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CLINICAL REVIEW

The value of cardiorespiratory parameters for sleep state classification in preterm infants: A systematic review

Eline R. de Groot [a, 1], Marit S. Knoop [a, 1], Agnes van den Hoogen [a], Xiaowan Wang [a, b], Xi Long [c, d], Sigrid Pillen [e], Manon Benders [a, b], Jeroen Dudink [a, b, *]

[a] Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Family Care Solutions, Philips Research, the Netherlands
[d] Department of Electrical Engineering, Eindhoven University of Technology, the Netherlands
[e] Sleep Medicine Center, Kempenhaeghe, Heeze, the Netherlands

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SUMMARY

Cardiorespiratory activity is highly associated with infants' sleep duration and quality. We performed a systematic literature search of PubMed and EMBASE databases to investigate if and how cardiorespiratory parameters can be used for sleep state classification in preterm infants and in what way maturation influences this relation. All retrieved citations were screened against predetermined inclusion and exclusion criteria. Only studies of preterm infants (<37 wk postmenstrual age during sleep state classification) admitted to a neonatal ward and of whom at least one sleep state and one cardiorespiratory parameter was measured, were included. Two researchers independently reviewed the included studies on methodological quality. Of the 1097 initially retrieved studies, 23 were included for analysis. Heart rate and respiration frequency are strongly correlated with active sleep and quiet sleep. In quiet sleep, as compared to active sleep, respiratory frequency is more stable, and the heart rate is lower and less variable. This association, however, differed across preterm birth subtypes (i.e., extremely, very or late preterm), indicating that maturation – in the form of both gestational and postnatal age – influences the cardiorespiratory characteristics of preterm sleep states. The knowledge gained from this review can help improve behavioral sleep classification and automated sleep classification algorithms for preterm infants.

Introduction

Every year, an estimated 15 million infants worldwide are born preterm – i.e., before 37 wk of gestation (37 wk GA) [1]. They are thus exposed to the extra-uterine environment during a critical period for brain growth, and, therefore, are at risk for adverse neurodevelopmental outcomes [2]. It is important that these vulnerable infants get enough sleep, seeing that sleep has been consistently found to have a protective effect on brain development in preterm infants [3–7].

Four behavioral states can be distinguished during the preterm sleep–wake cycle: active sleep (AS), quiet sleep (QS), intermediate sleep (IS) and wake (W) [8–11]. Some behavioral sleep scores label sleep states differently, but these states can be re-classified to the AS/QS/IS/W distinction based on corresponding behavioral criteria [12–16]. The AS state makes up 40–60% of the preterm total sleep time [17] and is considered important for endogenous stimulation of sensorimotor processing areas of the brain, facilitating activity-dependent development [7,11,18]. QS gains more importance in the last weeks of pregnancy and first moths of life and might induce experience-dependent synaptic remodeling via repetitive, synchronized activity within neuronal pathways [11,18]. IS considered mainly as a transitional state [19,20] and is scored as such when an infant's behavioral sleep state is unclear [8,21–23]. W is characterized as a state in which the infant is alert and/or crying [8–11]. In this state, the infant's eyes are often focused and scanning the environment, and frequent motor activity can be seen.

In the first months of life term born infants spend more time sleeping than they do awake. Preterm infants sleep even more. A longitudinal study of 34 preterm infants found that they slept approximately 87% of the time at 32 wk postmenstrual age (PMA),

* **Corresponding author.** Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Lundlaan 6, 3584, EA, Utrecht.
E-mail address: jdudink@umcutrecht.nl (J. Dudink).
[1] *Both authors contributed equally.*

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Abbreviations

ANS	autonomic nervous system
AS	active sleep
BP	blood pressure
BpE	beats per epoch
BW	birth weight
ECG	electrocardiogram
EEG	electroencephalogram
GA	gestational age
HF	high frequency
HR	heart rate
HRV	heart rate variability
IS	intermediate sleep
JBI	Joanna Briggs institute
LF	low frequency
LTV	long term variability
LZECG	Lemple–Ziv complexity measure on ECG
LZNN	Lempel–Ziv complexity measure on HRV
MeSH	medical subject headings
MF	mid frequency
NICU	neonatal intensive care unit
PMA	postmenstrual age
PNA	postnatal age
PRISMA	'preferred reporting items for systematic reviews'
QS	quiet sleep
RF	respiration frequency
RMSSD	root mean square of successive RR interval differences
SDANN	standard deviation of average normal-to-normal interval
SDNN	standard deviation of normal-to-normal interval
SDRR	standard deviation of RR-interval
SEAUC	sample entropy area under the curve
STV	short term variability
VLF	very low frequency
W	wake

