ABSTRACT

Background Neonatal heart rate variability (HRV) is widely used as a research tool. However, HRV calculation methods are highly variable making it difficult for comparisons between studies.

Objectives To describe the different types of investigations where neonatal HRV was used, study characteristics, and types of analyses performed.

Eligibility criteria Human neonates ≤1 month of corrected age.

Sources of evidence A protocol and search strategy of the literature was developed in collaboration with the McGill University Health Center's librarians and articles were obtained from searches in the Biosis, Cochrane, Embase, Medline and Web of Science databases published between 1 January 2000 and 1 July 2020.

Charting methods A single reviewer screened for eligibility and data were extracted from the included articles. Information collected included the study characteristics and population, type of HRV analysis used (time domain, frequency domain, non-linear, heart rate characteristics [HRC] parameters) and clinical applications (physiological and pathological conditions, responses to various stimuli and outcome prediction).

Results Of the 286 articles included, 171 (60%) were small single centre studies (sample size <50) performed on term infants (n=136). There were 138 different types of investigations reported: physiological investigations (n=162), responses to various stimuli (n=136), pathological conditions (n=109) and outcome predictor (n=30). Frequency domain analyses were used in 210 articles (73%), followed by time domain (n=139), non-linear methods (n=74) or HRC analyses (n=25).

Additionally, over 60 different measures of HRV were reported; in the frequency domain analyses alone there were 29 different ranges used for the low frequency band and 46 for the high frequency band.

Conclusions Neonatal HRV has been used in diverse types of investigations with significant lack of consistency in analysis methods applied. Specific guidelines for HRV analyses in neonates are needed to allow for comparisons between studies.

INTRODUCTION

Heart rate variability (HRV) refers to the fluctuation of beat-to-beat intervals over time and is the result of the continuous counter-balancing input from the parasympathetic and sympathetic branches of the autonomic nervous system. In neonates, a diversity of studies using HRV have been published during the last 20 years. HRV analyses were used in investigations of brain injuries,1–4 response to pain,5,6 effects of prenatal drug exposure7 and to assess physiological maturation of preterm infants.8–14 More recently the gradual integration of heart rate characteristics (HRC) monitoring (HeRO, Medical Predictive Science Corporation) into the neonatal intensive care unit (NICU) setting has also increased the use of neonatal HRV in clinical practice.

HRV indices can be processed in many different ways following three analysis approaches: time domain, frequency domain or non-linear methods.1 Time domain methods use summary statistics of the normal-to-normal beat (NN) interval (or R-wave-to-R-wave [RR] intervals), such as the SD of NN intervals (SDNN). Frequency domain methods use spectral analyses to break down the RR interval time series into a distribution
of the power as a function of frequency, which is then broken down into spectral ranges of interest. The third and more advanced type of HRV analysis is the nonlinear method, which includes various measures of chaos, unpredictability and self-similarity, such as sample entropy (SampEn) and the ddetrended fluctuation analysis (DFA).1

In 1996, the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology published specific guidelines for processing of HRV indices in adults that became the gold standard.15 Nevertheless, the majority of research projects did not strictly adhere to these standards.16 Such standards are important for consistency in the literature so that results of studies may be compared and combined accurately. In neonates, there are no specific guidelines for processing of HRV indices. Thus, in order to understand the full extent of neonatal HRV analysis and its various applications, a scoping review was conducted. The aim was to provide an overview of the current studies and population characteristics, analysis methods used, and clinical research applications in which HRV has been used in the neonatal population.

METHODS

Protocol
A comprehensive protocol and search strategy of the literature was developed in collaboration with the McGill University Health Center’s librarians. The study is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews.

Eligibility criteria
All articles that analysed human neonatal HRV were included. Articles were limited to the last 20 years (ie, from the year 2000 onwards) to review more contemporary research in neonatal HRV as methodologies and clinical care have evolved significantly making difficult to ascertain validity of studies performed and published more than 20 years ago. Articles in which human neonates of any gestational age (GA) and ≤1 month corrected age had HRV measured in at least five neonates were eligible. Articles performed in fetuses, animals, infants and children above 1 month corrected age, or adults were excluded. Other types of articles that analysed or discussed human neonatal HRV (reviews, case reports, commentaries, methodological papers, etc) were excluded from data collection. A tally of these different types of articles was maintained in order to understand the full degree to which neonatal HRV has been investigated or used.

Information sources and search
The search was performed in Biosis, Cochrane, Embase, Medline and Web of Science databases and included articles of HRV in neonates in all languages, published between 1 January 2000 and 1 July 2020. The search was performed twice: first in October 2017, then updated again in July 2020. Details of the search strategy used for all databases is provided as online supplemental file 1.

