3 (36.0-63.9)	0.433
		B (LF/HF)	0.1 (0.04-0.1)	0.1 (0.1-0.2)	0.014*
		HF _n +	0.96 (0.93-0.98)	0.96 (0.89-0.98)	0.021*
	No (30)	HR	87 (76.75-105.25)	87 (72-100.25)	0.097
		SBP	112 (99-124)	104 (96-107.5)	0.083
		RespR	19 (18-21)	18.5 (17-21.5)	0.228
		SDNN	70.1 (57.9-90.1)	53.6 (41.2-91.1)	0.039*
		RMSSD	58.3 (40.3-72.0)	29.3 (16.7-87.1)	0.027*
		pNN50	22.2 (15.8-37.0)	5.6 (0.9-28.3)	0.012*
		LF _n	1.7 (1.5-3.6)	1.9 (1.4-4.1)	0.275
		HF _n	43.1 (24.6-45.3)	38.2 (30.0-52.0)	0.509
		B (LF/HF)	0.1 (0.05-0.1)	0.1 (0.0-0.1)	0.446
		HF _n +	0.98 (0.97-0.99)	0.97 (0.96-0.98)	0.136

Values are expressed as median (IQR-interquartile range); *Significant difference between measures before and after surgery (p<0.05).

Table 3: HRV parameters according to Propofol, Sevoflurane and Fentanyl.

Fentanyl effect on HRV parameters was related to significant changes in RMSSD, SDNN, LF_n and in balance (B).

In those cases in which this drug was not used, significant decreases were observed in all time domain components. 88.8% of the patients who were not submitted to fentanyl did lumbar epidural anesthesia.

Discussion

Over the last years, literature has highlighted the relevance of HRV on assessing ANS status as a mean of predicting post-operative complications, considering surgery and all its implications (pain, anesthetic drugs, emotional distress) as a cause of autonomic disruption with effects on systemic homeostasis [5,16-18]. The analysis of HRV can complement the reasoning for invasive monitoring and may hopefully guide preventive strategies for risk reduction [24-26]. Thus, the post-operative period is a period of increased cardiovascular and respiratory risk and a decreased HRV is recognized to be a more powerful predictor for mortality [5].

On children, little information exists regarding surgery effects on HRV, which means that research in this area is required. With this study, we sought to determine HRV changes among healthy children submitted to minor surgery and presents descriptive information about each HRV parameter.

It is known that HRV reflects the fluctuation in autonomic inputs to the heart. Diminished HRV occurs when there's both autonomic inactivity and excessive sympathetic inputs [2], showing an ANS imbalance that may be induced by increased stress or autonomic neuropathy [30]. Time domain parameters (SDNN, RMSSD and pNN50) strongly reflect parasympathetic modulation of sinus node [4] and, although there's not a consensus among the scientific community about frequency domain parameters, most authors consider HF component as an expression of vagal activity influenced by respiration and LF component as a reflection of both cardiac sympathetic and parasympathetic activity with predominance of the sympathetic discharge [5]. Thus, LF/HF ratio represents a sympathovagal balance [5].

Regarding the results, with an overall analysis, it is possible to conclude that surgery influenced HRV values of the entire sample independently of other variables, as showed in Table 2. These findings suggest an increase in sympathetic control of the heart or a decrease in parasympathetic control of the heart. Probably, in younger children, surgery influences parasympathetic activity the most whereas, in the older children, it influences mostly the sympathetic activity as found in previous studies that suggest a decrease in the influence of parasympathetic activity that occurs with increasing age [8].

Normal ranges of respiratory rate in children are still under discussion. Fleming et al. [7] created new centiles of respiratory rate in children demonstrating a decline in respiratory rate from birth to early adolescence decreasing from a median of 44 breaths/minutes at birth to 26 breaths/minute at age of two. In our study only four children presented a respiratory rate over 24 breaths/minute (maximum RR of 28 breaths/minute). Since HF-HRV is defined in a spanning 0.15 to 0.4 Hz we calculated HFn+ to include the patients with RR >24 breaths/minute, but no significant differences were found from the HF-HRV.

Although sometimes conflicting, information in literature demonstrated age related changes in HRV due to ANS maturation [31,32]. Some authors describe a gradual decrease of the sympathetic activity in the first decade of life [3,31], while others describe an increase of parasympathetic activity in the same period of time,

reflected by increased values of all the time domain indices, followed by a gradual decrease [4, 32,33].

When comparing pre and post-surgical values between boys and girls, no significant differences were found in the same HRV parameters, which is consistent with previous studies that stated no differences in children HRV values according to gender [1,30].

Even though studies show a correlation between HRV and physical activity [1,34], in the present study, differences seen on HRV indices related to physical activity are probably biased by age because the group that practiced less than 2 h/week consists of younger children and the group that practiced more than 5 h/week is composed of the older participants.

Only the group in which surgery lasted from 30 to 60 min (Figure 1) revealed significant differences in time domain values, thus in parasympathetic modulation of ANS. One possible explanation could be the use of a lighter anesthesia used in short and less aggressive surgery with very low influence on ANS. There were only four cases in which surgery duration lasted more than 60 min (two adolescents), not enough cases to find any statistically difference.

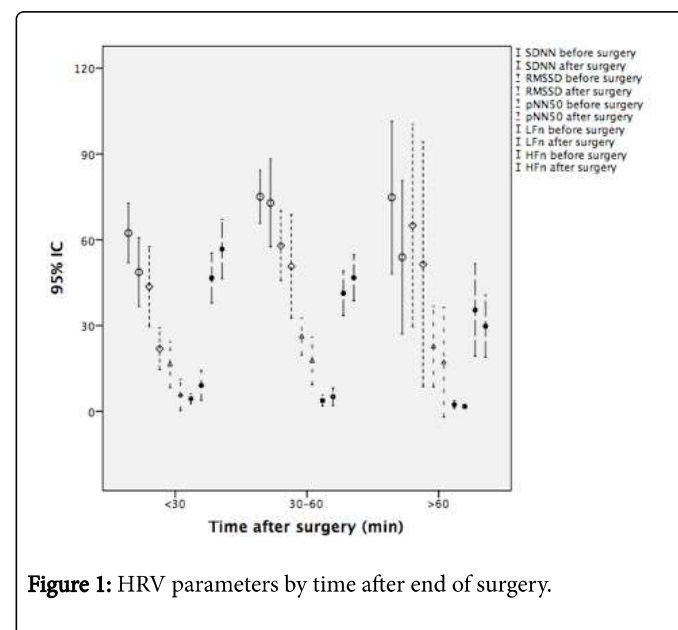


Figure 1: HRV parameters by time after end of surgery.

Results related to analysis of the time occurred from the end of the surgery until the measurement of HRV (Figure 2) showed a decreased parasympathetic activity in those patients whose HRV measurement was made in less than 30 min after surgery. A parasympathetic decrease and a sympathetic activity increase in those whose measurement was taken between 30 to 60 min after surgery was also found.

It is important to notice that, when measurements were taken after more than 60 min after surgery, no differences were found in HRV parameters. This can reflect a decreasing interference of surgery (and, possibly, the drugs used during the procedure) on ANS over time, with reestablishment of autonomic homeostasis. Despite the fact that our patients were only submitted to short duration anesthetic drugs, our study helps to support the time of 60 minutes as the minimum required period of standing in a post anesthesia care unit despite age or type of minor surgery.

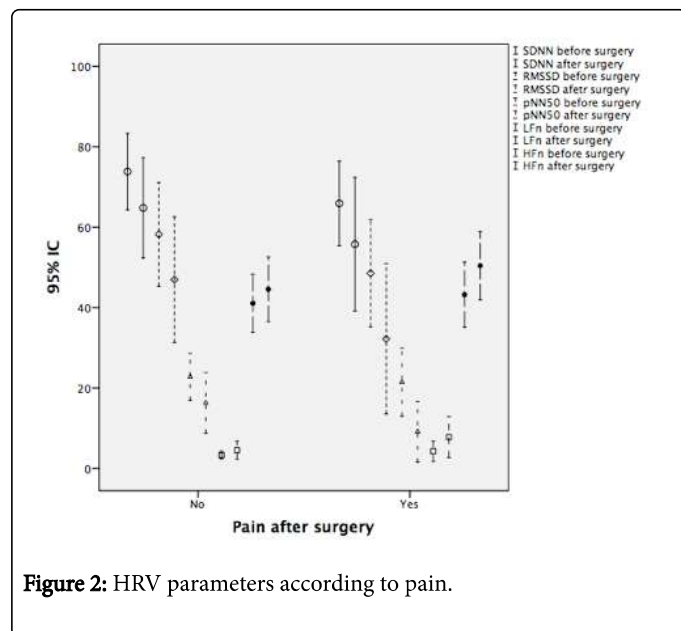


Figure 2: HRV parameters according to pain.

A diminished parasympathetic activity was seen on patients who have reported pain after surgery, as opposed to those who have not reported any pain (Figure 2). This result possibly leads to the establishment of a positive correlation between pain and parasympathetic inhibition and so a sympathetic dominance, also described in literature [35].

Anesthetics per se are known to affect ANS and HRV measurements. Despite this, during general anesthesia, anesthetic drugs may suppress autonomic activity oscillations and, depending on the combination of agents used, care must be taken when studying its influence on HRV [5,33]. Yet, inhalational anesthesia is known to negatively interfere with HRV indices [5].

HR decreases and SBP increases with age, this fact can explain why HR was lower and SBP higher, before and after surgery, in the cases submitted to propofol. Studies on propofol effect on HRV revealed a decrease in BP and HF proportional to the depth of anesthesia without any significant change on HR or LF, meaning that the cardiac parasympathetic nerve was inhibited to a higher degree than sympathetic nerve [5,36,37]. Other studies suggested propofol to induce cardiovascular depression by depressing sympathetic nervous activity [38].

In this study, results also showed an influence of propofol on the ANS activity. Patients who were submitted to propofol presented an increase of LF values and decrease of HF and HFn+ values after surgery. Reyes del Paso et al, suggested HRV power spectrum, including its LF component, is mainly determined by the parasympathetic system. These findings challenge the interpretation of the LF and LF/HF ratio as indices of sympathetic cardiac control and autonomic balance. According to this study findings we assume that our results suggests that propofol is an inhibitor of parasympathetic system that influenciate, in a higher proportion, the HF component. However, these results can have limited significance as propofol was only used in the older participants. In this population, induction of anesthesia with propofol was associated with a significant decrease in HR but not in SBP, as found in literature [36].

Sevoflurane was associated with decrease in BP or LF with little or no effect on the cardiac parasympathetic tone (5). The majority of our patients (93.6%) were submitted to sevoflurane so we cannot calculate the influence of this drug in our population. We found higher values of BP after surgery and no decrease of LF component. This finding could support the studies that suggest a mainly parasympathetic influence on LF component [38,39].

Few data on the effect of fentanyl on HRV are available [38]. Low dose fentanyl led to sympathetic withdrawal and is believed to reduce LF power reflecting an increased parasympathetic tone [5]. We found that children who were on fentanyl showed a significant increase in LF and decrease in RMSSD and HFn+ component supporting the vagomimetic properties of this drug.

There are a number of studies that report a strong positive correlation between mean R-R interval and various time domain indices of HRV (e.g., the standard deviation of normal beats, SDNN) [40-42] such that HRV was greater during longer mean R-R intervals (slower heart rates) than at shorter mean R-R intervals (faster heart rates). Frequency domain analysis of HRV is similarly affected by mean heart rate. Sacha and Pluta [43] found that LF was directly related, while HF was indirectly related, to the average heart rate of the subject. As a consequence, they further report that LF/HF varied depending on heart rate, lower at slower and higher at faster heart rates. Thus, heart rate per se can influence LF/HF independent of changes cardiac autonomic nerve activity [39].

Respiratory parameters can also alter heart rate and R-R interval variability independent of changes in cardiac autonomic regulation (i.e., against a constant background level of automatic regulation) [44-48]. It is now well established that increases in respiratory frequency reduce the amplitude of heart rate oscillations [44,46,47] conversely, reductions in respiratory frequency increase HRV [44,46,47]. Thus, it is important to control breathing (paced or timed breathing) in order to interpret HRV data accurately. Brown and co-workers reported that respiratory parameters not only altered HF power but also strongly influenced the LF components of the R-R interval power spectrum, a component that previously was viewed to vary independently of changes in respiration [39].

Some studies suggest that opioids predominantly reduce LF power (reflecting an increased parasympathetic tone) and that general anesthesia with fentanyl leads to sympathetic withdrawal [49,50]. Our study showed an overall parasympathetic tone reduction on the patients submitted to minor surgery independently of receiving fentanyl or not. This can be explained by the use of epidural lobar anesthesia in 88.8% of patients not submitted to fentanyl. Tanaka et al. found that lumbar epidural anesthesia resulted in a significant increase in the low-frequency/HF ratio of HRV and unchanged spontaneous sequence baroreflex indices, suggesting sympathetic predominance [51].

With respect to sevoflurane impact on HRV parameters, although previous data suggests that it has little or even no effect on parasympathetic tone [52], no reliable conclusion can be made because almost all (but three cases) of the sample was submitted to sevoflurane during induction of anesthesia.

The interpretation of the results of this study naturally is subject to certain limitations. The main limitation is the measurement position. Although not very different concerning the degrees of inclination (45° before surgery and 30° after surgery) subjects were in a chair and sitting position before surgery and in a bed and supine position after

surgery. Nepal et al. [39], found that a significant decreased in HRV parameters reflecting vagal activity and reciprocal increase in sympathetic activity in standing as compared to sitting and supine but there was no significant change in HRV in sitting as compared to supine.

Moreover, the small sample size compared with the diversity of the variables studied and the fact that the observed variables were not normally distributed is a strong impeditive to achieve more conclusions about some of the variables analyzed, particularly regarding multivariate analysis. No significant complications after surgery were found in our sample so any relation between ANS dysfunction and perioperative complications could be established.

Data in literature suggests that the measurement of HRV is a good tool to evaluate perioperative risk in patients with suspected autonomic dysfunction, select individuals who need further cardiac testing and optimize pre-operative status [5]. In this study, only healthy children with no surgical complications were studied and, still, they showed reduced HRV measurements. Further studies in children with suspected autonomic dysfunction or complicated surgery are necessary to better support the role of HRV monitoring on early prognosis prediction and risk stratification.

In addition, several other aspects that are known to influence HRV measurements were not taken into account, such as physical and emotional stress due to anticipation of the surgery, other drugs used during surgery, volemic status and changes in position [5]. Finally, because the studied population was composed of children and measurements were realized in the presence of other people, it was not always possible to have the desired and ideal quiet environment.

Conclusion

The measurement of HRV can be used as a helpful, non-invasive, bedside tool to evaluate the risk in patients who are going to be submitted to surgery. This study showed a decreased HRV in healthy children until one hour after being submitted to minor surgery in both time-domain and low frequency-domain parameters, reflecting a parasympathetic withdrawal and sympathetic predominance. When analyzing all patients no difference was found in HF domain and in balance.

Younger patients presented significant differences in HRV in time domain measures before and after surgery and older patients showed a difference in low frequency spectral component. In healthy children submitted to minor surgery no significant ANS dysfunction was found over 60 minutes after surgery. This data can support the time of 60 minutes as the required period for standing in post anesthesia care unit.

Nevertheless, it is important to notice that further investigation about this subject is required in order to a better comprehension of ANS behavior, particularly in the pediatric age group.

Acknowledgements

Authors would like to thank the director of Pediatric Surgery Department of Centro Hospitalar Sao Joao, José Estevão da Costa MD PhD, for giving permission to collect the data in his department.

Authors also acknowledge the support from Mortara Instr Inc., represented in Portugal by CardioSolutions, Lda. The first, third and sixth authors were partially supported by CMUP (UID/MAT/

00144/2013), which is funded by FCT (Portugal) with national (MEC) and European structural funds through the programs FEDER, under the partnership agreement PT2020.

This study was partially supported by projects TEC2010-21703-C03-02 and TEC2013-42140-R from the Ministerio de Economia y Competitividad (MINECO) with European Regional Development Fund (FEDER), Spain, and by Grupo Consolidado BSICoS (T-96) from DGA (Aragon, Spain) and European Social Fund (EU).

Statement

Ethics

The study was conducted according to the Declaration of Helsinki and the local Ethics Committee approved the project protocol. Written informed consent was obtained from the parents.

Disclosures

No conflicts of interest declared.

References

1. Michels N, Clays E, De Buyzere M, Huybrechts I, Marild S, et al. (2013) Determinants and reference values of short-term heart rate variability in children. *Eur J Appl Physiol* 113: 1477-1488.
2. Malik M, Bigger JT, Camm AJ, Kleiger RE, Malliani A, et al. (1996) Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 17: 354-381.
3. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS (2006) Heart rate variability: a review. *Med Biol Eng Comput* 44: 1031-1051.
4. Silvetti MS, Drago F, Ragonese P (2001) Heart rate variability in healthy children and adolescents is partially related to age and gender. *Int J Cardiol* 81: 169-174.
5. Mazzeo AT, La Monaca E, Di Leo R, Vita G, Santamaria LB (2011) Heart rate variability: a diagnostic and prognostic tool in anesthesia and intensive care. *Acta Anaesthesiol Scand* 55: 797-811.
6. Reyes del Paso, Langewitz W, Mulder LJ, van Roon A, Duschek S (2013) The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. *Psychophysiology* 50: 477-487.
7. Fleming S, Thompson M, Stevens R, Heneghan C, Pluddemann A, et al. (2011) Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* 377: 1011-1018.
8. Chen W, Zhang XT, Guo CL, Zhang SJ, Zeng XW, et al. (2016) Comparison of heart rate changes with ictal tachycardia seizures in adults and children. *Childs Nerv Syst* 32: 689-695.
9. Akinci A, Celiker A, Baykal E, Tezic T (1993) Heart rate variability in diabetic children: sensitivity of the time- and frequency-domain methods. *Pediatr Cardiol* 14: 140-146.
10. Chessa M, Butera G, Lanza GA, Bossone E, Delogu A, et al. (2002) Role of heart rate variability in the early diagnosis of diabetic autonomic neuropathy in children. *Herz* 27: 785-790.
11. Ozgur S, Ceylan O, Senocak F, Orun UA, Dogan V, et al. (2014) An evaluation of heart rate variability and its modifying factors in children with type 1 diabetes. *Cardiol Young* 24: 872-879.
12. Henslee JA, Schechtman VL, Lee MY, Harper RM (1997) Developmental patterns of heart rate and variability in prematurely-born infants with apnea of prematurity. *Early Hum Dev* 47: 35-50.

13. Van Ravenswaaij-Arts C, Hopman J, Kollée L, Stoeltinga G, Van Geijn H (1994) Spectral analysis of heart rate variability in spontaneously breathing very preterm infants. *Acta Paediatr* 83: 473-480.
14. Prietsch V, Knoepke U, Obladen M (1994) Continuous monitoring of heart rate variability in preterm infants. *Early Hum Dev* 37: 117-131.
15. Almeida R, Silva MJ, Rocha AP (2013) Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients, in *Computing in Cardiology Conference (CinC)* 61-64.
16. Perticone F, Ceravolo R, Maio R, Cosco C, Mattioli PL (1990) Heart rate variability and sudden infant death syndrome. *Pacing Clin Electrophysiol* 13: 2096-2099.
17. Antila KJ, Välimäki IA, Mäkelä M, Tuominen J, Wilson AJ, et al. (1990) Heart rate variability in infants subsequently suffering sudden infant death syndrome (SIDS). *Early Hum Dev* 22: 57-72.
18. Evans S, Seidman LC, Tsao JCI, Lung KC, Zeltzer LK, et al. (2013) Heart rate variability as a biomarker for autonomic nervous system response differences between children with chronic pain and healthy control children. *J Pain Res* 6: 449-457.
19. Laitio T, Jalonen J, Kuusela T, Scheinin H (2007) The role of heart rate variability in risk stratification for adverse postoperative cardiac events. *Anesth Analg* 105: 1548-1560.
20. Ushiyama T, Nakatsu T, Yamane S, Tokutake H, Wakabayashi H, et al. (2008) Heart rate variability for evaluating surgical stress and development of postoperative complications. *Clin Exp Hypertens* 30: 45-55.
21. Goldstein B, Ellenby MS (2000) Heart rate variability and critical illness: potential and problems. *Crit Care Med* 28: 3939-3940.
22. Bolea J, Almeida R, Laguna P, Sornmo L, Martínez JP (BioSigBrowser, biosignal processing interface (2009) Final Program and Abstract Book 9th International Conference on Information Technology and Applications in) BioSigBrowser, biosignal processing interface (2009) Final Program and Abstract Book 9th International Conference on Information Technology and Applications in Biomedicine, ITAB.
23. Martínez JP, Almeida R, Olmos S, Rocha AP, Laguna P (2004) A wavelet-based ECG delineator: evaluation on standard databases. *IEEE Trans Biomed Eng* 51: 570-581.
24. [Author not listed] (2007) Centers for Disease Control and Prevention and National Center for Health Statistics/CDC. CDC growth charts: United States 2002.
25. Tarvainen MP, Ranta-Aho PO, Karjalainen PA (2002) An advanced detrending method with application to HRV analysis. *IEEE Trans Biomed Eng* 49: 172-175.
26. Almeida R, Pueyo E, Martinez JP, Rocha AP, Olmos S, et al. (2003) A parametric model approach for quantification of short term QT variability uncorrelated with heart rate variability. *Comput Cardiol* 165-168.
27. Estafanous F, Brum J, Ribeiro M, Estafanous M, Starr N, et al. (1992) Analysis of heart rate variability to assess hemodynamic alterations following induction of anesthesia. *Cardiothorac Vasc Anesth* 6: 651-657.
28. Knugten D, Trojan S, Weber M, Wolf M, Wappler F (2005) Pre-operative measurement of heart rate variability in diabetics: a method to estimate blood pressure stability during anesthesia induction. *Anaesthesist* 54: 44-49.
29. Hanss R, Renner J, Ilies C, Moikow L, Buell O, et al. (2008) Does heart rate variability predict hypotension and bradycardia after induction of general anaesthesia in high risk cardiovascular patients? *Anaesthesia* 63: 129-135.
30. Seppälä S, Laitinen T, Tarvainen MP, Tompuri T, Veijalainen A, et al. (2014) Normal values for heart rate variability parameters in children 6-8 years of age: the PANIC Study. *Clin Physiol Funct Imaging* 34: 290-296.
31. Finley JP, Nugent ST, Hellenbrand W (1987) Heart-rate variability in children. Spectral analysis of developmental changes between 5 and 24 years. *Can J Physiol Pharmacol* 65: 2048-2052.
32. Finley JP, Nugent ST (1995) Heart rate variability in infants, children and young adults. *J Auton Nerv Syst* 51: 103-108.
33. Shannon D, Carley D, Benson H (1987) Aging and modulation of heart rate. *Am J Physiol* 19: 1334-1341.
34. Gutin B, Howe C, Johnson MH, Humphries MC, Snieder H, et al. (2005) Heart rate variability in adolescents: relations to physical activity, fitness, and adiposity. *Med Sci Sports Exerc* 37: 1856-1863.
35. Hamunen K, Kontinen V, Hakala E, Talke P, Paloheimo M, et al. (2012) Effect of pain on autonomic nervous system indices derived from photoplethysmography in healthy volunteers. *Br J Anaesth* 108: 838-844.
36. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A (2003) Differential effects of propofol and sevoflurane on heart rate variability. *Anesthesiology* 98: 34-40.
37. Win NN, Fukayama H, Kohase H, Umino M (2005) The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg* 101: 97-102, table of contents.
38. Unoki T, Grap MJ, Sessler CN, Best AM, Wetzel P, et al. (2009) Autonomic nervous system function and depth of sedation in adults receiving mechanical ventilation. *Am J Crit Care* 18: 42-50.
39. Nepal GB, Paudel BH (2012) Effect of posture on heart rate variability in school children. *Nepal Med Coll J* 14: 298-302.
40. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 59: 256-262.
41. Van Hoogenhuyze D, Weinstein N, Martin GJ, Weiss JS, Schaad JW, et al. (1991) Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 68: 1668-1676.
42. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, et al. (1992) Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 85:164-171.
43. Sacha J, Pluta W (2005) Different methods of heart rate variability analysis reveal different correlations of heart rate variability spectrum with average heart rate. *J Electrocardiol* 38: 47-53.
44. Angelone A, Coulter NA Jr (1964) Respiratory Sinus Arrhythmia: A Frequency Dependent Phenomenon. *J Appl Physiol* 19: 479-482.
45. Davies CT, Neilson JM (1967) Sinus arrhythmia in man at rest. *J Appl Physiol* 22: 947-955.
46. Melcher AH (1976) On the repair potential of periodontal tissues. *J Periodontol* 47: 256-260.
47. Hirsch JA, Bishop B (1981) Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *Am J Physiol* 241: H620-629.
48. Van De Borne P, Montano N, Narkiewicz K, Degaute JP, Malliani A, et al. (2001) Importance of ventilation in modulating interaction between sympathetic drive and cardiovascular variability. *Am J Physiol Heart Circ Physiol* 280: H722-729.
49. Billman G (2013) The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. In *heart rate variability: clinical applications and interaction between HRV and heart rate*. *Front Physiol* 4: 54-58.
50. Zickmann B, Hofmann HC, Pottkämper C, Knothe C, Boldt J, et al. (1996) Changes in heart rate variability during induction of anesthesia with fentanyl and midazolam. *J Cardiothorac Vasc Anesth* 10: 609-613.
51. Michaloudis D, Kochiadakis G, Georgopoulou G, Fridakis O, Chlouverakis G, et al. (1998) The influence of premedication on heart rate variability. *Anaesthesia* 53: 446-453.
52. Tanaka M, Goyagi T, Kimura T, Nishikawa T (2004) The Effects of Cervical and Lumbar Epidural Anesthesia on Heart Rate Variability and Spontaneous Sequence Baroreflex Sensitivity. *Anesth Analg* 99: 924 -929.

3.4 Paper IV

Cardiovascular responses as predictors of mortality in children with acute brain injury.

Silva, MJ; Gonçalves, H; Almeida, R; Camila, C; Almeida, AI; Rocha, AP; Granja, C; Baptista, MJ; Azevedo, I.

Pediatric Research (2024).

<https://doi.org/10.1038/s41390-024-03679-2>.

CLINICAL RESEARCH ARTICLE



Cardiovascular responses as predictors of mortality in children with acute brain injury

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BACKGROUND: Investigate the utility of cardiovascular responses such as heart rate (HR), blood pressure (BP), and heart rate variability (HRV) in the prognosis of children with acute acquired brain injury (ABI).

METHODS: Children under 18 years with severe acute acquired brain injury (ABI) who survived at least 12 h after PICU admission were included in a prospective observational cohort in a tertiary academic PICU. Physiological variables, neurological data, laboratory tests (chemistry and hematology), and medications were recorded within 12 h of admission. Linear and nonlinear HRV indices, CT scans, PICU scores, and survival rates were evaluated.

RESULTS: Seventy-two children, median age 10.7 years (IQR 4.1–13.6), were eligible for the study; 28 (38.9%) were diagnosed with brain death (BD). Tachycardia, SBP and MBP < 5th percentile, and MBP and DBP > 99th percentile were significantly associated with mortality. *Poincaré* SD1/SD2 was significantly associated with mortality after adjusting for age, sex and ongoing medication.

CONCLUSION: Tachycardia, systolic hypotension and median hypo and hypertension were associated to mortality in children with severe ABI. While further validation through larger, multicenter studies is necessary, the *Poincaré* SD1/SD2 ratio has shown promise as a prognostic tool for predicting mortality in children with severe ABI.

Pediatric Research; <https://doi.org/10.1038/s41390-024-03679-2>

IMPACT STATEMENT:

- This study explores cardiovascular changes, including heart rate and blood pressure, and linear/nonlinear HRV measures using ECG at 1000 Hz, and compare them with other prognostic factors like brain tomography and PICU scores. Tachycardia, hypo/hypertension in the early hours after admission are linked to early mortality in children with severe traumatic and non-traumatic brain injury. Linear/non-linear measures of HRV were also related to survival. Higher HRV values indicating better survival chances. We identified *Poincaré* SD1/SD2 ratio as a promising tool for predicting mortality in children with severe ABI.

INTRODUCTION

Acute acquired brain injury (ABI) refers to any sudden damage to the brain that occurs after birth, resulting from either traumatic or non-traumatic events. This type of injury can cause an immediate disruption in brain function, leading to a range of symptoms depending on the severity and location of the injury. Types of acute brain injuries include traumatic brain injury (TBI), and non-traumatic brain injury (NTBI) such as stroke, subarachnoid hemorrhage, hypoxic or anoxic brain injury, infections (such as meningitis or encephalitis), and metabolic or toxic insults.

More reliable predictors of neurological prognosis in children with severe ABI are needed.¹ Hemodynamic parameters like heart rate (HR), blood pressure (BP), and heart rate variability (HRV) can predict poor outcomes in severe ABI, but their significance and management

thresholds remain unclear in the pediatric population.² TBI and other forms of ABI can cause complex and unpredictable changes in autonomic function. HRV corresponds to the oscillations in the interval between consecutive instantaneous HR intervals that depend on the interactions between sympathetic and parasympathetic efferent impulses to the heart and offers a non-invasive indicator of autonomous nervous system (ANS) activity.³ Previous research found that HRV is a predictor of death irrespective of the cause.^{3,4} HRV can be assessed by calculation of indices based on statistical operations on R-R intervals (time domain analysis), by spectral (frequency domain) analysis of an array of R-R intervals or by non-linear mathematical analysis such as *Poincaré* plot analysis or Sample Entropy.^{5–7} Nonlinear indexes of HRV are not standardized^{5,6} but may be considered as alternatives to the other standard HRV measures.

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Received: 28 May 2024 Revised: 19 September 2024 Accepted: 14 October 2024

Published online: 15 November 2024

We hypothesize that cardiovascular monitoring at PICU admission for children with severe ABI (both traumatic and non-traumatic), specifically tracking HR, BP, and both linear and non-linear HRV measures, provides valuable early prognostic tools for mortality, offering potential advantages over other commonly used methods.

MATERIAL AND METHODS

The procedures followed were in accordance with the ethical standards of the responsible institute committee on human experimentation and with the Helsinki Declaration of 1975. This study was approved by the institutional Ethic Commission and by the Portuguese data protection authority (IRB number: 19776) on 27th July 2006. Parents have given signed informed consent for inclusion of their children in the database.

Study site

The PICU of São João University Hospital Center, a single tertiary multidisciplinary 10-bed pediatric critical care unit, serving both medical and surgical specialties that admitted an average of 274 patients per year, including all children with acute severe brain injury from the northern region of the country, averaging 17 patients per year (data from 2021–2023).

Study population

Children aged more than 27 days and less than 18 years-old, admitted to the PICU with severe ABI ($GCS \leq 10$), TBI and NTBI like stroke, meningoencephalitis or hypoxic-ischemic encephalopathy, from January 2006 to December 2017 were prospectively screened for recruitment. Patients were included if they had PICU length of stay (LOS) > 12 h.

Exclusion criteria: congenital heart disease, cardiac pace-maker, cardiac arrhythmias, previous epilepsy, diabetes mellitus or other peripheral neurologic impairment.

Patients that met the selection criteria were included based on the possibility of obtaining an electrocardiographic record upon admission by a research team member.

Data collection and management

High-resolution 12-lead ECG Holter recordings (1000 Hz sample frequency) were taken within the first 12 h after admission. ECG recordings were automatically annotated using a wavelet-based system previously developed and validated.⁸ Biological and physiological data were collected from the admission records and recorded within the first 12 h before the diagnosis of brain death was established. Blood pressure (BP) was recorded and classified into the following percentiles based on age and sex: <5th, 5th–10th, 10th–25th, 25th–50th, 50th–75th, 75th–95th, 95th–99th, or >99th, using previously published percentiles.⁹ Tachycardia was defined as follows: ≥ 180 cpm for those under 12 months old; ≥ 140 bpm for individuals aged 12 months to 10 years; and ≥ 120 bpm for those over 10 years old. Bradycardia was defined as $HR < 100$ bpm for those ≤ 12 months old; < 70 bpm for individuals aged 1–10 years; and < 60 bpm for those over 10 years old.¹⁰ All patients were registered in a database for the calculation of Pediatric Risk of Mortality Score III (PRISM III score).¹¹ Baseline data collected after PICU admission included age, weight, prior medical history and admission diagnoses, and HR, respiratory rate (RR), blood pressure (BP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), pupillary light reactivity, and body temperature registered hourly during the Holter registration. Hypothermia was defined as core temperature below 35 °C and hyperthermia when it was higher than 38 °C. Hypoglycemia was defined as < 60 mg/dL and hyperglycemia > 180 mg/dL.¹² PICU scoring systems—PRISM III score and Probability of Death, Glasgow Coma Scale (GCS) and GCS-Pupil Score at admission, Pediatric Index Mortality 3 (PIM –3), Pediatric Logistic Organ Dysfunction (PELOD), Pediatric Sequential Organ Failure Assessment (pSOFA), Injury Severity Score (ISS) and Pediatric Trauma Scale (PTS) were calculated and registered in the first 12 h after admission.¹³ We used the PRISMIII score cutoff value for mortality of 12, accordingly with the findings of other authors.¹⁴ CT images of all the patients were reviewed by a neuroradiologist, who classified them according to different CT scoring systems based on the type of intracranial injury.^{15,16} In patients with traumatic brain injury (TBI) Rotterdam, Helsinki, and Marshall CT scoring systems were used. In patients with intracerebral hemorrhage (ICH), the ICH score was applied and the presence of subarachnoid hemorrhage (SAH) and/or intraventricular hemorrhage (IVH) was assessed; in cases of aneurysmatic SAH, the

modified Fisher Grading Scale (Mfisher) was employed. Brain death suspicion was defined as having a $GCS = 3$ plus non-reactive mydriasis.¹⁷

Outcome

The primary outcome measure was surviving to PICU discharge or BD.

Data and statistical analysis

The wavelet system, a multi-scale wavelet-based ECG annotator previously developed and validated⁸ was applied. It obtains single lead (SL) based annotations from which multi lead-based R peaks (ML_R) were obtained as the median mark of the 8 SL annotators for R peak from leads I, III, V1–V6, excluding outliers. The interval $RR(n)$ related to the n^{th} beat is defined as the time from $(n-1)^{\text{th}}$ to the n^{th} beat measured between consecutive ML_R peaks. MATLAB R2022b was used in the implementation [ref: The MathWorks, Inc. (2022). MATLAB version: 9.13.0 (R2022b). Accessed: January 01, 2023. Available: <https://www.mathworks.com>.] HRV analysis was performed for all consecutive and non-overlapping 10-min segments of the tachograms (obtained after R peak detection on the ECG), including linear time-domain and frequency-domain analysis, as well as non-linear analysis. As used before for some of the authors,¹⁸ a 10-minute duration was chosen to effectively capture variability patterns, avoiding sequences with fewer than 300 data points in a 5-min segment where the average RR interval exceeds 1 s, which could potentially compromise the stability of entropy calculations.^{19,20} In order to account for considerable differences in the average beat-to-beat sampling across the sample, the tachograms were resampled using cubic spline interpolation at 4 Hz. After detecting the R-waves, the recordings were visually analyzed, and the traces with the highest quality, best signal stability, minimal artifacts, and absence of ectopic beats were selected. No other type of preprocessing was applied. In each case, only one visually selected 10-minute segment was chosen for in the first twelve hours after admission. Linear time-domain analysis included the NN interval mean (msec), the standard deviation of the average NN interval (SDNN, in msec) and the square root of the mean squared differences of successive NN intervals (RMSSD, in msec).^{3,21,22} The frequency domain analysis was based on the nonparametric estimation of the spectrum, particular the Welch method²² with a Hanning window, applied in each segment over sequences of length 256, with 62.5% of superposition between them. The following frequency bands were considered: very low frequency (VLF, msec^{-2}) at 0–0.04 Hz, low frequency (LF, msec^{-2}) at 0.04–0.15 Hz, and high frequency (HF, msec^{-2}) at 0.15–0.40 Hz. Given the wide variety of ages in the current sample (from 1 month to 18 years), the HF+ band at 0.15–1.00 Hz was also considered. The LF/HF index, as well as total power (TP, i.e., all the spectrum area), were also considered.³ For non-linear analysis, sample entropy (SampEn(m, r)) was calculated^{23,24} considering values $0.1 \times \text{SD}$, $0.15 \times \text{SD}$ and $0.2 \times \text{SD}$ for r and value 2 for m ²⁵ while N was 2400 points (10-min segments at 4 Hz). Additionally, the nonlinear indices computed from the *Poincaré* plot were also considered, namely SD1 (short-term variability), SD2 (long-term variability) and their ratio $\text{SD1}/\text{SD2}$.^{3,23} Results of descriptive statistics were expressed as a fraction of the total population, mean $\pm$ standard deviation (SD) and/or median with interquartile range (IQR). Continuous variables were compared using Student's t test if the variable was normally distributed or Wilcoxon test if not. The Chi-square statistic was used for categorical variables. A univariate and multivariable regression adjusting for age, sex, and medication was used to study the association between mortality and HRV indices estimating the odds ratio (OR) and their 95% confidence intervals. To quantify HRV measurements and try to determine clinically useful cutoff points, we used the precision-recall curve and selected a cut-off point based on a minimum precision value of 0.8. Following this, we identified HRV measurement cutoff points significantly associated with mortality. Results were considered statistically significant when the p -value was less than 0.05. All statistical analyses were using SPSS statistical software (SPSS, release 28.0, SPSS Inc., Chicago, IL).