and around 81% at 36 wk PMA [24]. Although preterm sleep is very similar to intra-uterine sleep [9], some differences might occur. For example, research by Mulder [25] has shown that, in fetuses, AS makes up about 50% of the time over a period of 32–40 wk GA. Furthermore, QS increases from about 7% at 32 wk GA to approximately 18% at 36 wk GA and finally 37% at 40 wk GA, while undefinable states decrease from 30% at 32 wk GA to almost 0% at 40 wk GA. All in all, one could conclude that fetuses spend at least 60–90% of their time asleep.

Outside of the protective intrauterine environment, preterm infants are suddenly exposed to excessive light, noise and treatments in the neonatal intensive care unit (NICU), which are all known to disturb sleep [26,27]. Sleep monitoring is thus thought to be very important, as monitoring can increase awareness of sleep duration and quality, give insight in factors negatively influencing sleep, and steer the timing of elective interventions [28].

Traditionally, preterm infants' sleep is monitored by the use of observational classification scores, using visual assessment of eye-movements, facial movements, body movements, and respiratory and heart rate patterns [8,29–31]. This, however, is labor intensive and time-consuming. Moreover, these scores often have a low interrater agreement [32] and differ with regard to the state criteria [8,13–15]. Polysomnography is considered the gold standard [29], but not the most frequently used measure to classify sleep states in infants admitted to the NICU. Polysomnography comprises a combination of EEG, eye-movements, chin muscle tone, heart rate and respiration [33]. However, polysomnography requires a high number of electrodes, which can damage the infant's skin. Furthermore, EEG patterns of preterm infant are GA specific, with early preterm EEG exhibiting an intermittent or discontinuous pattern (tracé discontinue), making the assessment less reliable before 32 wk PMA [34]. Because of this, it is necessary to investigate less intrusive measures that are of similar or higher accuracy during early preterm age. Amplitude-integrated EEG (aEEG) has been explored for its value in sleep state classification [35–42], but the only study comparing it to the gold standard [43] showed that the technique could not distinguish AS from wake. Furthermore, no consistent relationship has been found between aEEG and behavioral sleep states of infants younger than 32 wk GA [35,44].

By contrast, cardiorespiratory parameters such as heart rate (HR) and respiration frequency (RF) have shown correlations with sleep patterns [45]. Cardiorespiratory features are commonly incorporated in behavioral classification scores of preterm sleep [8,23,46–50], yet not consistently [51], and their characteristics are not unanimous between scores that do include them [8,23,46–50]. As HR and RF are measured regularly in each patient in the NICU, they are also attractive candidates for automated sleep classification algorithms. They have been successfully incorporated in automated sleep classification algorithms for adults [52,53] and children [54], and are now being explored for preterm infants [21,38,55,56]. To achieve an algorithm with a higher and more stable performance for classifying sleep states for individual infants, using multiple cardiorespiratory features is necessary [57]. Blood pressure (BP) is an additional cardiorespiratory parameter that might be linked to behavioral states, but its contributing value has not been investigated extensively [58]. Assessing how BP relates to preterm sleep states would be valuable, since it might serve as a back-up when more invasive HR and/or RF parameters cannot be measured – such as in extremely preterm infants (born before 28 wk GA), who cannot tolerate ECG electrodes on the skin.

In this systematic review, we investigated the value of cardiorespiratory parameters for sleep state classification in preterm infants. We did so by assessing the influence of preterm sleep states on cardiorespiratory characteristics. We put special effort in distinguishing between different features of the HRV, since the different HRV features are extensively researched in relation to sleep states [12–16] and used in automated classification models [46]. We also evaluated factors that influence cardiorespiratory parameters during sleep, with the aim to identify potential confounding factors that should be taken into account in future classification systems for preterm sleep. In this evaluation we focused specifically on different measures of age (gestational age at birth and postnatal age at time of sleep classification). This review will contribute to optimizing sleep classification, on both behavioral and automated levels.