Selection of articles
After duplicate removal, all titles and abstracts were screened for inclusion by one reviewer (SL) based on the eligibility criteria. Full-text articles were then obtained and reviewed by two reviewers (SL or JL) to confirm eligibility and extract data.

Data charting process
Two reviewers (SL or JL) extracted the data from the included articles using a predefined form which included the following sections and listed items below.

Study characteristics and population

Study characteristics
(a) Name of the journal, (b) region where the study was performed, (c) country where the study was performed, (d) type of study design and (e) single or multicentre.

Population details
(a) Sample size, (b) GA and birth weight (BW) categories based on the averages (or medians) of infants enrolled within the study (ie, not based on the study’s inclusion criteria) and using the following definitions: term (≥37 weeks GA), preterm (<37 weeks GA), late preterm (LPT; 34–366 weeks GA), moderate preterm (MPT; 32–346 weeks GA), very preterm (VP; 28–316 weeks GA), extremely preterm (<28 weeks GA), normal BW (≥2500 g), low BW (<2500 g), very low BW (<1500 g) and extremely low BW (<1000 g).

HRV analysis methods

Time domain parameters evaluated
(a) SDNN: SD of normal-to-normal (NN) or R-wave-to-R-wave intervals, (b) CVNN: coefficient of variation of NN intervals, (c) SDANN: SD of the averages of NN intervals in all 5 min segments of the entire recording, (d) SDNNi: mean of the SDs of all NN intervals for all 5 min segments of the entire recording, (e) RMSSD: root mean square of the differences between adjacent NN intervals, (f) SDSD: SD of differences between adjacent NN intervals, (g) NN50/pNN50: pairs of adjacent NN intervals differing by more than 50 ms (count or per cent), (h) NNx50/pNNx50: pairs of adjacent NN intervals differing by a time other than 50 ms (count or per cent), (i) triangular index: total number of all NN intervals divided by the height of the histogram of all NN intervals, (j) TINN: baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals measured, (k) histogram analyses: includes measures of skew, kurtosis and so on and (l) other; any other time domain parameter not listed previously.15

Frequency domain
(a) Total power (TP), (b) ultra low frequency (ULF), (c) very low frequency (VLF), (d) low frequency (LF), (e)
high frequency (HF), (f) LF/HF ratio and (g) other: any other frequency domain parameter not listed previously. Frequency ranges reported for each parameter were also collected.15

**Non-linear**
(a) Poincaré plot analyses (SD1 and SD2), (b) alpha (α): exponent of the 1/f pattern (power spectral density), (c) DFA α1 (short-term exponent), (d) DFA α2 (long-term exponent), (e) approximate entropy (ApEn), (f) sample entropy (SampEn) and (g) other: any other non-linear parameter not listed previously.17

**Heart rate characteristics**
 Classified as its own category given its specific combination of HRV parameters, and the gradual integration of Heart Rate Observation System (HeRO) monitors (Medical Predictive Science Corporation, USA) providing these values into the NICU setting.

**HRV application: studies were classified into four major groups**

**Physiological conditions**
HRV measured under normal, healthy, physiological conditions. Includes: (a) normative: study provides data on normal or healthy infants either with the purpose of providing normative data or as controls, (b) sleep state: includes quiet sleep, active sleep, quiet awake and active awake statuses, (c) longitudinal: study provides longitudinal data (repeated measures, maturation, etc), (d) age or weight: study examines the effect of age or weight in a cross-sectional fashion, (e) feeding, (f) position: supine or prone, (g) tilt: study examines the effect of different degrees of bed inclination, (h) sex: male or female and (i) other: any other physiological application not listed previously.

**Pathological conditions**
HRV measured in infants with certain conditions or diseases, including: (a) sepsis, (b) necrotising enterocolitis, (c) infection, (d) respiratory distress syndrome, (e) apnoea of prematurity (AOP), (f) extubation failure: peri-extubation measurements in relation to extubation outcome, (g) hypoxic ischaemic encephalopathy (HIE), (h) other brain injuries (eg, intraventricular haemorrhage, periventricular leukomalacia, etc), (i) seizures, (j) patent ductus arteriosus (PDA), (k) congenital heart disease or defects (CHD) (l) in-hospital mortality and (m) other (ie, any other condition or disease not listed previously).