RESULTS

Seventy-two children with ABI were eligible for the study. Of these, 45 (62.5%) had traumatic brain injury (TBI) and 27 (37.5%) had non-traumatic brain injury (NTBI). Among the TBI patients, only two had penetrating injuries; the rest experienced blunt trauma from incidents such as collisions, car accidents, or falls. In the NTBI group, 15 patients had strokes (11 hemorrhagic and 4 ischemic), five had meningoencephalitis or meningitis, and three

Table 1. Patient characteristics and physiologic data at the first 12 h after PICU admission and differences between the survivors and non-survivors.

Patient characteristics and physiologic data	Survivals (n = 44)	Brain death (n = 28)	p value ^a
Median age (IQR) at admission	11.08 years (5.47–14.14)	10.41 years (1.93–13.39)	0.116 ^b
Sex , n	33 males 11 females	18 males 10 females	0.238
Age group , n			0.060
<=2 years	3 (6.8%)	7 (25.0%)	
>2 years ≤12 years	25 (56.8%)	10 (35.7%)	
>12 years	16 (36.4%)	11 (39.3%)	
Diagnosis , n			0.064
-TBI	32	13	
-NTBI			
- Hemorrhagic stroke	7	4	
- Ischemic stroke	2	2	
- Meningoencephalitis/meningitis	1	4	
- Hypoxic Ischemic Encephalopathy	1	2	
- Brain Tumor	0	2	
- Status epilepticus	1	0	
- Cerebral edema secondary to hyponatremia	0	1	
GCS P (median, IQR)	6 (5–7.75)	1 (1–3)	<0.001 ^b
Pupils , n			<0.001
-Both reactive	36 (92.3%)	3 (7.7%)	
-Anisocoria	5 (62.5%)	3 (37.5%)	
-Mydriasis	3 (12.0%)	22 (88.0%)	
ICP (mmHg) Median (IQR)			<0.001 ^b
-Admission (n = 60)	16 (11–24)	59 (36–74)	
CPP (mmHg) Median (IQR)			<0.001 ^b
-Admission (n = 60)	62 (57.5–71.2)	16 (7.5–48)	
Minimum SBP (mmHg), n			0.009
<P5	9 (39.1%)	14 (60.9%)	
>P5	35 (71.4%)	14 (28.6%)	
Maximum SBP (mmHg), n			0.033
<P99	10 (43.5%)	13 (56.5%)	
>P99	34 (69.4%)	15 (30.6%)	
Minimum MBP (mmHg), n			0.018
<P5	5 (33.3%)	10 (66.7%)	
>P5	39 (68.4%)	18 (31.6%)	
Maximum MBP (mmHg), n			<0.001
<P99	37 (77.1%)	11 (22.9%)	
>P99	7 (29.2%)	17 (70.0%)	
Maximum DBP (mmHg), n			0.006
<P99	37 (71.2%)	15 (28.8%)	
>P99	7 (35.0%)	13 (65.0%)	
Tachycardia , n			0.008
-Yes	15 (44.1%)	19 (55.9%)	
-No	29 (76.3%)	9 (23.7%)	
Body temperature			0.001 ^a
<35 °C	9 (31.0%)	20 (69.0%)	
Mechanical ventilation days (Median, IQR)	10 (5–16)	3 (2–6)	<0.001 ^b
Days on vasoactive drugs (Median, IQR)	5 (3.5–9)	2 (1.2–4.5)	0.005 ^b
PICU Length of stay Observed (days)			<0.001 ^b
(Median, IQR)	11.5 (7.25–16.7)	3.0 (2.0–6.0)	

^aChi-Square test.^bMann–Whitey-test.

had hypoxic-ischemic encephalopathy due to suffocation or drowning. Additionally, two patients had brain tumors, one had refractory status epilepticus, and one had cerebral edema secondary to hyponatremia (Table 1). Patient characteristics and physiologic data are described in Table 1, according to the survival status. Twenty-eight (38.9%) progressed to BD (BD group) and 44 (61.1%) survived (S group). All patients who died were diagnosed with brain death (BD). All four patients less than 12 months-old died. The median age was 10.7 years old (IQR 4.1–13.7) and 70.8% of the patients were male.

Patients with TBI had lower mortality than those with NTBI (28.9% vs. 55.5%, $p = 0.045$). Moreover, NTBI patients presented a worse prognosis at admission, with significantly higher PELOD score and higher probability of death at admission (Supplementary Table 1). The presence of tachycardia was significantly associated with a worse outcome [OR 4.08 (95%CI : 1.48–11.19), $p = 0.008$]. The presence of bradycardia was not associated with mortality. Concerning blood pressure variables, adjusted for sex and age, SBP < 5th percentile [OR 3.88 (95%CI : 1.37–11.02), $p = 0.009$]; MBP < 5th percentile [OR 4.33 (95% CI: 1.29–14.53), $p = 0.018$]; DBP > 99th percentile [OR 8.16 (95% CI 2.69–24.63), $p < 0.001$] and DBP > 99th percentile [OR 4.58 (95%CI 1.52; 13.72), $p = 0.007$] were associated with a worst outcome. The 10 min ECG Holter records used ranged from 10th to 210th minute after admission, with a median of 50 min (IQR: 30–60 min). With the exception of *Poincaré* SD1/SD2, HRV measurements were lower in the BD than in the survival group, with the following measures reaching statistical significance : SDNN, RMSDD, mean NN, TP, VLF, LF, HF, HF +, *Poincaré* SD1 and *Poincaré* SD2. A trend without reaching statistical significance was observed for LFn and *Poincaré* SD1/SD2 and worse

outcome (Table 2). Apart from SampEn, *Poincaré* SD1/SD2, and LF/HF, HRV measurements increase with age. After adjusting for age and sex (Table 2), *Poincaré* SD1/SD2 was significantly associated with mortality, independent of ongoing medication. Higher time domain (SDNN, RMSDD, meanNN), frequency domain (LF, LFn, HF, VLF, HF +) and non-linear measures of HRV (*Poincaré* SD1 and *Poincaré* SD2) were associated with survival.

The median ICP at admission was significantly higher and CPP significantly lower among the BD group (Table 1). BD group presented a significant lower PICU length of stay, mechanical ventilation days and days on vasoactive drugs (Table 1). Prognostic and CT scoring in children with TBI are represented in Table 3. The absence or obliteration of basal cisterns and a higher score in Rotterdam, Marshall and Helsinki CT score system were significantly associated with a poor outcome. All the nine patients with basal cisterns obliteration progressed to BD [OR 9.00 (CI 3.57; 22.67), $p < 0.001$]. Median *Poincaré* SD1/SD2 was significantly higher in the patients with obliterated basal cisterns (0.315 (IQR 0.082–0.199) vs. 0.132 (IQR 0.192–0.347), $p = 0.001$).

All the PICU scoring systems calculated were significantly higher in the BD group (Table 4). Three out of the 19 patients with suspected brain death at admission survived, exhibiting higher values in most HRV measurements (Supplementary Table 2). BD group also presented a significantly higher sodium, ionized calcium, C-reactive protein (CPR) and PTT at admission (Supplementary Table 3). During the ECG recording 67 (93.1%) of the patients were under the effect of sedation, and 44 (61.1%) received vasopressor support (Supplementary Table 3).

A *Poincaré* SD1/SD2 ratio ≤ 0.27 was negatively associated with mortality [OR 0.13 (CI 0.03; 0.53), $p = 0.003$]. Thirteen patients

Table 2. HRV measurements and multivariable logistic regression analysis for the association of age, sex, and medication with outcome (mortality).

HRV measures median (IQR)	Survivals (n = 44)	Brain death (n = 28)	p value ^a	Midazolam ^b OR; p value	Fentanyl ^b OR, p value	Propofol ^b OR, p value	Thiopental ^b OR, p value
SDNN	11.70 (5.57–30.70)	5.42 (0.99–12.56)	0.007	1.00; 0.689	1.007; 0.613	1.013; 0.358	1.019; 0.185
RMSDD	2.89 (1.30–7.68)	1.48 (0.83–3.67)	0.010	1.025; 0.536	1.031; 0.460	1.046; 0.290	1.064; 0.152
Mean NN	661.95 (542.14–830.58)	528.80 (445.06–689.58)	0.005	1.000; 0.066	1.003; 0.091	1.000; 0.019	1.004; 0.032
TP	100.61 (17.62–610.76)	14.97 (2.89–50.70)	0.001	1.00; 0.869	1.000; 0.995	1.000; 0.822	1.000; 0.506
VLF	31.07 (6.14–146.56)	4.02 (0.61–10.96)	0.001	1.000; 0.953	1.000; 0.840	1.000; 0.696	1.001; 0.516
LF	19.42 (5.22–134.47)	1.73 (0.21–6.72)	0.001	0.999; 0.610	1.00; 0.761	1.000; 0.954	1.000; 0.686
LFn	34.80 (16.64–71.23)	23.34 (8.03–41.06)	0.052	1.015; 0.159	1.017; 0.102	1.017; 0.084	1.024; 0.022
HF	16.89 (2.32–135.50)	2.24 (0.24–7.91)	0.001	1.00; 0.869	1.000; 0.888	1.000; 0.968	1.000; 0.668
HF _n	37.48 (14.60–65.83)	30.16 (5.71–63.57)	0.220	0.976; 0.399	0.983; 0.594	0.980; 0.467	1.003; 0.729
LF/HF	0.98 (0.27–4.35)	0.54 (0.29–2.94)	0.690	1.006; 0.555	1.000; 0.590	1.007; 0.455	0.990; 0.701
HF +	20.82 (4.15–233.93)	5.15 (0.59–38.14)	0.010	1.00; 0.411	1.000; 0.668	1.00; 0.587	1.000; 0.737
SampEn2, 0.1	0.94 (0.80–1.21)	0.83 (0.74–1.24)	0.460	1.746; 0.431	1.911; 0.358	1.412; 0.601	1.272; 0.716
SampEn2, 0.15	0.73 (0.63–0.94)	0.72 (0.57–1.13)	0.730	1.368; 0.707	1.510; 0.613	1.083; 0.917	0.991; 0.990
SampEn2, 0.2	0.62 (0.53–0.78)	0.60 (0.47–0.96)	0.910	1.108; 0.914	1.261; 0.801	0.875; 0.878	0.795; 0.791
<i>Poincaré</i> SD1	2.04 (0.92–5.43)	1.05 (0.58–2.59)	0.010	1.034; 0.547	1.043; 0.469	1.064; 0.297	1.091; 0.154
<i>Poincaré</i> SD2	16.24 (7.58–43.12)	7.64 (3.76–17.57)	0.007	0.997; 0.591	0.998; 0.648	0.999; 0.892	1.000; 0.810
<i>Poincaré</i> SD1/SD2	0.13 (0.08–1.99)	0.18 (0.09–0.31)	0.067	0.001; 0.021	0.002; 0.028	0.003; 0.038	0.004; 0.036

IQR inter quartile range, OR odds ratio.

^aMann–Whitney Test.

^bMultivariable Logistic regression adjusted for age in months and sex.

Table 3. CT scoring systems and outcome in TBI children.

Prognostic and CT scoring systems TBI	Survivals (n = 32)	Brain death (n = 13)	p value
Rotterdam basal cisterns n			<0.001 ^a
-Normal	22 (68.8%)	2 (15.4%)	
-Compressed	10 (31.3%)	2 (15.4%)	
-Absent	0 (0.0%)	9 (69.2%)	
Rotterdam midline shift n			0.233 ^a
-No or < 5 mm	29 (90.6%)	10 (76.9%)	
-> 5 mm	3 (9.4%)	3 (23.1%)	
Rotterdam IVH SAH n			0.011^a
-Present	11 (91.7%)	1 (7.7%)	
-Absent	21 (63.6)	12 (36.4)	
Rotterdam sum score + 1 (Median, IQR)	3.00 (2.00–3.00)	5.00 (4.00–5.00)	<0.0012^a
Rotterdam epidural mass lesion n			0.052 ^a
-Present	9 (28.1%)	2 (15.4%)	
-Absent	11 (32.4)	23 (67.6)	
Marshall CT score n			<0.001 ^a
-Diffuse injury I	3 (9.4%)	0 (0.0%)	
-Diffuse injury II	25 (78.1%)	3 (23.1%)	
-Diffuse injury IIIr	4 (12.5%)	7 (53.8%)	
-Diffuse injury IV	0 (0.0%)	1 (7.7%)	
-EML	0 (0.0%)	2 (15.4%)	
Helsinki CT score Total (Median, IQR)	2.00 (0.25–5.00)	7.00 (6.00–10.00)	<0.001^b
Helsinki IVH n			0.043 ^a
-Present	7 (21.9)	7 (53.8)	
-Absent	25 (80.6)	6 (19.4)	
Mass lesion size > 25 cm³, n	0 (??%)	2 (100%)	0.079 ^a
Helsinki suprasellar cisterns, n			<0.001 ^a
-Normal	20 (62.5%)	3 (23.1%)	
-Compressed	11 (34.4%)	2 (15.4%)	
-Obliterated	1 (3.1%)	8 (61.5%)	
NTBI - Hemorrhagic stroke	(n = 7)	(n = 4)	
ICH score	2.5 (2.0–3.25)	3.0 (0.0–3.0)	0.182

IVH intraventricular hemorrhage, SAH subarachnoid hemorrhage, IQR inter quartile range, ICH score intracerebral hemorrhage score.

^aChi-Square test; ^bMann-Whitney Test.

exhibited a *Poincaré* SD1/SD2 value greater than 0.27, and among them, 76.9% of them progressed to brain death ($p = 0.003$) (Supplementary Table 4). In patients with a PRISMIII score greater than 12, ten patients (25.0%) progressed to BD, with nine of them (90.0%) exhibiting a *Poincaré* SD1/SD2 value exceeding 0.27 (Supplementary Table 4).

DISCUSSION

This exploratory study revealed three major findings: (1) Tachycardia and hypotension were significantly associated with mortality in children with severe ABI; (2) HRV time and frequency domains were higher in severe ABI children who survived; (3) The non linear HRV measure *Poincaré* SD1/SD2 ratio has shown promise as a prognostic tool for predicting mortality in children with severe ABI.

The presence of tachycardia was significantly associated with mortality. Although, tachycardia itself may not directly cause death in ABI children it can serve as a marker for the severity and overall physiological instability.²⁶ The correlation between hypotension, tachycardia and mortality appears to be multifactorial in nature.^{27,28} In major trauma, a primary complication is hemorrhagic hypovolemia, which can result in hypotension and tachycardia, contributing to high mortality rates. Accordingly with other authors, we found that patients with SBP and MBP <5th percentile, had a greater percentage of in-hospital mortality ($p < 0.001$).^{2,29–31} Possible reasons association between mortality and hypotension may be attributed to the secondary damage inflicted on the injured brain by low blood pressure. Like Freeman et al., we also found a relation between early hypertension, SBP >P99th percentile, and a better outcome.^{32,33} These findings corroborate recent recommendations advocating for pediatric-specific SBP targets after TBI that prioritize higher percentiles of SBP, underscoring the importance of preventing low SBP in the initial hours after admission.^{33,34}

In children, the parasympathetic system generally has a stronger influence, leading to lower LF/HF ratios and higher *Poincaré* SD1/SD2 ratios compared to adults. Both measures are usually useful in understanding the autonomic regulation of HR, but they provide complementary insights. Many studies have linked decreased LF, HF, LF/HF ratio with BD and increased mortality in ABI patients.^{35–37} However, in our sample, we did not find a significant association between LF/HF and mortality. Biswas et al.⁴ studied 15 children with TBI and suggested a link between a lower LF/HF ratio and poor outcomes, also associating elevated ICP (>30 mmHg) or reduced CPP (<40 mmHg) with autonomic dysfunction. Although our data showed lower LF/HF in patients with ICP > 30 mmHg [0.67 (0.29–1.50) vs. 1.00 (0.28–4.55), $p = 0.411$] and CPP < 40 mmHg [0.53 (0.25–1.70) vs. 1.00 (0.28–4.50), $p = 0.507$], these differences were not significant. We also tested the LF/HF cutoff of 1.2 proposed by Butera et al., but found no significant impact on survival or mortality, even after excluding outliers and adjusting for age (data not shown).³⁸ The LF/HF ratio was a poor predictor of mortality, particularly when compared to *Poincaré* SD1/SD2, as supported by other studies.³⁹ Unlike studies that used daily mean LF/HF ratios over 72 h,⁴ our HRV values were derived from a single 10-minute segment, which may not have captured the full complexity of autonomic fluctuations. The ANS response in brain injury is non-linear and rapidly changing, making a single LF/HF ratio insufficient for comprehensive assessment.⁴⁰ Additionally, medications like sedatives and analgesics can affect the LF/HF ratio independently of autonomic function. Given the dynamic and multifactorial nature of autonomic dysfunction in ABI, along with external influences like medication and ventilation, the LF/HF ratio in our sample was not a reliable predictor of mortality. One advantage of *Poincaré* plot method is that nonstationary data can be included in the analysis.²⁴ Elevated values of *Poincaré* SD1/SD2 may indicate an increased parasympathetic activity and/or reduced sympathetic drive.^{41,42} Notably, outliers have less influence on the *Poincaré* plot compared to traditional time and frequency domain measures of HRV. Other nonlinear measures like SampEn were not different between groups supporting the idea that it is a less sensitive marker.^{43,44} In addition to the undeniable importance of the association between reduced HRV measures and mortality, our data also highlight the importance of increased HRV measures as a prognostic factor for survival in children with severe ABI, TBI and NTBI, conveying the idea that patients with dynamic and elevated HRV are protected against death.

Additionally, our study data confirms and supports the findings of other authors, further solidifying the association of several well-established variables with mortality following ABI, such as GCS, PRISM, pupil reactivity, ICP, and CPP.¹⁴

Our study has limitations: (1) The small sample size and heterogeneity, which make it challenging to draw meaningful

Table 4. PICU scoring systems and outcome.

PICU scoring systems	Survivals (n = 44)	Brain death (n = 28)	p value ^a
PRISMIII (median, IQR)	10.0 (7.0–13.75)	25.5 (20.5–28.0)	<0.001
≤12	28 (87.5%)	4 (12.5%)	
>12	16 (40.0%)	24 (60.0%)	
Probability of death (median, IQR)	0.055(0.03–0.13)	0.563 (0.43–0.63)	<0.001
PIM 3 (median, IQR)	3.4 (3.2–4.3)	60.7 (7.1–72.6)	<0.001
PELOD (median, IQR)	11.0 (4.2–11.0)	30.5 (21.0–31.0)	<0.001
SOFA_p (median, IQR)	4.00 (4.0–6.75)	7.0 (5.0–10.5)	<0.001
ISS (median, IQR)	20.5 (16.0–27.0)	25.0 (25.0–34.0)	0.032
PTS (median, IQR)	8.5 (7.0–9.0)	6.0 (4.5–7.0)	<0.001

PRISM III Pediatric Risk of Mortality Score, PIM-3 Pediatric Index Mortality 3, PELOD Pediatric Logistic Organ Dysfunction, pSOFA Pediatric Sequential Organ Failure Assessment, ISS injury severity score, PTS pediatric trauma scale, ISS injury severity score, IQR inter quartile range.

^aMann–Whitney test.

conclusions. This was a single center study that used a convenience small and highly heterogeneous sample collected over an extended period of time; we did not consider a potential influence on HRV analysis following interventions such as tracheal aspiration, transport or sedation bolus. (2) This exploratory study was based on short ECG segments analysis and the decision to choose only one segment of 10 min could impact the outcomes of HRV measurements, as the results may stem from physiological factors in some instances, but in others, they could be influenced by signal loss or the failure to detect R waves. The manual selection of epochs can also be a source of bias. Longer HRV time series, which contain enough information to address slower fluctuations and therefore pose different physiological mechanisms of regulation, were not explored in this work and should be assessed in future projects as well. (3) The lack of spectral band references in the heterogeneous pediatric population led us to choose to consider the bands of adults.³ (4) The unknown timing between the TBI and admission. Despite being the only unit in the northern region of the country to receive children with severe ABI and these are always transferred directly to us, we do not have exact data on the time elapsed between the injury and the ECG recording analyzed.

Further studies comparing the predictive power of HRV measures to other well-known ECG morphology indicators in adults, such as depressed ST segments, abnormal T waves, and prolonged QTc intervals, could strengthen the case for using tachogram measures in mortality prediction.

One weakness of our study is that the sample is not sufficient to accurately determine cutoff points for key HRV measures. However, we believe it is important to mention the cutoff value we found, if for no other reason than to serve as a starting point for further studies with larger and multicenter samples. We found that a threshold value of 0.27 *Poincaré* SD1/SD2 demonstrated a good discrimination. *Poincaré* SD1/SD2 ≥ 0.27 added to PRISM III value > 12 (the average value of the PRISM score to predict mortality¹⁴) significantly increased the ability to predict mortality.¹⁴ Though further validation in subsequent studies is necessary, this cutoff value may be used as another vital sign in the future. Other measures of HRV were related to survival, but no cutoff points were mentioned due to the small sample size and the influence of age and medication. Nonetheless, it has the potential to be a valuable tool for identifying patients with better outcomes, pending validation in additional studies. Many factors increase the HRV and provide protection against cardiac disease, mortality and sudden death.⁴⁵

Strengths from the present study includes: (1) a high resolution 12-lead ECG Holter recordings with 1000 Hz-sample frequency, which we consider could be more precise, than the usual sampling frequency acceptable for HRV analysis.⁴⁶ (2) A wide variety of physiological, analytical, imaging data, and severity scores were

studied, allowing for an extensive analysis of the factors that may interfere with the prognosis of ABI children. (3) The ability to identify significant differences between changes in HR, BP, and HRV linear and non-linear indexes, in the first hours after admission to the PICU, and mortality, underscores the relevance of these findings as early predictors of mortality in children with a severe neurologic condition independently of age, sex, BI mechanism and medication used. (4) The heterogeneity of the sample may present a limitation, but it also serves as an advantage by enhancing the robustness and validity of the findings.

CONCLUSIONS

Tachycardia, systolic hypotension and median hypo and hypertension in the first hours after PICU admission were significantly associated to mortality in children with severe ABI. HRV measurements are essential for assessing autonomic function and cardiovascular health in children severely affected by ABI. High HRV values can serve as a prognostic factor for survival, conveying the idea that patients with dynamic and elevated HRV are protected against death. While further validation through larger, multicenter studies is necessary, the *Poincaré* SD1/SD2 ratio has shown promise as a prognostic tool for predicting mortality in children with severe ABI.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

- Johnson, A. R., DeMatt, E. & Salorio, C. F. Predictors of outcome following acquired brain injury in children. *Dev. Disabil. Res. Rev.* **15**, 124–132 (2009).
- Silva, M. J., Carneiro, B., Mota, R. & Baptista, M. J. Cardiovascular events in children with brain injury: A systematic review. *Int. J. Cardiol.* **387**, 1–10 (2023).
- Johnston, B. W., Barrett-Jolley, R., Krige, A. & Welters, I. D. Heart rate variability: Measurement and emerging use in critical care medicine. *J. Intensive Care Soc.* **21**, 148–157 (2020).
- Biswas, A. K., Scott, W. A. & Sommerauer, J. F. Heart rate variability after acute traumatic brain injury in children. *Crit Care Med.* **28**, 3907–3912 (2000).
- Francesco, B. et al. Linear and nonlinear heart rate variability indexes in clinical practice. *Comput. Math Methods Med.* **2012**, 219080 (2012).
- Sassi, R. et al. Advances in heart rate variability signal analysis: Joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace* **17**, 1341–1353 (2015).
- Taralov, Z. Z., Terziyski, K. V. & Kostianev, S. S. Heart rate variability as a method for assessment of the autonomic nervous system and the adaptations to different

- physiological and pathological conditions. *Folia Med. (Plovdiv)*. **57**, 173–180 (2015).
8. Martínez, J. P., Almeida, R., Olmos, S., Rocha, A. P. & Laguna, P. A Wavelet-based ECG delineator evaluation on standard databases. *IEEE Trans. Biomed. Eng.* **51**, 570–581 (2004).
 9. Martin, B., DeWitt, P. E., Albers, D. & Bennett, T. D. Development of a pediatric blood pressure percentile tool for clinical decision support. *JAMA Netw. Open*. **5**, 10 (2022).
 10. Fleming, S. et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. *Lancet* **377**, 1011–1018 (2011).
 11. Pollack, M. M., Patel, K. M. & Ruttimann, U. E. PRISM III: An updated pediatric risk of mortality score. *Crit. Care Med.* **24**, 743–752 (1996).
 12. Casertano, A. et al. An overview of hypoglycemia in children including a comprehensive practical diagnostic flowchart for clinical Use. *Front Endocrinol (Lausanne)* **12** (2021).
 13. Balakrishnan, B. et al. GCS-pupil score has a stronger association with mortality and poor functional outcome than GCS alone in pediatric severe traumatic brain injury. *Pediatr. Neurosurg.* **56**, 432–439 (2021).
 14. Anjali, M. M. & Unnikrishnan, D. T. Effectiveness of PRISM III score in predicting the severity of illness and mortality of children admitted to pediatric intensive care unit: a cross-sectional study. *Egypt. Pediatr. Assoc. Gaz.* **71**, 1–6 (2023).
 15. Beslow, L. A. et al. Pediatric intracerebral hemorrhage score: a simple grading scale for intracerebral hemorrhage in children. *Stroke* **45**, 66–70 (2014).
 16. Ryu, J. A. et al. Prognostic value of computed tomography score in patients after extracorporeal cardiopulmonary resuscitation. *Crit. Care*. **22**, 323 (2018).
 17. Nakagawa, T. A. et al. Clinical report - Guidelines for the determination of brain death in infants and children: An update of the 1987 task force recommendations. *Pediatrics* **128**, 2139–2155 (2011).
 18. Gonçalves, H., Rocha, A. P., Ayres-De-Campos, D. & Bernardes, J. Internal versus external intrapartum foetal heart rate monitoring: The effect on linear and nonlinear parameters. *Physiol. Meas.* **27**, 307–319 (2006).
 19. Yentes, J. M. et al. The appropriate use of approximate entropy and sample entropy with short data sets. *Ann. Biomed. Eng.* **41**, 349–365 (2013).
 20. McCamley, J. D., Denton, W., Arnold, A., Raffalt, P. C. & Yentes, J. M. On the calculation of sample entropy using continuous and discrete human gait data. *Entropy* **20**, 10 (2018).
 21. Novak, V., Saul, J. P. & Eckberg, D. L. Task Force report on heart rate variability. *Circulation* **96**, 1056–1057 (1997).
 22. Hayes, M. H. *Statistical Digital Signal Processing and Modelling*. (John Wiley & Sons, New York, 1996).
 23. Richman, J. S. & Moorman, J. R. Physiological time-series analysis using approximate entropy and sample entropy. *Am. J. Physiol. Heart Circ. Physiol.* **278**, H2039–H2049 (2000).
 24. Uzun, I. S., Asyali, M. H., Celebi, G. & Pehlivan, M. Nonlinear analysis of heart rate variability. *Annu. Int. Conf. IEEE Eng. Med. Biol.-Proc.* **2**, 1581–1584 (2001).
 25. Pincus, S. M. Approximate entropy as a measure of system complexity. *Proc. Natl Acad. Sci. USA* **88**, 2297–2301 (1991).
 26. Brasel, K., Guse, C., Gentilello, L. & Nirula, R. HR in TBI 2007 abstract. *J. Trauma*. **62**, 812–817 (2007).
 27. Reisner, A., Chen, X., Kumar, K. & Reifman, J. Prehospital heart rate and blood pressure increase the positive predictive value of the glasgow coma scale for high-mortality traumatic brain injury. *J. Neurotrauma* **31**, 906–913 (2014).
 28. Victorino, G. P., Battistella, F. D. & Wisner, D. H. Does tachycardia correlate with hypotension after trauma? *J. Am. Coll. Surg.* **196**, 679–684 (2003).
 29. Yao, S. H. W., Chong, S. L., James, V., Lee, K. P. & Ong, G. Y. K. Associations of initial haemodynamic profiles and neurological outcomes in children with traumatic brain injury: A secondary analysis. *Emerg. Med. J.* **39**, 527–533 (2022).
 30. Suttipongkaset, P. et al. Blood pressure thresholds and mortality in pediatric traumatic brain injury. *Pediatrics* **142**, 2 (2018).
 31. Erickson, S. L., Killien, E. Y., Wainwright, M., Mills, B. & Vavilala, M. S. Mean arterial pressure and discharge outcomes in severe pediatric traumatic brain injury. *Neurocrit Care*. **34**, 1017–1025 (2021).
 32. Freeman, A. D. et al. Does hypertension at initial presentation adversely affect outcomes in pediatric traumatic brain injury? *J. Pediatr. Surg.* **55**, 702–706 (2020).
 33. Lulla, A. et al. Prehospital guidelines for the management of traumatic brain injury.; 273rd Edition. *Prehosp. Emerg. Care*. **27**, 507–538 (2023).
 34. Lui, A., Kumar, K. K. & Grant, G. A. Management of severe traumatic brain injury in pediatric patients. *Front. Toxicol.* **24**, 1–14 (2022).
 35. Rapenne, T. et al. Could heart rate variability predict outcome in patients with severe head injury? A pilot study. *J. Neurosurg. Anesthesiol.* **13**, 260–268 (2001).
 36. Rapenne, T. et al. Could heart rate variability analysis become an early predictor of imminent brain death? A pilot study. *Anesth. Analg.* **91**, 329–336 (2000).
 37. Florez-Perdomo, W. A. et al. A systematic review and meta-analysis on effect of beta-blockers in severe traumatic brain injury. *Neurol. Res.* **43**, 609–615 (2021).
 38. Butera, G., Bonnet, D., Kachaner, J., Sidi, D. & Villain, E. Heart rate variability in children with hypertrophic cardiomyopathy. *Heart* **89**, 205–206 (2003).
 39. Bhogal, A. S. et al. Which heart rate variability index is an independent predictor of mortality in cirrhosis? *Digestive Liver Dis.* **51**, 695–702 (2019).
 40. Milecević, G. Low to high frequency ratio of heart rate variability spectra fails to describe sympatho-vagal balance in cardiac patients. *Coll. Antropol.* **29**, 295–300 (2005).
 41. Toichi, M., Sugiura, T., Murai, T. & Sengoku, A. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. *J. Auton. Nerv. Syst.* **62**, 79–84 (1997).
 42. Guzik, P. et al. Correlations between the Poincaré plot and conventional heart rate variability parameters assessed during paced breathing. *J. Physiol. Sci.* **57**, 63–71 (2007).
 43. Piantino, J. A. et al. Early heart rate variability and electroencephalographic abnormalities in acutely brain-injured children who progress to brain death*. *Pediatr. Crit. Care Med.* **20**, 38–46 (2019).
 44. Henriques, T. et al. Nonlinear methods most applied to heart-rate time series: A review. *Entropy* **22**, 309 (2020).
 45. Serafi, A. S. Heart rate variability rate (HRV) – analysis and clinical significance. *Int. J. Biol. Biotech.* **15**, 193–199 (2018).
 46. Kwon, O. et al. Electrocardiogram sampling frequency range acceptable for heart rate variability analysis. *Health. Inf. Res.* **24**, 198–206 (2018).

ACKNOWLEDGEMENTS

A.P.R., partially supported by CMUP, member of LASI, which is financed by national funds through FCT—Fundação para a Ciência e a Tecnologia, I.P., under the projects with reference UIDB/00144/2020 and UIDP/00144/2020.

AUTHOR CONTRIBUTIONS

Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data—M.J.S.; H.G.; R.A.; C.C.D.; A.I.A.; C.G.; A.P.R.; I.A. Drafting the article or revising it critically for important intellectual content—M.J.S.; M.J.B.; C.G.; R.A.; H.G.; C.C.D. Final approval of the version to be published—M.J.S.; I.A.; C.G.; M.J.B.; A.P.R.; R.A.; C.C.D.; H.G.

COMPETING INTERESTS

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41390-024-03679-2>.

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Supplemental Table 1.

Patient characteristics and physiologic data at the first 12 hours after PICU admission and differences according to the diagnosis.

Patient characteristics and physiologic data	TBI (n=45)	NTBI (n=27)	p- value
Median Age (IQR) at admission	136.0 (69.0-165.0)	120.0 (26.0-165.0)	0.436 ^b
Sex	36 male (80.0%)	15 male (55.6%)	0.035 ^a
Age group, n			
<=2 years	4 (8.9%)	6 (22.2%)	0.141 ^a
>2years ≤12 years	24 (53.3%)	11 (40.7%)	
>12 years	17 (37.8%)	10 (37.0%)	
Mortality (n, %)	13 (28.9%)	15 (55.5%)	0.045 ^b
GCS P (median, IQR)	6.0 (3.0-7.0)	4.0 (1.0-6.0)	0.058 ^b
Pupils, n			
-Both reactive	28 (62.2%)	11 (40.7%)	0.057 ^a
-Anisocoria	5 (11.1%)	3 (11.1%)	
-Mydriasis	12 (16.7%)	13 (48.1%)	
ICP (mmHg) Median (IQR)			
-Admission	16.0 (12.0-34.5)	26.0 (14.0-48.0)	0.348 ^b
CPP (mmHg) Median (IQR)			
-Admission	60.0 (50.0-68.2)	58.0 (30.0-71.0)	0.924 ^b
Minimum SBP (mmHg), n			
< P10	16 (35.6%)	11 (40.7%)	0.802 ^a
>P10	29 (64.4%)	16 (35.6%)	
Maximum SBP (mmHg), n			
<P99	11 (24.4%)	12 (44.4%)	0.117 ^a
>P99	34 (75.6%)	15 (55.6%)	
Minimum MBP (mmHg), n			
< P5	7 (15.6%)	8 (29.6%)	0.230 ^a
>P5	38 (84.4%)	19 (70.4%)	
Maximum MBP (mmHg), n			
<P95	31 (68.9%)	14 (51.9%)	0.462 ^a
>P95	14 (31.1%)	13 (48.1%)	
Maximum DBP (mmHg), n			
<P99	35 (77.8%)	17 (63.0%)	0.177 ^a
>P99	10 (22.2%)	10 (37.0%)	
Tachycardia, n			
-Yes	20 (44.4%)	14 (51.9%)	0.629 ^a
-No	25 (55.6%)	13 (48.1%)	
Mechanical ventilation days (Median, IQR)	7.0 (4.0-10.0)	5.5 (2.0-15.2)	0.751 ^b
Days on vasoactive drugs (Median, IQR)	5.0 (2.0-6.7)	2.0 (0.5-7.0)	0.124 ^b
PICU Length of stay Observed (days)			
(Median, IQR)	8.0 (5.2-12.0)	5.5 (2.0-16.0)	0.354 ^b
PRISM III (Median, IQR)	13.0 (7.5-22.0)	17.0 (7.0-24.0)	0.545 ^b
Death probability (Median, IQR)	1.3 (1.3-23.4)	20.7 (1.3-84.0)	0.047 ^b
PELOD (Median, IQR)	11.0 (11.0-21.5)	21.0 (11.0-31.0)	0.040 ^b
SOFAp (Median, IQR)	6.0 (4.0-8.0)	5.0 (4.0-7.0)	0.520 ^b

Supplemental Table 1 (continued).

