

INPLASY

Patterns of heart rate variability (HRV) responses to acute stress in neonates: A systematic review

INPLASY202480007

doi: 10.37766/inplasy2024.8.0007

Received: 01 August 2024

Published: 01 August 2024

Bucsea, O; Jasim, S; Cohen, E; Pillai Riddell, R.

Corresponding author:

Rebecca Pillai Riddell

rpr@yorku.ca

Author Affiliation:

Department of Psychology, Faculty of Health, York University, Toronto, Ontario, Canada.

ADMINISTRATIVE INFORMATION

Support - Dr. Rebecca Pillai Riddell, a core faculty member of the Clinical-Developmental Psychology program at York University, is responsible for initiating and managing the review. This research is funded by operating grants from the Canadian Institutes of Health Research Natural Sciences and Engineering Research Council, and Social Sciences and Humanities Research Council to Dr. Pillai Riddell. Ms. Bucsea received support from the Canadian Institutes of Health Research (CIHR), Ontario Graduate Scholarship (OGS), and Canadian Psychological Association (CPA).

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202480007

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 August 2024 and was last updated on 01 August 2024.

INTRODUCTION

Review question / Objective The overall objective of this systematic review is to synthesize the literature examining preterm and full-term newborns' acute heart rate variability (HRV) responses to painful and non-painful disruptive procedures. It will address the following research questions:

- 1) What patterns of HRV responses do newborns exhibit during acute painful and non-painful disruptive procedures?
- 2) How does procedural pain severity influence neonatal HRV response patterns during acute painful procedures?

Rationale Early neonatal exposure to repeated stressors, such as disruptive medical procedures in hospital settings, has been linked to impaired autonomic nervous system (ANS) stress responses. Furthermore, other clinical variables, such as prematurity, have been associated with an underdeveloped ANS, increasing the vulnerability of hospitalized newborns to stress exposure. Heart rate variability (HRV) measures capture the balance of both branches of the ANS (sympathetic nervous system [SNS] and parasympathetic nervous system [PNS]), thus providing a non-invasive measure of stress reactivity and recovery. However, in newborns, heart rate has been more widely used to index cardiac stress responding to acute stress and pain in clinical settings. Although HRV measures are widely used to capture stress

regulation in older ages, they need to be better understood in newborns and thus are currently being underused to measure acute stress physiology in healthcare settings. This systematic literature review seeks to examine patterns of HRV responses to acute stressors in newborns and variables that may influence these responses, such as gestational and postnatal age, type and severity of acute procedures, and phase of the acute stress response (reactivity vs. recovery). Furthermore, given the wide array of HRV metrics that have been uncovered in previous research, gaining a deeper understanding of these measures' potential to distinctively capture newborns' dynamic acute stress responding is warranted.

Condition being studied This review focuses on newborn infants exposed to any acute painful or non-painful disruptive procedures in the first month of life. Acute HRV responses during these procedures capturing newborns' distress reactivity and recovery patterns is the main outcome of interest. The influence of several factors (i.e., age, severity of acute procedure, type of HRV metric) on the main outcome of interest will be examined.

METHODS

Search strategy A search strategy was developed in collaboration with an academic librarian. The following databases were searched: Medline (PudMed), Embase, CINAHL, PsycINFO (Proquest and Ovid), Web of Science, and Scopus. The search was conducted on May 6, 2024, using the following search strategy:

1. newborn* OR new-born* OR neonate* OR infant* OR baby OR babies OR preterm OR pre-term OR prematurity OR premature OR "full term" OR "full-term" AND
2. pain* OR nociceptive OR stress* OR distress* OR noxious* AND
3. "heart rate variability" OR "heart-rate variability" OR HRV OR "respiratory sinus arrhythmia" OR RSA OR "vagal tone" OR "vagal withdrawal" OR "vagal regulation" OR "vagal reactivity" OR "NIPE" OR "Newborn Infant Parasympathetic Evaluation" OR "Newborn and Infant Parasympathetic Evaluation" OR "interbeat interval*" OR "inter-beat interval*" OR IBI OR "beat-to-beat interval*".

Participant or population The review will focus on all preterm and full-term newborns in the first month of life. Newborns exposed to additional risk factors alongside prematurity (e.g., low birth weight, infection) will also be considered given the high incidence of comorbid clinical vulnerabilities in this population.

Intervention All preterm and full-term newborn samples undergoing an acute painful (e.g., heel lance) or non-painful disruptive procedure (e.g., nurse handling) will be included. For RCTs investigating the effects of an intervention on newborns' acute HRV responses which is outside the scope of the current review, only the participants included in the control/standard care group will be considered.

Comparator Not applicable.

Study designs to be included Any original empirical article (both observational and RCT) will be considered eligible for inclusion. Review articles, commentaries, conference proceedings, case studies, and dissertations will not be included.

Eligibility criteria Studies that meet the following eligibility criteria are being selected for inclusion: 1) original empirical article; 2) study conducted in either preterm or full-term newborns within the first month of life; 3) includes an acute procedure that is considered either painful and/or stressful to newborns; and 4) HRV measures are being collected during the acute procedure. Studies are not excluded based on language, time frame, country or setting. Only peer-reviewed published studies will be included.

Information sources The following databases were searched: Medline (PudMed), Embase, CINAHL, PsycINFO (Proquest and Ovid), Web of Science, and Scopus. Google Scholar alerts are also being received weekly to identify additional eligible studies. Included and excluded abstracts from Google Scholar alerts will be tracked and included in the PRISMA flow chart. The reference lists of relevant reviews/chapters are also being manually inspected to ensure completeness.