Methods

Design

In this systematic review, we reviewed associations between sleep states (AS, QS and W) and cardiorespiratory parameters (HR

and RF). Our secondary aim was to assess a variety of additional factors that were found to influence cardiorespiratory outcome, such as age, sleeping position and birth weight. The principles of the 'preferred reporting items for systematic reviews' (PRISMA) statement were adhered to [59]. Intermediate sleep was not taken into account. This sleep state is scored if there is doubt about the nature of the sleep; thus, including it might skew the results.

The known clinical heterogeneity of included studies meant that a meta-analysis method would have been inappropriate. Therefore, we described our findings in a narrative manner. This review was registered with Prospero number 139247.

Information sources and search strategy

A systematic literature search of the PubMed and EMBASE databases was performed on February 1, 2019; an update search was performed on September 24, 2020. Search terms were formulated based on keywords including "sleep", "preterm infant", "respiration" and "heart rate", and their corresponding medical subject headings (MeSH) terms. The search string was optimized with the help of experts in the fields of sleep research, preterm research and systematic reviews, as well as a librarian proficient in systematic search techniques. The search terms and the search strategy are provided in Supplement 1.

Inclusion criteria and exclusion criteria

Studies on preterm infants (<37 wk PMA) admitted to a neonatal ward were included. Studies were only included if the patients were younger than 37 wk PMA at time of sleep/cardiorespiratory data acquisition. If the patient group also included preterm infants that were older than the 37 wk PMA criterium, that study was still selected, but only if it was possible to retrieve findings for the <37 wk PMA age group. Studies had to include at least one sleep state (AS/QS) or compare between sleep states and had to report at least one cardiorespiratory measure (HR or RF) during the sleep state or states. It was decided that studies using HR and RF that also related other cardiorespiratory measures (e.g., saturation and BP) to sleep states would also be included.

Animal studies were excluded. Furthermore, conference abstracts, case studies, systematic reviews and meta-analyses were excluded, as were all studies not written in English or Dutch.

Study selection

Each of two researchers (EG and MK) screened titles and abstracts of equally divided portions of retrieved citations from the database searches on relevance for the review. EG and MK independently screened the full-texts of selected studies against the inclusion criteria and exclusion criteria. They compared their judgements and decided which studies could be included for data analysis. During all stages of study selection, any uncertainties or discrepancies were discussed until consensus was achieved. If consensus was not reached, disagreements were resolved by discussing them with a third researcher (AH). The screening and study selection are visualized in the flowchart in Figure S1.

Methodological quality

The included studies were reviewed independently by EG and MK on methodological quality according to the Joanna Briggs institute (JBI) critical appraisal tool for cohort studies [60]. The JBI form contains 11 items (including risk of bias), each of which is assessed as 'yes', 'no', 'unclear' or 'not applicable'. Items scored as 'yes' are assigned a score 1; other assessments are not assigned a score. Since some items were not applicable to every study, the total score range varied between 0-7 and 0–10. The JBI manual does not state cut-off points. Therefore, we defined these within the research team for the 0–7 range (since this range occurred most often in literature), based on previous literature. We concluded that 6–7 points would be high quality; 4–5 points moderate quality; and 1–3 points low quality. In the studies where a higher total score range was used, a cut-off was considered that was relative to the generic cut-off. The critical appraisals by EG and MK were cross-checked; any differences were discussed until consensus was achieved. If consensus was not reached, disagreements were resolved by discussing these issues with AH.

Data extraction

The following data were extracted and entered in a data extraction form: author, publication year, aim, study design, sample size, patient's age at birth; patient's age at time of the sleep observation, inclusion/exclusion criteria, health of sample, method of sleep classification, sleep states classified, length of sleep observation, minutes per sleep state, cardiorespiratory parameters, results, conclusion, key findings, JBI critical appraisal score, and JBI quality verdict.

Synthesis

All results from the data extraction form were classified into HR, HR variability (HRV), RF, RF variability, BP, cardiorespiratory coupling, and factors influencing cardiorespiratory outcome (described below). Per parameter, subheadings were made for each sleep state. In the 'other factors influencing cardiorespiratory outcome' the results were divided into the following categories: GA at birth, postnatal age (PNA) at time of sleep observation, birthweight, type of delivery, sleep position, and other. These were not a-priori defined inclusion parameters, but rather they were collected and assessed when found in the studies that were included for analysis of the relation between sleep states and cardiorespiratory patterns. The methodological quality of the studies was color-coded by JBI verdict (red = low quality, orange = moderate quality, green = high quality). Next, data of different studies were merged by comparing the different results within one 'domain' (e.g., HR– AS). Finally, the different results per domain were compared and a conclusion was drawn based on the number of studies reporting a certain finding and the quality of these studies. In a subsequent analysis, GA and PNA were taken into account, so that potential influences of maturation could be assessed.