Patient characteristics and physiologic data	TBI (n=45)	NTBI (n=27)	p- value
Under medication (n, %)			
Midazolam	42 (93.3%)	19 (70.4%)	0.015^a
Fentanyl	39 (86.7%)	15 (55.6%)	0.005^a
Propofol	10 (22.2%)	6 (22.2%)	1.00 ^a
Thiopental	8 (17.8%)	11 (40.7%)	0.052 ^a
HRV measures (Median, IQR)			
SDNN	10.13 (5.23-31.24)	6.30 (3.69-14.60)	0.088 ^b
RMSDD	2.39 (1.27-6.70)	1.52 (0.84-4.18)	0.040^b
Mean RR	639.51 (8537.56-835.48)	561.76 (461.70-718.58)	0.242 ^b
TP median	78.23 (15.50-674.42)	15.36 (5.45-120.76)	0.019^b
VLF	17.62 (4.34-162.03)	6.59 (1.25-22.41)	0.025^b
LF	12.78 (3.44-147.38)	1.92 (0.38-16.09)	0.007^b
LFn	30.90 (16.78-71.87)	20.25 (7.77-47.82)	0.110 ^b
HF	9.34 (1.94-92.15)	2.59 (0.34-15.02)	0.033^b
HFn	36.13 (12.99-53.28)	56.72 (8.60-73.19)	0.589 ^b
LF/HF	0.98 (0.49-3.90)	0.31 (0.22-3.49)	0.252 ^b
HF+	19.43 (4.07-167.51)	5.11 (2.68-44.38)	0.072 ^b
SampEn2, 0.1	0.92 (0.79-1.22)	1.00 (0.76-1.19)	0.977 ^b
SampEn2, 0.15	0.70 (0.63-0.93)	0.79 (0.57-0.95)	0.714 ^b
SampEn2, 0.2	0.68 (0.53-0.78)	0.68 (0.49-0.80)	0.507 ^b
Poincaré SD1	1.69 (0.90-4.74)	1.07 (0.59-2.83)	0.037^b
Poincaré SD2	14.25 (7.26-43.80)	8.89 (5.08-20.56)	0.088 ^b
Poincaré SD1/SD2	0.14 (0.09-0.25)	0.16 (0.08-0.21)	0.680 ^b

^a Chi-Square test; ^b Mann-Whitney-test

Supplemental Table 2. HRV measurements in suspected brain death at admission (GCS=3 and mydriasis) and outcome (n=19).

HRV measurements median (IQR)	Survived (n=3)	Brain Death (n=16)	p-value^a
SDNN	39.17 (31.24-39.17)	4.75 (2.22-8.62)	0.014
RMSDD	9.48 (8.21-9.48)	1.10 (0.59-1.99)	0.007
Mean NN	909.76 (705.87-909.76)	503.41 (443.13-663.31)	0.010
TP	1077.95 (826.99-1077.95)	10.69 (1.70-25.95)	0.010
VLF	579.41 (192.19-579.41)	2.25 (0.44-8.54)	0.014
LF	264.44 (160.78-264.44)	0.63 (0.11-3.24)	0.014
LFn	41.65 (32.25-41.65)	23.34 (3.03-46.55)	0.260
HF	333.13 (313.14-333.14)	0.37 (0.13-5.99)	0.007
HF_n	52.48 (49.70-52.48)	0.89 (0.266-6.76)	0.140
HF+	370.34 (337.74-370.34)	3.15 (0.50-17.32)	0.019
LF/HF	0.79 (0.51-0.79)	0.89 (0.26-6.76)	0.910
SampEn 2,0.1	0.79 (0.59-0.79)	0.83 (0.74-1.43)	0.500
SampEn 2,0.15	0.64 (0.47-0.64)	0.72 (0.56-1.15)	0.460
SampEn 2,0.2	0.54 (0.39-0.54)	0.60 (0.42-0.98)	0.530
Poincaré SD1	6.70 (5.80-6.70)	0.77 (0.42-1.40)	0.007
Poincaré SD2	54.98 (43.80-54.90)	6.64 (2.77-11.41)	0.014
Poincaré SD1/SD2	0.122 (0.07-0.12)	0.20 (0.09-0.34)	0.310

^a Mann-Whitney test

Supplemental Table 3.

Other patient characteristics and physiologic data at the first 12 hours after PICU admission and differences between the survivors and non-survivors.

Patient characteristics and physiologic data	Survivals (n=44)	Brain Death (n=28)	p- value
Weight in Kg, Median (IQR)	36.5 (22.0-51.5)	29.0 (12.0-42.2)	0.188 ^b
GCS Median (IQR)	6 (5-8)	3 (3-4.75)	< 0.001 ^b
SBP Median (IQR)			
-Minimum	97.5 (82.5-104.0)	82.0 (62.0-89.5)	<0.001 ^b
-Maximum	136.0 (123.0-142.0)	126.5 (110.5-153.7)	0.993 ^b
MBP Median (IQR)			
-Minimum	72.0 (61.0-80.0)	63.0 (55.75-75.50)	0.075 ^b
-Maximum	85.0 (78.5-96.0)	91.5 (82.5-108.5)	0.004 ^b
DBP Median (IQR)			
-Maximum	72.5 (63.5-80.0)	75.0 (66.2-91.0)	0.034 ^b
HR Median (IQR)			
-Admission	95.0 (76.0-112.0)	110.0 (83.5-135.0)	0.047 ^b
-Minimum	73.5 (65.2-92.0)	98.0 (61.2-124.0)	0.045 ^b
-Maximum	119(102.5-136.5)	157.5 (127.5-170)	<0.001 ^b
Bradycardia , n (%)			
-Yes	24 (70.1%)	10 (29.4%)	0.149 ^a
-No	20 (52.6%)	18 (47.4%)	
RR Median (IQR)			
-Admission	18 (15-20)	18 (15.5-21.5)	0.820 ^b
-Minimum	17.0 (14.0-20.0)	18.0 (12.0-20.0)	0.683 ^b
-Maximum	22 (18.5-28)	24.5 (20.2-29.5)	0.307 ^b
Lactate (mmol/L) Median (IQR)	1.4 (.7-3.2)	2.2 (1.5-3.9)	0.15 ^b
PCO2 (mmHg) Median (IQR)			
-Minimum	29.8 (26.4-32)	28 (24.2-31.7)	0.315 ^b
-Maximum	39.3 (34-44.9)	38.3 (36.2-51.5)	0.145 ^b
Minimum PaO2 (mmHg) Median (IQR)	120.8 (97.1-145.0)	111.6 (86.2-155.0)	0.560 ^b
Bicarbonate (mmol/L) Median (IQR)			
-Minimum	19.6 (18-20.7)	18.3 (16.1-20.8)	0.071 ^b
-Maximum	22.5 (20-23.7)	21.6 (19.4-23.0)	0.496 ^b
pH Median (IQR)			
-Minimum	7.34 (7.30-7.40)	7.32 (7.19-7.42)	0.046 ^b
-Maximum	7.44 (7.41-7.49)	7.45 (7.38-7.52)	0.518 ^b
Na (mmol/L) Median (IQR)			
-Minimum	139 (138-140.5)	138.5 (135.5-140)	0.931 ^b
-Maximum	141 (139-144)	145.5 (142-151.7)	0.002 ^b
K (mmol/L) Median (IQR)			
-Minimum	3.4 (3.0-3.8)	3.3 (3.1-3.8)	0.725 ^b
-Maximum	4 (3.8-4.2)	4.3 (3.8-4.7)	0.085 ^b
Higher BUN (mmol/L) Median (IQR)	12.8 (10.7-16.5)	14.2 (10.8-20.3)	0.059 ^b
Creatinine (mg/dL) Median (IQR)			
-Maximum	0.5 (0.39-0.70)	0.5 (0.35-0.77)	0.559 ^b

Supplemental Table 3 (continued).

Patient characteristics and physiologic data	Survivals (n=44)	Brain Death (n=28)	p- value
Glucose (mg/dL) Median (IQR)			
-Minimum	109 (97-117)	133 (97.5-153)	0.019^b
-Maximum	144.5 (118.5-183.2)	194.0 (162-246.7)	<0.001^b
Ca⁺⁺ (mmol/L) Median (IQR)			
-Minimum	1.12 (1.09-1.18)	1.08 (1.01-1.18)	0.083 ^b
-Maximum	1.20 (1.17-1.25)	1.24 (1.18-1.31)	0.009^b
Total bilirubin (mg/dL) Median (IQR)			
-Maximum	0.48 (0.35-0.59)	0.44 (0.33-0.62)	0.324 ^b
Hemoglobin (mg/dL) Median (IQR)			
-Minimum	9.8 (8.5-10.8)	9.9 (8.5-12.69)	0.420 ^b
-Maximum	11.5 (10.45-12.5)	11.4 (10.2-13.1)	0.724 ^b
WBC count (cellsx10⁹/L) Median (IQR)			
-Minimum	12.29 (8.40-14.28)	14.01 (9.43-17.04)	0.363 ^b
-Maximum	17.98 (13.45-22.72)	17.79 (13.23-22.50)	0.784 ^b
Platelet count (cellsx10⁹/L) Median (IQR)			
-Minimum	201 (157.7-247)	191.2 (104-223.5)	0.816 ^b
-Maximum	238.5 (203.5-266)	225.5 (151-322.7)	0.715 ^b
Body temperature (°C), n			
<35 °C	9 (31.0%)	20 (69.0%)	<0.001^a
35-38°C	21 (80.8%)	5 (19.2%)	
>38°C	14 (82.4%)	3 (17.6%)	
C Protein (mg/dL) median (IQR)			
-Admission	10 (2-35.7)	17.4 (2.7-105.2)	0.036^b
Glycemia (mg/dL), n			
< 60	0 (0%)	0 (0%)	0.003^a
≥60 ≤ 180	32 (76.2%)	10 (23.8%)	
> 180 mg/dL	12 (40.0%)	18 (60.0%)	
Higher PTT (seconds) Median (IQR)			
	14.35 (13.27-15.42)	16.3 (13.42-18.85)	0.016^b
Higher PT (seconds) Median (IQR)			
	30.65 (26.05-32.85)	36.3 (29.47-47.17)	0.666 ^b
EVD placement, n			
-Yes	5 (33.3%)	10 (66.7%)	0.007^a
- No	39 (68.4%)	18 (31.6%)	
Decompressive craniotomy, n			
-Yes	8 (72.7%)	3 (27.3%)	0.51 ^a
- No	36 (59.0)	25 (41.0%)	
Sedation, n			
-Yes	44 (65.7%)	23 (34.3%)	0.070 ^a
-No	0 (0%)	5 (100%)	
Catecholamines, n			
-Yes	20 (47.6%)	22 (52.4%)	0.007^a
- No	24 (80.0%)	6 (20.0%)	
Midazolan, n			
-Yes	42 (68.9 %)	19 (31.1%)	0.002^a
-No	2 (18.2%)	9 (81.8%)	

Supplemental Table 3 (continued).

Patient characteristics and physiologic data	Survivals (n=44)	Brain Death (n=28)	p- value
Tiopental, n			
-Yes	14 (73.7%)	5 (26.3%)	0.150 ^a
-No	30 (56.6%)	23 (43.4%)	
Propofol, n			
-Yes	8 (50.0%)	8 (50.0%)	0.227 ^a
-No	36 (64.3%)	20 (35.7%)	
Fentanil, n			
-Yes	38 (70.4%)	16 (29.6%)	0.011^a
-No	6 (33.3%)	12 (66.7%)	
Rocuronium, n			
-Yes	17 (81.0%)	4 (19.0%)	0.023^a
-No	27 (52.9%)	24 (47.1%)	
Dopamine, n			
-Yes	4 (28.6%)	10 (71.4%)	0.012^a
-No	40 (69.0% %)	18 (31.0%)	
Noradrenaline, n			
-Yes	16 (48.5%)	17 (51.5%)	0.037^a
-No	28 (71.8%)	11 (28.2%)	
Adrenaline, n			
-Yes	2 (66.7%)	1 (33.3%)	0.666 ^a
-No	42 (60.9%)	27 (39.1%)	

^a Chi-Square test; ^b Mann-Whitney-test

Supplemental Table 4. Relation between *Poincaré* SD1/SD2 cutoff values and outcome.

Outcome and prognostic tools		<i>Poincaré</i> SD1/SD2		p-value
		≤0.27 (n= 59)	>0.27 (n=13)	
Survived		*	*	
-Yes		41 (69.5%)	3 (23.1%)	0.003^a
-No		18 (30.5%)	10 (76.9%)	
PRISM III (median, IQR)		13 (7-20)	23 (10.5-27.5)	0.035^b
PRISM III ≤ 12 (n=32)	Survived	26 (44.1%)	2 (15.4%)	0.340 ^a
	BD	3 (5.1%)	1 (7.7%)	
PRISM III >12 (n= 40)	Survived	15 (25.4%)	1 (7.7%)	0.027^a
	BD	15 (25.4%)	9 (69.2%)	

^a Chi Square test; ^b Mann-Whitney test. PRISM III- Pediatric Risk of Mortality;

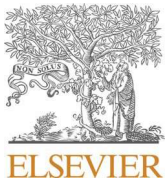
3.5 Paper V

The role of early cardiovascular response after severe acute brain injury in children in long-term prognosis – a pilot study.

Silva, MJ; Gonçalves, H; Almeida, R; Camila, C; Almeida, AI; Rocha, AP; Granja, C; Baptista, MJ; Azevedo, I.

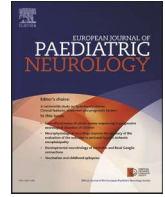
European Journal of Paediatric Neurology 56 (2025): 38-45.

<https://doi.org/10.1016/j.ejpn.2025.04.009>



Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Original article

The role of cardiovascular response as a predictor of neurologic disability in children with brain injury – a pilot study

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ARTICLE INFO

Keywords:

Brain injury

Prognosis

Outcome

Morbidity

Disability

Children

Heart rate variability

Blood pressure

Heart rate

ABSTRACT

Objective: We aimed to assess medium-to long-term neurological outcomes in children with severe acute brain injury (ABI) and to identify cardiovascular predictors associated with unfavorable outcomes, such as heart rate (HR), blood pressure (BP), and heart rate variability (HRV). HRV refers to the oscillations in the intervals between consecutive heartbeats, reflecting the dynamic interplay between sympathetic and parasympathetic impulses to the heart. It provides a non-invasive indicator of autonomic nervous system (ANS) activity.

Design: Prospective observational cohort.

Setting: Tertiary academic pediatric intensive care unit (PICU).

Patients: Children >27 days and <18 years old admitted to the PICU after severe ABI who survived to PICU discharge. Children suspected of being brain dead at PICU admission or with cardiac arrhythmias were excluded.

Interventions: None.

Measure: ments: Physiological variables, neurological data, chemistry and hematologic tests and medication were collected within the initial 12 h following admission to the PICU. Linear and nonlinear indices of HRV obtained from electrocardiogram (ECG) Holter recordings, computerized tomography (CT) and PICU scores, as well as survival rates within the PICU, were evaluated. The primary outcome measure was global functional outcome as measured by the Pediatrics Glasgow Outcome Scale Extended (GOSE-Peds) at 3 and 12 months after injury. These data were taken by reviewing the medical records. The outcome was dichotomized into favorable and unfavorable based on predefined cutoffs. None to mild disability (GOSE-E PEDS category ≤2) was categorized as favorable outcome, whereas moderate to severe disability was categorized as unfavorable (GOSE-E PEDS category ≥3).

Main results: Thirty-one children with ABI were eligible for the study. Twenty-four were male (77.4 %) and they had the median age of 11.3 years old (IQR 5.6–14.3). Twenty-two (71.0 %) patients had traumatic brain injury (TBI) and five (16.1 %) cerebral hemorrhage. Sixteen children (51.6 %) had a favorable outcome at 3 months and twenty-one (67.7 %) at 12 months. The presence of tachycardia or bradycardia was not related to the prognosis. Patients with systolic arterial blood pressure (SBP) above the 95th percentile in the first 12 h after admission to the PICU exhibited a significantly better neurological outcome [15 (68.2 %) vs. 9 (31.8 %), $p = 0.006$] at 3 months, and [20 (83.3 %) vs. 4 (16.7 %), $p = 0.002$] at 12 months. Calculated HRV values were higher, both on

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<https://doi.org/10.1016/j.ejpn.2025.04.009>

Received 11 December 2024; Received in revised form 15 April 2025; Accepted 17 April 2025

Available online 19 April 2025

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admission and 12 h after admission, in patients with a favorable prognosis at 3 and 12 months. However, these results were statistically significant only for RMSSD, LF, TP, and *Poincaré* SD1 and SD2 at 12 h after admission and for outcomes at 3 months. Patients with $LF > 70.0 \text{ ms}^2$ at 12 h after admission had a significantly better outcome at 12 months [11.0 (91.7 %) vs 1.0 (8.3 %), $p = 0.046$]. 87.5 % of patients with $SDNN > 35.0 \text{ ms}$ and 70.5 % of patients with $RMSSD > 3.2 \text{ ms}$, at 12 h after admission, showed a statistically significant better outcome at 3 months. Patients who had a more unfavorable prognosis spent significantly more time on mechanical ventilation and had a longer length of stay (LOS) in the PICU.

Conclusions: This study suggests that elevated early SBP and HRV indices—particularly LF power measured 12 h after PICU admission—may serve as independent, non-invasive predictors of long-term neurological outcomes in children with severe ABI. These findings support the role of early autonomic activation as a marker of favorable prognosis and underscore the potential value of incorporating cardiovascular and autonomic monitoring into prognostic models and individualized neuroprotective strategies in pediatric neurocritical care.

1. Introduction

Acute acquired brain injury (ABI) refers to any sudden damage to the brain that occurs after birth, caused by either traumatic or non-traumatic factors. These injuries lead to an abrupt disruption of brain function, with symptoms that vary depending on the injury's severity and the affected brain regions. ABI can be categorized into traumatic brain injury (TBI) and non-traumatic brain injury (NTBI). NTBI includes conditions such as stroke, subarachnoid hemorrhage, hypoxic or anoxic brain injury, central nervous system infections (e.g., meningitis or encephalitis), and metabolic or toxic insults. There is an increasing need for reliable, early predictors of neurological outcomes in children following these types of brain injuries, as timely and accurate prognostication is crucial for guiding treatment and rehabilitation strategies [1,2].

Cardiovascular abnormalities, like heart rate (HR), blood pressure (BP) and heart rate variability (HRV), arising from brain injury, may have a role as prognostic factors [1,3]. HRV is a simple, widely used non-invasive measure of the cardiac autonomic nervous system (ANS), indicating heart-brain interactions and potentially assessing functional outcomes [4,5]. Studies link increased HRV with better neurological functions in adults with ABI [5]. HRV research, as defined by the Task Force, traditionally relies on linear time-domain and frequency-domain methods to assess physiological states, psychological conditions, and various pathologies. These approaches offer valuable insights into ANS regulation and its impact on health, providing a framework for understanding the relationship between HRV and both normal and abnormal physiological processes [6,7]. While linear methods remain well-established and are widely regarded as the “gold standard” in HRV analysis, non-linear methods are less frequently employed in clinical practice. However, non-linear approaches have the potential to provide additional insights into autonomic regulation, especially in more complex or dynamic conditions. These methods can uncover aspects of HRV that linear techniques may miss, thus offering complementary perspectives. While linear analysis remains essential, the growing use of non-linear methods is emphasizing their increasing importance in advancing our understanding of HRV and its clinical relevance. These techniques hold promise in elucidating the intricate interactions between the parasympathetic and sympathetic nervous systems, offering a more detailed and comprehensive understanding of R-R interval variations [7,8].

HRV measurements are essential for assessing ANS function and cardiovascular health in children severely affected by ABI. In a previous study, the authors examined 72 children with severe ABI and found that tachycardia, systolic hypotension, and median hypo- and hypertension during the first hours after PICU admission were significantly associated with mortality. Additionally, they discovered that higher HRV values acted as a prognostic factor for survival, suggesting that patients with dynamic and elevated HRV are better protected against death [1].

Improvements in the immediate care of ABI decrease the risk of death but can result in various levels of functional impairment, thereby increasing the rehabilitation requirements for survivors. The ability to

foresee the medium-to-long-term outcome trajectory assists clinicians in setting priorities and refining the approach to customize rehabilitation needs for each patient. Children are extremely vulnerable to internal and external insults such as ischemia, hypoxia, traumatic force and infection.

This study evaluated the prognostic value of cardiovascular monitoring at PICU admission in children with severe ABI (both traumatic and non-traumatic). Specifically, it tracked heart rate (HR), blood pressure (BP), and both linear and non-linear HRV measures, aiming to provide valuable early prognostic tools for predicting neurological outcomes (GOSE-E Peds) at 3 and 12 months. The study also compared these measures with other established prognostic factors.

2. Material and methods

The procedures followed were in accordance with the ethical standards of the responsible institute committee on human experimentation and with the Helsinki Declaration of 1975. This study, titled *Analysis of cardiovascular variability in critical illness: follow-up and prognosis*, was approved by the institutional Ethic Commission and by the Portuguese data protection authority (IRB number: 19776) on July 27, 2006. Parents have given signed informed consent for inclusion of their children in the database.

2.1. Study site

The PICU of São João University Hospital Center is a single tertiary multidisciplinary 10-bed pediatric critical care unit, serving both medical and surgical specialties.

2.2. Study population

Children aged more than 27 days and less than 18 years-old, admitted to the PICU with ABI, from January 2006 to December 2017 were prospectively screened for recruitment. Patients were included if they had PICU length of stay (LOS) > 12 h and survived to PICU discharge.

Exclusion criteria: moderate or severe neurologic disability pre-ABI, suspected brain dead (BD) at admission (defined as Glasgow Coma Scale 3 and mydriasis) [9,10], congenital heart disease, cardiac arrhythmias, previous epilepsy, diabetes mellitus or other peripheral neurologic impairment.

Patients who met the selection criteria were included if there was the possibility of obtaining an electrocardiographic record upon admission and after 12 h by a member of the research team and if it was feasible to assess the GOSE E-Peds through clinical records up to 12 months after discharge from the PICU.

2.3. Data collection and management

Physiologic data was collected from the admission record and registered in the first 12 h. Baseline data collected after PICU admission included age, weight, prior medical history and admission diagnoses,

and heart rate (HR), respiratory rate (RR), blood pressure (BP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), pupillary light reactivity, and body temperature registered hourly during the Holter registration. The minimum and maximum values recorded during each hour were used.

BP was recorded and classified into the following percentiles based on age and gender: ≤ 5 th, 5th–95th and ≥ 95 th, using previously published percentiles [11]. Tachycardia was defined as follows: ≥ 180 cpm for those under 12 months old; ≥ 140 bpm for individuals aged 12 months to 10 years; and ≥ 120 bpm for those over 10 years old. Bradycardia was defined as HR < 100 bpm for those ≤ 12 months old; < 70 bpm for individuals aged 1–10 years; and < 60 bpm for those over 10 years old [12,13]. Hypothermia was defined when core temperature was below 35 °C and hyperthermia when it was higher than 38 °C. Hypoglycemia was defined as < 60 mg/dL and hyperglycemia > 180 mg/dL [14]. PICU scoring systems - Pediatric Risk of Mortality Score (PRISM III) and Probability of Death, Glasgow Coma Scale (GCS) and GCS-Pupil Score at admission, Pediatric Index Mortality 3 (PIM -3), Pediatric Logistic Organ Dysfunction (PELOD), Pediatric Sequential Organ Failure Assessment (pSOFA), Injury Severity Score (ISS) and Pediatric Trauma Scale (PTS) were calculated and registered in the first 12 h after admission [15,16]. High-resolution 12-lead ECG Holter recordings (1000 Hz sample frequency) were taken within the first 12 h after admission. ECG recordings were automatically annotated using a wavelet-based system previously developed and validated [17]. CT images of all the patients were reviewed by a neuroradiologist, who classified them according to different CT scoring systems based on the type of intracranial injury [18–21]. In patients with traumatic brain injury (TBI) Rotterdam, Helsinki, and Marshall CT scoring systems were used. In patients with intracerebral hemorrhage (ICH), the ICH score was applied and the presence of subarachnoid hemorrhage (SAH) and/or intraventricular hemorrhage (IVH) was assessed.

2.4. Data and statistical analysis

A multi-scale wavelet-based ECG annotator previously developed and validated [17] was applied to obtain single lead (SL) based annotations and multi-lead based peak annotations obtained as the median mark of the 8 SL annotators for R peak from leads I, III, V1–V6, excluding outliers. The interval RR(n) related to the nth beat is defined as the time from (n-1)th to the nth beat measured between consecutive R multi-lead based annotated R peaks. HRV analysis was performed (the linear and non-linear HRV measures used are explained in Supplemental Table 1) for all consecutive and non-overlapping 10-min segments of the tachograms (obtained after R peak detection on the ECG), including linear time-domain and frequency-domain analysis, as well as non-linear analysis. As used before for some of the authors [22], a 10-min duration was chosen to effectively capture variability patterns, avoiding sequences with fewer than 300 data points in a 5-min segment where the average RR interval exceeds 1 s, which could potentially compromise the stability of entropy calculations [23,24]. In order to account for considerable differences in the average beat-to-beat sampling across the sample, the tachograms were resampled using cubic spline interpolation at 4 Hz. After detecting the R-waves, the recordings were visually analyzed, and the traces with the highest quality, best signal stability, minimal artifacts, and absence of ectopic beats were selected. No other type of preprocessing was applied. In each case, two visually selected 10-min segment was chosen for its signal stability in the first two and 12 h after admission.

To study the ANS in our sample, we assessed HRV. We used a combination of linear and non-linear methods to evaluate HRV, as described below and shown in Supplemental Table 1. We calculated linear time-domain measures including [25]: Mean RR interval (in milliseconds), which represents the average time between consecutive heartbeats; SDNN (Standard Deviation of RR intervals in milliseconds), which reflects the overall variability of HR and RMSSD (Root Mean Square of

Successive Differences, in milliseconds) which measures short-term variations in HR. For the frequency domain analysis, we used a method called the Welch method (with a Hanning window) [25], which breaks down the heart rate signal into different frequency bands. We looked at: Very Low Frequency (VLF) (0–0.04 Hz); Low Frequency (LF) (0.04–0.15 Hz); High Frequency (HF) (0.15–0.40 Hz) and, given the wide age range in our sample (from 1 month to 18 years), we also considered an extended HF + band (0.15–1.00 Hz). Additionally, we calculated the LF/HF ratio [26], which shows the balance between sympathetic and parasympathetic activity, and Total Power (TP), which represents the overall variability in the heart rate signal. For non-linear analysis, we calculated Sample Entropy (SampEn) [27,28], which measures the complexity of the heart rate time series, using different tolerance values (0.1xSD, 0.15xSD, 0.2xSD) and an embedding dimension of 2 [29]. We used 2400 data points, corresponding to 10-min segments sampled at 4Hz. Lastly, we computed non-linear indices from the Poincaré plot, including SD1 (short-term variability), SD2 (long-term variability), and their ratio (SD1/SD2) [26,27]. This comprehensive analysis allowed us to evaluate autonomic regulation and better understand the physiological dynamics of our sample.

Descriptive statistics were expressed as a fraction of the total population, mean $\pm$ standard deviation (SD), and/or median with inter-quartile range (IQR). Continuous variables were compared using the Student's t-test if normally distributed, or the Mann-Whitney test if not normally distributed. Categorical variables were compared using the Chi-square statistic. No corrections for multiple comparisons were applied, as the aim was to explore preliminary associations. To quantify HRV measures and identify clinically relevant cut-off points for neurological outcomes, we employed the precision-recall curve. A cut-off value was selected based on a minimum precision threshold of 0.8. Statistical significance was determined when the p-value was below 0.05. A multivariable binary logistic regression was performed to assess the association between HRV indices (using pre-defined cut-off values) and functional outcomes at one year, while controlling for age and sex. Odds ratios (OR) with corresponding 95 % confidence intervals (CI) were calculated. All statistical analyses were using SPSS statistical software (SPSS, release 28.0, SPSS Inc., Chicago, IL, USA).

2.5. Outcomes assessment

The primary outcome measure was global functional outcome as measured by the Pediatrics Glasgow Outcome Scale Extended (GOSE-Peds) at 3 and 12 months after injury [30]. These data were taken by reviewing the medical records (Appendix). The outcome was dichotomized into favorable and unfavorable based on predefined cutoffs (Table 1). None to mild disability (GOSE-E PEDS category ≤ 2) was categorized as favorable outcome, whereas moderate to severe disability was categorized as unfavorable (GOSE-E PEDS category ≥ 3). We aimed to assess medium-to-long-term neurological outcomes in children with severe ABI and identify cardiovascular predictors linked to unfavorable outcomes.

Table 1
Assessment tool used in the study.

Outcome	Examination/Tool	Description
Neurologic	GOSE-E Peds ^a	Scores: 6: Lower severe disability (lower SD) 5: Upper severe disability (upper SD) 4: Lower moderate disability (lower MD) 3: Upper moderate disability (upper MD) 2: Lower good recovery (lower GR) 1: Upper good recovery (upper GR) Favorable outcome: Score 1–2 Unfavorable outcome: Score 3–6

^a GOSE-Peds - Glasgow Outcome Scale-extended Pediatric version.

3. Results

Thirty-one children with ABI were selected based on convenience sampling. These cases met the predefined inclusion criteria, had ECG data available, and were included during periods when the investigator was available to collect and process the data. Twenty-four were male (77.4 %) and they had the median age of 11.3 years old (IQR 5.6–14.3). Twenty-two (71.0 %) patients had traumatic brain injury (TBI), five (16.1 %) cerebral hemorrhage and the others meningoencephalitis, stroke, hypoxic-ischemic encephalopathy and *status epilepticus* (Supplemental Table 2 and Table 2). Patients with TBI presented a better outcome (Supplemental Table 2). No significant difference between outcome and age or gender was found (Table 2). According with GOSE E-Peds, sixteen children (51.6 %) had a favorable outcome at 3 months and twenty-one (67.7 %) at 12 months (Table 2).

When studying HR and BP as predictors of neurological outcomes in pediatric patients, we found that the presence of tachycardia or

bradycardia was not associated with prognosis (Table 2). However, patients with systolic blood pressure (SBP) above the 95th percentile during the first 12 h after admission to the PICU showed significantly better neurological outcomes. At 3 months, 68.2 % (15 patients) with SBP >95th percentile had a good outcome, compared to 31.8 % (9 patients) with SBP <95th percentile ($p = 0.006$). At 12 months, 83.3 % (20 patients) with SBP >95th percentile had a good outcome, compared to 16.7 % (4 patients) with SBP <95th percentile ($p = 0.002$) (Table 2).

The calculated HRV values were higher, both at admission and 12 h after admission, in patients with a favorable prognosis at 3 and 12 months. However, only some of the HRV values at 12 h post-admission were statistically significant in relation to the 3- and 12-month GOSE-Peds outcomes (Table 3).

In this exploratory study, we aimed to quantify HRV measurements and identify clinically relevant cut-off points for neurological outcomes. We used the precision-recall curve to select a cut-off point based on a minimum precision value of 0.8.

Table 2

Patient characteristics and physiologic data at the first 12 h after PICU admission and differences between favorable and unfavorable outcome at 3 and 12 months according to Glasgow Outcome Scale-Extended Pediatric (GOSE-E Peds).

Patient characteristics and physiologic data	Total (n = 31)	GOSE-E Peds 3 months			GOSE-E Peds 12 months		
		Favorable outcome (n = 16)	Unfavorable outcome (n = 15)	p-value	Favorable outcome (n = 21)	Unfavorable outcome (n = 10)	p-value
Median Age (IQR) at admission	11.3 years (5.6–14.3)	9.0 years (5.7–12.2)	13.0 (2.6–15.1)	0.252 ^b	11.33 years (5.83–13.75)	12.13 years (2.50–15.67)	0.612 ^b
Age group, n (%)				0.096 ^a			0.361 ^a
≤2 years	2 (6.5 %)	1 (50.0 %)	1 (50.0 %)		1 (4.8 %)	1 (10.0 %)	
>2 years ≤ 5 years	4 (12.9 %)	1 (25.0 %)	3 (75.0 %)		2 (9.5 %)	2 (20.0 %)	
>5 years ≤ 12 years	13 (41.9 %)	10 (76.9 %)	3 (23.1 %)		11 (52.4 %)	2 (20.0 %)	
>12 years	12 (38.7 %)	4 (33.3 %)	8 (66.7 %)		7 (33.3 %)	5 (50.0 %)	
GCS P (median, IQR)	6.0 (5.0–8.0)	7.5 (6.0–8.0)	6.0 (4.0–7.0)	0.020 ^b	7.0 (5.5–8.0)	6.0 (3.7–6.2)	0.082 ^b
Pupils, n (%)				0.600 ^a			1.00 ^a
- Both reactive	28 (90.3 %)	15 (93.8 %)	13 (86.7 %)		19 (67.9 %)	9 (32.1 %)	
- Anisocoria	3 (9.7 %)	1 (6.3 %)	2 (13.3 %)		2 (66.7 %)	1 (33.3 %)	
ICP (mmHg)				0.695 ^b			0.445 ^b
Median (IQR)	15.5 (11.0–24.5)	15.0 (11.0–23.0)	18.0 (11.5–25.5)		16 (10.0–25.0)	16 (10.0–22.0)	
- Admission				0.747 ^b			0.231 ^b
CPP (mmHg)							
Median (IQR)							
- Admission	60.5 (56.8–70.2)	60.0 (55.0–71.0)	64.0 (57.2–68.5)	1.00 ^a	60.0 (55.0–67.0)	65.0 (59.0–72.0)	0.381 ^a
Minimum SBP (mmHg), n (%)							
< P5	8 (25.8 %)	4 (50.0 %)	4 (50.0 %)		4 (50.0 %)	4 (50.0 %)	
> P5	23 (74.2 %)	12 (52.2 %)	11 (47.8 %)	0.037 ^a	17 (73.9 %)	6 (26.1 %)	0.002 ^a
Maximum SBP (mmHg), n (%)							
< P95	7 (22.6 %)	1 (14.3 %)	6 (85.7 %)		1 (14.3 %)	6 (85.7 %)	
> P95	24 (77.4 %)	15 (62.5 %)	9 (37.5 %)	1.00 ^a	20 (83.3 %)	4 (16.7 %)	1.00 ^a
Minimum MBP (mmHg), n (%)							
< P5	3 (9.7 %)	2 (66.7 %)	1 (33.3 %)		2 (66.7 %)	1 (33.3 %)	
> P5	28 (90.3 %)	14 (50.0 %)	14 (50.0 %)	1.00 ^a	19 (67.9 %)	9 (32.1 %)	0.417 ^a
Maximum MBP (mmHg), n (%)							
< P95	22 (71.0 %)	11 (50.0 %)	11 (50.0 %)		16 (72.7 %)	6 (27.3 %)	
> P95	9 (29.0 %)	5 (55.6 %)	4 (44.4 %)	1.00 ^a	5 (55.6 %)	4 (44.4 %)	1.00 ^a
Maximum DBP (mmHg), n (%)							
< P95	22 (71.0 %)	11 (50.0 %)	11 (50.0 %)		15 (68.2 %)	7 (31.8 %)	
> P95	9 (29.0 %)	5 (55.6 %)	4 (44.4 %)	0.458 ^a	6 (66.7 %)	3 (33.3 %)	0.685 ^a
Tachycardia, n (%)							
- Yes	10 (32.2 %)	4 (40.0 %)	6 (60.0 %)	0.484 ^a	6 (28.6 %)	4 (40.0 %)	1.00 ^a
- No	21 (67.7 %)	12 (57.1 %)	9 (42.9 %)		15 (71.4 %)	6 (60.0 %)	
Bradycardia, n (%)							
- Yes	2 (6.5 %)	2 (100.0 %)	0 (0.0 %)		2 (9.5 %)	0 (0.0 %)	
- No	29 (93.5 %)	14 (48.3 %)	15 (51.7 %)		19 (90.5 %)	10 (100.0 %)	
Mechanical ventilation days (Median, IQR)	10.0 (5.0–16.2)	7.5 (5.0–10.0)	18.5 (11.5–24.5)	0.026 ^b	8.0 (5.0–10.0)	18.0 (15.0–20.0)	0.001 ^b
Days on vasoactive drugs (Median, IQR)	5.0 (2.0–8.5)	5.0 (4.0–6.0)	6.0 (0.0–10.0)	0.613 ^b	5.0 (3.0–7.0)	7.0 (1.0–10.0)	0.379 ^b
PICU Length of stay Observed (days) (Median, IQR)	11.0 (7.2–16.7)	9.0 (6.0–11.0)	17.0 (11.0–23.0)	0.007 ^b	10.0 (6.0–12.0)	20.0 (16.0–24.0)	<0.001 ^b

IQR – inter quartile; GCS P- Pupillary Glasgow Coma Scale; ICP- intracranial pressure; CPP – cerebral perfusion pressure; SBP- systolic blood pressure; MBP – median blood pressure; DBP – diastolic blood pressure; PICU – Pediatric Intensive Care Unit.

^a Chi-Square test.

^b Mann-Whitney-test.