**Response to certain exposures, stimuli or external factors**
Includes: (a) pain, (b) medication, (c) sensory stimuli (light, sound or touch), (d) non-nutritive sucking (pacifiers), (e) kangaroo care (skin-to-skin), (f) sucrose, (g) procedures, (h) maternal factors and (i) other stimuli or responses not listed previously. Details regarding the types of medications, procedures and maternal factors were also collected.
with all references organised by each data collection item (figshare.com, DOI: 10.6084/m9.figshare.14750865).18

Table 1  Top 10 journals publishing articles concerning neonatal heart rate variability

<table>
<thead>
<tr>
<th>Journal name</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Human Development</td>
<td>26 (9.1)</td>
</tr>
<tr>
<td>Pediatric Research</td>
<td>24 (8.4)</td>
</tr>
<tr>
<td>Biology of the Neonate/Neonatology</td>
<td>11 (3.8)</td>
</tr>
<tr>
<td>Acta Paediatrica</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Institute of Electrical and Electronics Engineers (IEEE)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Journal of Perinatology</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Developmental Psychobiology</td>
<td>9 (3.1)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Journal of Pediatrics</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Physiological Measurement</td>
<td>6 (2.1)</td>
</tr>
</tbody>
</table>

Table 1  Top 10 journals publishing articles concerning neonatal heart rate variability

Study population
Most articles enrolled a small number of infants (table 2). For the largest cohorts, n=6 articles enrolled >1000 patients, with n=3 (1%) between 1000 and 1999 and n=3 (1%) between 2000 and 2999. However, it should be noted that two of the three published articles that had between 2000 and 2999 infants recruited were analyses of the same large cohort study. Term infants with BW ≥2500 were the most common GA and BW categories studied (table 2). BW was more frequently omitted in articles than GA (n=46 vs n=11 not reported) and 18 articles (6.3%) reported including preterm patients, without specifying the ages (table 2).

HRV analysis methods
The list of all HRV analysis methods and their references is provided as table 3.

Time domain HRV
Time domain was the second most commonly employed type of HRV analysis (n=139; 48.6%), mostly by calculating SDNN (n=125; 43.7%) and RMSSD (n=83; 29.0%) (table 3). Some articles reported other time domain parameters (n=18), including: SDNN/SD delta NN, log MSSD, SDNN/RMSSD, variance NN, long-term variability, short-term variability, interval index, differential index, long-term irregularity, expiration/inspiration ratio, percentage of successive changes in NN intervals sustained over two consecutive increases and decreases, temporally scaled SDNN, temporally scaled CVNN, log variance of heart rate, IQRs, per cent of NN intervals of transient decelerations, SD of NN intervals of transient decelerations, average acceleration and deceleration response, and an undefined variable ‘X’.

Frequency domain HRV
Frequency domain was the most common type of HRV analysis used (n=210; 73.4%) (table 3). The most frequently used parameters were the LF (n=168; 58.7%), HF (n=188; 65.7%) and LF/HF ratio (n=117; 40.9%) (table 3). Many articles also reported other frequency domain parameters (n=41), including: mid-frequency (MF, reported at various ranges), super HF, ultra HF, VLF/HF ratio, MF/HF ratio, LF/LF+VLF.
Among the frequency domain parameters, there were two different reported ranges used for ULF frequency band (upper border limit 0.003 (n=1), 0.0033 (n=2)), 13 different ranges for the VLF band, 29 different ranges used for the LF band and 46 different ranges used for the HF band (figure 4 and online supplemental file 2). The most common VLF and LF ranges were 0.003–0.04 Hz (n=8) and 0.04–0.15 Hz (n=60) (figure 4A and B), respectively, which follow the Task Force guidelines for adults. For the HF range, the most common was 0.2–2 Hz (n=20), which is different from the Task Force guidelines range of 0.15–0.4 Hz (n=19) recommended for adults (figure 4C). Of the 210 articles using frequency domain analyses, only 17 (8.1%) articles