Results

Because of heterogeneity of the included studies a meta-analysis could not be performed, and results are written in a narrative way.

Study selection

The database searches yielded 1496 citations. Three additional articles were added on the recommendation by an expert in the field [61–63]. Eventually, 23 studies were included for qualitative data analysis. For an overview of the study selection process, see the PRISMA statement Figure S1.

Study characteristics

The included studies had been first published between August 7, 1976 and November 6, 2019. All included studies predominantly

assessed cardiorespiratory parameters in relation to preterm sleep using a prospective cohort study design [12,13,45,61,64–72], sometimes including follow-up [14,15,62,63,73–77]. One study used a retrospective cohort design, including follow-up [16]. In case of a follow-up design, data of the follow-up measurement was only included for analysis if the infants had not exceeded the age of 37 wk PMA at the time of follow-up data collection.

All studies were conducted in a hospital. A total of 15 studies included preterm infants who, based on clinical and neurological assessments, did not show overt complications related to preterm birth [14,15,63–69,72,73,75–77]. Four studies divided their patients into a healthy group and an unhealthy group [13,70,71,74]. Two studies divided infants into multiple groups [12,16]. Two studies did not specify infant health [45,61] and one comprised convalescent preterm infants [62]. In total, 547 preterm infants had been assessed. At time of sleep data collection, PMA ranged from 23 to 37 wk PMA, and postnatal ages ranged from 0 to 84 d. The characteristics of included studies are shown in Table S1.

Sleep characteristics

Of the included studies, five assessed cardiorespiratory parameters only during QS [64,74–77]. Eleven studies included both AS and QS [16,45,63,65–68,71–73]; three included AS, QS and IS [15,69,70]; two included AS, QS and W [13,14]; and three studies included all four sleep states [12,61,62]. For generalizability purposes, we relabeled sleep states that were not labeled according to the AS/QS/IS/W classification introduced by Anders et al. [8]. Correct relabeling was ensured by thorough exploration of the behavioral attributes of the classified sleep states (See Supplement 2). Table S2 presents the associations between sleep states and cardiorespiratory parameters addressed in included studies.

Quality assessment

Eleven studies were of high methodological quality [15,16,45,61–64,66,69,72,73,75,77], six of moderate quality [12–14,67,68,70], and four of low quality [65,71,74,76], as assessed with the JBI critical appraisal tool and based on cutoffs we proposed (Table S1).

Results of individual studies shown by subcategory

A qualitative data-analysis was applied, in which results and key findings of each article were collected and compared, while taking the quality scores into account. It should be noted that although reported in Tables S1 and S2, findings of low quality studies were only included in the qualitative data-analysis when they are considered to add context to other findings. Findings from the qualitative analysis were divided into five categories HR, HRV, RF, BP and potential confounding factors influencing cardiorespiratory–sleep associations. The latter category included GA at birth, PNA at time of sleep classification, birth weight, sleep position and other factors. An overview of the results regarding sleep and cardio-respiration can be found in Table S2.

Heart rate

Of the included studies, 14 studies addressed changes in HR features in relation to preterm sleep states. High sampling frequency of the electrocardiogram (ECG) allows for accurate extraction of the beat-to-beat interval, also known as the RR interval, which reflects the distance between the peaks of a heartbeat. Four studies compared RR interval length between AS and QS. Apart from Reulecke et al. [67], who showed no difference between states, all studies found a longer RR interval in QS than in AS. This indicates a slower heart rate during QS versus AS [15,65,68]. Additionally, QS was related to a lower frequency and duration of bradycardias [73]. Interestingly, Werth et al. [61] used 34 features of HR to develop a classification algorithm and beats per epoch (BpE; the number of R peaks in an interval of 300 s) was one of five features that provided the best classification. In that study, BpE was higher in AS, compared to QS.

Heart rate variability

The degree of variation in the length between RR intervals is an indicator of HRV. This can be divided into different features of HRV: linear time-domain indices (estimating the variability of the RR intervals), linear frequency-domain indices (estimating the distribution of HR spectral power in different frequency bands), and non-linear dynamics indices (quantifying the complexity and unpredictability of a HR series). These HRV features can further be attributed to short-term HR variability, the beat-to-beat differences between two heart beats, and long-term HR variability, the overall variability in interval length between a number of RR intervals. The definitions of the specific HRV features used by the included studies are provided in Table S3.