Table 3
HRV measurements and outcome at 3 and 12 months (GOSE-E Peds).

HRV measures (median, IQR)	Total (n = 31)	GOSE-E Peds 3 months			GOSE E-Peds 12 months		
		Favorable outcome (n = 16)	Unfavorable outcome (n = 15)	p-value	Favorable outcome (n = 21)	Unfavorable outcome (n = 10)	p-value
Mean NN							
- Admission	706.62 (560.77–859.87)	672.21 (552.53–874.63)	718.58 (597.59–835.48)	0.711 ^b	679.15 (555.28–866.75)	714.13 (562.91–885.25)	0.520 ^b
– 12th hours	764.22 (613.24–907.87)	804.66 (578.29–919.60)	687.66 (613.24–907.87)	0.520 ^b	777.28 (599.28–909.09)	701.93 (561.33–926.21)	0.603 ^{hb}
SDNN							
- Admission	12.35 (5.55–25.80)	16.50 (5.66–27.22)	11.37 (4.82–25.80)	0.323 ^b	15.72 (5.64–25.80)	10.03 (4.80–18.48)	0.375 ^b
– 12th hours	16.51 (5.08–35.35)	27.71 (5.06–40.21)	10.10 (5.08–23.61)	0.236 ^b	21.40 (4.83–36.98)	13.31 (5.83–23.61)	0.735 ^b
RMSDD							
- Admission	3.82 (1.30–6.59)	4.41 (1.90–9.77)	2.70 (1.08–4.65)	0.192 ^b	4.18 (1.65–8.04)	2.89 (1.08–4.61)	0.331 ^b
– 12th hours	4.12 (2.00–12.50)	8.30 (2.97–15.29)	2.75 (0.89–6.99)	0.014 ^b	5.21 (2.33–15.00)	2.77 (1.08–8.26)	0.190 ^b
TP							
- Admission	120.76 (14.63–419.76)	177.9 6 (27.41–594.98)	112.20 (9.75–270.30)	0.304 ^b	125.84 (24.31–674.42)	83.64 (13.89–164.35)	0.390 ^b
– 12th hours	171.43 (16.54–930.26)	615.0 (28.6–1392.48)	57.0 (6.53–412.33)	0.027 ^b	412.33 (18.40–1070.97)	91.39 (9.84–293.76)	0.310 ^b
VLF							
- Admission	22.40 (5.27–34.53)	26.19 (6.34–159.21)	13.70 (3.38–104.37)	0.363 ^b	29.98 (6.29–150.57)	12.10 (4.85–52.89)	0.272 ^b
– 12th hours	31.78 (3.65–148.53)	100.60 (6.09–304.0)8	29.48 (2.10–101.81)	0.069 ^b	86.36 (5.72–236.25)	29.59 (3.65–93.24)	0.254 ^b
LF							
- Admission	16.09 (3.44–95.75)	32.83 (5.8–4132.66)	16.09 (0.8–167.79)	0.304 ^b	16.09 (5.21–147.38)	17.26 (0.81–17.97)	0.331 ^b
– 12th hours	27.16 (2.76–128.35)	84.39 (5.04–247.42)	13.55 (0.67–66.81)	0.033 ^b	79.63 82.98–185.32)	17.97 (0.72–42.36)	0.205 ^b
LFn							
- Admission	28.13 (14.69–62.58)	29.92 (14.30–59.87)	20.25 (16.59–69.30)	0.984 ^b	28.95 (14.43–67.26)	19.81 (14.12–59.96)	0.663 ^b
– 12th hours	23.58 (11.78–37.84)	25.05 (12.12–34.95)	16.17 (11.74–39.59)	1.00 ^b	25.04 (12.45–35.89)	15.67 (10.68–64.51)	0.950 ^b
HF							
- Admission	29.26 (2.34–92.15)	52.24 (4.01–197.99)	15.02 (2.34–86.00)	0.453 ^b	51.47 (4.61–149.96)	17.17 (2.34–66.28)	0.612 ^b
– 12th hours	44.49 (2.49–335.03)	171.56 (16.07–679.34)	3.96 (2.32–162.02)	0.123 ^b	158.49 (2.32–176.59)	4.46 (2.32–176.59)	0.422 ^b
HFn							
- Admission	48.73 (15.56–70.69)	36.79 (14.73–70.29)	56.97 (19.10–70.69)	0.446 ^b	37.45 (15.30–65.46)	65.61 (18.17–78.06)	0.268 ^b
– 12th hours	54.94 (32.05–71.79)	50.82 (25.45–68.83)	60.86 (42.48–76.12)	0.264 ^b	51.11 (35.64–66.70)	68.79 (15.10–82.42)	0.287 ^b
LF/HF							
- Admission	0.78 (0.24–3.27)	1.00 (0.23–2.03)	0.30 (0.24–3.90)	0.813 ^b	0.97 (0.27–2.23)	0.29 (0.22–3.90)	0.583 ^b
– 12th hours	0.42 (0.18–1.44)	0.52 (0.20–1.63)	0.23 (0.14–0.79)	0.502 ^b	0.45 (0.20–0.85)	0.22 (0.14–24.0)	0.833 ^b
HF +							
- Admission	37.31 (5.88–167.51)	80.38 (10.13–291.23)	19.86 (4.08–98.08)	0.268 ^b	74.28 (6.11–256.07)	24.00 (4.08–82.65)	0.176 ^b
– 12th hours	49.65 (5.46–521.15)	229.61 (21.34–983.29)	7.27 (3.88–195.84)	0.020 ^b	165.11 (7.27–647.62)	7.13 (4.10–219.34)	0.291 ^b
SampEn2, 0.1							
- Admission	0.94 (0.81–1.24)	0.99 (0.86–1.29)	0.92 (0.71–1.22)	0.192 ^b	0.98 (0.83–1.29)	0.91 (0.76–1.13)	0.291 ^b
– 12th hours	0.92 (0.76–1.11)	0.95 (0.76–1.20)	0.86 (0.71–1.04)	0.465 ^b	0.95 (0.76–0.71)	0.85 (0.71–1.03)	0.245 ^b
SampEn2, 0.15							
- Admission	0.74 (0.66–0.95)	0.76 (0.69–0.98)	0.71 (0.56–0.95)	0.185 ^b	0.755 (0.69–0.97)	0.70 (0.57–0.88)	0.254 ^b
– 12th hours	0.72 (0.58–0.90)	0.75 (0.61–0.93)	0.68 (0.57–0.81)	0.323 ^b	0.76 (0.62–0.93)	0.64 (0.57–0.61)	0.151 ^b
SampEn2, 0.2							
- Admission	0.62 (0.58–0.80)	0.64 (0.59–0.80)	0.61 (0.49–0.80)	0.295 ^b	0.62 (0.58–0.80)	0.61 (0.56–0.75)	0.176 ^b
– 12th hours	0.62 (0.49–0.70)	0.63 (0.50–0.77)	0.61 (0.45–0.69)	0.502 ^b	0.64 (0.50–0.77)	0.52 (0.45–0.68)	0.272 ^b
Poincaré SD1							
- Admission	2.46 (0.92–43.66)	3.11 (1.34–6.91)	1.90 (0.76–3.29)	0.155 ^b	2.96 (1.1–5.68)	2.05 (0.76–3.05)	0.272 ^b
– 12th hours	2.91 (1.33–10.09)	7.18 (2.07–11.36)	1.94 (0.63–4.94)	0.014 ^b	3.68 (1.52–10.60)	1.96 (0.76–13.92)	0.163 ^b
Poincaré SD2							
- Admission	17.45 (7.51–35.80)	23.13 (8.43–37.98)	15.74 (6.63–35.80)	0.343 ^b	21.96 (7.99–35.80)	13.92 (6.63–24.62)	0.375 ^b
– 12th hours	23.2 (8.22–49.20)	45.42 (14.44–56.24)	10.07 (4.33–31.59)	0.006 ^b	35.53 (10.07–55.03)	11.90 (7.13–0.14)	0.063 ^b
Poincaré SD1/SD2							
- Admission	0.14 (0.09–0.20)	0.15 (0.10–0.22)	0.11 (0.08–0.20)	0.313 ^b	0.14 (0.10–0.20)	0.14 (0.09–0.20)	0.688 ^b
– 12th hours	0.17 (0.08–0.21)	0.18 (0.10–0.21)	0.13 (0.07–0.21)	0.333 ^b	0.17 (0.10–0.20)	0.12 (0.07–0.21)	0.321 ^b
SDNN 12 h (n, %)				0.037 ^a			0.222 ^a
≤35.0	23 (74.2 %)	9 (39.1 %)	14 (60.9 %)		14 (60.9 %)	9 (39.1 %)	
>35.0	8 (25.8 %)	7 (87.5 %)	1 (12.5 %)		7 (87.5 %)	1 (12.5 %)	
RMSSD 12 h (n, %)				0.032 ^a			0.121 ^a
≤3.2	14 (45.2 %)	4 (28.6 %)	10 (71.4 %)		7 (50.0 %)	7 (50.0 %)	
>3.2	17 (54.8 %)	12 (70.5 %)	5 (29.4 %)		14 (82.4 %)	3 (17.6 %)	

(continued on next page)

Table 3 (continued)

HRV measures (median, IQR)	Total (n = 31)	GOSE-E Peds 3 months			GOSE E-Peds 12 months		
		Favorable outcome (n = 16)	Unfavorable outcome (n = 15)	p-value	Favorable outcome (n = 21)	Unfavorable outcome (n = 10)	p-value
Poincaré SD2				0.029 ^a			0.129 ^a
12 h (n, %)							
≤32.0	18 (58.1 %)	6 (33.3 %)	12 (66.7 %)		10 (55.6 %)	8 (44.4 %)	
>32.0	13 (41.9 %)	10 (76.9 %)	3 (23.1 %)		11 (84.6 %)	2 (15.4 %)	
LF 12 h (n, %)				0.066 ^a			0.046 ^a
≤70.0	19 (61.3 %)	7 (36.8 %)	12 (63.2 %)		10 (52.6 %)	9 (47.4 %)	
>70.0	12 (31.7 %)	9 (75.0 %)	3 (25.0 %)		11 (91.7 %)	1 (8.3 %)	

IQR – inter quartil range.

^a Chi-Square test.

^b Mann-Whitey-test.

At 12 h after admission, 87.5 % of patients with SDNN >35.0 m, 70.5 % of patients with RMSSD >3.2 ms and 76.9 % of patients with *Poincaré* SD2 > 32.0 ms, showed a statistically significant better outcome at 3 months (Table 3). In our logistic regression models assessing predictors of 3-month functional outcomes, SDNN, RMSSD, and *Poincaré* SD2 at 12 h post-injury emerged as significant independent predictors of recovery. The SDNN values below 35 ms were significantly associated with poorer recovery, with children exhibiting SDNN <35 ms having significantly lower odds of achieving good recovery (OR = 0.073, 95 % CI: 0.007–0.756, p = 0.028). The value of RMSSD at 12 h post-injury was also a significant predictor of recovery, with lower RMSSD values being associated with reduced odds of good recovery (OR = 0.098, 95 % CI: 0.015–0.646, p = 0.016). Similarly, *Poincaré* SD2 values at 12 h post-injury were significantly associated with functional outcome, with lower *Poincaré* SD2 values corresponding to lower odds of good recovery (OR = 0.081, 95 % CI: 0.011–0.575, p = 0.012). Neither age nor sex were statistically significant predictors in any of the models (p = 0.121 for age and p = 0.257 for sex in the RMSSD model; p = 0.083 for age and p = 0.381 for sex in the *Poincaré* SD2 model). For the SDNN model, the overall accuracy was 74.2 %, with a sensitivity of 75.0 % for good recovery and a specificity of 73.3 % for moderate to severe disability. For the RMSSD model, the classification accuracy was 74.2 %, with similar sensitivity and specificity. The *Poincaré* SD2 model showed lower accuracy, with an overall classification accuracy of 64.5 %, sensitivity of 75.0 % for good recovery, and specificity of 53.3 % for moderate to severe disability.

Patients with LF > 70.0 ms² at 12 h after PICU admission had a significantly better outcome at 12 months [11 (91.7 %) vs 1 (8.3 %), p = 0.046] than patients with a lower value. In a logistic regression model including LF power at 12 h (LF T12), gender, and age. Children with LF T12 > 70 ms² had 11.4 times higher odds of achieving a good recovery after 12 months compared to those with lower values (OR = 11.4; 95 % CI: 1.15–112.88; p = 0.037). Gender and age were not statistically significant predictors. The model correctly classified 74.2 % of cases overall, with high sensitivity (85.7 %) for identifying good outcomes but lower specificity (50.0 %) for predicting poor outcomes.

The Pupillary Glasgow Coma Scale (GCS) score was lower upon admission in children who later experienced unfavorable outcomes, as indicated by GOSE E-Peds [(6.0, IQR 4.0–7.0) vs. 7.5 (IQR 6.0–8.0), p = 0.020], showing statistical significance at 3 months. However, this significance did not persist at 12 months [6.0 (IQR 3.7–6.2) vs. 7.0 (IQR 5.5–8.0), p = 0.082] (Table 2). Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) at admission did not exhibit a significant relationship with the outcome (Table 2). Patients who had a more unfavorable prognosis spent significantly more time on mechanical ventilation and had a longer length of stay (LOS) in the PICU (Table 2). All 31 patients were under the effects of sedation and invasive mechanical ventilation at the time of data collection. Although pH and oxygen arterial pressure (PaO₂) were not related to the prognosis, patients with a worse prognosis exhibited significantly higher values of lactate and lower values of bicarbonate in the first 12 h after admission

(Supplemental Table 2). The presence of hypothermia (body temperature <35 °C) was associated with a worse neurological prognosis [6 (75.0 %) vs 2 (25.0 %), p = 0.121] at 3 month and [5 (62.5 %) vs 3 (37.5 %), p = 0.035] at 12 months (Supplemental Table 2). CT scoring systems did not show a significant association with outcome, as shown in Supplemental Table 3. PICU scoring systems (PRISM III, Probability of death, ISS and SOFA) exhibited lower scores in cases of unfavorable outcomes at 3 and 12 months; however, statistical significance was not observed (Table 4).

4. Discussion

This study highlights the prognostic significance of early cardiovascular and autonomic markers in children with severe ABI. Our findings suggest that both elevated SBP in the immediate post-injury period and HRV indices derived from high-resolution ECG Holter recordings can serve as independent indicators of long-term neurological outcome. Higher HRV metrics at the first 12 h following admission were associated with a favorable neurologic outcome at 3 and 12 months after injury. This finding is consistent with previous pediatric studies [2].

Children with systolic blood pressure (SBP) values above the 95th percentile within the first 12 h of PICU admission demonstrated significantly better neurological outcomes at both 3 and 12 months post-injury. These findings support the hypothesis that early post-injury hypertension may reflect preserved cerebral autoregulation, potentially offering a neuroprotective benefit. This is consistent with the observations of Silva et al. [1], who reported that children with severe ABI and systolic hypertension (SBP >99th percentile) at admission had higher mortality rates. Similarly, Freeman et al. [31] found that, in contrast to the adult literature, pediatric patients with severe traumatic brain injury and hypertension on presentation did not exhibit worse outcomes compared to normotensive patients. However, they did observe a trend toward increased mortality at the extremes of age-adjusted hypertension. These results align with prior evidence suggesting that hemodynamic patterns early in the course of ABI carry important prognostic value [1,3,32].

In parallel, HRV analysis based on 10-min ECG segments demonstrated that autonomic indices measured 12 h after PICU admission were predictive of favorable neurological outcomes. Specifically, elevated values of SDNN, RMSSD, *Poincaré* SD2, and LF power were significantly associated with improved neurological recovery. These findings suggest that the autonomic mechanisms reflected by these HRV indices—capturing overall HRV, short-term parasympathetic activity, and baroreflex-mediated control—are particularly responsive to the physiological impact of pediatric acute brain injury. We utilized high-resolution 12-lead Holter ECG recordings with a sampling frequency of 1000 Hz, which likely provided more precise data than the lower frequencies commonly employed in standard HRV analysis.

In this cohort of children, higher HRV metrics at the first 12 h following admission were associated with a favorable neurologic outcome at 3 and 12 months after injury. This finding is consistent with

Table 4
PICU scoring systems and outcome at 3 and 12 months (GOSE-E Peds).

PICU scoring systems	Total (n = 31)	GOSE E-Peds 3 months			GOSE E-Peds 12 months		
		Favorable (n = 16)	Unfavorable (n = 15)	p-value ^a	Favorable (n = 16)	Unfavorable (n = 15)	p-value ^a
PRISMIII (Median, IQR)	10.0 (7.0–13.0)	10.0 (8.0–13.7)	7.0 (5.0–12.0)	0.080	10.0 (7.0–13.0)	8.5 (5.0–13.2)	0.418
Probability of death (Median, IQR)	0.05 (0.02–0.12)	0.06 (0.04–0.14)	0.03 (0.02–0.08)	0.055	0.05 (0.03–0.12)	0.04 (0.02–0.1)	0.446
PIM 3 (Median, IQR)	3.3 (3.2–4.3)	3.4 (3.2–4.3)	3.3 (3.2–3.6)	0.403	3.3 (3.2–3.9)	3.3 (3.2–4.6)	0.965
PELOD (Median, IQR)	11.0 (2.0–12.0)	11.0 (2.0–18.7)	11.0 (11.0–12.0)	0.552	11.0 (2.0–12.0)	11.5 (11.0–21.0)	0.083
SOFAp (Median, IQR)	4.0 (4.0–7.0)	5.0 (3.2–8.0)	4.0 (4.0–6.0)	0.441	5.0 (3.4–7.5)	4.0 (4.0–6.2)	0.488
ISS (Median, IQR)	18.0 (16.0–25.2)	19.0 (16.0–31.2)	18.0 (16.0–25.0)	0.481	18.0 (16.0–25.5)	16.0 (16.0–25.5)	0.402

PRISM III - Pediatric Risk of Mortality Score; PIM-3 Pediatric Index Mortality 3; PELOD - Pediatric Logistic Organ Dysfunction; pSOFA - Pediatric Sequential Organ Failure Assessment; ISS- Injury Severity Score; ISS - Injury Severity score. IQR - Inter quartile range. ¹Mann-Whiney test.

^a Mann-Whitney-test.

previous pediatric studies [2].

Notably, an LF power exceeding 70 ms² was linked to an 11.4-fold increase in the odds of a favorable outcome at 12 months, underscoring its potential utility as a non-invasive biomarker for early risk stratification. In contrast, HRV indices recorded at the time of admission did not show a significant association with outcome. This temporal distinction suggests that HRV values obtained immediately post-injury may primarily reflect acute physiological instability, whereas measurements obtained after the initial stabilization period may better capture sustained autonomic function with prognostic relevance. Gender and age were not statistically significant predictors in our models.

Despite the encouraging nature of these findings, our study has several limitations. It was conducted at a single center and involved a small, heterogeneous sample collected over an extended time period, limiting generalizability and the precision of HRV cutoff values. While no significant differences in outcomes were observed over the extended study period, evolving critical care practices may have influenced patient management. Throughout the study period, all patients were managed in a dedicated PICU with consistent application of core neuroprotective strategies, including sedation and analgesia, control of intracranial pressure, and maintenance of normoxia, normocapnia, and normotension. These practices were aligned with international pediatric neurocritical care guidelines and remained stable despite incremental advancements in monitoring and supportive care.

The exploratory nature of our HRV analysis relied on short-duration ECG segments (10 min at admission and at 12 h), which may be affected by signal quality issues such as R-wave detection errors, brief signal loss, or bias in manual segment selection. Future research using longer or continuous ECG recordings may provide more robust insight into slower autonomic dynamics.

This study focused exclusively on neurological outcomes, assessed retrospectively through medical records, without direct input from patients or caregivers—an approach that may limit the depth and accuracy of outcome evaluation. Incorporating additional dimensions such as behavioral and functional outcomes, quality of life, and academic performance would have provided a more comprehensive understanding of the long-term impact on these patients.

Our ability to establish definitive cutoff values for key HRV measures is limited by the sample size, and these preliminary thresholds require validation in larger, multicenter studies.

Although our center receives severe pediatric ABI cases directly, without prior transfers, we did not systematically record the exact time elapsed between injury and the first ECG acquisition, which could introduce some variability into early measurements. Nonetheless, all recordings were obtained within the first 12 h post-admission, during a clinically relevant window for prognostic assessment.

Finally, although we included multivariable regression models adjusting for age and sex, the overall statistical approach remains exploratory and was not corrected for multiple comparisons. Therefore, the risk of type I error cannot be excluded. These findings should be interpreted as hypothesis-generating and warrant confirmation in larger, multicenter cohorts with broader multivariable analyses.

Future studies with larger sample sizes, multivariate analyses, and longer recording periods are needed to validate these observations and further elucidate the prognostic potential of HRV in pediatric ABI, including its impact on cardiovascular risk, psychiatric outcomes, and rehabilitation progress.

Additional observations include that patients with a worse neurological prognosis experienced longer PICU stays and required more days of ventilation. Like Appavu et al. [33], we did not find any association between PICU scoring systems or CT scores systems and GOSE-Peds scores at three and 12 months. Not even the Helsinki CT score that is a proposed novel method for predicting long-term outcome in patients with TBI [18]. Despite examining a comprehensive array of physiological, analytical, imaging data, and severity scores, no other cardiovascular variables (besides early SBP and LF) emerged as significant prognostic markers for 12-month outcomes. This further highlights the distinctive prognostic value of early cardiovascular and autonomic parameters in this patient population.

Although all patients were mechanically ventilated and under continuous sedoanalgesia, which helped standardize the sample to some extent, we acknowledge that the 12 h period used for prognostic assessment is relatively short, especially when considering medium-to long-term outcomes. This time frame was selected for convenience, allowing for comparison with established severity scores such as PRISM III, which is calculated within the first 12 h after admission. However, we recognize that this short interval may not fully capture the longer-term dynamics of physiological responses, potentially limiting the accuracy of our prognostic predictions.

Five patients who had an unfavorable outcome at 3 months demonstrated meaningful recovery by 12 months, transitioning to the favorable outcome group. This observation illustrates that early outcome assessments may not fully reflect the trajectory of neurological recovery in pediatric patients with severe ABI, reinforcing the value of long-term follow-up in this population.

5. Conclusions

This study suggests that both elevated early SBP and HRV indices—particularly LF power recorded 12 h after PICU admission—may serve as independent, non-invasive predictors of long-term neurological outcome in children with severe ABI. These preliminary findings support the notion that autonomic activation in the early hours following severe

ABI is indicative of a better neurological outcome. They also highlight the potential value of integrating early cardiovascular and autonomic monitoring into prognostic frameworks and personalized neuro-protective strategies in pediatric neurocritical care.

Financial disclosure statement

Ana Paula Rocha, partially supported by CMUP, member of LASI, which is financed by national funds through FCT – Fundação para a Ciência e a Tecnologia, I.P., under the projects with reference UIDB/00144/2020 and UIDP/00144/2020.

The other authors declare that they have no relevant financial relationships with ineligible companies or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpn.2025.04.009>.

References

- [1] M.J. Silva, H. Gonçalves, R. Almeida, C.C. Dias, A.I. Almeida, A.P. Rocha, et al., Cardiovascular responses as predictors of mortality in children with acute brain injury, *Pediatr. Res.* (2024), <https://doi.org/10.1038/s41390-024-03679-2>.
- [2] S. Martin, G. Du Pont-Thibodeau, A.J.E. Seely, G. Emeriaud, C.L. Herry, M. Recher, et al., Heart rate variability in children with moderate and severe traumatic brain injury: a prospective observational study, *J. Pediatr. Intensive Care* (2022), <https://doi.org/10.1055/s-0042-1759877>.
- [3] M.J. Silva, B. Carneiro, R. Mota, M.J. Baptista, Cardiovascular events in children with brain injury: a systematic review, *Int. J. Cardiol.* 387 (2023).
- [4] G. Ernst, Hidden signals—the history and methods of heart rate variability, *Front. Public Health* 5 (2017).
- [5] Y. Lee, R.J. Walsh, M.W.M. Fong, M. Sykora, M.M. Doering, A.W.K. Wong, Heart rate variability as a biomarker of functional outcomes in persons with acquired brain injury: systematic review and meta-analysis, *Neurosci. Biobehav. Rev.* 131 (2021).
- [6] American Heart Association, Task force of the European society of cardiology and the north American society of pacing and electrophysiology (membership of the task force listed in the appendix), *Eur. Heart J.* 17 (1996).
- [7] J. Aftyka, J. Staszewski, A. Dębiec, A. Pogoda-Wesołowska, J. Żebrowski, Heart rate variability as a predictor of stroke course, functional outcome, and medical complications: a systematic review, *Front. Phys.* 14 (2023).
- [8] R. Sassi, S. Cerutti, F. Lombardi, M. Malik, H.V. Huikuri, C.K. Peng, et al., Advances in heart rate variability signal analysis: joint position statement by the e-cardiology ESC working group and the European heart rhythm association co-endorsed by the asia pacific heart rhythm society, *Europace* 17 (9) (2015 Jul 29) 1341–1353.
- [9] T.A. Nakagawa, S. Ashwal, M. Mathur, M. Mysore, Committee for Determination of Brain Death in Infants C. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations-executive summary, *Ann. Neurol.* [Internet] 71 (4) (2012) 573–585.
- [10] T.A. Nakagawa, S. Ashwal, M. Mathur, M. Mysore, L. Kolinski, L. Retford, et al., Clinical report - guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations, *Pediatrics* 128 (2011).
- [11] B. Martin, P.E. DeWitt, D. Albers, T.D. Bennett, Development of a pediatric blood pressure percentile tool for clinical decision support, *JAMA Netw. Open* [Internet] 5 (10) (2022) e2236918, 20221003rd ed.
- [12] S. Fleming, M. Thompson, R. Stevens, C. Heneghan, A. Plüddemann, I. MacOnochie, et al., Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies, *Lancet* 377 (9770) (2011) 1011–1018.
- [13] F. O'Leary, A. Hayen, F. Lockie, J. Peat, Defining normal ranges and centiles for heart and respiratory rates in infants and children: a cross-sectional study of patients attending an Australian tertiary hospital paediatric emergency department, *Arch. Dis. Child.* 100 (8) (2015).
- [14] A. Casertano, A. Rossi, S. Fecarotta, F.M. Rosanio, C. Moracas, F. Di Candia, et al., An overview of hypoglycemia in children including a comprehensive practical diagnostic flowchart for clinical use, *Front. Endocrinol.* 12 (2021).
- [15] P. Emami, P. Czorlich, F.S. Fritzsche, M. Westphal, J.M. Rueger, R. Lefering, et al., Impact of glasgow coma scale score and pupil parameters on mortality rate and outcome in pediatric and adult severe traumatic brain injury: a retrospective, multicenter cohort study, *J. Neurosurg.* 126 (3) (2017).
- [16] B. Balakrishnan, H. Vandongen-Trimmer, I. Kim, S.J. Hanson, L. Zhang, P. M. Simpson, et al., GCS-pupil score has a stronger association with mortality and poor functional outcome than GCS alone in pediatric severe traumatic brain injury, *Pediatr. Neurosurg.* 56 (5) (2021).
- [17] J.P. Martínez, R. Almeida, S. Olmos, A.P. Rocha, P. Laguna, A wavelet-based ECG delineator evaluation on standard databases, *IEEE Trans. Biomed. Eng.* 51 (4) (2004 Apr) 570–581.
- [18] R. Raj, J. Siironen, M.B. Skrifvars, J. Hernesniemi, R. Kivisaari, Predicting outcome in traumatic brain injury: development of a novel computerized tomography classification system (Helsinki computerized tomography score), *Neurosurgery* [Internet] 75 (6) (2014) 632–646, discussion 646–7.
- [19] L.A. Beslow, R.N. Ichord, M.C. Gindville, J.T. Kleinman, K. Engelmann, R. A. Bastian, et al., Pediatric intracerebral hemorrhage score: a simple grading scale for intracerebral hemorrhage in children, *Stroke* [Internet] 45 (1) (2014) 66–70, 20131126th ed, <https://www.ncbi.nlm.nih.gov/pubmed/24281231>.
- [20] S. Chakraborty, S.P. Symons, M. Chapman, R.I. Aviv, A.J. Fox, Diffuse ischemia in noncontrast computed tomography predicts outcome in patients in intensive care unit, *Can. Assoc. Radiol. J.* [Internet] 63 (2) (2012) 129–134, 20110727th ed.
- [21] J.A. Ryu, Y.H. Lee, C.R. Chung, Y.H. Cho, K. Sung, K. Jeon, et al., Prognostic value of computed tomography score in patients after extracorporeal cardiopulmonary resuscitation, *Crit. Care* 22 (1) (2018) 323 [Internet]. 20181122nd ed.
- [22] H. Gonçalves, A.P. Rocha, D. Ayres-De-Campos, J. Bernardes, Internal versus external intrapartum foetal heart rate monitoring: the effect on linear and nonlinear parameters, *Physiol. Meas.* 27 (3) (2006 Mar 1) 307–319.
- [23] J.M. Yentes, N. Hunt, K.K. Schmid, J.P. Kaipust, D. McGrath, N. Stergiou, The appropriate use of approximate entropy and sample entropy with short data sets, *Ann. Biomed. Eng.* 41 (2) (2013 Feb 1) 349–365.
- [24] J.D. McCamley, W. Denton, A. Arnold, P.C. Raffalt, J.M. Yentes, On the calculation of sample entropy using continuous and discrete human gait data, *Entropy* 20 (10) (2018 Oct 1).
- [25] M.H. Hayes, *Statistical Digital Signal Processing and Modelling*, John Wiley & Sons, New York, 1996.
- [26] B.W. Johnston, R. Barrett-Jolley, A. Krige, I.D. Welters, Heart Rate Variability: Measurement and Emerging Use in Critical Care Medicine, in: *Journal of the Intensive Care Society*, vol. 21, SAGE Publications Inc., 2020, pp. 148–157.
- [27] J.S. Richman, J.R. Moorman, Physiological time-series analysis using approximate entropy and sample entropy, *Am. J. Physiol. Heart Circ. Physiol.* [Internet] 278 (6) (2000) H2039–H2049.
- [28] I.S. Uzun, M.H. Asyali, G. Celebi, M. Pehlivan, Nonlinear analysis of heart rate variability, in: *Annual International Conference of the IEEE Engineering in Medicine and Biology-Proceedings* 2, 2001, pp. 1581–1584.
- [29] S.M. Pincus, Approximate entropy as a measure of system complexity, *Proc. Natl. Acad. Sci. U S A.* [Internet] 88 (6) (1991) 2297–2301. <https://www.ncbi.nlm.nih.gov/pubmed/11607165>.
- [30] S.R. Beers, S.R. Wisniewski, P. Garcia-Filion, Y. Tian, T. Hahner, R.P. Berger, et al., Validity of a pediatric version of the glasgow outcome scale-extended, *J. Neurotrauma* 29 (6) (2012) 1126–1139, 20120410th ed.
- [31] A.D. Freeman, C.A. Fitzgerald, K.J. Baxter, L.P. Neff, C.E. McCracken, L.N. Bryan, et al., Does hypertension at initial presentation adversely affect outcomes in pediatric traumatic brain injury? *J. Pediatr. Surg.* 55 (4) (2020).
- [32] M.J. Silva, N. Antunes, The utility of heart rate variability as a prognostic factor in children with traumatic brain injury, *Brain Inj.* 34 (13–14) (2020).
- [33] B. Appavu, M. Hamed Temkit, S. Foldes, B.T. Burrows, M. Kuwabara, A. Jacobson, et al., Association of outcomes with model-based indices of cerebral autoregulation after pediatric traumatic brain injury, *Neurocrit Care* 35 (3) (2021).

Supplemental table 1. Linear and non-linear HRV measures calculated.

Variability analysis	Parameters	Units	Description
Time domain			
Statistical	Mean NN	ms	The average duration of normal-to-normal RR intervals
	SDNN	ms	Standard deviation of the NN interval.
	RMSSD	ms	Square of the root of the mean of the sum of square differences between adjacent NN intervals.
Frequency domain			
	Total power (TP)	ms ²	Variance of the NN intervals over the temporal segment.
	VLF	ms ²	Power of very low frequency range (0.0033 Hz–0.04 Hz).
	LF	ms ²	Power of the low frequency range (0.04 Hz–0.15 Hz).
	LFn	n.u.	Normalized low-frequency power, calculated as $LF / (Total\ Power - VLF) \times 100$
	HF	ms ²	Power of the high frequency HF in normalized units (0.15 Hz–0.40 Hz).
	HFn	n.u.	Normalized high-frequency power, calculated as $HF / (Total\ Power - VLF) \times 100$
	HF+	ms ²	Power of the high frequency HF+ in normalized units (0.15 Hz–1.00 Hz).
	LF/HF	n.u.	Low frequency/High frequency ratio.
Non-linear measures			
Poincaré	SD1	ms	Standard deviation perpendicular to the line of identity in a <i>Poincaré</i> Plot.
	SD2	ms	Standard deviation along the line of identity in a <i>Poincaré</i> Plot.
	SD1/SD2	ms	Ratio of SD1 to SD2.
Entropy analysis	SampEn		Sample entropy, measures the regularity and complexity associated with a time series.

ms- milliseconds; n.u. - normalized units.

Adapted from: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, Standards of measurement of HRV guidelines and Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri H V., Peng CK, et al. Advances in heart rate variability signal analysis: Joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace*. 2015 Jul 29;17(9):1341–53.

Supplemental table 2. Patient Characteristics and Physiologic Data at the First 12 Hours After PICU Admission and Differences Between Favorable and Unfavorable Outcomes at 3 and 12 Months According to Glasgow Outcome Scale-Extended Pediatric (GOSE-E Peds).

This supplemental table presents additional variables collected during the first 12 hours after PICU admission, not addressed in the main text. The data is stratified by outcomes at 3 and 12 months, as classified by the Glasgow Outcome Scale-Extended Pediatric (GOSE-E Peds), distinguishing between favorable and unfavorable outcomes.