Table 3  Heart rate variability analysis methods

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time domain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>125</td>
<td>(43.7)</td>
</tr>
<tr>
<td>CVNN</td>
<td>26</td>
<td>28 30 40 44 46 49 109 110 149 176 213 242</td>
</tr>
<tr>
<td>SDANN</td>
<td>20</td>
<td>(7.0)</td>
</tr>
<tr>
<td>SDNNi</td>
<td>9</td>
<td>86 90 91 130 175 187 190 193 248 253 259 261 275</td>
</tr>
<tr>
<td>RMSSD</td>
<td>83</td>
<td>(29.0)</td>
</tr>
<tr>
<td>SDSD</td>
<td>14</td>
<td>(4.9)</td>
</tr>
<tr>
<td>NN50</td>
<td>33</td>
<td>(11.5)</td>
</tr>
<tr>
<td>NNxx</td>
<td>15</td>
<td>(5.2)</td>
</tr>
<tr>
<td>TINN</td>
<td>7</td>
<td>(2.4)</td>
</tr>
<tr>
<td>Triangular index</td>
<td>14</td>
<td>(4.9)</td>
</tr>
<tr>
<td>Histogram</td>
<td>17</td>
<td>(5.9)</td>
</tr>
<tr>
<td>Other*</td>
<td>18</td>
<td>(6.3)</td>
</tr>
<tr>
<td><strong>Frequency domain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power</td>
<td>78</td>
<td>(27.3)</td>
</tr>
<tr>
<td>Ultra low frequency</td>
<td>5</td>
<td>(1.7)</td>
</tr>
<tr>
<td>Very low frequency</td>
<td>42</td>
<td>(14.7)</td>
</tr>
<tr>
<td>Low frequency</td>
<td>168</td>
<td>(58.7)</td>
</tr>
<tr>
<td>High frequency</td>
<td>188</td>
<td>(65.7)</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>117</td>
<td>(40.9)</td>
</tr>
<tr>
<td>Other*</td>
<td>41</td>
<td>(14.3)</td>
</tr>
<tr>
<td><strong>Non-linear</strong></td>
<td>74</td>
<td>(25.9)</td>
</tr>
<tr>
<td>Poincaré</td>
<td>29</td>
<td>(10.1)</td>
</tr>
<tr>
<td>Alpha (α)</td>
<td>4</td>
<td>(1.4)</td>
</tr>
<tr>
<td>DFA α1</td>
<td>28</td>
<td>(9.8)</td>
</tr>
<tr>
<td>DFA α2</td>
<td>25</td>
<td>(8.7)</td>
</tr>
<tr>
<td>ApEn</td>
<td>19</td>
<td>(6.6)</td>
</tr>
<tr>
<td>SampEn</td>
<td>22</td>
<td>(7.7)</td>
</tr>
<tr>
<td>Other*</td>
<td>48</td>
<td>(16.8)</td>
</tr>
</tbody>
</table>

Continued
had both their LF and HF ranges following the Task Force guidelines. Nine of these articles also included VLF measures, of which seven also matched the Task Force guidelines for VLF ranges, while the other two used the slightly altered range of 0.0033–0.04 Hz.15 A summary of the number of articles adhering to the frequency ranges from the Task Force guidelines is provided as table 4. A few articles reported using an individualised approach to determine the range for each patient, often by taking into consideration the breathing frequency: fully individualised range (n=8) and upper limit individualised (n=3) (figure 4C).

Non-linear HRV
A total of 74 articles reported using non-linear HRV analysis (table 3). The parameters used were evenly distributed between the Poincaré plot analyses (n=29; 10.1%), DFA α1 (n=28; 9.8%) and α2 (n=25; 8.7%), approximate entropy (n=19; 6.6%) and sample entropy (n=22; 7.7%). Most frequently, however, articles reported using some other non-linear parameters (n=48; 16.8%) (table 3) such as: DFA RMS1 and/or RMS2, Shannon entropy,28 36 43 44 46 84–87 deceleration/acceleration capacity24 25 86 90–93 and numerous (n=26) other combinations of measures, indices, exponents and dimensions of various chaos, fractality, sample asymmetry, correlations and graphical analyses.21 28 30 36 37 48 72 84–87 93–107

Heart rate characteristics
N=25 articles reported using HRC (table 3). Most of them (n=20) come from within the same group of researchers. However, since 2016, other groups have begun using HRC.

HRV applications
The list of all HRV applications and their references is provided as table 5.

Physiological condition
N=162 articles (56.6%) included some form of physiological application of HRV (table 5). The most common form was the use of longitudinal design or repeated measures (n=80). There were 14 articles that examined HRV in relation to 13 other types of normal physiological application or parameters: QT interval,108 EEG bursts,109 110 respiratory,33 47 111 112 heart rate,113 blood pressure,111 112 oxygen saturation,114 fetal HRV,115 movements,114 crying frequency,115 body fat percentage,116 ethnicity,117 height-for-age ratio118 and the Neonatal Behavior Assessment Scale.62

Pathological conditions
N=109 articles included an investigation of a specific condition or disease. The list of the conditions studied and their references is provided as table 5. The most commonly studied conditions were sepsis (n=20) and HIE (n=19) (table 5). There were 37 articles that examined 27 other conditions: cardiorespiratory events,30 119 120 abnormal

Table 3  Continued

<table>
<thead>
<tr>
<th>Heart rate characteristics</th>
<th>N (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (8.7)</td>
<td>2 100 119 124 135 140 142 145 164 166 251 263 269 272 283 284 292 293 296–302</td>
</tr>
</tbody>
</table>

*Others are described in detail within the manuscript text (with references).