Main outcome(s) The main outcomes of interest will include:

- Newborn HRV responses before, during, and after an acute disruptive procedure. Time-domain, frequency-domain, and non-linear types of HRV metrics will be included.

Additional outcome(s) In order to address the second aim of this review, acute painful procedures will be given a severity score based on a previously published system (Laudiano-Dray et al., 2020). The influence of procedural pain severity on the main outcome (HRV response patterns) will then be investigated.

Data management Three authors (OB, SJ, EC) will be responsible for conducting title/abstract screening and full-text review to identify articles that meet criteria for inclusion. Disagreements will be discussed with senior author RPR. Data extraction will then be performed by the same three authors using a data extraction template developed in consultation with RPR. Inter-rater reliability will be assessed and tracked during the title/abstract screening, full-text review, and data extraction processes and disagreements will be resolved via discussion and consultation with RPR, as needed.

The following data will be extracted from each study:

- Participant data, such as gestational age at birth, postnatal age at time of study, sex, sample size, country of recruitment, setting of data collection, average birth weight, infant positioning during study (e.g., sitting upright in parent arms (away from parent), sitting upright in parent arms (facing into parent), supine in incubator/cot, sitting upright in skin-to-skin contact), and details of the painful/disruptive stimuli (e.g. pain severity index, type of painful procedure, time duration of stressor).

- Newborn sample-specific heart rate variability (HRV) measures (e.g. respiratory sinus arrhythmia, power in high-frequency or low-frequency bands, LF/HF ratio, etc.)

- Descriptive statistics for newborn heart rate variability (HRV) measures (absolute values or changes from baseline)

Covidence software and Microsoft Excel will be used to record inclusion/exclusion decisions throughout the systematic review process, as well as for data extraction and risk of bias judgements. R software (metafor package) and Comprehensive Meta-Analysis software will be used for statistical analyses.

Quality assessment / Risk of bias analysis Three authors (OB, SJ, EC) will independently assess the risk of bias of included studies using an adapted risk of bias tool developed for the current review and informed by the NIH National Heart, Blood, and Lung Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, the Risk of Bias in Non-Randomized Studies – of Exposure (ROBINS-E) tool, and published guidelines pertaining to best practices in the measurement and analysis of heart rate variability (HRV) outcome measures. Inter-rater reliability will be assessed, and disagreements will be resolved via discussion and consultation with the senior author (RPR).

Strategy of data synthesis Each study's participant characteristics, acute procedure, study

methodology, and study quality will be evaluated, as well as any outcomes and statistical analyses that pertain to the research question (i.e., patterns of newborn HRV responses to various acute procedures). Given that several variables are expected to influence the pattern of HRV responses, findings will be stratified by 1) gestational age at birth; 2) postnatal age at study; 3) nature of acute procedure; and 4) HRV measure.

To address the first aim, standardized mean differences (Cohen's d) will be used to examine differences in HRV responses (continuous outcome) across the phases of acute responding within a procedure (baseline, reactivity, and recovery) and across procedures. These effect sizes will then be meta-analysed using a random-effects model. I2 coefficients will be used to assess the heterogeneity among effect sizes.

However, should a meta-analysis not be feasible due to significant variability across studies in sample characteristics, study methodology, outcomes, and statistical analyses, a narrative synthesis will be selected over meta-analysis techniques. Cohen's d effect sizes will still be computed as described above but they will be compared in a qualitative manner. A formal framework for conducting narrative reviews would be employed to consolidate the relevant studies and draw conclusions that address our research question (Popay et al., 2006).

To address the second aim of the review, meta-regression techniques will be employed to examine how the severity of acute painful procedures is related to variation in the main effect sizes (Cohen's d) across studies.

The most recent PRISMA 2020 guidelines (Page et al., 2021) will be followed when reporting the review findings.

Subgroup analysis Patterns of HRV responses to acute procedures will be examined separately based on gestational age, postnatal age, nature of the acute stressor, and type of HRV metric.

Sensitivity analysis Should considerable heterogeneity emerge across study effect sizes, studies with outlier effect sizes will be further inspected for sample, methodological, or statistical differences.

Language restriction No language restrictions were imposed in the search strategy.

Country(ies) involved Canada.

Keywords Newborn; pain; stress; heart rate variability; HRV.

Dissemination plans Review findings will be published in a peer-reviewed journal and presented at academic conferences.

Contributions of each author

Author 1 - Oana Bucsea - The author was responsible for conceiving the review, designing the review, coordinating the review, data collection, data management, analysis of data, interpretation data, and writing the protocol and review.

Email: obucsea@yorku.ca

Author 2 - Sara Jasim The author assisted with data collection and data management.

Email: sjasim@yorku.ca

Author 3 - Estreya Cohen - The author assisted with data collection and data management.

Email: estco@yorku.ca

Author 4 - Rebecca Pillai Riddell - The author was responsible for conceiving the review, designing the review, interpretation data, writing the protocol and review, and providing funding.

Email: rpr@yorku.ca

References

Laudiano-Dray MP, Pillai Riddell R, Jones L, Iyer R, Whitehead K, Fitzgerald M, Fabrizi L, Meek J. Quantification of neonatal procedural pain severity: A platform for estimating total pain burden in individual infants. *Pain*. 2020 Jun 1;161(6):1270-7.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021 Mar 29;372.

Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, Britten N, Roen K, Duffy S. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme Version. 2006 Apr 1;1(1):b92.