Patient characteristics and physiologic data	Total (n=31)	GOSE-E Peds 3 months			GOSE-E Peds 12 months		
		Favorable outcome (n=16)	Unfavorable outcome (n=15)	p-value	Favorable outcome (n=21)	Unfavorable outcome (n=10)	p-value
Sex n (%)	Female, 7 (22.6%) Male, 24 (77.4%)	Female 4 (57.1%) Male 12 (50.0%)	Female 3 (42.9%) Male 12 (50.0%)	1.00 ^a	Female 5 (71.4%) Male 16 (66.7%)	Female 2 (28.6%) Male 8 (33.3%)	1.00 ^a
Weight Median (IQR)	35.0 Kg (22.0-55.0)	30.0 Kg (22.3-48.0)	40.0 Kg (13.6-58.0)	0.342 ^b	32.0 Kg (22.7-56.5)	39.0 Kg (13.2-48.2)	0.983 ^b
Diagnosis, n (%)				0.064 ^a			0.012 ^a
-TBI	22 (71.0%)	15 (68.2%)	7 (31.8%)		19 (86.4%)	3 (13.6%)	
-Cerebral hemorrhage	5 (16.1%)	1 (20.0%)	4 (80.0%)		2 (40.0%)	3 (60.0%)	
-Meningoencephalitis	1 (3.2%)	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	
-Stroke	1 (3.2%)	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	
-HI Encephalopathy	1 (3.2%)	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	
-Status epilepticus	1 (3.2%)	0 (0.0%)	1 (100.0%)		0 (0.0%)	1 (100.0%)	
GCS (median, IQR)	6.0 (5.0-8.0)	7.5 (6.0-8.0)	6.0 (4.0-7.0)	0.024 ^b	7.0 (5.5-8.0)	6.0 (4.0-6.2)	0.075 ^b
GCS group, n (%)				0.600 ^a			1.00 ^a
3-8	27 (87.1%)	13 (48.1%)	14 (51.9%)		18 (66.7%)	9 (33.3%)	
9-12	4 (12.9%)	3 (75.0%)	1 (25.0%)		3 (75.0%)	1 (25.0%)	
SBP Median (IQR)							
-Minimum	96.0 (81.0-103.0)	90.5 (78.7-103.2)	100.0 (82.0-103.0)	0.342 ^b	98.0 (84.5-103.5)	92.0 879.5-105.0)	0.833 ^b
-Maximum	137.0 (123.0-143.0)	138.0 (127.0-145.0)	137.0 (120.0-142.0)	0.464 ^b	140.0 (128.0-145.0)	129.0 (107.2-139.0)	0.060 ^b
MBP Median (IQR)							
-Minimum	71.0 (61.0-77.0)	71.5 (62.0-80.7)	70.0 860.0-76.0)	0.514 ^b	71.0 (63.0-80.5)	70.0 (59.7-76.2)	0.783 ^b
-Maximum	85.0 (78.0-97.0)	83.5 (78.0-94.5)	85.0 (80.0-98.0)	0.678 ^b	83.0 (78.0-95.0)	87.0 (79.2-101.0)	0.409 ^b
DBP Median (IQR)							
-Maximum	72.0 (65.0-79.0)	74.0 (65.2-80.7)	70.0 (63.0-83.0)	0.828 ^b	73.0 (65.5-79.0)	70.0 (58.0-84.2)	0.735 ^b
HR Median (IQR)							
-Admission	91.5 (71.5-110.0)	92.0 (66.0-117.0)	91.0 (76.0-110.0)	0.967 ^b	88.5 (66.2-109.7)	93.0 (82.0-113.2)	0.597 ^b
-Minimum	72.0 (65.0-91.0)	78.0 (69.7-93.5)	70.0 (65.0-75.0)	0.109 ^b	73.0 (67.0-93.0)	68.0 (64.5-79.0)	0.262 ^b
-Maximum	115.0 (99.0-143.0)	115.5 (99.5-141.0)	115.0 (97.0-149.0)	0.984 ^b	115.0 (99.0-139.0)	116.0 (100.7-149.7)	0.627 ^b
RR Median (IQR)							
-Admission	18.0 (15.0-20.0)	18.0 (17.0-20.0)	16.0 (15.0-20.0)	0.284 ^b	22.0 (20.5-29.0)	22.0 (16.0-27.7)	0.608 ^b
-Minimum	16.0 (14.0-20.0)	18.0 (14.2-20.0)	16.0 (14.0-20.0)	0.705 ^b	16.0 (14.5-20.0)	15.0 (14.0-20.5)	0.701 ^b
-Maximum	22.0 (20.0-28.0)	23.5 (21.2-29.5)	20.0 (18.0-28.0)	0.211 ^b			0.319 ^b
Lactate (mmol/L) median (IQR)	1.49 (0.74-3.45)	0.78 (0.61-1.41)	3.07 (1.20-3.68)	0.035 ^b	0.75 (0.61-1.44)	3.31 (1.54-4.44)	0.005 ^b
PCO2 (mmHg)							
Median (IQR)							
-Minimum	29.7 (26.8-31.7)	29.2 (28.0-32.2)	29.0 (26.0-31.1)	0.280 ^b	29.5 (27.0-31.4)	30.3 (24.4-33.1)	0.946 ^b
-Maximum	39.4 (34.7-45.3)	42.1 (36.4-50.8)	37.5 (33.0-43.4)	0.114 ^b	42.0 (36.6-46.8)	36.0 (32.6-43.2)	0.108 ^b
PaO ₂ Minimum (mmHg) median (IQR)	119.4 (100.2-139.7)	119.5 (105.6-137.7)	116.1 (91.1-160.2)	0.506 ^b	114.9 (103.1-141.5)	124.4 (90.2-168.6)	0.635 ^b
Bicarbonate (mmol/L)							
Median (IQR)							
-Minimum	19.5 (17.8-20.5)	19.8 (19.1-22.6)	18.1 (17.4-20.1)	0.029 ^b	19.6(18.1-21.1)	19.2 (16.4-20.2)	0.189 ^b
-Maximum	22.7 (20.0-23.5)	23.1 (22.6-23.8)	20.3 (19.5-22.3)	0.010 ^b	23.0 (20.7-23.8)	20.0 (19.4-22.6)	0.042 ^b
pH Median (IQR)							
-Minimum	7.34 (7.30-7.40)	7.36 (7.30-7.42)	7.34 (7.30-7.37)	0.441 ^b	7.35 (7.30-7.40)	7.34 (7.28-7.38)	0.634 ^b
-Maximum	7.44 (7.41-7.49)	7.45 (7.41-7.49)	7.43 (7.41-7.47)	0.380 ^b	7.44 (7.41-7.49)	7.42 (7.40-7.47)	0.159 ^b
Na (mmol/L) (IQR)							
-Minimum	139.0 (138.0-140.5)	138.0 (134.5-140.5)	139.5 (139.0-141.5)	0.126 ^b	139.0 (136.5-141.0)	139.0 (138.5-141.0)	0.582 ^b
-Maximum	141.0 (139.0-144.0)	141.0 (139.0-143.7)	142.0 (139.0-148.0)	0.349 ^b	141.0 (139.0-144.0)	142.0 (139.0-147.2)	0.496 ^b
K (mmol/L) Median (IQR)							
-Minimum	3.3 (3.1-3.7)	3.5 (3.3-3.7)	3.2 (2.7-3.7)	0.303 ^b	3.4 (3.3-3.7)	3.2 (2.7-3.6)	0.197 ^b
-Maximum	4.0 (3.8-4.2)	4.0 (3.8-4.4)	4.1 (3.7-4.2)	0.921 ^b	4.0 (3.7-4.2)	4.2 (3.9-4.2)	0.444 ^b
BU/N (mmol/L) Median (IQR)	14.0 (10.7-17.2)	14.9 (11.7-16.8)	11.6 (10.2-17.7)	0.593 ^b	14.4 (11.2-17.0)	12.8 (10.6-17.9)	0.751 ^b

Supplemental table 2 (continued).

Patient characteristics and physiologic data	Total (n=31)	GOSE-E Peds 3 months			GOSE-E Peds 12 months		
		Favorable outcome (n=16)	Unfavorable outcome (n=15)	p-value	Favorable outcome (n=21)	Unfavorable outcome (n=10)	p-value
Creatinine (mg/dL) Median (IQR)	0.50 (0.40-0.67)	0.57 (0.42-0.74)	0.50 (0.35-0.67)	0.451 ^b	0.60 (0.44-0.74)	0.49 (0.33-0.55)	0.144 ^b
Glucose (mg/dL) Median (IQR) -Minimum -Maximum	106.0 (93.5-115.0) 137.0 (113.0-181.0)	99.5 (84.2-115.0) 144.5 (120.0-190.0)	109.0 (101.5-119.0) 124.0 (98.0-148.0)	0.188 ^b 0.172 ^b	100.0 (88.0-113.0) 144.0 (121.0-189.0)	109.5 (104.5-128.2) 116.5 (85.7-145.0)	0.129 ^b 0.047^b
Ca⁺⁺(mmol/L) Median (IQR) -Minimum -Maximum	2.1 (1.9-2.2) 1.1 (1.1-1.2)	1.12 (1.10-1.16) 1.19 (1.15-1.23)	1.14 (1.05-1.18) 1.22 (1.17-1.25)	0.981 ^b 0.478 ^b	1.13 (1.10-1.18) 1.19 (1.16-1.25)	1.12 (1.05-1.18) 1.21 (1.18-1.25)	0.536 ^b 0.510 ^b
Total bilirubin (mg/dL) Median (IQR)	0.5 (0.3-0.6)	0.5 (0.3-0.6)	0.4 (0.3-0.6)	0.389 ^b	0.5 (0.3-0.6)	0.4 (0.2-0.7)	0.263 ^b
Hemoglobin (mg/dL) Median (IQR) -Minimum -Maximum	11.5 (10.3-12.7) 9.6 (8.4-10.8)	9.7 (8.3-10.8) 11.7 (11.0-13.0)	9.6 (8.4-11.2) 11.2 (9.5-12.3)	0.961 ^b 0.220 ^b	10.2 (8.5-10.8) 11.7 (10.7-12.9)	9.0 (8.2-11.1) 10.9 (9.4-12.4)	0.734 ^b 0.300 ^b
WBC count (cellsx10⁹/L) Median (IQR) -Minimum -Maximum	12.4 (8.0-15.9) 18.0 (11.0-22.8)	11.4 (7.7-15.1) 18.2 (16.2-22.8)	13.7 (10.2-19.3) 17.1 (7.6-22.8)	0.283 ^b 0.295 ^b	12.4 (7.9-14.2) 18.1 (16.9-22.9)	14.7 (8.5-21.4) 10.0 (5.4-22.6)	0.497 ^b 0.063 ^b
Platelet count (cellsx10⁹/L) Median (IQR) -Minimum -Maximum	204.0 (154.0-225.0) 244.0 (187.0-268.0)	196.5 (163.0-208.2) 250.0 (181.7-266.7)	204.0 (146.0-310.0) 226.0 (197.0-319.0)	0.770 ^b 0.984 ^b	204.0 (158.0-208.5) 250.0 (184.5)	235.0 (149.5-313.0) 220.5 (189.0-320.5)	0.571 ^b 0.833 ^b
Body temperature (°C), n (%) <35 °C 35-38°C >38°C	8 (25.8%) 15 (48.4%) 8 (25.8%)	2 (25.0%) 8 (53.3%) 6 (75.0%)	6 (75.0%) 7 (46.7%) 2 (25.0%)	0.121 ^a	3 (37.5%) 11 (73.3%) 7 (87.5%)	5 (62.5%) 4 (26.7%) 1 (12.5%)	0.035^a
C Protein (mg/dL) Median (IQR)	14.0 (2.0-40.6)	13.5 (1.6-74.1)	14.8 (2.4-40.6)	0.937 ^b	14.0 (1.4-53.1)	10.0 (3.0-30.1)	0.767 ^b
Glicemia (mg/dL) n (%) ≥60 ≤ 180 > 180 mg/dL	23 (74.2%) 8 (25.8%)	11 (47.8%) 5 (62.5%)	12 (52.2%) 3 (37.5%)	0.685 ^a	14 (60.9%) 7 (87.5%)	9 (39.1%) 1 (12.5%)	0.222 ^a
Higher PTT (seconds) Median (IQR)	30.3 (25.7-32.5)	28.5 (23.8-32.7)	31.1 (26.0-33.0)	0.547 ^b	29.8 (24.3-32.6)	31.4 (26.0-33.5)	0.684 ^b
Higher PT (seconds) Median (IQR)	14.6 (13.2-15.5)	14.5 (13.2-15.3)	14.7 813.3-16.1)	0.917 ^b	14.7 (13.3-16.2)	14.2 (12.9-14.8)	0.319 ^b
Craniotomy -Yes -No	6 (19.4%) 25 (80.6%)	1 (16.7%) 15 (60.0%)	5 (83.3%) 10 (40.0%)	0.083 ^a	3 (50.0%) 18 (72.9%)	3 (50.0%) 7 (28.0%)	0.358 ^a
Anti-edematous medication, n (%) -Yes -No	18 (60.0%) 12 (40.0%)	10 (55.6%) 6 (50.0%)	8 (44.4%) 6 (50.0%)	1.00 ^a	13 (72.2%) 7 (58.3%)	5 (27.8%) 5 (41.7%)	0.461 ^a
EVD, n (%) -Yes -No	3 (9.7%) 28 (90.3%)	0 (0.0%) 16 (51.6%)	3 (100.0%) 12 (42.9%)	0.101 ^a	1 (33.3%) 20 (71.4%)	2 (66.7%) 8 (28.6%)	0.237 ^a
Catecholamine, n (%) -Yes -No	14 (45.2%) 17 (54.8%)	7 (50.0%) 9 (52.9%)	7 (50.0%) 8 (47.1%)	1.00 ^a	10 (71.4%) 11 (64.7%)	4 (28.6%) 6 (35.3%)	1.00 ^a

^a Chi-square test; ^b Mann-Whitney Test.

EVD – external ventricular deviation; HI – Hypoxic-ischemic; PaO2- oxygen arterial pressure; PTT – Partial Thromboplastin Time; PT- Prothrombin Time.

Supplemental table 3. CT Scoring Systems and Their Association with Outcomes at 3 and 12 Months (GOSE-E Peds) in Pediatric Traumatic Brain Injury Patients.

This table outlines the CT scoring systems used to assess traumatic brain injury (TBI) and their correlation with patient outcomes at 3 and 12 months, as measured by the Glasgow Outcome Scale-Extended Pediatric (GOSE-E Peds).

Prognostic and CT scoring systems	Total (n=22)	GOSE-E Peds 3 months			GOSE-E Peds 12 months		
		Favorable outcome (n=15)	Unfavorable outcome (n=7)	p-value ^a	Favorable outcome (n=19)	Unfavorable outcome (n=3)	p-value ^a
Rotterdam basal cisterns n (%)				0.630			1.00
-Normal	15 (68.1%)	11 (73.3%)	4 (26.7%)		13 (86.7%)	2 (13.3%)	
-Compressed	7 (31.8%)	4 (57.1%)	3 (42.9%)		6 (85.7%)	1 (14.3%)	
Rotterdam midline shift n (%)				1.00			1.00
- < 5mm	20 (90.9%)	14 (70.0%)	6 (30.0%)		17 (85.0%)	3 (15.0%)	
- ≥ 5 mm	2 (9.1%)	1 (50.0%)	1 (50.0%)		2 (100.0%)	0 (0.0%)	
Rotterdam IVH SAH n (%)				0.648			1.00
-Present	9 (40.9%)	7 (77.8%)	2 (22.2%)		8 (88.9%)	1 (11.1%)	
-Absent	13 (59.1%)	8 (61.5%)	5 (38.5%)		11 (84.6%)	2 (15.4%)	
Rotterdam sum score + 1 (Median, IQR)	3.0 (1.7-3.0)	3.0 (1.0-3.0)	3.0 (2.0-3.0)	0.416	3.0 (1.0-3.0)	2.0 (2.0-2.0)	0.581
Rotterdam epidural mass lesion n (%)				0.350			1.00
-Present	7 (31.8%)	6 (85.7%)	1 (14.3%)		6 (85.7%)	1 (14.3%)	
-Absent	15 (68.2%)	9 (60.0%)	6 (40.0%)		13 (86.7%)	2 (13.3%)	
Marshall CT score n (%)				0.703			0.334
-Diffuse injury I	2 (9.1%)	1 (50.0%)	1 (50.0%)		2 (100.0%)	0 (0.0%)	
-Diffuse injury II	18 (81.8%)	13 (72.2%)	5 (27.8%)		16 (88.9%)	2 (11.1%)	
-Diffuse injury IIIr	2 (9.1%)	1 (50.0%)	1 (50.0%)		1 (50.0%)	1 (50.0%)	
Helsinki CT score Total (Median, IQR)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	1.00	2.0 (2.0-2.0)	2.0 (2.0-2.0)	0.155
Helsinki IVH n (%)				0.227			0.371
-Present	3 (13.6%)	1 (33.3%)	2 (66.7%)		2 (66.7%)	1 (33.3%)	
-Absent	19 (86.4%)	14 (73.7%)	5 (26.3%)		17 (89.5%)	2 (10.5%)	
Helsinki suprasellar cisterns n (%)				0.303			0.478
-Normal	13 (59.1%)	10 (76.9%)	3 (23.1%)		12 (92.3%)	1 (7.7%)	
-Compressed	8 (36.4%)	4 (50.0%)	4 (50.0%)		6 (75.0%)	2 (25.0%)	
-Obliterated	1 (4.5%)	1 (100.0%)	0 (0.0%)		1 (100.0%)	0 (0.0%)	

^a Chi-Square Test.

IVH – Intraventricular hemorrhage; SAH - Subarachnoid hemorrhage. IQR – inter quartile range.

ANNEX

PEDIATRIC GLASGOW OUTCOME SCALE–EXTENDED (GOSE E-Peds)

Appendix A. Glasgow Outcome Scale-Extended Pediatric Version (GOS-E Peds) (Sue R. Beers, PhD, Anna Skold, MS, Thomas Hahner, & P. David Adelson, MD Children's Hospital of Pittsburgh)

Information obtained (select one): ☐ In person
☐ By phone
☐ From records

NOTE: Only problems that have developed or become markedly worse since the head injury should be considered when completing the GOS-E Peds. That is, the child's premorbid status must be weighed when answering all questions.

1. CONSCIOUSNESS

1a) Is the head-injured person able to obey simple commands or say any words?

Or for younger patients...

Can he or she act/react/interact beyond reflexes? ☐ No ☐ Yes (Skip to 2.)

Vegetative State (VS)
Skip to end of form and record
GOS- E Peds Score=7

An individual who shows the ability to obey even simple commands or utter any word or communicate specifically in any other way is no longer considered to be in a vegetative state. Eye movements are not reliable evidence of meaningful responsiveness; corroborate with nursing staff and the child's parents when possible. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines. However, for infants, actively following the movement of a parent or people/object with eyes, grasping for objects, making faces, etc. are interactions; breast feeding and crying continuously can be reflexes.

2. INDEPENDENCE IN THE HOME

2a) Is the assistance of another person at home essential every day for some activities of daily living?

Or for younger patients...

Is the child dependent upon a care taker more so than is expected based on age?

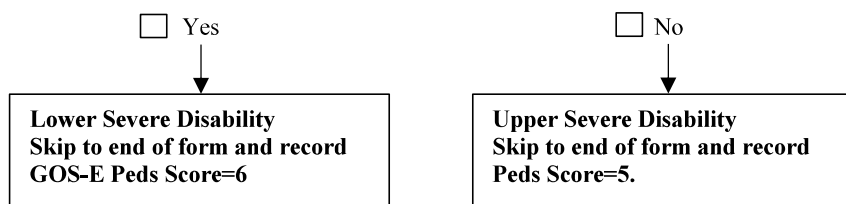
☐ Yes (Go to 2b.) ☐ No (Skip to 3.)

For an older child, complete independence and a 'no' answer should mean that the person can get washed, put clean clothes without prompting, prepare food for themselves, deal with callers, and handle minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone for an age appropriated period. Young children should be able to accomplish age appropriated developmental milestones without assistance (see Vineland Daily Living Skills). If a child compensates for physical disability to the point where developmental milestones are only mildly compromised, question parents to determine the level of independence (i.e., A child with a hemiparesis who is still able to complete tasks that other children of that age can be rated as independent).

2b) Does the child need frequent help or for someone to be around at home most of the time?

Or for younger patients...

Does the child need frequent help from a caretaker to accomplish tasks that a child this age should be able to accomplish (If child sometimes functions at an age appropriated level, then answer 'no.')

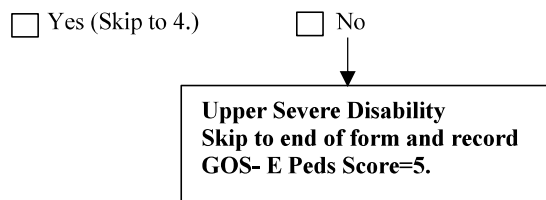


3. INDEPENDENCE OUTSIDE THE HOME

3a) Is the child able to shop and travel without assistance?

Or for younger patients...

Does the child behave age appropriately outside the home?



This item considers activities such as shopping and traveling, always in the context of age appropriated behaviors. This includes being able to plan what to buy, take care of money, and behave appropriately in public. The individual need not normally shop, but must be able to do so. A younger child must behave age appropriately in public. An older child may drive or use public transit to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and give instruction the driver. Older children who sometimes were allowed to travel independently before the injury should be able to walk to a neighbor's house, take a school bus, ride a bike, or take public transportation.

4. SCHOOL/WORK

4a) Can the child function at work or in school at his or her previous capacity?

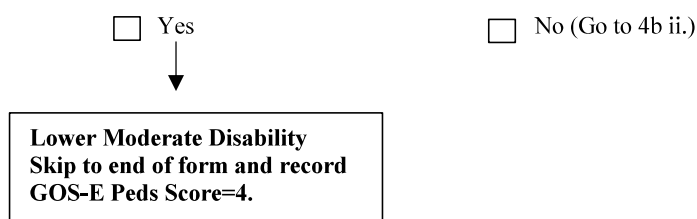
☐ Yes (Skip to 5.)

☐ No (Go to 4b.)

If an adolescent was working before the injury, then his or her current capacity for work should be at the same level. If the individual was seeking work before, then the injury should not have adversely affected chances of obtaining work or the level of work for which he or she is eligible. If the patient was in preschool or a student before the injury, then capacity for school work and school activities should not be adversely affected.

4b) Level of restriction:

i) Able to work only in a sheltered workshop or non-competitive job, in a school setting for severely impaired children or tutored at home, or currently unable to work or go to school.



ii) Reduced work or school capacity.

☐ Yes



Upper Moderate Disability
Skip to end of form and record GOS-
E Peds Score=3.

5. SOCIAL & LEISURE ACTIVITIES

5a) Is the child able to resume regular social and leisure activities?

☐ Yes (Skip to 6.)

☐ No (Go to 5b.)

The individual may not have resumed all previous leisure activities, but should not be prevented from doing so by physical or mental impairment. If he or she has stopped the majority of activities because of loss of interest or motivation, then this is considered a disability. For younger children, social and leisure activities can include games and toys played with caretakers, siblings or other children as well as the ability to interact in a playful manner with others.

5b) What is the extent of restrictions on social and leisure activities?

i) Unable to participate: Rarely, if ever, take part.

☐ Yes



Lower Moderate Disability
Skip to end of form and
record GOS-E Peds Score=4.

☐ No (Go to 5b ii.)

ii) Participate much less: Less than half as often.

☐ Yes



Upper Moderate Disability
Skip to end of form and record GOS-E
Peds Score=3.

☐ No (go to 5b iii.)

iii) Participate a bit less: At least half as often as before injury.

☐ Yes



Lower Good Recovery
Skip to end of form and
record GOS-E Peds Score=2.

☐ No (Skip to 6.) Y

6. FAMILY & FRIENDSHIPS

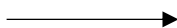
6a) Are there psychological problems that have resulted in ongoing disruption with respect to either family or friendships?

☐ Yes (Go to 6b.) ☐ No (Skip to 7.)

Typical post-traumatic personality changes: quick temper, irritability, anxiety, aggressive acts, insensitivity to others, mood swings, depression, and unreasonable or childish behavior that is not age appropriate.

6b) What is the extent of disruption or strain?

☐ Constant – daily and intolerable.



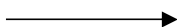
Lower Moderate Disability
Skip to end of form and record GOS-E Peds Score=4.

☐ Frequent – once a week or more, but tolerable.



Upper Moderate Disability
Skip to end of form and record GOS-E Peds Score = 3.

☐ Occasional – less than weekly.



Lower Good Recovery
Skip to end of form and record GOS-E Peds Score =2.

7. RETURN TO NORMAL LIFE

7a) Are there any other problems relating to the injury that affect daily life?

☐ Yes



Lower Good Recovery
Skip to end of form and record GOS-E Peds Score

☐ No



Upper Good Recovery
Skip to end of form and record GOS-E Peds Score =1.

Typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, concentration problems, or other problems.

RECORD GOS-E PEDS Score

SCORE:

Scoring caveat: Remember to consider premorbid status when assigning category scores to an outcome of injury; problems in functioning should have deteriorated from premorbid level.

8 – Death

7 - Vegetative State (VS)

6 - Lower Severe Disability (Lower SD)

5 - Upper Severe Disability (Upper SD)

4 - Lower Moderate Disability (Lower MD)

3 - Upper Moderate Disability (Upper MD)

2 - Lower Good Recovery (Lower GR)

1 - Upper Good Recovery (Upper GR)

GOS-E Peds Score: _____

(Adapted from Wilson, Pettigrew, and Teasdale, 1998)

3.6 Other papers

1- Exploring QT variability dependence from heart rate in coma and brain death on pediatric patients.

R. Almeida, M. J. Silva; A. P. Rocha

Computing in Cardiology 2013, Zaragoza, Spain, 2013, pp. 61-64.

<https://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=6712411>

2- Long-term HRV in critically ill pediatric patients: Coma versus brain death.

A.P. Rocha, R. Almeida, A. Leite, M. J. Silva; M. E. Silva

Computing in Cardiology 2014, Cambridge, MA, USA, 2014, pp. 89-92.

<https://ieeexplore.ieee.org/abstract/document/7042986>

3- Reliability Loss with Sampling Rate Reduction.

P. Sousa, R. Almeida, M. J. Silva; A. P. Rocha.

Computing in Cardiology 2015, Nice, France, 2015, pp. 689-692.

<https://ieeexplore.ieee.org/document/7411004>

4- Autonomic nervous system in newborns: a review based on heart rate variability.

Cardoso, S., Silva, M.J.; Guimarães, H. *Childs Nerv Syst* 33, 1053–1063 (2017).

<https://link.springer.com/article/10.1007/s00381-017-3436-8>

4. Discussion and Future Perspectives

4.1 Main findings

4.1.1 Paper I

In our first study we conducted a literature review to investigate the hypothesis that altered ANS regulation, specifically a decrease in HRV, is associated with worse outcomes and could serve as a prognostic factor in children with TBI.

We performed a search across three databases (Pubmed, Web of Science and Scopus) covering the period from 1996 to 2017, focusing on studies that evaluated HRV in children with TBI. Seven relevant studies were identified and analyzed.

Although this review was narrative in nature and did not adhere to PRISMA guidelines, a rigorous and structured methodology was employed to identify, select, evaluate, and synthesize the available evidence on this specific topic. The main finding of this study is that HRV can be useful when determining the severity of neurological damage and as a prognostic factor for recovery in pediatric TBI.

The results indicated that the severity of neurological damage correlates with poorer prognosis and lower HRV.

Patients who progressed to brain death exhibited a markedly lower LF/HF ratio, with a significant decline observed within the first few hours of hospitalization. Conversely, patients with more favorable prognoses had significantly higher LF/HF ratios. Despite the limited number of studies on this topic, the reviewed evidence consistently demonstrated that HRV was significantly reduced in children who progressed to BD following TBI.

4.1.2 Paper II

We conducted a systematic review to assess the hemodynamic consequences of BI in the pediatric population through an electronic literature search in *Pubmed*, *Scopus* and *Web of Science*, up to October 3, 2022. This is the first systematic review focusing specifically on the systemic hemodynamic consequences of BI in children. Our aim was to compile and report clinical evidence regarding abnormalities in systemic hemodynamics, electrocardiographic changes, arrhythmias, and elevation of cardiovascular damage markers resulting from BI, in the pediatric population, to set a path to determine management goals and achieve better outcomes.

Thirteen articles were included in the review, addressing the effects of BI in BP, rhythm disturbances and biomarkers of myocardial injury. The key findings of this study are as follows:

- 1 Systolic Blood Pressure: An SBP measure below the 5th percentile for age and sex, particularly within the first 6 h post-TBI, is associated with worse discharge outcomes.
- 2 Hypertension: while hypertension may have a protective role at a later stage after BI, it may be associated with higher mortality during the initial hours post-injury.
- 3 QTc Prolongation: BI may result in prolonged QTc intervals, which are linked to cardiac arrhythmias.
- 4 Neurogenic Stunned Cardiomyopathy: NSC is commonly observed after BI and perceived as a rise in serum troponin levels.

- 5 Tachycardia: Age-adjusted tachycardia at admission may be the most common presentation of NSC. Age-adjusted admission tachycardia was identified as a risk factor for myocardial injury after TBI (AUC 0.82, $p < 0.001$), being observed in 72.7% of children with isolated TBI and elevated cardiac troponin I levels, which suggests it might be the most common presentation of myocardial injury. The high incidence of myocardial injury in patients with isolated TBI, and its association with tachycardia, suggests a neurogenic origin due to high levels of circulating catecholamines, which mainly occurs in the first 6 days after hospital admission.
- 6 Hypotension and Mortality: Ten studies assessed the effect of BI in arterial BP. Hypotension is a marker of worse prognosis and higher mortality, as it reflects decreased cerebral blood flow and brain ischemia ^{388,389}. In adults it might be easier to set a target, as mortality increases as SBP decreases below 120 mmHg ³⁹⁰. In children, all efforts should focus on raising and maintaining SBP above the 5th percentile for age and sex, especially within the critical first 6 hours post-injury, as this period represents a time-sensitive therapeutic window ^{391–393}. Erickson also emphasizes the importance of monitoring MAP in children after severe TBI, since it's an essential factor in predicting cerebral perfusion pressure (CPP), alongside ICP. In settings where ICP monitoring is unavailable, maintaining MAP above the 10th percentile for age and sex is associated with better outcomes.
- 7 Hypertension and Mortality: Hypertension could also be a predictor of higher morbidity and mortality. In adults, Zafar et al. ³⁹⁰described the relationship between BP and mortality, following moderate to severe TBI, as bimodal, with mortality increasing both when SBP was below 120 mmHg and when

above 140 mmHg. One possible interpretation is that hypertension generates excessive flow through the breakdown of the blood-brain barrier, causing hemorrhage, hyper-perfusion injury, infarction and vasogenic edema, due to a failure of the vascular autoregulation in the injured brain. Hypertension as a prognostic marker remains understudied in pediatrics, with mixed results reported. While most studies did not report worse prognosis when SBP was higher at admission ^{388,394,395}, Johnson described a U-shaped curve between mortality and admission SBP ³⁹⁶, Kanter identified hypertension as a common and fatal finding predicting permanent neurological damage and death ³⁹⁷, and, finally, Freeman reported a higher need for neurosurgical intervention as SBP rose and a trend towards increased mortality with rising SBP ³⁹⁸.

- 8 Neurogenic Cardiac Injury Score (NCIS): Hasanin et al. ³⁹⁹ introduced the NCIS, which evaluates hemodynamic status by incorporating cardiac dysfunction, cardiac injury, and hypotension. Both myocardial dysfunction and a higher NCIS (>1) were associated with increased mortality and thus NCIS may represent a valuable tool in pediatric populations.

4.1.3 Paper III

The aim of this study was to investigate the potential impact of minor surgeries, along with the associated stress, pain, and medication, on HRV in healthy children by assessing HRV both before and after surgery. Since children can breathe at higher rates than 24/min we also calculated HF_n+ corresponding to frequencies higher than 0.15 Hz and include all high rates of breathing.

This observational prospective cohort study included a convenience cohort population of 47 children who were scheduled for elective minor surgery at the Pediatric Surgery Department of a tertiary hospital. The surgeries included phimosis correction (76.7% of

cases) and inguinal, umbilical, or abdominal wall hernia repairs. The study considered several dimensions, including the drugs used, pain levels, airway management, and surgical stress.

Our findings showed significant differences in HRV time domain indices before and after surgery in younger patients and in frequency domain in the older ones. They also demonstrated decreased HRV indices until one hour (60 minutes) after being submitted to surgery in both time domain and LF parameters, reflecting a parasympathetic withdrawal and sympathetic predominance. It is important to notice that, when measurements were taken after more than 60 min after surgery, no differences were found in HRV parameters. This may reflect a gradual reduction in the impact of surgery, including the associated stress and potentially the drugs used during the procedure, on the ANS over time, leading to the reestablishment of autonomic homeostasis. Even though our patients were only submitted to short duration anesthetic drugs, our study helps to support the time of 60 minutes as the minimum required period of standing in a post anesthesia care unit despite age or type of minor surgery.

Concerning the post-operative period, it is known, in adults, the correlation between ANS dysfunction and life-threatening complications after surgery ^{400–402}. The effect of anesthetics per se also affects ANS function. The ANS dysfunction represents a serious source of anesthetic risk affecting the outcome of patients undergoing surgery ³⁸⁷. However, no significant complications after surgery were found in our sample so any relation between ANS dysfunction and perioperative complications could be established. The main limitation is the measurement position. Although not very different concerning the degrees of inclination (45° before surgery and 30° after surgery) subjects were in a chair and sitting position before surgery and in a bed and supine position after surgery. Moreover, the small sample size compared with the diversity of the variables studied and

the fact that the observed variables were not normally distributed is a strong impeditive to achieve more conclusions about some of the variables analyzed, particularly regarding multivariate analysis.

4.1.4 Paper IV

We analyzed cardiovascular responses such as HR, BP and various measures of HRV in children with severe ABI who survived at least 12 hours after admission to the PICU. These parameters were compared with other prognostic indicators to determine their utility in predicting mortality and survival.

The key findings are as follows:

1. Cardiovascular Parameters and Mortality:

- Tachycardia, SBP and MBP < 5th percentiles, and MBP and DBP > 99th percentiles were significantly associated with mortality.
- Early systolic hypertension (SBP > 99th percentile) was associated with better outcomes, in contrast to findings from some prior studies.
- No association between mortality and the presence of bradycardia was found, unlike other studies^{186,403,404}.

2. HRV Measures:

- HRV time and frequency domains were significantly lower in children who progressed to BD. However, these measures were more effective in predicting survival than mortality.
- The *Poincaré* SD1/SD2 ratio was significantly associated with mortality after adjusting for age, sex, and ongoing medications. Higher values were observed in the BD group, with a cutoff point of 0.27 further enhancing its predictive capacity for mortality.

3. Predictive Cutoffs:

- Exploratory analysis revealed that HRV cutoffs (e.g., SDNN > 14.65 and LF > 9.17) improved identification of survivors, though statistical significance was limited by the small sample size.

4. Severity Scoring and Mortality Prediction:

- Combining an *Poincaré* SD1/SD2 cutoff > 0.27 with a PRISM III score > 12 enhanced mortality prediction.
- The Helsinki CT score demonstrated better prognostic performance compared to Marshall and Rotterdam CT scores for short-term outcomes.

The general discussion of this study addresses key aspects of HRV as a prognostic marker, its relationship with mortality, and associated clinical implications, while also highlighting important pathophysiological insights and study limitations:

1. **HRV and Mortality:** Reduced HRV measures are consistently associated with higher mortality rates. Conversely, increased HRV measures may serve as protective markers for survival in severe ABI, traumatic (TBI), and non-traumatic (NTBI). This study reinforces the potential of HRV as a vital prognostic indicator.
2. **Age and Sex Factors:** No significant differences in HR or HRV parameters were observed between sexes or across different age groups, suggesting that these parameters are age-independent prognostic markers in pediatric ABI.
3. **Pathophysiological Insights:** Our findings align with Valimaki et al. ⁴⁰⁵, who speculated that vagal modulation is disrupted in BD due to vagal nucleus destruction or blockage of vagal pathways, while sympathetic reflexes persist.

This may explain why the HF component was markedly reduced in the BD group, despite an insignificant change in the LF/HF ratio.

4. **Nonlinear HRV Measures:** The *Poincaré* plot and related indices (e.g., SD1 and SD2) offer valuable insights into autonomic balance. While traditional frequency methods require signal stationarity and are prone to artifacts, *Poincaré* plot provide robust data, even in nonstationary conditions. The nonlinear measure SampEn did not differ significantly between groups supporting the notion, found by other authors, that it may be a less sensitive marker⁴⁰⁶. Elevated *Poincaré* SD1/SD2 values in BD do not signify increased variability but rather indicate total autonomic failure, with relatively greater preservation of residual short-term fluctuations. Long-term variability, which typically depends on ANS modulation, virtually disappears in patients with BD due to the loss of balance between SNS and PSNS inputs.
5. **Clinical Implications:** BP monitoring remains critical. Hypotension (SBP/MBP < 5th percentiles) and hypertension (MBP /DBP > 99th percentile) within the first 12 hours post-admission was linked to higher mortality. Similarly, obliterated basal cisterns on CT imaging were strongly associated with poor outcomes, including a reduction in HRV measures.
6. **Limitations:** The small sample size limited the statistical power for multivariate analyses and definitive cutoff determination. Further studies are needed to validate these findings and refine HRV-based predictive models.

4.1.5 Paper V

In this study we investigated medium-to-long-term neurological outcomes in children with severe ABI, who survived to PICU discharge, aiming to identify cardiovascular predictors linked to unfavorable outcomes, particularly BP and HRV measures.

We selected 31 children, of which 24 (77.4%) were male, with a median age of 11.3 years old (IQR 5.6-14.3). Twenty-two (71.0%) patients had TBI and five (16.1%) cerebral hemorrhage. Sixteen children (51.6%) had a favorable neurological outcome at 3 months and twenty-one (67.7%) at 12 months.

The primary outcome measure was global functional outcome as measured by the Pediatrics Glasgow Outcome Scale Extended (GOSE-Peds) at 3 and 12 months after injury ⁴⁰⁷. These data were taken by reviewing the medical records. The outcome was dichotomized into favorable and unfavorable based on predefined cutoff. None to mild disability (GOSE-E PEDS category ≤ 2) was categorized as favorable outcome, whereas moderate to severe disability was categorized as unfavorable (GOSE-E PEDS category ≥ 3).