ApEn, approximate entropy; CVNN, coefficient of variation of NN intervals; DFA, detrended fluctuation analysis; LF/HF ratio, low frequency/high frequency ratio; NN, normal-to-normal beat intervals; NN50, pairs of adjacent NN intervals differing by more than 50 ms (count or per cent); NNxx, pairs of adjacent NN intervals differing by a time other than 50 ms (count or per cent); SampEn, sample entropy; SDANN, SD of the averages of NN intervals in all 5 min segments of the entire recording; SDNN, standard deviation of NN intervals; SDNNi, mean of the SDs of all NN intervals for all 5 min segments of the entire recording; SDSD, SD of differences between adjacent NN intervals; TINN, triangular interpolation of NN intervals.
fetal status, un规划ed intubation, hypotension, abnormal polgyomomaphy, neonatal abstinence syndrome, Transport Risk Index of Physiologic Stability score, hyperbilirubinaemia, Score for Neonatal Acute Physiology score, delivery complications, clinical course score, risk of neurodevelopmental impairment, gastro-esophageal reflux disease, bronchopulmonary dysplasia, inflammatory cytokines, fetal growth restriction, cardiovascular development, APGAR score (newborn health assessment of Appearance, Pulse, Grmace, Activity, and Respiration), retinopathy of prematurity, in-trathoracic masses, stroke, antibiotic use, non-benign tachyarrhythmia, death/disability score, T-wave alternans, epigenetic ageing, and Clinical Risk Index for Babies (CRIB) score.

Response
N=136 articles investigated HRV in response to certain stimuli. The list of the responses studied and their references is shown in table 5. The most common stimuli studied were response to pain (n=32), followed by light, sound or touch (n=22) and procedures (n=22; table 5). There were 11 different medication or medication groups, 9 different procedures, and 21 different maternal factors studied; a list of these 3 subgroups and their references is provided as table 6. There were 38 articles examining 17 other stimuli: respiratory support, delivery mode, phototherapy, consoling devices, electromagnetic field, stress, cocon/swaredd, transport, hypoxic hypercapnia, feeding protocol, environmental tobacco smoke, caregiving, incubator temperature, non-invasive electrical stimulation at acupuncture points, CRIB versus incubator, self-consoling behaviour, and family nurture intervention.

Outcome prediction
N=30 articles examined HRV in relation to long-term outcomes at discharge and beyond. The list of outcomes studied and their references is provided as table 5. The most common outcome examined was neurodevelopmental impairment (n=12) (table 5). There were 11 articles that included 9 other outcome measures: days on antibiotics, days on oxygen, days off mechanical ventilation, days alive, death, feeding skill or type of feeding at discharge, abnormal polgyomomaphy, ‘unfavourable’ outcome (multifactorial) and cardiovascular development (echocardiography and blood pressure measurements).

DISCUSSION
Study and population characteristics
In the last 20 years, there has been an increasing interest in neonatal HRV, with a notable increase from 2017 onward. Indeed, in this scoping review, we also found 118 review articles that mentioned neonatal HRV, further pointing to its potential usefulness as a clinical tool. Interestingly, the majority of published articles were single-centre investigations that enrolled a small number of infants (<50). It is possible that sample sizes may increase over time as a consequence of advances in monitoring technology and in-hospital data storage systems, which will allow access to ECG signals recorded during hospital stay rather than performing separate signal collection for specific research projects.

There were notably fewer articles in MPT and LPT infants than in the other GA groups despite the fact that these infants account for the majority of preterm infants admitted to the NICUs. These patients still encounter a variety of clinical issues such as respiratory problems requiring different types of respiratory support, feeding and thermoregulation difficulties, and prolonged hospitalisation. This is a population where further HRV studies may show clinical benefit.

HRV analysis methods
A large variety of HRV analyses methods were noted. This review identified 37 additional parameters used for HRV analysis, primarily within the non-linear analyses. Furthermore, the 46 different frequency ranges reported for the HF frequency domain parameter demonstrates how a single HRV parameter can have multiple definitions. Few articles fully adhered to the Task Force guidelines for the frequency domain ranges; however, guidelines for the adult population may not be appropriate for use in neonates given the differences in respiratory and heart rates. Moreover, this review did not collect certain aspects and details concerning ECG signal or HRV analysis, such as the duration of the ECG segment and handling of artefacts, which can also vary between studies.