HRV time-domain

HRV time-domain measures were investigated in association with sleep states in eight studies [12–14,16,45,61,65,66]. Short-term variability features standard deviation of normal-to-normal interval (SDNN) and standard deviation of RR-interval (SDRR) were assessed in three studies [16,45,61], showing an increase of SDRR during AS [16,45] and supporting higher median and IQR scores for SDNN during AS [61]. Additionally, the long-term variability feature “standard deviation of average normal-to-normal interval” (SDANN) was one of three top-performing HRV features in a classification algorithm based on the ECG signal [61]. Three studies found an increased HRV during AS compared to QS. This was quantified by long-term variability features variation in RR interval [13] and the range of instantaneous HR series [14,65]. Another study assessed HRV with the HR differential index and HR interval difference index and did not find significant differences between sleep states [66]. Finally, the root mean square of successive RR interval differences (RMSSD) was found to be higher during AS than QS in three studies [16,45,61].

Overall, HRV time-domain features show an increase during AS, compared to QS [12–14,16,45,61,65,66]. Of these HRV time-domain features, the features related to long-term HRV show the strongest, unanimous distinction in preterm sleep states [12,14,61,65,66].

HRV frequency domain

Five studies [15,45,61,67,68] assessed the association between sleep states and frequency-domain features of HRV. Frequency domain features estimate the absolute or relative power of the heart rate in different frequency bands, in which ‘power’ is the signal energy of heart rate. Commonly used frequency bands are very low frequency (VLF), low frequency (LF), mid frequency (MF) and high frequency (HF), in which VLF and LF reflect long-term variability features of HR, and HF reflects a short-term HRV feature.

Sleep states in relation to VLF HR (0.003/0.017–0.04 Hz, see Table S3) were assessed in three studies [15,45,68]. All three studies found that VLF HR is stronger in AS compared to QS. LF HR power (0.04–0.2/1.5 Hz, see Table S3) in relation to sleep states was assessed in five studies [15,45,61,67,68]. Werth et al. [45,61] and Reulecke et al. [67] also assessed normalized LF power. Four studies found a stronger (normalized) LF HR power in AS compared to QS [15,45,67,68]. The fifth study [61] assessed which features performed the best at classification between AS and QS. Interestingly,

LF HR was one of three most relevant features for optimal sleep state classification based on ECG signal [61].

One study assessed sleep classification in relation to MF HR [68] (Table S3). They did not find a change in MF HR in AS versus QS. The final frequency band, HF HR (0.15/0.2–0.4/1 Hz, see Table S3), was assessed in four studies [15,45,67,68]. Reulecke et al. [67] found a significant increase in normalized HF power in QS. Werth et al. [45] reported increased median and IQR of HF HR during AS, but this was not statistically tested. Two of the four studies did not find a change in HF HR between AS and QS [15,68]. The results for HF HR, thus, are inconclusive, for also no uniform pattern appeared when considering methodological quality of the four studies.

The two studies by Werth et al. [45,61] implemented additional HF bands, pHF1 (0.4–0.7 Hz) and pHF2 (0.7–1.5 Hz), with higher upper bandwidths to accommodate the increased cardiorespiratory rates in preterm infants compared to adults. Notably, Werth et al., 2017 [45] found that pHF1 was the only frequency-band HRV feature present in the optimal feature subset (n = 6 features) for automated classification between AS and QS. They further reported higher median and IQR ranges of pHF1 during AS. Similarly, Werth et al., 2019 [61] also identified pHF1 (then named 'sHF') as one of four HRV features, including LF HR, that produce the most optimal classification performance, based on the ECG signal.

The ratio between low and high frequency components (LF/HF ratio) of HRV may serve as an indication of the sympatho-vagal balance. This HRV feature was assessed in relation to sleep states by three studies [45,61,67]. The findings are inconclusive. Werth et al. [61] did not identify LF/HF ratio as a top-performing feature for AS-QS classification. Werth et al. [45] reported an increase in LF/HF ratio during QS compared to AS. Reulecke et al. [67] found an increase in LF/HF ratio during AS, compared to QS, yet this trend was not significant. The latter study [67] is of moderate methodological quality whereas the Werth et al. studies [45,61] were scored as high methodological quality.