The major findings suggested Key Prognostic Indicators:

- i. Systolic BP: Hypertension (SBP > 95th percentile), within the first 12 hours after PICU admission was significantly associated with better neurological outcomes at 3 and 12 months. Patients with SBP > 95th percentile exhibited a significantly better neurological outcome at 3 months (68.2% vs. 31.8%, $p=0.006$), and at 12 months (83.3% vs. 16.7%, $p=0.002$) than those with worse neurological outcome.
- ii. HRV Measures: HRV values were higher, both on admission and 12 hours after admission in patients with a favorable prognosis at 3 and 12 months. Higher values of HRV parameters (RMSSD, LF, TP, and *Poincaré* SD1 and SD2) at 12 hours post-admission was only significantly associated with favorable outcomes at 3 months.
- iii. HRV Cutoffs and Outcomes: Although the sample size was too small to establish valid cutoff values, we found that patients with LF >70.0 ms² at 12 h after PICU

admission had a significantly better outcome at 12 months [11 (91.7 %) vs 1 (8.3 %), $p = 0.046$] than patients with a lower value. In a logistic regression model including LF power at 12 h (LF T12), gender, and age. Children with LF T12 >70 ms² had 11.4 times higher odds of achieving a good recovery after 12 months compared to those with lower values (OR =11.4; 95 % CI: 1.15–112.88; $p = 0.037$). Gender and age were not statistically significant predictors. The model correctly classified 74.2 % of cases overall, with high sensitivity (85.7 %) for identifying good outcomes but lower specificity (50.0 %) for predicting poor outcomes.

The presence of tachycardia or bradycardia was not related to the prognosis.

The major limitation of our study is that neurological outcomes were assessed solely through medical records. Behavioral, functional, and quality-of-life outcomes, including school performance, were not evaluated. The absence of interviews or direct inquiries with patients, families, or caregivers may limit the precision of disability assessments.

Elevated BP and HRV may reflect autonomic activation, particularly a sympathetic response, which seems protective in the context of severe ABI. Our data suggest that early ANS activation, reflected by hypertension and higher HRV measures, like LF, in the early hours following PICU admission, appears to be an indicator of better neurological outcomes and thus may serve as valuable, non-invasive predictors of neurological recovery in children with severe ABI. These findings highlight the importance of monitoring cardiovascular parameters during the critical early hours of PICU admission.

4.1.6 Other contributing papers

Exploring QT Variability Dependence from Heart Rate in Coma and Brain Death on Pediatric Patients

In this study we aimed to explore the potential of QT vs. RR uncoupling as a clinical tool for differentiating disease progression in children with ABI and as an early prognostic indicator of BD.

We selected a cohort of 12 children aged 11–14 years with ABI, of which 41.6 % with BD outcome. A parametric approach was applied to assess the short-term linear dependency of QT variability on HRV from Holter recordings. HRV, QT variability, and the QT variability fraction driven by HRV were quantified and compared across different outcomes and timepoints.

We showed that changes in QT variability -HRV relationships correlated with the severity of ABI. Therefore, uncoupling of QT vs RR has clinical potential in differentiating the progression of the disease within children with ABI, and can contribute for a better individual adjustment in treatment type and timing, and as early prognostic predictor of BD. Our findings support the clinical utility of QT variability measures in improving treatment decisions and timing.

Long-term HRV in critically ill pediatric patients: coma versus brain death

In this exploratory study, our objective was to characterize HRV in pediatric patients with ABI using advanced statistical models to try to identify parameters predictive of BD.

We analyzed HRV series from 15 patients with ABI admitted in a PICU, of which five has BD confirmed, one patient died during the recording and nine patients survived. We applied the AutoRegressive Fractionally Integrated Moving Average models with Generalized AutoRegressive Conditional Heteroscedastic errors (AFIRMA -GARCH).

The long memory is estimated by the parameter d of the ARFIMA-GARCH model, that indicates stability in mean HRV; whilst the time-varying conditional variance parameters u and v characterize the short-range and persistence in the conditional variance.

Previous studies indicate that for normal subjects these parameters show circadian variation. In our study, survivors showed circadian variations in HRV parameters (d , u , and v). Non-survivors exhibited reduced stability ($0.5 \leq d < 1$), indicating less stability in mean HRV, and lower persistence in volatility, with 90% of beats modeled as non-persistent ($v = 0$).

Findings: The parameter d has lowest values, $0 < d < 0.5$, during the night period with mean (std) 0.35 (0.05) and the parameters u , v present, for the same period, values of 0.17 (0.06) and 0.64 (0.05), respectively, indicating persistence in the conditional volatility. For non survivors the values of $0.5 \leq d < 1$ indicate less stability in mean HRV. Additionally lower persistence in volatility was noticed, with 90% of beats modeled with non-persistent ($v = 0$) volatility.

The long memory and time-varying conditional variance parameters estimated by ARFIMA-GARCH modeling significantly differ between groups. Our results indicated that persistence in volatility may be used to discriminate between survivors and non-survivors and holds promise as an early BD indicator, a finding that merits to be further explored.

Reliability loss with sampling rate reduction

We aimed to evaluate the reliability of beat-to-beat RR, RT, QT, and QTc interval measures, using low sampling frequency, typically available at bedside ECG monitoring systems. The reliability of beat-to-beat measures using low sampling frequency was quantified with respect to the original high sampling rate.

Methodology: We analyzed ECG records in intensive care patients. ECG recordings, originally at 1000 Hz, were down sampled to 500 Hz and 250 Hz. Automatic delineation was applied to extract beat-to-beat intervals. The reliability was assessed using concordance correlation coefficient (CCC), intraclass correlation coefficient (ICC), and the Information–based measure of disagreement (IBMD).

Results indicated that even at the lowest sampling rate 250 Hz, all time interval series are still reliable, with small measurement errors in comparison to the true differences between subjects. Therefore, these results suggest the feasibility of using low-frequency ECG data for clinical analysis, despite the limitations in high-frequency data availability. Indeed, high sampling frequency is not usually available in hospital monitoring systems.

Autonomic nervous system in newborns: a review based on heart rate variability

The aims of this review were to assess the evidence on the impact of gestational age (GA) on ANS maturation and autonomic control in preterm (PT) and term (TN) newborns, using HRV parameters.

Electronic databases (PubMed, World of Science, and Scopus) were searched for studies examining HRV (time and frequency domains) in PT and TN, from 1997 to 2017, who followed the 1996 Task Force guidelines. Ten studies met our inclusion criteria and were analyzed.

Key Findings: The available evidence indicated that advanced GA correlated with increased HRV, reflecting a marked progressive parasympathetic activity maturation relative to sympathetic activity in newborns.

Frequency-domains were more commonly used on the studies included on this review. HF power was the most used and showed significant relevance in measuring vagal maturation. The maturation of ANS requires at least 37 weeks of intrauterine development to reach a threshold value ^{408,409}. The maturation of ANS in PTN is

accompanied by an increase of HRV indices ^{410,411}. Parasympathetic development plays a critical role and thus it is important to consider the increasing importance of the development of the parasympathetic branch of ANS in PTN ⁴¹². This can be applied to newborns, especially preterm neonates (PTN), whose ANS is not yet fully developed ^{97,413}. In conclusion, HRV is an important tool to evaluate ANS development, particularly in preterm infants. However, standard recommendations for newborn HRV assessment are yet to be fully defined.

4.2 General Discussion and Implications for Clinical Practice

Despite all technological and scientific advancements, predicting the prognosis of children with severe ABI remains challenging, particularly regarding mortality and medium- to long-term morbidity. Established prognostic factors, such as intracranial pressure, cerebral perfusion pressure, severity scores, and pupillary response, are widely used ^{363,364,414}. However, cardiovascular response—particularly HRV, alongside BP, HR, and cardiac biomarkers measured early during admission to intensive care— have emerged as promising tools for early prognostication, shortly after admission, and for guiding appropriate interventions ^{160,379,383,384}.

Cardiovascular responses may be affected by several factors that are present in intensive care environments, such as stress, pain, anesthetic medication, analgesia, and sedation ^{129,169,186,208,372,390,415–417}.

We conducted two complementary review articles on this topic: one focused exclusively on HRV, while the other examined the other forms of cardiovascular response. Our findings underscore the potential of cardiovascular responses as prognostic indicators. However, despite years of research, these metrics have yet to be integrated into clinical practice for managing children with severe brain injuries.

Why, after all these years of research [PubMed currently lists >17 000 publications ²⁴⁴], has HRV not yet used in the daily clinical management of these children? Several of the following reasons may explain this ⁴¹⁸.

Complexity of HRV Signal Analysis

The signal used for HRV analysis is complex and influenced by numerous confounding factors, making interpretation challenging ^{40,419}. Additionally, accurate analysis of N-N intervals is crucial, but difficult to achieve in real-time clinical settings. Retrospective analyses, though clinically significant, are temporally impractical for immediate use.

Preprocessing HRV data for analyses is time consuming and labor-intensive, requiring typically, high-frequency ECG data collection (e.g., 250–1000 Hz); R-peak identification in the ECG signal for RR interval calculation; noise and ectopic beat removal through interpolation or filtering; and ensuring stationarity for accurate frequency-domain analysis ^{16,42,83,420}.

Moreover, HR correction is essential since HRV parameters are influenced by average HR ^{244,247}. Common correction methods include scaling correction (adjusting time-domain parameters for mean RR intervals), normalization (normalizing frequency-domain parameters to account for HR) and regression models (adjusting HRV parameters based on HR); or the use of HR-independent indices (computing ratios like LF/HF or *Poincaré* SD1/SD2) ⁴²¹.

In our studies we used higher sampling rates, such as 1000 Hz, to provide superior signal quality, but to try to overcome some challenges we demonstrated that reliable analyses can also be achieved at lower rates, such as 250 Hz ^{422,423}. This suggests that robust, non-invasive technologies can be developed for real-time HRV monitoring in intensive care

settings, enabling integration into daily clinical practice without significant added complexity.

Continuous non-invasive monitoring technologies for parasympathetic tone, such as the Newborn Infant Parasympathetic Evaluation Index (N.I.P.E) — the neonatal version of the Autonomic Nervous Index (ANI) used in adults — illustrate the potential of such advancements ^{424,425}. These systems have been successfully employed to evaluate and monitor the parasympathetic function of the ANS, assess pain during surgery and painful procedures, and predict intra- and postoperative pain ⁴²⁵. ANI monitoring under general anesthesia has proven valuable in reducing intraoperative opioid use and improving pain management throughout the perioperative period ⁴²⁴.

Developing a user-friendly, non-invasive devices that automatically provide real-time HRV values corrected for HR would not only improve workflow efficiency but also represent a significant step toward large-scale validation and broader clinical adoption, especially in pediatric intensive care settings.

Variability of HRV Measures and Lack of Standardization

The existence of multiple HRV measures obtained through different methods (as time domain, frequency domain, geometric, and non-linear) contributes to the variability in the results and is one of the current limitations for clinical use ^{17,83}. Focusing on one or two more representative measures could improve outcomes, enhance understanding of cutoff values across different ages, and facilitate the development of a user-friendly, real-time technological model. Streamlining clinical reasoning to concentrate on one or two key HRV parameters could enhance decision-making and reduce the dispersion caused by evaluating numerous existing measures.

Ratios such as *Poincaré* SD1/SD2 or LF/HF could be potential candidates. These parameters are relatively robust to HR changes but may still benefit from HR correction to ensure their reliability ^{62,244,247}. The LF/HF ratio, as traditionally calculated, does not account for HR variations. HR correction methods can make the ratio more representative of autonomic function by minimizing the confounding effect of HR ⁵². Also, *Poincaré* SD1/SD2 ratio is relatively robust to HR changes, as it represents the proportional relationship between short-term and long-term variability ^{61,66,68,82,426}. However, extreme HR can still indirectly affect the ratio, so HR correction might be considered.

Correcting for HR ensures that HRV analysis reflects autonomic function rather than skewness by the average HR. This is particularly important in pediatrics, to overcome the added complexity due to wide HR ranges in children, that makes challenging to establish age-specific cutoff values or predictive thresholds for mortality or morbidity ^{101,103,107,263,427,428}.

Task Force Guidelines and Pediatric Studies

The Task Force guidelines were published in 1996 and are outdated ¹⁷. Many articles have been published since then, and no updates have been made ⁴¹⁸. Sassi et al. ⁸³ investigated and summarized the value of HRV methods that were not included in the original standards ¹⁷, which have yielded medically relevant results in recent literature. However, their findings were limited in scope and extent. Moreover, guidelines lack pediatric-specific adaptations. Standard values may not apply to children and different authors used different frequency bands ^{14,429}.

Most available research predominantly involves adults, and only a small number of children, limiting pediatric-specific conclusions on the importance of HRV and its role in

the prognosis of children with ABI ³⁸³. Studies in children in intensive care with severe ABI often involve small sample sizes due to age restrictions and the rarity and severity of the condition ^{14,131,430,431}. Multicenter research collaborations could increase sample sizes and strengthen findings. Developing pediatric-specific HRV guidelines and standards would facilitate broader clinical applicability.

Bridging Gaps in Existing Knowledge

Cardiovascular responses in intensive care environments may be influenced by factors such as stress, pain, anesthetic medication, analgesia, and sedation, prompting us to first investigate HRV changes in healthy children undergoing surgery ^{129,169,186,208,372,390,415–417}. Our findings showed that, regardless of age, the presence of pain, medication, or type of surgery, no significant differences were observed in HRV measures 60 minutes after surgery, showing that ANS homeostasis is rapidly re-established when these factors are removed. This study helped to better understand the effect of these factors on the ANS response in healthy children and support the usual 60-minute stay in the post-anesthesia recovery room. However, prolonged persistence of stress may hinder recovery, despite the potential for ANS normalization.

In our study of children with severe ABI from diverse etiologies, the *Poincaré* SD1/SD2 ratio demonstrated a strong correlation with mortality, independent of sex, age, and ongoing medication. We identified a cutoff value that requires validation in larger studies due to the small sample size but highlights the importance of focusing on fewer prognostic measures of mortality. Among nonlinear methods, the *Poincaré* SD1/SD2 ratio emerged as a more robust measure, less sensitive to biases in our sample, and was the only metric

associated with mortality, unlike the widely discussed LF/HF ratio. This finding may be coincidental but, if validated in larger samples, it could represent a valuable parameter for further exploration as both a complementary indicator in BD diagnosis and a short-term mortality predictor.

HRV measures also proved valuable in predicting medium-term outcomes among survivors^{159,432–434}. Rather than serving as a marker of poor prognosis, higher HRV within the first few hours of admission were indicative of favorable outcomes, even in the presence of other severity indicators. Measures such as LF, SDNN and RMSSD emerged as strong predictive tools for both PICU survival and short-to-medium-term morbidity⁴³⁴. As expected, the identified cutoff values differ survival prediction and neurological outcome evaluation. These merely indicative values provide a good starting point for validation in studies with larger sample sizes.

Studies Limitations

Several limitations affected our findings. Firstly, data was collected from a small, convenience and heterogeneous, single-center sample of children with ABI, over an extended period. Also, we do not have exact data on the time elapsed between the injury and the ECG recording analyzed, although we are the only unit in the northern region of the country to receive children with severe ABI, that are always transferred directly to us. Moreover, factors like tracheal aspiration, transport, or sedation bolus that may affect HRV analysis were not considered^{161,203,435,436}. All these factors make it challenging to draw robust conclusions.

Secondly, technical issues should be taken in consideration. In our exploratory study, analysis was based on 10-minute ECG segments analysis. Our decision could impact the

outcomes, as short segments may be potentially impacted by physiological factors or even by signal loss or failure to detect R waves^{33,437}. The presence of artifact in some ECG waveform may alter HRV values. The manual selection of epochs can also be a source of bias. Also, frequency bands for adults were used due to the lack of pediatric-specific references³⁰.

We did not address other interesting areas of research. Longer HRV time series, which contain enough information to address slower fluctuations and different physiological mechanisms of regulation, were not explored in our work and should be explored in future research^{438–440}. High parasympathetic activity leads to immune suppression and sepsis, further contributing to higher mortality rates^{147,160}. Thus, it would have been interesting to assess whether HRV is related to the development of infections complications, such as sepsis or pneumonia, during the hospitalization⁴⁴¹.

Neurological outcomes were assessed solely through medical records, without interviews or inquiries with the patient, families, or caregivers. This approach may limit the precision of our perception regarding the extent of disabilities. We only addressed neurologic outcome in the survivors, and it could be interesting to evaluate behavioral and functional outcome and quality of life and school performance. Future studies should address these limitations to improve the robustness of findings.

4.3 Future Perspectives

Although HRV has shown promise in predicting mortality and morbidity, its potential as a prognostic tool in critical care, particularly among pediatric populations, requires further investigation. The possibility of elevated HRV serving as a protective factor remains an open area of study. Future research should focus on solidifying HRV's role not only as a prognostic marker but also as a potential therapeutic target. Defining and

validating specific cut-off values for key HRV parameters, in conjunction with HR and BP, could enhance the predictive accuracy for mortality and survival outcomes. Establishing these thresholds would represent a significant advancement in clinical prognostication. Additionally, creating a real-time data collection method would increase the prognostic accuracy of HRV assessments and improve its clinical relevance, as a continuous monitoring approach while providing a better understanding of a patient's condition. This real-time analysis could prove invaluable in complex diagnostic scenarios, such as determining BD, where autonomic responses may offer critical diagnostic insights. This technology could support clinicians to make rapid, informed decisions and adjust treatment protocols dynamically, ultimately optimizing survival outcomes. Furthermore, comparative studies examining the predictive value of HRV against well-established ECG parameters for adults, such as depressed ST segments, abnormal T waves and prolonged corrected QT interval (QTc interval), would provide valuable insights into the relative strengths of these markers in mortality prediction of critical care patients, particularly in pediatric settings where established predictive models are less established.

We did not assess cardiac dysfunction through echocardiography or serum troponins measurements. Future investigations should address this gap by computing the neurogenic cardiac injury score (NCIS) and evaluating its potential to predict mortality, in cases where both myocardial dysfunction and an elevated NCIS score are present. Replicating and extending the findings of Hasanin *et al.*³⁹⁹ could provide further evidence of the clinical relevance of the NCIS in pediatric populations.

Additionally, examining the potential relationship between QTc and HRV in predicting outcomes in children with severe ABI could provide new insights into the mechanisms underlying cardiac and autonomic dysregulation in this cohort. Evaluating and validating

the NCIS through echocardiographic assessments and cardiac enzyme measurements upon admission, could help to correlate these factors with prognosis and guide clinical decision making.

By advancing our understanding of these parameters and their interplay, future research has the potential to significantly improve prognostication and therapeutic strategies in critically ill pediatric patients.

Artificial Intelligence (AI) has the potential to play a transformative role in the real-time analysis of HRV and prognosis in critical care settings. By providing dynamic, individualized prognostic insights and helping to optimize treatment decisions, AI could improve patient outcomes, reduce mortality, and streamline clinical workflows. However, to realize this potential, it will be crucial to overcome technical, ethical, and regulatory challenges and ensure that AI systems are interpretable, rigorously validated and integrated into clinical practice in a way that complements and enhances human decision-making. As research and technology continue to evolve, the combination of AI and HRV monitoring may offer unprecedented opportunities for improving prognostication and personalized care in pediatric intensive care units and beyond.

5. Concluding remarks

Our study highlights the importance of early management of HR and BP in children with severe ABI to improve in-hospital outcomes. Specifically, we recommend that HR be controlled to avoid tachycardia and BP be maintained within the 5th to 99th percentiles during the first hours following PICU admission. These measures may play a critical role in reducing in-hospital mortality and enhancing patient prognosis.

The *Poincaré* SD1/SD2 ratio has emerged as a robust predictor of mortality in our cohort, showing significant potential both for predicting PICU mortality and for diagnosing brain death in children with traumatic and non-traumatic ABI. Notably, this measure operates independently of key demographic factors such as sex and age, and of pharmacological interventions, underscoring its utility as a generalizable biomarker.

Furthermore, HRV metrics have proven to be reliable indicators of patients' survival rather than mortality, allowing to identify patients with more favorable prognoses. Key HRV parameters, including the LF, SDNN, and RMSSD have demonstrated significant prognostic value. These measures, with distinct cutoff values, appear to be strong predictors not only of mortality but also of short-to-medium-term morbidity in survivors, supporting their potential use as prognostic tools in the clinical management of pediatric ABI.

In conclusion, our findings suggest that HRV, particularly through the *Poincaré* SD1/SD2 measure, alongside controlled HR and BP management, may significantly enhance the early prognosis and clinical decision-making in children with severe ABI. Future studies should further investigate these relationships, aiming to refine HRV-based prognostic models and establish actionable clinical thresholds for improved patient outcomes.

6. References

1. Novak V, Saul JP, Eckberg DL. Task Force report on heart rate variability. *Circulation*. 1997;96(3):1056–7.
2. IEEE Engineering in Medicine and Biology Society. Annual Conference (33rd: 2011: Boston Mass), Institute of Electrical and Electronics Engineers. 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society: [proceedings]: August 30-September 3, 2011, Boston, MA, USA. IEEE; 2011.
3. Taralov ZZ, Terziyski K V., Kostianev SS. Heart Rate Variability as a Method for Assessment of the Autonomic Nervous System and the Adaptations to Different Physiological and Pathological Conditions. Vol. 57, *Folia medica*. 2015. p. 173–80.
4. Karemaker JM. An introduction into autonomic nervous function. Vol. 38, *Physiological Measurement*. IOP Publishing Ltd; 2017. p. R89–118.
5. McCorry LK. Physiology of the autonomic nervous system. *Am J Pharm Educ*. 2007;71(4).
6. Tiwari R, Kumar R, Malik S, Raj T, Kumar P. Analysis of Heart Rate Variability and Implication of Different Factors on Heart Rate Variability. *Curr Cardiol Rev*. 2021 Jan 1;17(5).
7. van Ravenswaaij-Arts CKAHJSG van GHP. Heart Rate Variability. *Ann Intern Med*. 1993; 118:436–47.
8. Kreibig SD. Autonomic nervous system activity in emotion: A review. Vol. 84, *Biological Psychology*. 2010.
9. Lewis ME, Al-Khalidi AH, Bonser RS, Clutton-Brock T, Morton D, Paterson D, et al. Vagus nerve stimulation decreases left ventricular contractility in vivo in the human and pig heart. *Journal of Physiology*. 2001;534(2).

10. Kent KM, Epstein SE, Cooper T, Jacobowitz DM. Cholinergic innervation of the canine and human ventricular conducting system. Anatomic and electrophysiologic correlations. *Circulation*. 1974;50(5).
11. Purkayastha S, Stokes M, Bell KR. Autonomic nervous system dysfunction in mild traumatic brain injury: a review of related pathophysiology and symptoms. Vol. 33, *Brain Injury*. 2019.
12. Silva MJ, Antunes N. The utility of heart rate variability as a prognostic factor in children with traumatic brain injury. *Brain Inj*. 2020;34(13–14).
13. American Heart Association. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (Membership of the Task Force listed in the Appendix). *Eur Heart J*. 1996;17.
14. Conte E, Pieralice M, Laterza V, Losurdo A, Santacroce N, Conte S, et al. Traditional and a new methodology for analysis of heart rate variability: a review by physiological and clinical experimental results. *IJRRAS*. 2012;13(1):206.
15. Jelinek HF, Cornforth DJ, Koenig A, Riener R, Karmakar C, Imam MH, et al. Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Heart Rate Variability. *Eur Heart J*. 1996 Mar 1;5(93):1043–65.
16. Tarvainen MP, Ranta-Aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. *IEEE Trans Biomed Eng*. 2002;49(2):172–5.
17. DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: The SUDEP-7 Inventory. *Epilepsy and Behavior*. 2010;19(1).
18. Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: Re-examining a widely used heart rate variability measure. *Heart*. 2002;88(4).

19. Vanderlei LCM, Pastre CM, Freitas IF, Godoy MF de. Geometric indexes of heart rate variability in obese and eutrophic children. *Arq Bras Cardiol.* 2010;95(1).
20. Kleiger RE, Stein PK, Bigger JT. Heart rate variability: Measurement and clinical utility. Vol. 10, *Annals of Noninvasive Electrocardiology.* 2005.
21. İşler Y, Kuntalp M. Combining classical HRV indices with wavelet entropy measures improves to performance in diagnosing congestive heart failure. *Comput Biol Med.* 2007;37(10).
22. Kuusela T. Methodological aspects of heart rate variability analysis. In: *Heart Rate Variability (HRV) Signal Analysis: Clinical Applications.* 2016.
23. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol.* 2014;5.
24. Ebadi H, Shirazi AH, Mani AR, Jafari GR. Inverse statistical approach in heartbeat time series. *Journal of Statistical Mechanics: Theory and Experiment.* 2011;2011(8).
25. De Souza NM, Vanderlei LCM, Garner DM. Risk evaluation of diabetes mellitus by relation of chaotic globals to HRV. *Complexity.* 2015;20(3).
26. Bailly F, Longo G, Montevil M. A 2-dimensional geometry for biological time. Vol. 106, *Progress in Biophysics and Molecular Biology.* 2011.
27. Stein PK, Reddy A. Non-linear heart rate variability and risk stratification in cardiovascular disease. Vol. 5, *Indian Pacing and Electrophysiology Journal.* 2005.
28. Costa M, Goldberger AL, Peng CK. Multiscale Entropy Analysis of Complex Physiologic Time Series. *Phys Rev Lett.* 2002;89(6).
29. Johnston BW, Barrett-Jolley R, Krige A, Welters ID. Heart rate variability: Measurement and emerging use in critical care medicine. Vol. 21, *Journal of the Intensive Care Society.* SAGE Publications Inc.; 2020. p. 148–57.

30. Kuo TBJ, Lin T, Yang CCH, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. Vol. 46, *Heart Circ. Physiol.* 1999.
31. Kunikullaya U K, Kunnivil R, Vijayadas, Goturu J, Prakash VS, Murthy NS. Normative data and gender differences in heart rate variability in the healthy young individuals aged 18–30 years, a South Indian cross-sectional study. *Indian Pacing Electrophysiol J.* 2021 Mar 1;21(2):112–9.
32. Gonçalves H, Rocha AP, Ayres-De-Campos D, Bernardes J. Internal versus external intrapartum foetal heart rate monitoring: The effect on linear and nonlinear parameters. *Physiol Meas.* 2006 Mar 1;27(3):307–19.
33. Smith AL, Owen H, Reynolds KJ. Heart rate variability indices for very short-term (30 beat) analysis. Part 1: Survey and toolbox. *J Clin Monit Comput.* 2013 Oct;27(5):569–76.
34. Stojmenski A, Gusev M, Chorbev I, Tudjarski S, Poposka L, Vavlukis M. Age and Gender Impact on Heart Rate Variability towards Noninvasive Glucose Measurement. *Sensors (Basel).* 2023 Oct 25;23(21).
35. Nayak SK, Pradhan B, Mohanty B, Sivaraman J, Ray SS, Wawrzyniak J, et al. A Review of Methods and Applications for a Heart Rate Variability Analysis. Vol. 16, *Algorithms.* Multidisciplinary Digital Publishing Institute (MDPI); 2023.
36. Berntson GG, Bigger Jr. JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology.* 1997;34(6):623–48.
37. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: A review. Vol. 44, *Medical and Biological Engineering and Computing.* 2006. p. 1031–51.
38. Kamath M V., Watanabe MA, Upton ARM. Heart rate variability (HRV) signal analysis: clinical applications. Taylor & Francis; 2012. 513 p.

39. Ernst G. Hidden Signals—The History and Methods of Heart Rate Variability. *Front Public Health*. 2017 Oct 16;5.
40. Tarvainen MP, Lipponen JA, Kuoppa P. Analysis and preprocessing of HRV-Kubios HRV software. In: *ECG Time Series Variability Analysis: Engineering and Medicine*. 2017.
41. Sztajzel J. Heart rate variability: A noninvasive electrocardiographic method to measure the autonomic nervous system. Vol. 134, *Swiss Medical Weekly*. 2004.
42. Schumacher A. Linear and nonlinear approaches to the analysis of R-R interval variability. Vol. 5, *Biological research for nursing*. 2004.
43. Burr RL. Interpretation of Normalized Spectral Heart Rate Variability Indices In Sleep Research: A Critical Review. *Sleep*. 2007 Jul;30(7):913–9.
44. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. Vol. 90, *Heart*. 2004.
45. Furlan R, Barbic F, Piazza S, Tinelli M, Seghizzi P, Malliani A. Modifications of cardiac autonomic profile associated with a shift schedule of work. *Circulation*. 2000;102(16).
46. Thomas BL, Claassen N, Becker P, Viljoen M. Validity of Commonly Used Heart Rate Variability Markers of Autonomic Nervous System Function. *Neuropsychobiology*. 2019;78(1):14–26.
47. Heathers JAJ. Everything Hertz: methodological issues in short-term frequency-domain HRV. *Front Physiol*. 2014 May 7;5.
48. Amekran Y, Damoun N, El Hangouche AJ. Analysis of frequency-domain heart rate variability using absolute versus normalized values: implications and practical concerns. Vol. 15, *Frontiers in Physiology*. Frontiers Media SA; 2024.

49. Amekran Y, El hangouche AJ. Effects of Exercise Training on Heart Rate Variability in Healthy Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Cureus*. 2024 Jun 16.
50. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Vol. 4 FEB, *Frontiers in Physiology*. 2013.
51. Montano N, Porta A, Cogliati C, Costantino G, Tobaldini E, Casali KR, et al. Heart rate variability explored in the frequency domain: A tool to investigate the link between heart and behavior. Vol. 33, *Neuroscience and Biobehavioral Reviews*. 2009. p. 71–80.
52. Reyes del Paso GA, Langewitz W, Mulder LJM, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. Vol. 50, *Psychophysiology*. Blackwell Publishing Inc.; 2013. p. 477–87.
53. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991;84(2).
54. Hadase M, Azuma A, Zen K, Asada S, Kawasaki T, Kamitani T, et al. Very Low Frequency Power of Heart Rate Variability is a Powerful Predictor of Clinical Prognosis in Patients with Congestive Heart Failure. *Circulation Journal*. 2004;68(4).
55. Kop WJ, Stein PK, Tracy RP, Barzilay JI, Schulz R, Gottdiener JS. Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression. *Psychosom Med*. 2010;72(7).
56. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science* (1979). 1981;213(4504).

57. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation*. 1993;88(3).
58. Francesco B, Maria Grazia B, Emanuele G, Valentina F, Sara C, Chiara F, et al. Linear and nonlinear heart rate variability indexes in clinical practice. *Comput Math Methods Med*. 2012.
59. Henriques T, Ribeiro M, Teixeira A, Castro L, Antunes L, Costa-Santos C. Nonlinear methods most applied to heart-rate time series: A review. Vol. 22, *Entropy*. MDPI AG; 2020.
60. Bigger JT, Albrecht P, Steinman RC, Rolnitzky LM, Fleiss JL, Cohen RJ. Comparison of time- and frequency domain-based measures of cardiac parasympathetic activity in Holter recordings after myocardial infarction. *Am J Cardiol*. 1989 Sep;64(8):536–8.
61. Kamen PW, Krum H, Tonkin AM. Poincare plot of heart rate variability allows quantitative display of parasympathetic nervous activity in humans. *Clin Sci*. 1996;91(2).
62. Brennan M, Palaniswami M, Kamen P. Poincaré plot interpretation using a physiological model of HRV based on a network of oscillators. *Am J Physiol Heart Circ Physiol*. 2002;283(5 52-5).
63. Guzik P, Piskorski J, Krauze T, Schneider R, Wesseling KH, Wykrętowicz A, et al. Correlations between the Poincaré plot and conventional heart rate variability parameters assessed during paced breathing. *Journal of Physiological Sciences*. 2007 Feb;57(1):63–71.
64. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Vol. 5, *Frontiers in Public Health*. Frontiers Media S.A.; 2017.

65. Kamen PW, Tonkin AM. Application of the Poincaré plot to heart rate variability: a new measure of functional status in heart failure. *Aust N Z J Med*. 1995;25(1).
66. Tulppo MP, Mäkikallio TH, Takala TES, Seppänen T, Huikuri H V. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. *Am J Physiol Heart Circ Physiol*. 1996;271(1 40-1).
67. McCamley JD, Denton W, Arnold A, Raffalt PC, Yentes JM. On the calculation of sample entropy using continuous and discrete human gait data. *Entropy*. 2018 Oct 1;20(10).
68. Yentes JM, Hunt N, Schmid KK, Kaipust JP, McGrath D, Stergiou N. The appropriate use of approximate entropy and sample entropy with short data sets. *Ann Biomed Eng*. 2013 Feb 1;41(2):349–65.
69. Beckers F, Ramaekers D, Aubert AE. Approximate entropy of heart rate variability: validation of methods and application in heart failure. *Cardiovascular Engineering: An International Journal*. 2001;1(4):177–82.
70. Ernst G. Heart rate variability. Springer London. *Heart Rate Variability*. 2014.
71. Laitio T, Jalonen J, Kuusela T, Scheinin H. The role of heart rate variability in risk stratification for adverse postoperative cardiac events. Vol. 105, *Anesthesia and Analgesia*. 2007.
72. Bravi A, Longtin A, Seely AJE. Review and classification of variability analysis techniques with clinical applications. Vol. 10, *BioMedical Engineering Online*. 2011.
73. Costa MD, Peng CK, Goldberger AL. Multiscale analysis of heart rate dynamics: Entropy and time irreversibility measures. *Cardiovascular Engineering*. 2008;8(2).
74. Lippman N, Stein KM, Lerman BB. Comparison of methods for removal of ectopy in measurement of heart rate variability. *American Journal of Physiology-Heart and Circulatory Physiology*. 1994 Jul 1;267(1):H411–8.

75. Webber CL, Zbilut JP. Dynamical assessment of physiological systems and states using recurrence plot strategies. *J Appl Physiol.* 1994;76(2).
76. Marwan N, Carmen Romano M, Thiel M, Kurths J. Recurrence plots for the analysis of complex systems. Vol. 438, *Physics Reports.* 2007.
77. Marwan N, Wessel N, Meyerfeldt U, Schirdewan A, Kurths J. Recurrence-plot-based measures of complexity and their application to heart-rate-variability data. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics.* 2002;66(2).
78. Zbilut JP, Webber CL. Embeddings and delays as derived from quantification of recurrence plots. *Phys Lett A.* 1992;171(3–4).
79. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. *Front Physiol.* 2013;4.
80. Voss BA, Schulz S, Schroeder R, Baumert M, Caminal P. Methods derived from nonlinear dynamics for analysing heart rate variability. Vol. 367, *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences.* Royal Society; 2009. p. 277–96.
81. Schumacher A. Linear and nonlinear approaches to the analysis of R-R interval variability. Vol. 5, *Biological research for nursing.* 2004. p. 211–21.
82. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri H V., Peng CK, et al. Advances in heart rate variability signal analysis: Joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace.* 2015 Jul 29;17(9):1341–53.
83. Fatissou J, Oswald V, Lalonde F. Influence diagram of physiological and environmental factors affecting heart rate variability: An extended literature overview. Vol. 11, *Heart International.* 2016.

84. Sammito S, Böckelmann I. Factors influencing heart rate variability. *International Cardiovascular Forum Journal*. 2016;6.
85. Omerbegovic M. Analysis of heart rate variability and clinical implications. Vol. 63, *Medicinski arhiv*. 2009.
86. Stein PK, Kleiger RE, Rottman JN. Differing effects of age on heart rate variability in men and women. *American Journal of Cardiology*. 1997;80(3).
87. Bonnemeier H, Wiegand UKH, Brandes A, Kluge N, Katus HA, Richardt G, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: Differing effects of aging and gender on heart rate variability. *J Cardiovasc Electrophysiol*. 2003;14(8).
88. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, Stein PK. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation*. 1995;91(7).
89. Abhishekh HA, Nisarga P, Kisan R, Meghana A, Chandran S, Trichur Raju, et al. Influence of age and gender on autonomic regulation of heart. *J Clin Monit Comput*. 2013;27(3).
90. Rechlin T, Weis M, Ott C, Bleichner F, Joraschky P. Alterations of autonomic cardiac control in anorexia nervosa. *Biol Psychiatry*. 1998;43(5).
91. Poirier P, Hernandez TL, Weil KM, Shepard TJ, Eckel RH. Impact of diet-induced weight loss on the cardiac autonomic nervous system in severe obesity. *Obes Res*. 2003;11(9).
92. Kimura T, Matsumoto T, Akiyoshi M, Owa Y, Miyasaka N, Aso T, et al. Body fat and blood lipids in postmenopausal women are related to resting autonomic nervous system activity. *Eur J Appl Physiol*. 2006;97(5).