Table 4 Articles using frequency domain analyses that follow the Task Force guideline’s frequency ranges

<table>
<thead>
<tr>
<th>Frequency range</th>
<th>Task Force ranges</th>
<th>Number of articles following Task Force ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF 0.003–0.04 Hz</td>
<td>8/210 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>LF 0.04–0.15 Hz</td>
<td>60/210 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>HF 0.15–0.4 Hz</td>
<td>18/210 (8.5%)</td>
<td></td>
</tr>
<tr>
<td>LF+HF 0.04–0.15 and 0.15–0.4 Hz</td>
<td>17/210 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>VLF+LF+HF 0.003–0.04, 0.04–0.15 and 0.15–0.4 Hz</td>
<td>7/210 (3.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Data reported as n/N (%), where N=number of articles using frequency domain analyses (N=210). HF, high frequency; LF, low frequency; VLF, very low frequency.
Table 5  Neonatal heart rate variability applications

<table>
<thead>
<tr>
<th>Condition</th>
<th>n (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normative</td>
<td>162 (56.6)</td>
<td>13 30 33 40 41 47 60 76 86 88-93 107 113 117 118 130 131 141 160 163 178 193 195 208 210 213 215 218 223 229 232 233 243 247 248 253 264–266 271 274 294 295 296 299 303</td>
</tr>
<tr>
<td>Age or weight</td>
<td>49 (17.1)</td>
<td>10 13 19 21 25 33 40 41 62 73 76 89 93 95 98 102 107 111 113 115 116 118 122 125 132 134 137 141 181 183 202–204 208 241 243 250 258 259 265 266 271 274 275 280 294–296 303</td>
</tr>
<tr>
<td>Feeding</td>
<td>16 (5.6)</td>
<td>10 13 19 21 25 33 40 41 62 73 76 89 93 95 98 102 107 111 113 115 116 118 122 125 132 134 137 141 181 183 202–204 208 241 243 250 258 259 265 266 271 274 275 280 294–296 303</td>
</tr>
<tr>
<td>Position</td>
<td>13 (4.5)</td>
<td>19 23–25 111 146 182 201 205 211 232 233 273</td>
</tr>
<tr>
<td>Tilt</td>
<td>7 (2.4)</td>
<td>96 111 197 200 209 233 303</td>
</tr>
<tr>
<td>Sex</td>
<td>6 (2.1)</td>
<td>33 55 73 86 111 151</td>
</tr>
<tr>
<td>Other*</td>
<td>14 (4.9)</td>
<td>33 47 62 108–118</td>
</tr>
<tr>
<td><strong>Pathological conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>20 (7.0)</td>
<td>35 92 97 100 119 126 135 164 166 191 212 251 252 278 282 296 298–300 302</td>
</tr>
<tr>
<td>NEC</td>
<td>7 (2.4)</td>
<td>74 76 119 131 135 263 302</td>
</tr>
<tr>
<td>Infection</td>
<td>8 (2.8)</td>
<td>76 119 137 145 186 283 298 301</td>
</tr>
<tr>
<td>RDS</td>
<td>2 (0.7)</td>
<td>39 139</td>
</tr>
<tr>
<td>AOP</td>
<td>1 (0.3)</td>
<td>231</td>
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<tr>
<td>Extubation failure</td>
<td>7 (2.4)</td>
<td>87 140 148 149 225 269 284</td>
</tr>
<tr>
<td>HIE</td>
<td>19 (6.6)</td>
<td>2 4 28 52 65 72 75 81–83 142 151 169 190 218 230 237 244 285</td>
</tr>
<tr>
<td>Other brain injury</td>
<td>7 (2.4)</td>
<td>135 175 199 210 217 242 293</td>
</tr>
<tr>
<td>Seizures</td>
<td>6 (2.1)</td>
<td>28 42–44 46 241</td>
</tr>
<tr>
<td>PDA</td>
<td>2 (0.7)</td>
<td>73 224</td>
</tr>
<tr>
<td>CHD</td>
<td>8 (2.8)</td>
<td>79 194 206 214 221 228 256 275</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>9 (3.1)</td>
<td>26 65 72 135 164 166 293 297 298</td>
</tr>
<tr>
<td>Other*</td>
<td>37 (12.9)</td>
<td>21 29 30 45 56 78 81 101 104 105 107 119–144</td>
</tr>
<tr>
<td><strong>Responses</strong></td>
<td>136 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>32 (11.2)</td>
<td>36 48 50 57 59 63 64 67 69 71 85 103 106 132 133 150 153 154 162 185 199 222 220 240 249 254 260 262 268 276 277 281</td>
</tr>
<tr>
<td>Medication</td>
<td>18 (6.3)</td>
<td>2 4 70 73 78 125 132 134 146 180 192 196 203 231 246 249 267 284</td>
</tr>
<tr>
<td>Light, sound or touch</td>
<td>22 (7.7)</td>
<td>22 29 64 68 146 153–155 160 184 187 227 238 239 245 255 257 262 264 273 281 282</td>
</tr>
<tr>
<td>NNS</td>
<td>5 (1.7)</td>
<td>49 127 232 233 281</td>
</tr>
<tr>
<td>Kangaroo care</td>
<td>13 (4.5)</td>
<td>31–34 61 66 165 179 185 188 194 220 264</td>
</tr>
<tr>
<td>Sucrose</td>
<td>3 (1.0)</td>
<td>59 162 281</td>
</tr>
<tr>
<td>Procedure</td>
<td>22 (7.7)</td>
<td>2 26 50 65 67 72 82 117 119 125 126 146 168 169 196 214 221 226 260 261 267 272 285</td>
</tr>
<tr>
<td>Other*</td>
<td>38 (13.3)</td>
<td>20 23 32 34 48 55 59 64 69 77 104 112 118 121–123 128 129 137 145–163</td>
</tr>
<tr>
<td><strong>Outcome prediction</strong></td>
<td>30 (10.5)</td>
<td></td>
</tr>
<tr>
<td>NDI</td>
<td>12 (4.2)</td>
<td>4 5 57 58 65 72 100 114 126 167 175 190 293</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5 (1.7)</td>
<td>4 100 114 126 175</td>
</tr>
<tr>
<td>LOS or GA at discharge</td>
<td>5 (1.7)</td>
<td>129 164 165 175 256</td>
</tr>
</tbody>
</table>

