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# Patterns of heart rate variability (HRV) responses to acutely painful procedures in neonates: A systematic review

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## 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 31 October 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 acutely painful medical procedures. It will address the following research questions:
1) What normative patterns of HRV responses do newborns exhibit during acute painful procedures?
2) How to moderators/covariates influence newborns' HRV responses during acutely painful procedures?

**Rationale** Early neonatal exposure to repeated stressors, such as painful 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 pain in newborns and variables that may influence these responses, such as gestational and postnatal age, as well as phase of the acute pain-related stress response (reactivity vs. recovery).

**Condition being studied** This review focuses on newborn infants exposed to any acute painful procedures in the first month of life. Acute HRV responses during these procedures capturing newborns' pain-related distress reactivity and recovery patterns is the main outcome of interest. The influence of several factors (i.e., gestational age, postnatal age) 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., brain injury, 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) procedure 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 painful 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 painful procedure. Time-domain, frequency-domain, and non-linear types of HRV metrics will be included, as well as the Newborn and Infant Parasympathetic Evaluation (NIPE) index.

**Additional outcome(s)** To address the second aim, the relationship between covariates/moderators and newborn HRV responses during and after an acute painful procedure will be examined.

**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, average birth weight, illness severity, sample size, country of recruitment, setting of data collection, study beginning and end dates, inclusion/exclusion criteria, and details of the methodology and painful stimuli (e.g. type of painful procedure, description of procedure, time duration of procedure, description of baseline activity/handling, infant body positioning during study, pain management received during painful procedure).

• Duration of measurement for HRV measures (e.g. 15 seconds, 30 seconds, 1 minute)

• Information on newborn sample-specific HRV measures (i.e., how measures were recorded, edited, calculated, and interpreted)

• Descriptive statistics for newborn HRV measures (absolute values or changes from baseline)

• Results of statistical analyses examining trends in HRV responses during the acute painful procedure

• Any covariates and/or moderators (i.e., brain injury, prenatal exposure, birthweight, degree of prematurity, use of sucrose, medication status in inclusion/exclusion criteria, infant state during baseline [alert, drowsy, etc.], illness severity) examined in relation to the HRV responses

• Methodological limitations and future recommendations pertaining to HRV research in newborns

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 RevMan 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; and 3) type of 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).

Given that a preliminary examination of the studies revealed significant heterogeneity in measurement outcomes and statistical analyses across studies, a narrative synthesis was selected over meta-analysis techniques to synthesize the quantitative findings. Cohen's d effect sizes will still be computed as described above but they will be summarized in a narrative manner. A formal framework for conducting narrative reviews will 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, the influence of covariates/moderators on trends in newborn HRV responses (changes in magnitude and direction) will be discussed narratively.

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

**Subgroup analysis** Patterns of HRV responses to acutely painful procedures will be examined separately based on gestational age, postnatal age, HRV outcomes reflecting sympathetic nervous system (SNS) versus parasympathetic nervous system (PNS) activity, and pain response phase (baseline, reactivity, and recovery).

**Sensitivity analysis** Should considerable heterogeneity emerge across study effect sizes, studies with outlier effect sizes will be narratively inspected for sample (i.e., medication status, illness severity, infant state), methodological (i.e.,

type of acute painful procedure), or statistical (i.e., outcomes reported) differences.

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

**Country(ies) involved** Canada.

**Keywords** Newborn, pain, acute, 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 – responsible for conceiving the review; designing the review; coordinating the review; data collection; data management; data analysis; data interpretation; writing the protocol or review.
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