93. Choi JB, Hong S, Nelesen R, Bardwell WA, Natarajan L, Schubert C, et al. Age and ethnicity differences in short-term heart-rate variability. *Psychosom Med*. 2006;68(3).
94. Reed KE, Warburton DER, Whitney CL, McKay HA. Differences in heart rate variability between Asian and Caucasian children living in the same Canadian community. *Applied Physiology, Nutrition and Metabolism*. 2006;31(3).
95. Goto M, Nagashima M, Baba R, Nagano Y, Yokota M, Nishibata K, et al. Analysis of heart demonstrates effects on vagal modulation healthy children rate variability of development of heart rate in. *J Pediatr*. 1997; 130:725–9.
96. Finley JP, Nugent ST. Heart rate variability in infants, children and young adults. *J Auton Nerv Syst* [Internet]. 1995;51(2):103–8.
97. Bobkowski W, Stefaniak ME, Krauze T, Gendera K, Wykretowicz A, Piskorski J, et al. Measures of heart rate variability in 24-h ECGs depend on age but not gender of healthy children. *Front Physiol*. 2017 May 18;8(MAY).
98. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-Four Hour Time Domain Heart Rate Variability and Heart Rate: Relations to Age and Gender Over Nine Decades. 1998.
99. Silvetti M, Drago F, Ragonese P. Heart rate variability in healthy children and adolescents is partially related to age and gender. *Int J Cardiol*. 2001; 81:169–74.
100. Finley JP, Nugent ST. Autonomic Nervous System Heart rate variability in infants, children and young adults. Vol. 51, *Journal of the Autonomic Nervous System*. 1995.
101. van den Berg ME, Rijnbeek PR, Niemeijer MN, Hofman A, Herpen G van, Bots ML, et al. Normal values of corrected heart-rate variability in 10-second electrocardiograms for all ages. *Front Physiol*. 2018 Apr 27;9(APR).

102. Finley JP, Nugent ST, Hellenbrand W. Heart-rate variability in children. Spectral analysis of developmental changes between 5 and 24 years. *Can J Physiol Pharmacol*. 1987 Oct 1;65(10):2048–52.
103. Clairambault J, Curzi-Dascalova L, Kauffmann F, Médigue C, Leffler. Heart rate variability in normal sleeping full-term and preterm neonates. *Early Hum Dev*. 1992;28(2):169–83.
104. Massin M, Von Bernuth G. Normal ranges of heart rate variability during infancy and childhood. *Pediatr Cardiol*. 1997;18(4).
105. Galeev Zepp A. Heart Rate Variability in Healthy Six-to Sixteen-Year-Old Children. 2002.
106. Joanna Rękawek med, Rękawek J, Miszczak-Knecht M, Kawalec W, Mielniczuk J. Heart rate variability in healthy children. *Folia Cardiol*. 2003; 10:203–11.
107. Lenard Z, Studinger P, Mersich B, Kocsis L, Kollai M. Maturation of cardiovagal autonomic function from childhood to young adult age. *Circulation*. 2004 Oct 19;110(16):2307–12.
108. Fukuba Y, Sato H, Sakiyama T, Endo MY, Yamada M, Ueoka H, et al. Autonomic nervous activities assessed by heart rate variability in pre-and post-adolescent japanese. *J Physiol Anthropol*. 2009;28(6):269–73.
109. Cysarz D, Linhard M, Edelhäuser F, Längler A, van Leeuwen P, Henze G, et al. Unexpected course of nonlinear cardiac interbeat interval dynamics during childhood and adolescence. *PLoS One*. 2011;6(5).
110. Moodithaya S, Avadhany ST. Gender differences in age-related changes in cardiac autonomic nervous function. *J Aging Res*. 2012.

111. Michels N, Clays E, De Buyzere M, Huybrechts I, Marild S, Vanaelst B. Determinants and reference values of short-term heart rate variability in children. *Eur J Appl Physiol*. 2013;(113):1477–88.
112. Sharma VK, Subramanian SK, Arunachalam V, Rajendran R. Heart rate variability in adolescents – Normative data stratified by sex and physical activity. *Journal of Clinical and Diagnostic Research*. 2015 Oct 1;9(10):CC08-CC13.
113. Gasior JS, Sacha J, Jeleń PJ, Pawlowski M, Werner B, Dabrowski MJ. Interaction between heart rate variability and heart rate in pediatric population. *Front Physiol*. 2015;6(DEC).
114. Stejskal P, Šlachta R, Elfmark M, Salinger J, Retek T, Vychodil R, et al. The effect of age on short-term heart rate variability. Vol. 29. 1999.
115. Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Vol. 141, *International Journal of Cardiology*. 2010. p. 122–31.
116. Krislal-Boneh E, Raifel M, Froom P, Ribak J. Heart rate variability in health and disease. Vol. 2, *Reviews Scand J Work Environ Health*. 1995.
117. Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincaré plot geometry reflect nonlinear features of heart rate variability? *IEEE Trans Biomed Eng*. 2001;48(11).
118. Guzik P, Piskorski J, Krauze T, Wykretowicz A, Wysocki H. Heart rate asymmetry by Poincaré plots of RR intervals. In: *Biomedizinische Technik*. 2006.
119. de Zambotti M, Javitz H, Franzen PL, Brumback T, Clark DB, Colrain IM, et al. Sex- and Age-Dependent Differences in Autonomic Nervous System Functioning in Adolescents. *Journal of Adolescent Health*. 2018 Feb 1;62(2):184–90.

120. Ramaekers D. Heart rate variability and heart rate in healthy volunteers. Is the female autonomic nervous system cardioprotective? *Eur Heart J.* 1998 Sep;19(9):1334–41.
121. Seppälä S, Laitinen T, Tarvainen MP, Tompuri T, Veijalainen A, Savonen K, et al. Normal values for heart rate variability parameters in children 6-8 years of age: The PANIC Study. *Clin Physiol Funct Imaging.* 2014;34(4):290–6.
122. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: A meta-analysis. Vol. 64, *Neuroscience and Biobehavioral Reviews.* Elsevier Ltd; 2016. p. 288–310.
123. Jarrin DC, McGrath JJ, Poirier P, Séguin L, Tremblay RE, Montplaisir JY, et al. Short-term heart rate variability in a population-based sample of 10-year-old children. *Pediatr Cardiol.* 2015 Jan 1;36(1):41–8.
124. Bobkowski W, Stefaniak ME, Krauze T, Gendera K, Wykretowicz A, Piskorski J, et al. Measures of heart rate variability in 24-h ECGs depend on age but not gender of healthy children. *Front Physiol.* 2017 May 18;8(MAY).
125. Galeev AR, Igisheva L.N., Kazin E.M. Heart rate variability in healthy six- to sixteen-year-old children. *Hum Physiol.* 2002; 28:428–32.
126. Farland L V., Correia KF, Wise LA, Williams PL, Ginsburg ES, Missmer SA. P-values and reproductive health: What can clinical researchers learn from the American Statistical Association? Vol. 31, *Human Reproduction.* Oxford University Press; 2016. p. 2406–10.
127. Bravi A, Green G, Herry C, Wright HE, Longtin A, Kenny GP, et al. Do physiological and pathological stresses produce different changes in heart rate variability? *Front Physiol.* 2013;4 JUL.

128. Papaioannou V, Pneumatikos I, Maglaveras N. Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: Current strengths and limitations. Vol. 4 JUL, *Frontiers in Physiology*. 2013.
129. Mellekjaer L, Hammarström L, Andersen V, Yuen J, Heilmann C, Barington T, et al. Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: A combined Danish and Swedish study. *Clin Exp Immunol*. 2002;130(3).
130. Jarczok MN, Kleber ME, Koenig J, Loerbroeks A, Herr RM, Hoffmann K, et al. Investigating the associations of self-rated health: Heart rate variability is more strongly associated than inflammatory and other frequently used biomarkers in a cross-sectional occupational sample. *PLoS One*. 2015;10(2).
131. Dehghan A, Kardys I, De Maat MPM, Uitterlinden AG, Sijbrands EJG, Bootsma AH, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes*. 2007;56(3).
132. Kudat H, Akkaya V, Sozen AB, Salman S, Demirel S, Ozcan M, et al. Heart rate variability in diabetes patients. *Journal of International Medical Research*. 2006;34(3).
133. Badke CM, Carroll MS, Weese-Mayer DE, Sanchez-Pinto LN. Association between Heart Rate Variability and Inflammatory Biomarkers in Critically Ill Children*. *Pediatric Critical Care Medicine*. 2022;23(6).
134. Alcamo A, Weiss SL. Is Heart Rate Variability the Spice of Life? Vol. 23, *Pediatric Critical Care Medicine*. 2022.
135. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59(4).

136. Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation*. 1992;85(1).
137. Sessa F, Anna V, Messina G, Cibelli G, Monda V, Marsala G, et al. Heart rate variability as predictive factor for sudden cardiac death. Vol. 10, *Aging*. 2018.
138. Wiggers H, Bøtker HE, Egeblad H, Christiansen EH, Nielsen TT, Mølgaard H. Coronary artery bypass surgery in heart failure patients with chronic reversible and irreversible myocardial dysfunction: Effect on heart rate variability. *Cardiology*. 2002;98(4).
139. Mahajan R, Viangteeravat T, Akbilgic O. Improved detection of congestive heart failure via probabilistic symbolic pattern recognition and heart rate variability metrics. *Int J Med Inform*. 2017;108.
140. Havlicekova Z, Jurko A. Heart rate variability changes in children after cardiac transplantation. *Bratisl Lek Listy*. 2005;106(4–5).
141. Giardino ND, Chan L, Borson S. Combined heart rate variability and pulse oximetry biofeedback for chronic obstructive pulmonary disease: Preliminary findings. *Applied Psychophysiology Biofeedback*. 2004;29(2).
142. Cohen H, Benjamin J. Power spectrum analysis and cardiovascular morbidity in anxiety disorders. Vol. 128, *Autonomic Neuroscience: Basic and Clinical*. 2006.
143. Jönsson P. Respiratory sinus arrhythmia as a function of state anxiety in healthy individuals. *International Journal of Psychophysiology*. 2007;63(1).
144. Paniccia M, Paniccia D, Thomas S, Taha T, Reed N. Clinical and non-clinical depression and anxiety in young people: A scoping review on heart rate variability. Vol. 208, *Autonomic Neuroscience: Basic and Clinical*. 2017.

145. Hon EH, Lee ST. Electronic evaluation of fetal heart rate. VIII. Patterns preceding fetal death, further observations. *Am J Obstet Gynecol.* 1963;87.
146. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, Blood Pressure, and Heart Rate Variability: The Atherosclerosis Risk in Communities (ARIC) Study. *Hypertension.* 2003;42(6).
147. Ewing DJ, Campbell IW, Clarke BF. Mortality in diabetic autonomic neuropathy. *The Lancet.* 1976;307(7960).
148. La Fountaine MF, Wecht JM, Spungen AM, Bauman WA. Intra-inter visit reproducibility of short-term linear and nonlinear measurement of heart rate variability in tetraplegia and neurologically intact controls. *Physiol Meas.* 2010;31(3).
149. Barnaby DP, Fernando SM, Ferrick KJ, Herry CL, Seely AJE, Bijur PE, et al. Use of the low-frequency/high-frequency ratio of heart rate variability to predict short-term deterioration in emergency department patients with sepsis. *Emergency Medicine Journal.* 2018;35(2).
150. Abrahamovych O, Abrahamovych M, Farmaha M, Tolopko S. The peculiarities of the state of the autonomic nervous system estimated by the method of heart rate variability in patients with cirrhosis and syntropic damages of cardiovascular system. *Georgian Med News.* 2017;(273).
151. Dekker JM, Schouten EG, Klootwijk P, Pool J, Swenne CA, Kromhout D. Heart rate variability from short electrocardiographic recordings predicts mortality from all causes in middle-aged and elderly men. The Zutphen Study. *Am J Epidemiol.* 1997;145(10).

152. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham heart study. *Circulation*. 1994;90(2).
153. Serafi AS. Heart rate variability-analysis and clinical significance. Vol. 15, *Int. J. Biol. Biotech*. 2018.
154. Pagani M, Malfatto G, Pierini S, Casati R, Masu AM, Poli M, et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst*. 1988;23(2).
155. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP. Components of heart rate variability measured during healing of acute myocardial infarction. *Am J Cardiol*. 1988;61(4).
156. Ewing DJ, Neilson JMM, Travis P. New method for assessing cardiac parasympathetic activity using 24-hour electrocardiograms. *Br Heart J*. 1984;52(4).
157. Wolf MM, Varigos GA, Sloman JG. Sinus arrhythmia in acute myocardial infarction. *Medical Journal of Australia*. 1978;2(2).
158. Webb SW, Adgey AAJ, Pantridge JF. Autonomic Disturbance at Onset of Acute Myocardial Infarction. *Br Med J*. 1972;3(5818).
159. McAreavey D, Neilson JMM, Ewing DJ, Russell DC. Cardiac parasympathetic activity during the early hours of acute myocardial infarction. *Br Heart J*. 1989;62(3).
160. Luria MH, Sapoznikov D, Gilon D, Zahger D, Weinstein JM, Weiss AT, et al. Early heart rate variability alterations after acute myocardial infarction. *Am Heart J*. 1993;125(3).
161. Bento L, Fonseca-Pinto R, Póvoa P. Autonomic nervous system monitoring in intensive care as a prognostic tool. Systematic review. Vol. 29, *Revista Brasileira de Terapia Intensiva*. Associacao de Medicina Intensiva Brasileira - AMIB; 2017. p. 481–9.

162. Tulen JHM, Man In 't Veld AJ, Van Roon AM, Moleman P, Van Steenis HG, Blankestijn PJ, et al. Spectral analysis of hemodynamics during infusions of epinephrine and norepinephrine in men. *J Appl Physiol*. 1994;76(5).
163. Galletly DC, Buckley DHF, Robinson BJ, Corfiatis T. Heart rate variability during propofol anaesthesia. *Br J Anaesth*. 1994;72(2).
164. Riznyk L, Fijałkowska M, Przesmycki K. Effects of thiopental and propofol on heart rate variability during fentanyl-based induction of general anesthesia. *Pharmacological Reports*. 2005;57(1).
165. Vettorello M, Colombo R, De Grandis CE, Costantini E, Raimondi F. Effect of fentanyl on heart rate variability during spontaneous and paced breathing in healthy volunteers. *Acta Anaesthesiol Scand*. 2008;52(8).
166. Michaloudis D, Kochiadakis G, Georgopoulou G, Fraidakis O, Chlouverakis G, Petrou A, et al. The influence of premedication on heart rate variability. *Anaesthesia*. 1998;53(5).
167. Unoki T, Grap MJ, Sessler CN, Best AM, Wetzel P, Hamilton A, et al. Autonomic nervous system function and depth of sedation in adults receiving mechanical ventilation. *American Journal of Critical Care*. 2009 Jan;18(1):42–51.
168. Howell SJ, Wanigasekera V, Young JD, Gavaghan D, Sear JW, Garrard CS. Effects of propofol and thiopentone, and benzodiazepine premedication on heart rate variability measured by spectral analysis. *Br J Anaesth*. 1995;74(2).
169. Yi CH, Chen CL, Kuo TBJ, Yang CCH. The effect of acid suppression on sleep and cardiac autonomic regulation in GERD. *Hepatogastroenterology*. 2008;55(86–87).
170. MacFadyen RJ, Barr CS, Struthers AD. Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and reduces early morning rise in heart rate in heart failure patients. *Cardiovasc Res*. 1997;35(1).

171. Davies JJ, Band M, Morris A, Struthers AD. Spironolactone impairs endothelial function and heart rate variability in patients with Type 2 diabetes. *Diabetologia*. 2004;47(10).
172. Deschamps A, Denault A. Analysis of heart rate variability: a useful tool to evaluate autonomic tone in the anesthetized patient? *Can J Anesth*. 2009;4(55):208–13.
173. Kanaya N, Hirata N, Kurosawa S, Nakayama M, Namiki A. Differential Effects of Propofol and Sevoflurane on Heart Rate Variability [Internet]. Vol. 98, *Anesthesiology*. 2003.
174. Pfeifer R, Hopfe J, Ehrhardt C, Goernig M, Figulla HR, Voss A. Autonomic regulation during mild therapeutic hypothermia in cardiopulmonary resuscitated patients. *Clinical Research in Cardiology*. 2011 Sep 8;100(9):797–805.
175. Riordan WP, Norris PR, Jenkins JM, Morris JA. Early Loss of Heart Rate Complexity Predicts Mortality Regardless of Mechanism, Anatomic Location, or Severity of Injury in 2178 Trauma Patients. *Journal of Surgical Research*. 2009 Oct;156(2):283–9.
176. Kahraman S, Dutton RP, Hu P, Stansbury L, Xiao Y, Stein DM, et al. Heart Rate and Pulse Pressure Variability are Associated with Intractable Intracranial Hypertension After Severe Traumatic Brain Injury. *J Neurosurg Anesthesiol*. 2010 Oct;22(4):296–302.
177. Mowery NT, Norris PR, Riordan W, Jenkins JM, Williams AE, Morris JA. Cardiac uncoupling and heart rate variability are associated with intracranial hypertension and mortality: A study of 145 trauma patients with continuous monitoring. *Journal of Trauma - Injury, Infection and Critical Care*. 2008 Sep;65(3):621–6.
178. Norris PR, Stein PK, Morris JA. Reduced heart rate multiscale entropy predicts death in critical illness: A study of physiologic complexity in 285 trauma patients. *J Crit Care*. 2008 Sep;23(3):399–405.

179. Papaioannou V, Giannakou M, Maglaveras N, Sofianos E, Giala M. Investigation of heart rate and blood pressure variability, baroreflex sensitivity, and approximate entropy in acute brain injury patients. *J Crit Care*. 2008;23(3):380–6.
180. Grogan EL, Morris JA, Norris PR, France DJ, Ozdas A, Stiles RA, et al. Reduced heart rate volatility: An early predictor of death in trauma patients. *Ann Surg*. 2004;240(3).
181. Rapenne T, Moreau D, Lenfant F, Vernet M, Boggio V, Cottin Y, et al. Could heart rate variability predict outcome in patients with severe head injury? A pilot study. *J Neurosurg Anesthesiol* [Internet]. 2001;13(3):260–8.
182. Winchell RJ, Hoyt DB. Analysis of heart-rate variability: A noninvasive predictor of death and poor outcome in patients with severe head injury. *Journal of Trauma - Injury, Infection and Critical Care*. 1997;43(6).
183. Schmidt H, Hoyer D, Hennen R, Heinroth K, Rauchhaus M, Prondzinsky R, et al. Autonomic dysfunction predicts both 1- and 2-month mortality in middle-aged patients with multiple organ dysfunction syndrome. *Crit Care Med*. 2008;36(3).
184. Gujjar AR, Sathyaprabha TN, Nagaraja D, Thennarasu K, Pradhan N. Heart Rate Variability and Outcome in Acute Severe Stroke: Role of Power Spectral Analysis. *Neurocrit Care*. 2004;1(3):347–54.
185. Haji-Michael PG, Vincent JL, Degaute JP, van de Borne P. Power spectral analysis of cardiovascular variability in critically ill neurosurgical patients. *Crit Care Med*. 2000 Jul;28(7):2578–83.
186. Papaioannou VE, Maglaveras N, Houvarda I, Antoniadou E, Vretzakis G. Investigation of altered heart rate variability, nonlinear properties of heart rate signals, and organ dysfunction longitudinally over time in intensive care unit patients. *J Crit Care*. 2006 Mar;21(1):95–103.

187. Yien HW, Hseu SS, Lee LC, Kuo TBJ, Lee TY, Chan SHH. Spectral analysis of systemic arterial pressure and heart rate signals as a prognostic tool for the prediction of patient outcome in the intensive care unit. *Crit Care Med*. 1997 Feb;25(2):258–66.
188. Winchell RJ, Hoyt DB. Spectral analysis of heart rate variability in the ICU: A measure of autonomic function. *Journal of Surgical Research*. 1996. Jun;63(1):11-6.
189. Bodenes L, N’Guyen QT, Le Mao R, Ferrière N, Pateau V, Lellouche F, et al. Early heart rate variability evaluation enables to predict ICU patients’ outcome. *Sci Rep*. 2022 Dec 1;12(1).
190. Norris PR, Morris JA, Ozdas A, Grogan EL, Williams AE. Heart rate variability predicts trauma patient outcome as early as 12 h: Implications for military and civilian triage. *Journal of Surgical Research*. 2005;129(1).
191. Proctor KG, Atapattu SA, Duncan RC. Heart rate variability index in trauma patients. *Journal of Trauma - Injury, Infection and Critical Care*. 2007;63(1).
192. Morris JA, Norris PR, Ozdas A, Waitman LR, Harrell FE, Williams AE, et al. Reduced Heart Rate Variability: An Indicator of Cardiac Uncoupling and Diminished Physiologic Reserve in 1,425 Trauma Patients. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2006 Jun;60(6):1165–74.
193. Huang CT, Tsai YJ, Lin JW, Ruan SY, Wu HD, Yu CJ. Application of heart-rate variability in patients undergoing weaning from mechanical ventilation. *Crit Care*. 2014;18(1): R21.
194. Shen HN, Lin LY, Chen KY, Kuo PH, Yu CJ, Wu HD, et al. Changes of Heart Rate Variability During Ventilator Weaning. *Chest*. 2003 Apr;123(4):1222–8.
195. Tang SC, Jen HI, Lin YH, Hung CS, Jou WJ, Huang PW, et al. Complexity of heart rate variability predicts outcome in intensive care unit admitted patients with acute stroke. *J Neurol Neurosurg Psychiatry*. 2015 Jan;86(1):95–100.

196. Oh J, Cho D, Park J, Na SH, Kim J, Heo J, et al. Prediction and early detection of delirium in the intensive care unit by using heart rate variability and machine learning. *Physiol Meas*. 2018 Mar 27;39(3):035004.
197. Oh J, Cho D, Kim J, Heo J, Park J, Na SH, et al. Changes in heart rate variability of patients with delirium in intensive care unit. In: 2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2017. p. 3118–21.
198. Broucqsault-Dédrie C, De Jonckheere J, Jeanne M, Nseir S. Measurement of Heart Rate Variability to Assess Pain in Sedated Critically Ill Patients: A Prospective Observational Study. *PLoS One*. 2016 Jan 25;11(1): e0147720.
199. Papaioannou V, Chouvarda I, Gaertner E, Benyamina M, Ferry A, Maurel V, et al. Heart rate variability and cardiac baroreflex inhibition-derived index predicts pain perception in burn patients. *Burns*. 2016 Nov;42(7):1445–54.
200. Nagaraj SB, Biswal S, Boyle EJ, Zhou DW, McClain LM, Bajwa EK, et al. Patient-Specific Classification of ICU Sedation Levels from Heart Rate Variability*. *Crit Care Med*. 2017 Jul;45(7): e683–90.
201. Billman GE. Heart rate variability - a historical perspective. *Front Physiol* [Internet]. 2011;129th ed. 2011; 2:86.
202. Eckberg DL. Sympathovagal Balance. *Circulation*. 1997 Nov 4;96(9):3224–32.
203. Houle MS, Billman GE. Low-frequency component of the heart rate variability spectrum: a poor marker of sympathetic activity. *American Journal of Physiology-Heart and Circulatory Physiology*. 1999 Jan 1;276(1):H215–23.
204. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. *J Appl Physiol*. 1993 Nov 1;75(5):2310–7.

205. Kollai M, Mizsei G. Respiratory sinus arrhythmia is a limited measure of cardiac parasympathetic control in man. *J Physiol.* 1990 May;424(1):329–42.
206. Hainsworth R. Circulatory responses from lung inflation in anesthetized dogs. *American Journal of Physiology-Legacy Content.* 1974 Feb 1;226(2):247–55.
207. Hadase M, Azuma A, Zen K, Asada S, Kawasaki T, Kamitani T, et al. Very Low Frequency Power of Heart Rate Variability is a Powerful Predictor of Clinical Prognosis in Patients with Congestive Heart Failure. *Circulation Journal.* 2004;68(4):343–7.
208. Hamilton DJ, Ignatavicius DD. Interventions for clients with vascular problems. In: Ignatavicius DD, Workman ML, editors. *Medical-surgical nursing: Critical thinking for collaborative care.* Pennsylvania: W.B.Saunders.; 2002.
209. Perrin KO. Assessment of the cardiovascular system. In: Ignatavicius DD, Workman ML, editors. *Medical-surgical nursing: Critical thinking for collaborative care.* Pennsylvania: W.B.Saunders.; 2002.
210. Esler M, Straznicki N, Eikelis N, Masuo K, Lambert G, Lambert E. Mechanisms of sympathetic activation in obesity-related hypertension. Vol. 48, *Hypertension.* 2006.
211. Grassi G, Mark A, Esler M. The Sympathetic Nervous System Alterations in Human Hypertension. Vol. 116, *Circulation Research.* 2015.
212. Grassi G. Sympathomodulatory Effects of Antihypertensive Drug Treatment. *Am J Hypertens.* 2016;29(6).
213. DeLalio LJ, Sved AF, Stocker SD. Sympathetic Nervous System Contributions to Hypertension: Updates and Therapeutic Relevance. Vol. 36, *Canadian Journal of Cardiology.* Elsevier Inc.; 2020. p. 712–20.
214. Pal GK, Ganesh V, Karthik S, Nanda N, Pal P. The Effects of Short-Term Relaxation Therapy on Indices of Heart Rate Variability and Blood Pressure in Young Adults. *Am J Health Promot.* 2014;29(1):23–8.

215. Mussalo H, Vanninen E, Ikäheimo R, Laitinen T, Laakso M, Länsimies E, et al. Heart rate variability and its determinants in patients with severe or mild essential hypertension. *Clinical Physiology*. 2001 Sep 24;21(5):594–604.
216. Leon DF, Shaver JA, Leonard JJ. Reflex heart rate control in man. *Am Heart J*. 1970;80(6).
217. Rajashekar RK, Niveditha Y, Ghosh S. Blood pressure response to cold pressor test in siblings of hypertensives. *Indian J Physiol Pharmacol*. 2003;47(4).
218. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res*. 1986;59(2).
219. Barbosa TC, Vianna LC, Fernandes IA, Prodel E, Rocha HNM, Garcia VP, et al. Intrathecal fentanyl abolishes the exaggerated blood pressure response to cycling in hypertensive men. *Journal of Physiology*. 2016;594(3).
220. Songcharern N, Ruangthai R, Tumnark P, Phoemsapthawee J. Improved arterial stiffness after combined aerobic and resistance training: correlation with heart rate variability change in prehypertensive offspring of hypertensive parents. *J Exerc Rehabil*. 2022;18(6).
221. Schneider GM, Jacobs DW, Gevirtz RN, O'Connor DT. Cardiovascular haemodynamic response to repeated mental stress in normotensive subjects at genetic risk of hypertension: Evidence of enhanced reactivity, blunted adaptation, and delayed recovery. *J Hum Hypertens*. 2003;17(12).
222. Ni H, Cho S, Mankoff J, Yang J, Dey A k. Automated recognition of hypertension through overnight continuous HRV monitoring. *J Ambient Intell Humaniz Comput*. 2018 Nov 8;9(6):2011–23.

223. Lan K chan, Raknim P, Kao WF, Huang JH. Toward Hypertension Prediction Based on PPG-Derived HRV Signals: a Feasibility Study. *J Med Syst*. 2018 Jun 21;42(6):103.
224. Martinez PF, Okoshi MP. Heart Rate Variability in Coexisting Diabetes and Hypertension. *Arq Bras Cardiol*. 2018. Jul;111(1):73-74.
225. Poddar MG, Birajdar AC, Virmani J, Kriti. Automated Classification of Hypertension and Coronary Artery Disease Patients by PNN, KNN, and SVM Classifiers Using HRV Analysis. In: *Machine Learning in Bio-Signal Analysis and Diagnostic Imaging*. Elsevier; 2019. p. 99–125.
226. Goldberger JJ, Johnson NP, Subacius H, Ng J, Greenland P. Comparison of the physiologic and prognostic implications of the heart rate versus the RR interval. *Heart Rhythm*. 2014 Nov 1;11(11):1925–33.
227. Billman GE. The effect of heart rate on the heart rate variability response to autonomic interventions. *Front Physiol*. 2013;4 AUG.
228. Ungi I, Thury A, Csanády M. Investigation of The Correlation Between Heart Rate and Heart Rate Variability. *Computers in Cardiology*. 1995:189-191.
229. Panina G, Khot UN, Nunziata E, Cody RJ, Binkley PF. Assessment of autonomic tone over a 24-hour period in patients with congestive heart failure: Relation between mean heart rate and measures of heart rate variability. *Am Heart J*. 1995;129(4).
230. La Rovere MT, Mortara A, Pantaleo P, Maestri R, Cobelli F, Tavazzi L. Scopolamine improves autonomic balance in advanced congestive heart failure. *Circulation*. 1994;90(2).
231. Mccraty R, Shaffer F. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health Risk. *Glob Adv Health Med*. 2015 Jan 1;4(1):46–61.

232. Carter R, Hinojosa-Laborde C, Convertino VA. Sex comparisons in muscle sympathetic nerve activity and arterial pressure oscillations during progressive central hypovolemia. *Physiol Rep*. 2015;3(6).
233. Estévez-Báez M, Machado C, Leisman G, Brown-Martínez M, Jas-García JD, Montes-Brown J, et al. A procedure to correct the effect of heart rate on heart rate variability indices: Description and assessment. *International Journal on Disability and Human Development*. 2016 Aug 1;15(3):277–92.
234. Monfredi O, Lyashkov A, Johnsen A, Inada S, Schneider H, Wang R, et al. Biophysical Characterization of the Underappreciated and Important Relationship Between Heart Rate Variability and Heart Rate. *Hypertension [Internet]*. 2014; 64:1334–43.
235. Nieminen T, Kähönen M, Kööbi T, Nikus K, Viik J. Heart rate variability is dependent on the level of heart rate. *Am Heart J*. 2007 Jul;154(1): e13.
236. Sacha J, Sobon J, Sacha K, Barabach S. Heart rate impact on the reproducibility of heart rate variability analysis. *Int J Cardiol*. 2013 Oct;168(4):4257–9.
237. Sacha J. Interaction between Heart Rate and Heart Rate Variability. *Annals of Noninvasive Electrocardiology*. 2014 May 6;19(3):207–16.
238. Sacha J. Interplay between heart rate and its variability: a prognostic game. *Front Physiol*. 2014 Sep 12;5.
239. Sacha J. Heart rate contribution to the clinical value of heart rate variability. *Kardiol Pol*. 2014 Oct 15;72(10):919–24.
240. Sacha J, Barabach S, Statkiewicz-Barabach G, Sacha K, Müller A, Piskorski J, et al. How to select patients who will not benefit from ICD therapy by using heart rate and its variability? 2013.

241. Sacha J, Barabach S, Statkiewicz-Barabach G, Sacha K, Müller A, Piskorski J, et al. How to strengthen or weaken the HRV dependence on heart rate — Description of the method and its perspectives. *Int J Cardiol.* 2013 Sep;168(2):1660–3.
242. Sacha J, Barabach S, Statkiewicz-Barabach G, Sacha K, Müller A, Piskorski J, et al. Gender differences in the interaction between heart rate and its variability — How to use it to improve the prognostic power of heart rate variability. *Int J Cardiol.* 2014 Feb;171(2): e42–5.
243. Pradhapan P, Tarvainen MP, Nieminen T, Lehtinen R, Nikus K, Lehtimäki T, et al. Effect of heart rate correction on pre- and post-exercise heart rate variability to predict risk of mortality - an experimental study on the FINCAVAS cohort. *Front Physiol.* 2014 Jun 3;5.
244. Billman GE. The effect of heart rate on the heart rate variability response to autonomic interventions. *Front Physiol.* 2013;4 Aug.
245. Virtanen M, Kähönen M, Nieminen T, Karjalainen P, Tarvainen M, Lehtimäki T, et al. Heart rate variability derived from exercise ECG in the detection of coronary artery disease. *Physiol Meas.* 2007 Oct 1;28(10):1189–200.
246. Melenovsky V, Simek J, Sperl M, Malik J, Wichterle D. Relation between actual heart rate and autonomic effects of beta blockade in healthy men. *Am J Cardiol.* 2005 Apr;95(8):999–1002.
247. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Determinants of heart rate variability. *J Am Coll Cardiol.* 1996 Nov;28(6):1539–46.
248. Karlsson M, Hörnsten R, Rydberg A, Wiklund U. Automatic filtering of outliers in RR intervals before analysis of heart rate variability in Holter recordings: a comparison with carefully edited data. *Biomed Eng Online.* 2012 Dec 11;11(1):2.

249. Rijnbeek P. New normal limits for the paediatric electrocardiogram. *Eur Heart J*. 2001 Apr 15;22(8):702–11.
250. Yilmaz M, Kayancicek H, Cekici Y. Heart rate variability: Highlights from hidden signals. *J Integr Cardiol*. 2018;4(5).
251. Sammito S, Thielmann B, Klussmann A, Deußen A, Braumann KM, Böckelmann I. Guideline for the application of heart rate and heart rate variability in occupational medicine and occupational health science. Vol. 19, *Journal of Occupational Medicine and Toxicology*. BioMed Central Ltd; 2024.
252. Britton A, Shipley M, Malik M, Hnatkova K, Hemingway H, Marmot M. Changes in Heart Rate and Heart Rate Variability Over Time in Middle-Aged Men and Women in the General Population (from the Whitehall II Cohort Study). *Am J Cardiol*. 2007 Aug;100(3):524–7.
253. Eyre ELJ, Duncan MJ, Birch SL, Fisher JP. The influence of age and weight status on cardiac autonomic control in healthy children: A review. Vol. 186, *Autonomic Neuroscience: Basic and Clinical*. Elsevier B.V.; 2014. p. 8–21.
254. Kuo TBJ, Lin T, Yang CCH, Li CL, Chen CF, Chou P. Effect of aging on gender differences in neural control of heart rate. *American Journal of Physiology-Heart and Circulatory Physiology*. 1999 Dec 1;277(6):H2233–9.
255. Felber Dietrich D, Schindler C, Schwartz J, Barthélémy JC, Tschopp JM, Roche F, et al. Heart rate variability in an ageing population and its association with lifestyle and cardiovascular risk factors: results of the SAPALDIA study. *EP Europace*. 2006 Jul 1;8(7):521–9.
256. Alvares GA, Quintana DS, Hickie IB, Guastella AJ. Autonomic nervous system dysfunction in psychiatric disorders and the impact of psychotropic medications: a

systematic review and meta-analysis. *Journal of Psychiatry and Neuroscience*. 2016 Mar 1;41(2):89–104.

257. Alberto U. F. Modifications of the Cardiovascular System with Aging. *Am J Geriatr Cardiol*. 2002 Jan 6;11(1):30–4.

258. Fukusaki C, Kawakubo K, Yamamoto Y. Assessment of the primary effect of aging on heart rate variability in humans. *Clinical Autonomic Research*. 2000 Jun;10(3):123–30.

259. Greiser KH, Kluttig A, Schumann B, Swenne CA, Kors JA, Kuss O, et al. Cardiovascular diseases, risk factors and short-term heart rate variability in an elderly general population: the CARLA study 2002–2006. *Eur J Epidemiol*. 2009 Mar 7;24(3):123–42.

260. Shioyai Y, Stefanovska A, McClintock PVE. Nonlinear dynamics of cardiovascular ageing. *Phys Rep*. 2010 Mar;488(2–3):51–110.

261. Voss A, Heitmann A, Schroeder R, Peters A, Perz S. Short-term heart rate variability—age dependence in healthy subjects. *Physiol Meas*. 2012 Aug 1;33(8):1289–311.

262. Zhang J. Effect of Age and Sex on Heart Rate Variability in Healthy Subjects. *J Manipulative Physiol Ther*. 2007 Jun;30(5):374–9.

263. Abhishekh HA, Nisarga P, Kisan R, Meghana A, Chandran S, Trichur Raju, et al. Influence of age and gender on autonomic regulation of heart. *J Clin Monit Comput*. 2013 Jun 8;27(3):259–64.

264. Fagard RH. A population-based study on the determinants of heart rate and heart rate variability in the frequency domain. Vol. 63, *Verhandelingen - Koninklijke Academie voor Geneeskunde van België*. 2001.

265. Boudreau P, Yeh WH, Dumont GA, Boivin DB. Circadian Variation of Heart Rate Variability Across Sleep Stages. *Sleep*. 2013 Dec 1;36(12):1919–28.
266. Sammito S, Sammito W, Böckelmann I. The circadian rhythm of heart rate variability. *Biol Rhythm Res*. 2016 Sep 2;47(5):717–30.
267. Hill LK, Hu DD, Koenig J, Sollers JJ, Kapuku G, Wang X, et al. Ethnic Differences in Resting Heart Rate Variability. *Psychosom Med*. 2015 Jan;77(1):16–25.
268. Faisal Lutfi M, Yosif Sukkar M, Professor of Physiology A, of Physiology P. The effect of gender on heart rate variability in asthmatic and normal healthy adults. Vol. 5, *International Journal of Health Sciences*. 2011.
269. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: A meta-analysis. *Neurosci Biobehav Rev*. 2016 May; 64:288–310.
270. Snieder H, van Doornen LJP, Boomsma DI, Thayer JF. Sex Differences and Heritability of Two Indices of Heart Rate Dynamics: A Twin Study. *Twin Research and Human Genetics*. 2007 Apr 1;10(2):364–72.
271. Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindbland LE, Jensen-Urstad M. Heart rate variability in healthy subjects is related to age and gender. *Acta Physiol Scand*. 1997 Jun 7;160(3):235–41.
272. Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, et al. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. *Clinical Autonomic Research*. 2001 Apr;11(2):99–108.
273. Barante M, Krauss T, Ortak J, Lieb W, Reppel M, Burgdorf C, et al. Effects of Gender and Aging on Differential Autonomic Responses to Orthostatic Maneuvers. *J Cardiovasc Electrophysiol*. 2008 Dec 24;19(12):1296–303.