Continued
but is not often clearly reported. As a result, the methodological variation and lack of consensus in neonatal HRV analysis makes synthesis and comparisons between investigations very difficult, if not impossible. As a result, analysis of neonatal HRV data have been limited to simplified interpretations of trends or shifts in HRV before and after any intervention or condition.

**HRV applications**

Neonatal HRV was used in numerous clinical applications well over the 34 different applications prespecified in this review. Including the applications listed within the ‘other’ categories, as well as the subgroups of responses to medications, procedures and maternal factors, a total of 138 clinical applications have been identified in this

<table>
<thead>
<tr>
<th>Response subgroup</th>
<th>Medications (n=18)</th>
<th>Maternal factors (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoactives</td>
<td>3</td>
<td>73 125 180</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>3</td>
<td>2 472</td>
</tr>
<tr>
<td>Morphine</td>
<td>3</td>
<td>4 128 132</td>
</tr>
<tr>
<td>Caffeine</td>
<td>3</td>
<td>146 231 246</td>
</tr>
<tr>
<td>Thiopental</td>
<td>1</td>
<td>196</td>
</tr>
<tr>
<td>EMLA</td>
<td>1</td>
<td>249</td>
</tr>
<tr>
<td>Cisapride</td>
<td>1</td>
<td>203</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>1</td>
<td>192</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2</td>
<td>73 284</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1</td>
<td>267</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>Procedures (n=22)</td>
<td>6</td>
<td>2 65 72 82 169 285</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response subgroup</th>
<th>Medications (n=18)</th>
<th>Maternal factors (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation</td>
<td>2</td>
<td>146 196</td>
</tr>
<tr>
<td>Surgery</td>
<td>7</td>
<td>50 117 119 168 214 221 260</td>
</tr>
<tr>
<td>Immunisation</td>
<td>2</td>
<td>226 267</td>
</tr>
<tr>
<td>ECMO</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>UVC</td>
<td>1</td>
<td>261</td>
</tr>
<tr>
<td>IAC</td>
<td>1</td>
<td>125</td>
</tr>
<tr>
<td>Chest tube insertion</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1</td>
<td>272</td>
</tr>
</tbody>
</table>

*Others are described in detail within the manuscript text (with references).

AOP, apnoea of prematurity; CHD, congenital heart defects or disease; GA, gestational age; HIE, hypoxic ischaemic encephalopathy; LOS, length of stay; MV, mechanical ventilation; NDI, neurodevelopmental impairment; NEC, necrotising enterocolitis; NNS, non-nutritive sucking (eg, pacifier); PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; SIDS, sudden infant death syndrome.
review. The articles evaluating physiological conditions and responses to stimuli articles should be particularly useful in highlighting certain considerations when planning a research study. It is encouraging that many studies used a longitudinal or repeated measures design, as this allows each patient to act as their own control which is important in the absence of established normative data. The context within these designs is key in interpreting, for example, in which state or condition is the newborn stressed versus relaxed, or the system’s balanced versus disorganised and dysfunctional. It is important that future research also consider performing similar and multiple HRV measures, with the goal of quantitatively combining the results of several investigations. Furthermore, this review highlights areas where more in-depth reviews and larger scale studies could be worth pursuing such as AOP and various long-term outcomes.