274. Abhishekh HA, Nisarga P, Kisan R, Meghana A, Chandran S, Trichur Raju, et al. Influence of age and gender on autonomic regulation of heart. *J Clin Monit Comput*. 2013 Jun 8;27(3):259–64.
275. Fagard RH, Pardaens K, Staessen JA. Influence of demographic, anthropometric and lifestyle characteristics on heart rate and its variability in the population. *J Hypertens*. 1999 Nov;17(11):1589–99.
276. Ramaekers D, Ector H, Demyttenaere K, Rubens A, Van de Werf F. Association between Cardiac Autonomic Function and Coping Style in Healthy Subjects. *Pacing and Clinical Electrophysiology*. 1998 Aug 30;21(8):1546–52.
277. Huang W, Zhu T, Pan X, Hu M, Lu SE, Lin Y, et al. Air Pollution and Autonomic and Vascular Dysfunction in Patients with Cardiovascular Disease: Interactions of Systemic Inflammation, Overweight, and Gender. *Am J Epidemiol*. 2012 Jul 15;176(2):117–26.
278. Bouvy ML. Predicting mortality in patients with heart failure: a pragmatic approach. *Heart*. 2003 Jun 1;89(6):605–9.
279. Lombardi F, Sandrone G, Mortara A, La Rovere MT, Colombo E, Guzzetti S, et al. Circadian variation of spectral indices of heart rate variability after myocardial infarction. *Am Heart J*. 1992 Jun;123(6):1521–9.
280. Kovar D, Cannon CP, Bentley JH, Charlesworth A, Rogers WJ. Does initial and delayed heart rate predict mortality in patients with acute coronary syndromes? *Clin Cardiol*. 2004 Feb 5;27(2):80–6.
281. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting Heart Rate in Cardiovascular Disease. *J Am Coll Cardiol*. 2007 Aug;50(9):823–30.

282. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP. Components of heart rate variability measured during healing of acute myocardial infarction. *Am J Cardiol.* 1988 Feb;61(4):208–15.
283. Guzzetti S, Magatelli R, Borroni E, Mezzetti S. Heart rate variability in chronic heart failure. *Autonomic Neuroscience.* 2001 Jul;90(1–2):102–5.
284. Davies LC, Colhoun H, Coats AJS, Piepoli M, Francis DP. A noninvasive measure of baroreflex sensitivity without blood pressure measurement. *Am Heart J.* 2002 Mar;143(3):441–7.
285. Carthy ER. Autonomic dysfunction in essential hypertension: A systematic review. *Annals of Medicine & Surgery.* 2014 Mar;3(1):2–7.
286. Fakhrzadeh H, Yamini-Sharif A, Sharifi F, Tajalizadekhoob Y, Mirarefin M, Mohammadzadeh M, et al. Cardiac Autonomic Neuropathy Measured by Heart Rate Variability and Markers of Subclinical Atherosclerosis in Early Type 2 Diabetes. *ISRN Endocrinol.* 2012 Dec 4; 2012:1–7.
287. Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinol.* 2012 Jul 28;8(7):405–16.
288. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, et al. Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. *PLoS One.* 2018 Apr 2;13(4): e0195166.
289. Kuehl M, Stevens MJ. Cardiovascular autonomic neuropathies as complications of diabetes mellitus. *Nat Rev Endocrinol.* 2012 Jul 28;8(7):405–16.
290. Karayannis G, Giamouzis G, Cokkinos D V, Skoularigis J, Triposkiadis F. Diabetic cardiovascular autonomic neuropathy: clinical implications. *Expert Rev Cardiovasc Ther.* 2012 Jun 10;10(6):747–65.

291. Stein PK, Barzilay JI, Domitrovich PP, Chaves PM, Gottdiener JS, Heckbert SR, et al. The relationship of heart rate and heart rate variability to non-diabetic fasting glucose levels and the metabolic syndrome: The Cardiovascular Health Study. *Diabetic Medicine*. 2007 Aug 2;24(8):855–63.
292. Min K, Min J, Paek D, Cho S. The Impact of the Components of Metabolic Syndrome on Heart Rate Variability: Using the NCEP-ATP III and IDF Definitions. *Pacing and Clinical Electrophysiology*. 2008 May 24;31(5):584–91.
293. Liao D, Sloan RP, Cascio WE, Folsom AR, Liese AD, Evans GW, et al. Multiple Metabolic Syndrome Is Associated with Lower Heart Rate Variability: The Atherosclerosis Risk in Communities Study. *Diabetes Care*. 1998 Dec 1;21(12):2116–22.
294. Koskinen T, Kähönen M, Jula A, Mattsson N, Laitinen T, Keltikangas-Järvinen L, et al. Metabolic syndrome and short-term heart rate variability in young adults. *Diabetic Medicine*. 2009 Apr 6;26(4):354–61.
295. Hemingway H, Shipley M, Brunner E, Britton A, Malik M, Marmot M. Does Autonomic Function Link Social Position to Coronary Risk? *Circulation*. 2005 Jun 14;111(23):3071–7.
296. Chang YW, Lin JD, Chen WL, Yen CF, Loh CH, Fang WH, et al. Metabolic syndrome and short-term heart rate variability in adults with intellectual disabilities. *Res Dev Disabil*. 2012 Nov;33(6):1701–7.
297. Assoumou HGN, Pichot V, Barthelemy JC, Dauphinot V, Celle S, Gosse P, et al. Metabolic Syndrome and Short-Term and Long-Term Heart Rate Variability in Elderly Free of Clinical Cardiovascular Disease: The PROOF Study. *Rejuvenation Res*. 2010 Dec;13(6):653–63.

298. Stuckey MI, Tulppo MP, Kiviniemi AM, Petrella RJ. Heart rate variability and the metabolic syndrome: a systematic review of the literature. *Diabetes Metab Res Rev*. 2014 Nov 14;30(8):784–93.
299. Koenig J, hum sc, Falvay D, Clamor A, Wagner J, Jarczok MN, et al. Systematic Review Pneumogastric (Vagus) Nerve Activity Indexed by Heart Rate Variability in Chronic Pain Patients Compared to Healthy Controls: A Systematic Review and Meta-Analysis. *Pain Physician*. 2016 Jan;19(1): E55-78.
300. Dehghan H, Mortazavi SB, Jafari MJ, Maracy MR. Cardiac Strain between Normal Weight and Overweight Workers in Hot/Humid Weather in the Persian Gulf [Internet]. Vol. 4, *International Journal of Preventive Medicine*. 2013.
301. Mark AL. Selective leptin resistance revisited. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2013 Sep 15;305(6): R566–81.
302. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-Induced Hypertension. *Circ Res*. 2015 Mar 13;116(6):991–1006.
303. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. *Obesity Reviews*. 2005 Nov 20;6(4):275–81.
304. Huang CJ, Webb HE, Zourdos MC, Acevedo EO. Cardiovascular reactivity, stress, and physical activity. *Front Physiol*. 2013;4.
305. Dishman RK, Nakamura Y, Garcia ME, Thompson RW, Dunn AL, Blair SN. Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. *International Journal of Psychophysiology*. 2000 Aug;37(2):121–33.
306. Benschop RJ, Geenen R, Mills PJ, Naliboff BD, Kiecolt-Glaser JK, Herbert TB, et al. Cardiovascular and Immune Responses to Acute Psychological Stress in Young and Old Women. *Psychosom Med*. 1998;60(3):290–6.

307. Looser RR, Metzenthin P, Helfricht S, Kudielka BM, Loerbroks A, Thayer JF, et al. Cortisol Is Significantly Correlated with Cardiovascular Responses During High Levels of Stress in Critical Care Personnel. *Psychosom Med*. 2010 Apr;72(3):281–9.
308. Chandola T, Britton A, Brunner E, Hemingway H, Malik M, Kumari M, et al. Work stress and coronary heart disease: what are the mechanisms? *Eur Heart J*. 2008 Mar 1;29(5):640–8.
309. Jarvelin-Pasanen S, Sinikallio S, Tarvainen MP. Heart rate variability and occupational stress—systematic review. *Ind Health*. 2018;56(6):500–11.
310. Clays E, De Bacquer D, Crasset V, Kittel F, de Smet P, Kornitzer M, et al. The perception of work stressors is related to reduced parasympathetic activity. *Int Arch Occup Environ Health*. 2011 Feb 1;84(2):185–91.
311. Chandola T, Heraclides A, Kumari M. Psychophysiological biomarkers of workplace stressors. *Neurosci Biobehav Rev*. 2010 Sep;35(1):51–7.
312. Eckberg DL. The human respiratory gate. *J Physiol*. 2003 Apr 15;548(2):339–52.
313. Badra LJ, Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KUO, et al. Respiratory modulation of human autonomic rhythms. *American Journal of Physiology-Heart and Circulatory Physiology*. 2001 Jun 1;280(6):H2674–88.
314. Hill L, Siebenbrock A. Are all measures created equal? Heart rate variability and respiration - biomed 2009. *Biomed Sci Instrum*. 2009;71–6.
315. Schaffer T, Hensel B, Weigand C, Schüttler J, Jeleszcov C. Evaluation of techniques for estimating the power spectral density of RR-intervals under paced respiration conditions. *J Clin Monit Comput*. 2014 Oct 19;28(5):481–6.
316. Kanters JK, Hojgaard M V., Agner E, Holstein-Rathlou NH. Influence of forced respiration on nonlinear dynamics in heart rate variability. *American Journal of*

Physiology-Regulatory, Integrative and Comparative Physiology. 1997 Apr 1;272(4): R1149–54.

317. GRAHAM TE. Thermal, metabolic, and cardiovascular changes in men and women during cold stress. *Med Sci Sports Exerc.* 1988 Oct;20(Sup 1): S185–92.

318. Huang CM, Chang HC, Kao ST, Li TC, Wei CC, Chen C, et al. Radial Pressure Pulse and Heart Rate Variability in Heat- and Cold-Stressed Humans. *Evidence-Based Complementary and Alternative Medicine.* 2011 Jan 14;2011(1).

319. Bortkiewicz A, Gadzicka E, Szymczak W, Szyjewska A, Koszoda-Włodarczyk W, Makowiec-Dąbrowska T. Physiological Reaction to Work in Cold Microclimate. *Int J Occup Med Environ Health.* 2006 Jan 1;19(2).

320. Ren C, O'Neill MS, Park SK, Sparrow D, Vokonas P, Schwartz J. Ambient Temperature, Air Pollution, and Heart Rate Variability in an Aging Population. *Am J Epidemiol.* 2011 May 1;173(9):1013–21.

321. Wilson TE, Crandall CG. Effect of Thermal Stress on Cardiac Function. *Exerc Sport Sci Rev.* 2011 Jan;39(1):12–7.

322. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev.* 1974 Jan;54(1):75–159.

323. Wu S, Deng F, Liu Y, Shima M, Niu J, Huang Q, et al. Temperature, traffic-related air pollution, and heart rate variability in a panel of healthy adults. *Environ Res.* 2013 Jan; 120:82–9.

324. Bhaumik G, Dass D, Bhattacharyya D, Sharma YK, Singh SB. Heart rate variability changes during first week of acclimatization to 3500 m altitude in Indian military personnel. *Indian J Physiol Pharmacol.* 2013;57(1):16–22.

325. Dhar P, Sharma VK, Hota KB, Das SK, Hota SK, Srivastava RB, et al. Autonomic Cardiovascular Responses in Acclimatized Lowlanders on Prolonged Stay at High Altitude: A Longitudinal Follow Up Study. *PLoS One*. 2014 Jan 3;9(1): e84274.
326. Gross R, Kirchheim H. Effects of bilateral carotid occlusion and auditory stimulation on renal blood flow and sympathetic nerve activity in the conscious dog. *Pflügers Archiv European Journal of Physiology*. 1980 Feb;383(3):233–9.
327. VETERNIK M, TONHAJZEROVA I, MISEK J, JAKUSOVA V, HUDECKOVA H, JAKUS J. The Impact of Sound Exposure on Heart Rate Variability in Adolescent Students. *Physiol Res*. 2018 Oct 31;695–702.
328. Schnell I, Potchter O, Epstein Y, Yaakov Y, Hermesh H, Brenner S, et al. The effects of exposure to environmental factors on Heart Rate Variability: An ecological perspective. *Environmental Pollution*. 2013 Dec; 183:7–13.
329. Lee GS, Chen ML, Wang GY. Evoked response of heart rate variability using short-duration white noise. *Autonomic Neuroscience*. 2010 Jun;155(1–2):94–7.
330. Kraus U, Schneider A, Breitner S, Hampel R, Rückerl R, Pitz M, et al. Individual Daytime Noise Exposure during Routine Activities and Heart Rate Variability in Adults: A Repeated Measures Study. *Environ Health Perspect*. 2013 May;121(5):607–12.
331. Rubiano AM, Carney N, Chesnut R, Puyana JC. Global neurotrauma research challenges and opportunities. Vol. 527, *Nature*. Nature Publishing Group; 2015. p. S193–7.
332. Chan V, Pole JD, Keightley M, Mann RE, Colantonio A. Children and youth with non-traumatic brain injury: A population-based perspective. *BMC Neurol*. 2016 Jul 20;16(1).
333. Silvetti S, Drago F, Ragonese PR. Heart rate variability in healthy children and adolescents is partially to age and gender. *Int J Cardiol*. 2001; 81:169–74.

334. Daley M, Cameron S, Ganesan SL, Patel MA, Stewart TC, Miller MR, et al. Pediatric severe traumatic brain injury mortality prediction determined with machine learning-based modeling. *Injury*. 2022 Mar 1;53(3):992–8.
335. Morrissey K, Fairbrother H. Severe Traumatic Brain Injury in Children: An Evidence-Based Review of Emergency Department Management. Vol. 13, *Pediatric emergency medicine practice*. 2016.
336. Chung CY, Chen CL, Cheng PT, See LC, Tang SFT, Wong AMK. Critical Score of Glasgow Coma Scale for Pediatric Traumatic Brain Injury. *Pediatr Neurol*. 2006;34(5).
337. Campbell CGN, Kuehn SM, Richards PMP, Ventureyra E, Hutchison JS. Medical and cognitive outcome in children with traumatic brain injury. Vol. 31, *Canadian Journal of Neurological Sciences*. 2004.
338. Alharfi IM, Stewart TC, Kelly SH, Morrison GC, Fraser DD. Hypernatremia is associated with increased risk of mortality in pediatric severe traumatic brain injury. *J Neurotrauma*. 2013;30(5).
339. Stewart TC, Alharfi IM, Fraser DD. The role of serious concomitant injuries in the treatment and outcome of pediatric severe traumatic brain injury. *Journal of Trauma and Acute Care Surgery*. 2013;75(5).
340. Hochstadter E, Stewart TC, Alharfi IM, Ranger A, Fraser DD. Subarachnoid Hemorrhage Prevalence and Its Association with Short-Term Outcome in Pediatric Severe Traumatic Brain Injury. *Neurocrit Care*. 2014;21(3).
341. Alofisan TO, Algarni YA, Alharfi IM, Miller MR, Charyk Stewart T, Fraser DD, et al. Paroxysmal Sympathetic Hyperactivity after Severe Traumatic Brain Injury in Children: Prevalence, Risk Factors, and Outcome*. *Pediatric Critical Care Medicine*. 2019;20(3).

342. Fortune PM, Shann F. The motor response to stimulation predicts outcome as well as the full Glasgow Coma Scale in children with severe head injury. *Pediatric Critical Care Medicine*. 2010;11(3).
343. Alhelali I, Stewart TC, Foster J, Alharfi IM, Ranger A, Daoud H, et al. Basal skull fractures are associated with mortality in pediatric severe traumatic brain injury. *Journal of Trauma and Acute Care Surgery*. 2015;78(6).
344. Fulkerson DH, White IK, Rees JM, Baumanis MM, Smith JL, Ackerman LL, et al. Analysis of long-term (median 10.5 years) outcomes in children presenting with traumatic brain injury and an initial Glasgow Coma Scale score of 3 or 4. *J Neurosurg Pediatr*. 2015;16(4).
345. Rosario BL, Horvat CM, Wisniewski SR, Bell MJ, Panigrahy A, Zuccoli G, et al. Presenting characteristics associated with outcome in children with severe traumatic brain injury: A secondary analysis from a randomized, controlled trial of therapeutic hypothermia. *Pediatric Critical Care Medicine*. 2018;19(10).
346. Emami P, Czorlich P, Fritzsche FS, Westphal M, Rueger JM, Lefering R, et al. Impact of glasgow coma scale score and pupil parameters on mortality rate and outcome in pediatric and adult severe traumatic brain injury: A retrospective, multicenter cohort study. *J Neurosurg*. 2017;126(3).
347. Saadat SMS, Bidabadi E, Saadat SNS, Mashouf M, Salamat F, Yousefzadeh S. Association of persistent hyperglycemia with outcome of severe traumatic brain injury in pediatric population. *Child's Nervous System*. 2012;28(10).
348. Smith RL, Lin JC, Adelson PD, Kochanek PM, Fink EL, Wisniewski SR, et al. Relationship between hyperglycemia and outcome in children with severe traumatic brain injury. *Pediatric Critical Care Medicine*. 2012;13(1).

349. Podolsky-Gondim GG, Furlanetti LL, Viana DC, Ballesterio MFM, de Oliveira RS. The role of coagulopathy on clinical outcome following traumatic brain injury in children: analysis of 66 consecutive cases in a single center institution. *Child's Nervous System*. 2018;34(12).
350. Liras IN, Caplan H, Stensballe J, Wade C, Cox C, Cotton B. Prevalence and Impact of Admission Acute Traumatic Coagulopathy on Treatment Intensity, Resource Use, and Mortality: An Evaluation of 956 Severely Injured Children and Adolescents. *J Am Coll Surg*. 2017;224(4).
351. Whittaker B, Christians SC, Altice JL, Chen MK, Bartolucci AA, Morgan CJ, et al. Early coagulopathy is an independent predictor of mortality in children after severe trauma. *Shock*. 2013;39(5).
352. Alharfi IM, Stewart TC, Foster J, Morrison GC, Fraser DD. Central diabetes insipidus in pediatric severe traumatic brain injury. *Pediatric Critical Care Medicine*. 2013;14(2).
353. Kochanek PM, Tasker RC, Carney N, Totten AM, Adelson PD, Selden NR, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Pediatric Critical Care Medicine*. 2019;20(3).
354. Pedersen SH, Lilja-Cyron A, Astrand R, Juhler M. Monitoring and Measurement of Intracranial Pressure in Pediatric Head Trauma. Vol. 10, *Frontiers in Neurology*. 2020.
355. Nacoti M, Fazzi F, Biroli F, Zangari R, Barbui T, Kochanek PM. Addressing Key Clinical Care and Clinical Research Needs in Severe Pediatric Traumatic Brain Injury: Perspectives from a Focused International Conference. Vol. 8, *Frontiers in Pediatrics*. Frontiers Media S.A.; 2021.

356. Gregory T, Smith M. Cardiovascular complications of brain injury. *Continuing Education in Anaesthesia, Critical Care and Pain*. 2012;12(2).
357. Tavazzi G, Zanierato M, Via G, Iotti GA, Procaccio F. Are Neurogenic Stress Cardiomyopathy and Takotsubo Different Syndromes with Common Pathways? *Etiopathological Insights on Dysfunctional Hearts*. Vol. 5, JACC: Heart Failure. 2017.
358. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-Heart Interaction: Cardiac Complications after Stroke. Vol. 121, *Circulation Research*. 2017.
359. Vakilian A, Iranmanesh F, Nadimi A, Kahnali J. Heart Rate Variability and QT Dispersion Study in Brain Death Patients and Comatose Patients with Normal Brainstem Function. *Journal of the College of Physicians and Surgeons Pakistan*. 2011;21(3):130133.
360. Lowensohn RichardI, Weiss M, Hon EdwardH. Heart rate variability in brain damaged adults. In: *The Lancet*. 1977. p. 626–8.
361. Rapenne T, Moreau D, Lenfant F, Boggio V, Cottin Y, Freysz M. Could heart rate variability analysis become an early predictor of imminent brain death? A pilot study. *Anesth Analg*. 2000;91(2):329–36.
362. Conci F. Blood pressure and heart rate variability and baroreflex sensitivity before and after brain death. *J Neurol Neurosurg Psychiatry*. 2001 Nov 1;71(5):621–31.
363. Meglič B, Kobal J, Osredkar J, Pogačnik T. Autonomic Nervous System Function in Patients with Acute Brainstem Stroke. *Cerebrovascular Diseases*. 2001;11(1):2–8.
364. Baillard C, Vivien B, Mansier P, Mangin L, Jasson S, Riou B, et al. Brain death assessment using instant spectral analysis of heart rate variability. 2002.
365. Ryan ML, Ogilvie MP, Pereira BMT, Gomez-Rodriguez JC, Manning RJ, Vargas PA, et al. Heart Rate Variability Is an Independent Predictor of Morbidity and Mortality

in Hemodynamically Stable Trauma Patients. *Journal of Trauma: Injury, Infection & Critical Care*. 2011 Jun;70(6):1371–80.

366. Machado-Ferrer Y, Estévez M, Machado C, Hernández-Cruz A, Carrick FR, Leisman G, et al. Heart rate variability for assessing comatose patients with different Glasgow Coma Scale scores. *Clinical Neurophysiology*. 2013 Mar;124(3):589–97.

367. Sykora M, Czosnyka M, Liu X, Donnelly J, Nasr N, Diedler J, et al. Autonomic impairment in severe traumatic brain injury: A multimodal neuromonitoring study. *Crit Care Med*. 2016 Jun 1;44(6):1173–81.

368. Goldstein B, Fiser D, Kelly M, Mickelsen D, Ruttimann U, Pollack M. Decomplexification in critical illness and injury: Relationship between heart rate variability, severity of illness, and outcome. *Pediatric Critical Care*. 1998;26(2):352–6.

369. Biswas AK, Scott WA, Sommerauer JF. Heart rate variability after acute traumatic brain injury in children. *Pediatric Critical Care*. 2000. 28(12):3907-3912.

370. Martin S, Du Pont-Thibodeau G, Seely AJE, Emeriaud G, Herry CL, Recher M, et al. Heart Rate Variability in Children with Moderate and Severe Traumatic Brain Injury: A Prospective Observational Study. *J Pediatr Intensive Care*. 2022.

371. Florez-Perdomo WA, García-Ballestas E, Moscote-Salazar LR, Konar SK, Raj S, Chouksey P, et al. Heart Rate Variability as a Predictor of Mortality in Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Vol. 148, *World Neurosurgery*. Elsevier Inc.; 2021. p. 80–9.

372. Hart S, Lannon M, Chen A, Martyniuk A, Sharma S, Engels PT. Beta blockers in traumatic brain injury: a systematic review and meta-analysis. *Trauma Surg Acute Care Open*. 2023;8(1).

373. Talbert LD, Kaelberer Z, Gleave E, Driggs A, Driggs AS, Baldwin SA, et al. A Systematic Review of the Relationship Between Traumatic Brain Injury and Disruptions in Heart Rate Variability. *Applied Psychophysiology Biofeedback*. 2024 Dec 1.
374. Silva MJ, Carneiro B, Mota R, Baptista MJ. Cardiovascular events in children with brain injury: A systematic review. *Int J Cardiol*. 2023;387.
375. Reisner A, Chen X, Kumar K, Reifman J. Prehospital heart rate and blood pressure increase the positive predictive value of the glasgow coma scale for high-mortality traumatic brain injury. *J Neurotrauma*. 2014 May 15;31(10):906–13.
376. Alam MB, Jones G, Seely AJE, Poehlman W.F.S., Kamath M V. Heart Rate Variability Signal Analysis: Clinical Applications. 1st ed. Markad V. Kamath, Mari Watanabe, Adrian Upton, editors. 2013. 203–221 p.
377. Mazzeo AT, La Monaca E, Di Leo R, Vita G, Santamaria LB. Heart rate variability: A diagnostic and prognostic tool in anesthesia and intensive care. Vol. 55, *Acta Anaesthesiologica Scandinavica*. 2011. p. 797–811.
378. Ushiyama T, Nakatsu T, Yamane S, Tokutake H, Wakabayashi H, Ishimura K, et al. Heart rate variability for evaluating surgical stress and development of postoperative complications. *Clin Exp Hypertens*. 2008;30(1).
379. Goldstein B, Ellenby MS. Heart rate variability and critical illness: Potential and problems. Vol. 28, *Critical Care Medicine*. 2000.
380. Suttipongkaset P, Chaikittisilpa N, Vavilala MS, Lele A V, Watanitanon A, Chandee T, et al. Blood Pressure Thresholds and Mortality in Pediatric Traumatic Brain Injury. *Pediatrics* [Internet]. 2018;142(2).
381. Ozdemir D, Ozdemir N, Unal N, Tektas S. QTc Dispersion in Children with Severe Head Trauma. *Pediatr Emerg Care*. 2005 Oct;21(10):658–61.

382. Zafar SN, Millham FH, Chang Y, Fikry K, Alam HB, King DR, et al. Presenting Blood Pressure in Traumatic Brain Injury: A Bimodal Distribution of Death. *Journal of Trauma: Injury, Infection & Critical Care*. 2011 Nov;71(5):1179–84.
383. Coates BM, Vavilala MS, Mack CD, Muangman S, Suz P, Sharar SR, et al. Influence of definition and location of hypotension on outcome following severe pediatric traumatic brain injury. *Crit Care Med*. 2005;33(11).
384. Samant IV UB, Mack CD, Koepsell T, Rivara FP, Vavilala MS. Time of hypotension and discharge outcome in children with severe traumatic brain injury. *J Neurotrauma*. 2008;25(5).
385. Yao SHW, Chong SL, James V, Lee KP, Ong GYK. Associations of initial haemodynamic profiles and neurological outcomes in children with traumatic brain injury: A secondary analysis. *Emergency Medicine Journal*. 2022;39(7).
386. Erickson SL, Killien EY, Wainwright M, Mills B, Vavilala MS. Mean Arterial Pressure and Discharge Outcomes in Severe Pediatric Traumatic Brain Injury. *Neurocrit Care*. 2021 Jun 1;34(3):1017–25.
387. Vavilala MS, Bowen A, Lam AM, Uffman JC, Powell J, Winn HR, et al. Blood Pressure and Outcome after Severe Pediatric Traumatic Brain Injury. *The Journal of Trauma: Injury, Infection, and Critical Care*. 2003 Dec;55(6):1039–44.
388. Johnson MA, Borgman MA, Cannon JW, Kuppermann N, Neff LP. Severely elevated blood pressure and early mortality in children with traumatic brain injuries: The neglected end of the spectrum. *Western Journal of Emergency Medicine*. 2018;19(3).
389. Kanter RK, Carroll JB, Post EM. Association of Arterial Hypertension with Poor Outcome in Children with Acute Brain Injury. *Clin Pediatr (Phila)*. 1985;24(6).

390. Freeman AD, Fitzgerald CA, Baxter KJ, Neff LP, McCracken CE, Bryan LN, et al. Does hypertension at initial presentation adversely affect outcomes in pediatric traumatic brain injury? *J Pediatr Surg*. 2020;55(4).
391. Hasanin A, Kamal A, Amin S, Zakaria D, El Sayed R, Mahmoud K, et al. Incidence and outcome of cardiac injury in patients with severe head trauma. *Scand J Trauma Resusc Emerg Med [Internet]*. 20160427th ed. 2016; 24:58.
392. Berry C, Ley E, Mirocha J, Margulies D, Salim A. The Optimal Heart Rate to Reduce Mortality after Traumatic Brain Injury. *Journal of Surgical Research*. 2010 Feb;158(2):412.
393. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, MacOnochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: A systematic review of observational studies. *The Lancet*. 2011;377(9770):1011–8.
394. Kero P, Antilla K, Ylitalo V, Valimaki I. Decreased Heart Rate Variation in Decerebration Syndrome: Quantitative Clinical Criterion of Brain Death? *Pediatrics*. 1978;62(3):307–11.
395. Piantino JA, Lin A, Crowder D, Williams CN, Perez-Alday E, Tereshchenko LG, et al. Early Heart Rate Variability and Electroencephalographic Abnormalities in Acutely Brain-Injured Children Who Progress to Brain Death*. *Pediatric Critical Care Medicine*. 2019 Jan 1;20(1):38–46.
396. Beers SR, Wisniewski SR, Garcia-Filion P, Tian Y, Hahner T, Berger RP, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. *J Neurotrauma [Internet]*. 20120410th ed. 2012;29(6):1126–39.
397. Gagnon R, Campbell K, Hunse C, Patrick J. Patterns of human fetal heart rate accelerations from 26 weeks to term. *Am J Obstet Gynecol*. 1987;157(3).

398. Purisch SE, Gyamfi-Bannerman C. Epidemiology of preterm birth. Vol. 41, *Seminars in Perinatology*. 2017.
399. Clairambault J, Curzi-Dascalova L, Kauffmann F, Médigue C, Leffler C. Heart rate variability in normal sleeping full-term and preterm neonates. *Early Hum Dev*. 1992;28(2).
400. Cabal LA, Siassi B, Zanini B, Hodgman JE, Hon EE. Factors affecting heart rate variability in preterm infants. *Pediatrics*. 1980;65(1).
401. Verklan MT, Padhye NS. Spectral analysis of heart rate variability: An emerging tool for assessing stability during transition to extrauterine life. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing*. 2004;33(2).
402. Selig FA, Tonolli R, Vinicius É, Moreira Da Silva C, Fernandes De Godoy M. Heart Rate Variability in Preterm and Term Neonates. *Arq Bras Cardiol*. 2011;96(6).
403. Bhandarkar P, Munivenkatappa A, Roy N, Kumar V, Samudrala VD, Kamble J, et al. On-admission blood pressure and pulse rate in trauma patients and their correlation with mortality: Cushing's phenomenon revisited. *Int J Crit Illn Inj Sci*. 2017;7(1).
404. Johnston BW, Barrett-Jolley R, Krige A, Welters ID. Heart rate variability: Measurement and emerging use in critical care medicine. Vol. 21, *Journal of the Intensive Care Society*. SAGE Publications Inc.; 2020. p. 148–57.
405. Michels N, Sioen I, Clays E, De Buyzere M, Ahrens W, Huybrechts I, et al. Children's heart rate variability as stress indicator: association with reported stress and cortisol. *Biol Psychol [Internet]*. 20130902nd ed. 2013;94(2):433–40.
406. Tan G, Wang P, Ginsberg J. Heart Rate Variability and Posttraumatic Stress Disorder. *Biofeedback*. 2013;41(3).

407. Win NN, Fukayama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg*. 2005 Jul;101(1):97–102.
408. Karemaker JM. Interpretation of Heart Rate Variability: The Art of Looking Through a Keyhole. *Front Neurosci*. 2020 Dec 21;14.
409. Serafi AS. Heart rate variability (HRV) - analysis and clinical significance. Vol. 15, *INT. J. BIOL. BIOTECH*. 2018.
410. Mateo J, Laguna P. Analysis of heart rate variability in the presence of ectopic beats using the heart timing signal. *IEEE Trans Biomed Eng [Internet]*. 2003;50(3):334–43.
411. Estévez-Báez M, Machado C, Leisman G, Brown-Martínez M, Jas-García JD, Montes-Brown J, et al. A procedure to correct the effect of heart rate on heart rate variability indices: description and assessment. *International Journal on Disability and Human Development*. 2016 Jan 1;15(3).
412. Kwon O, Jeong J, Kim H Bin, Kwon IH, Park SY, Kim JE, et al. Electrocardiogram sampling frequency range acceptable for heart rate variability analysis. *Healthc Inform Res*. 2018 Jul 1;24(3):198–206.
413. Sousa P, Almeida R, Silva MJ, Rocha AP. Reliability Loss with Sampling Rate Reduction. In: *Computing in Cardiology*. 2015.
414. Kim MK, Choi GJ, Oh KS, Lee SP, Kang H. Pain Assessment Using the Analgesia Nociception Index (ANI) in Patients Undergoing General Anesthesia: A Systematic Review and Meta-Analysis. Vol. 13, *Journal of Personalized Medicine*. Multidisciplinary Digital Publishing Institute (MDPI); 2023.
415. Sakthivel M, Su V, Nataraja RM, Pacilli M. Newborn and Infant Parasympathetic Evaluation (NIPETM) Monitor for Assessing Pain During Surgery and Interventional

Procedures: A Systematic Review. Vol. 59, Journal of Pediatric Surgery. W.B. Saunders; 2024. p. 672–7.

416. Tayel M, AlSaba E. Poincaré Plot for Heart Rate Variability. World Academy of Science, Engineering and Technology International Journal of Biomedical and Biological Engineering. 2015;9.

417. Rodríguez-Núñez I, Rodríguez-Romero N, Álvarez A, Zambrano L, da Veiga GL, Romero F. Heart rate variability in children: methodological issues and clinical applications. Arch Cardiol Mex. 2022;92(2).

418. Galeev A, Igisheva L, Kazin E. Heart Rate Variability in Healthy Six-to-Sixteen-Year-Old Children. Hum Physiol. 2002;28(4):428–32.

419. Cardoso S, Silva MJ, Guimarães H. Autonomic nervous system in newborns: a review based on heart rate variability. Child's Nervous System. 2017;33(7).

420. Rodríguez N, Febrer A, Meléndez M. Autonomic dysfunction in children with traumatic brain injury. Rev Neurol. 2006;43(3).

421. Krach LE, Kriel RL, Morris WF, Warhol BL, Luxenberg MG. Central Autonomic Dysfunction Following Acquired Brain Injury in Children. Neurorehabil Neural Repair. 1997;11(1).

422. Blake TA, McKay CD, Meeuwisse WH, Emery CA. The impact of concussion on cardiac autonomic function: A systematic review. Vol. 30, Brain Injury. Taylor and Francis Ltd; 2016. p. 132–45.

423. Mercier LJ, Batycky J, Campbell C, Schneider K, Smirl J, Debert CT. Autonomic dysfunction in adults following mild traumatic brain injury: A systematic review. Vol. 50, NeuroRehabilitation. IOS Press BV; 2022. p. 3–32.

424. Lee Y, Walsh RJ, Fong MWM, Sykora M, Doering MM, Wong AWK. Heart rate variability as a biomarker of functional outcomes in persons with acquired brain injury:

Systematic review and meta-analysis. Vol. 131, Neuroscience and Biobehavioral Reviews. 2021.

425. Huang HH, Chan HL, Lin PL, Wu CP, Huang CH. Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia. *Br J Anaesth*. 1997;79(6).

426. Lu HY, Huang APH, Kuo LT. Prognostic value of variables derived from heart rate variability in patients with traumatic brain injury after decompressive surgery. *PLoS One*. 2021 Feb 1;16(2 February).

427. Karmali SN, Sciusco A, May SM, Ackland GL. Heart rate variability in critical care medicine: a systematic review. *Intensive Care Med Exp*. 2017 Dec 12;5(1):33.

428. McNamara J, Aboy M. Reliability and accuracy of heart rate variability metrics versus ECG segment duration. *Med Biol Eng Comput*. 2006 Sep 22;44(9):747–56.

429. Hilz MJ, Wang R, Markus J, Ammon F, Hösl KM, Flanagan SR, et al. Severity of traumatic brain injury correlates with long-term cardiovascular autonomic dysfunction. *J Neurol*. 2017;264(9).

430. Rocha AP, Almeida R, Leite A, Silva MJ, Silva ME. Long-term HRV in critically ill pediatric patients: Coma versus brain death. In: *Computing in Cardiology*. 2014.

431. Hayano J, Yuda E. Assessment of autonomic function by long-term heart rate variability: beyond the classical framework of LF and HF measurements. Vol. 40, *Journal of Physiological Anthropology*. BioMed Central Ltd; 2021.

432. Hall S, Kumaria A, Belli A. The role of vagus nerve overactivity in the increased incidence of pneumonia following traumatic brain injury. *Br J Neurosurg*. 2014;28(2).