Harmonising neonatal HRV

Until a consensus is reached and a guideline is made available, neonatal HRV will continue to have varied methodologies, with simplified interpretability and limited meta-analytic potential. Without the ability to combine results from multiple studies, establishing normative data within this population is not possible. While waiting for an established neonatal HRV methodology to be recommended, we provide a table of suggested reporting items for all studies of neonatal HRV (table 7). Consistency in reporting will ensure, at least, that methodologies can be adequately compared, which will in turn allow certain studies with matching methodologies to be compared and combined. Indeed, with the ever-expanding capabilities of storing large amounts of data, such as the ECGs used for HRV analysis, it may be possible to re-analyse past datasets while applying a newly standardised methodology.

Limitations

This scoping review has some limitations. First, with the intent of keeping the review contemporary, we did not include articles published before 2000. Second, a single reviewer performed both the screening and data collection, but any questions or conflicts were discussed among all reviewers. Third, as previously mentioned, additional details concerning ECG signal or HRV analysis (eg, duration of the ECG segment and handling of artefacts) were not collected since they are not clearly reported in a number of publications. However, this review provides an updated and comprehensive view on neonatal HRV that can be used as reference for future investigations.

CONCLUSION

This scoping review highlights the growing interest in neonatal HRV, with numerous applications being investigated. Most importantly, it reveals the lack of consistency in calculating and reporting HRV, likely due to the lack of consensus and published guidelines for neonatal HRV. Future investigations will benefit from a consensus guideline for neonatal HRV, and this review may help in the planning of that.

Acknowledgements

We would like to thank Elena Guadagno and Ibtisam Mahmoud (McGill University Health Center librarians) for their guidance and for performing the literature searches.

Table 7  Suggested reporting items for neonatal HRV

<table>
<thead>
<tr>
<th>Reporting item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodology</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>Acquisition Describe the acquisition set-up, including devices and software used, sampling frequency, sleep state and positioning of the newborn, and details of the period during which ECG is recorded (eg, 1 hour prior to extubation, immediately after feeding, etc).</td>
</tr>
<tr>
<td></td>
<td>Segment Describe the segment length used to calculate HRV and methods used to select the segment (if any).</td>
</tr>
<tr>
<td></td>
<td>Handling Describe any filtering applied to the ECG or artefact removal methods, including any software used.</td>
</tr>
<tr>
<td>HRV</td>
<td>R-wave identification Describe the algorithms or software used to identify beats (R-waves).</td>
</tr>
<tr>
<td></td>
<td>Handling Describe any filtering, selection or artefact removal methods applied to the RR intervals, including any software used.</td>
</tr>
<tr>
<td></td>
<td>Parameters Describe all HRV parameters calculated with definitions and methods for obtaining the values, with references where appropriate and including any software used. Report all frequency domain ranges.</td>
</tr>
<tr>
<td></td>
<td>Results Demographics Report the baseline demographics of all patients and subgroups of patients where HRV was investigated, including weights, gestational ages and day of life.</td>
</tr>
<tr>
<td></td>
<td>Reporting Report all values for all HRV parameters calculated, regardless of statistical significance.</td>
</tr>
</tbody>
</table>

HRV, heart rate variability.
Open access

Contributors SL consulted with the medical librarians for the search protocol, drafted the data collection form, performed the eligibility screening, extracted the data, summarised the data and drafted the manuscript. JL assisted in the data extraction. WS contributed to the design of the review and provided critical input into the data summarisation and writing of the manuscript. GS (guarantor) supervised the design and execution of the review, and provided critical input into the data summarisation and writing of the manuscript.

Funding This work was supported by the Montreal Children’s Foundation research funds for GS. In addition, SL and WS were both supported from Fonds de la recherche en santé du Québec (FRQS) doctoral research awards in partnership with the Fondation Des Étoiles (award numbers: N/A).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. The references and extracted data items included in this scoping review are provided and organised within an EndNote file (X7, Clarivate Analytics) and an Excel file (Microsoft) available on Fighshare (figshare.com, DOI: 10.6084/m9.figshare.14750865).

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Objective assessment


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