In conclusion, HRV frequency-domain measures are influenced by preterm sleep states. Overall, the strength of the power spectra of the (very) low frequency bands increases during AS compared to QS. The frequency-domain feature that shows the largest distinction between preterm sleep states appears to be LF HR. Moreover, extreme-HF bands seem more able to detect HF HR changes in sleep states, and suggest a stronger pHF1 in AS compared to QS. Yet, statistical analysis is required to make more conclusive claims. LF/HF ratio could relate to sleep states, but this is supported by only one study. Together, the data on frequency-domain measures of HRV suggest a clear influence of preterm sleep states on long-term variability features LF and VLF HR. This was found in a patient age group collectively ranging from 27 to 37 wk PMA. Inconclusive results were found for the influence of sleep states on short-term variability spectral power indices. However, the two studies that did not find an association included extremely preterm infants in their patient groups (with the youngest age at testing being 28 wk PMA) [12,66]. In contrast, the study by Vandeput et al. [16], which found a significantly lower HF HR in QS, included only late-preterm infants (36 wk PMA). Thus, the influence of preterm sleep states on STV might be influenced by PMA.

Nonlinear HRV measures

Complementary to linear measures of HRV, nonlinear HRV features reflect the complex behavior of the underlying control system of HR. They can be used as indicators of HR complexity and unpredictability during sleep states. The association between preterm sleep states and nonlinear HRV dynamics was investigated in three of the included studies [16,61,67].

Vandeput et al. [16] used a numerical noise titration technique of HRV, which provides a numerical test of chaos and chaotic intensity. They found that QS is accompanied by lower noise limit values of HRV, meaning that RR interval series are less chaotic in QS compared to AS. Werth et al. [61] assessed sleep states with HRV features from the following nonlinear techniques: sample entropy (SE), quadratic sample entropy (QSE), the Lempel–Ziv complexity measure (LZ), and the sample entropy area under the curve (SEAUC) (see Table S3). Feature optimization of their classification algorithm identified SEAUC, Lemple–Ziv complexity measure on ECG (LZECG) and Lempel–Ziv complexity measure on HRV (LZNN) as top-performing features for the distinction between AS and QS.

Reulecke et al. [67] assessed sleep states in relation to HRV with nonlinear indices from symbolic dynamics (SD), compression entropy (CE), detrended fluctuation analysis (DFA), Poincaré plot analysis and conditional entropy (CEn) (see Table S3). Overall, nonlinear analysis supported that HR complexity and HRV are lower in QS compared to AS [67]. Furthermore, STV and LTV showed a loss of fractal-like dynamics in QS [67]. CE analysis showed a decrease in degree of compressibility of the RR interval in QS. DFA analysis showed a decrease in mean value of short-term DFA scaling exponent during QS. CEn analysis did not reveal HRV differences between QS and AS. Interestingly, this study included both linear and nonlinear assessment of HRV, and found that indices from nonlinear symbolic dynamics analysis demonstrated changes in HRV with sleep states much clearer than linear features from the HRV time domain.

All in all, nonlinear analyses show that the RR interval series are less chaotic in QS [16], while also showing that HR complexity and HRV are lower in QS compared to AS [67]. Moreover, nonlinear symbolic dynamics analysis demonstrated changes in HRV with sleep states much clearer than linear time domain features [67], with SEAUC, LZECG and LZNN being identified as top-performing features for the distinction between AS and QS [61].

Conclusion of HRV

Overall, HRV time-domain features show an increase during AS, compared to QS [12–14,16,45,61,65,66]. HRV frequency-domain features show increased power of the (very) low frequency bands during AS compared to QS [15,45,67,68]. The relation between HF HRV and sleep states is inconclusive [15,45,67,68], yet extreme-HF band power seems to increase more in AS [45,61]. This distinction between LF and HF bands might be supported by higher LF/HF ratio during QS [45]. Moreover, preterm sleep states show a clear association with LTV measures of HR (increase during AS) [12,14,15,45,61,65–68]. The influence of sleep states on STV appears less conclusive [12,15,16,45,61,66–68] and might be influenced by PMA [12,16,66]. Finally, nonlinear analyses show that the RR interval series are less chaotic in QS [16], while also showing that HR complexity and HRV are lower in QS compared to AS [67].

Respiration frequency

Four studies assessed the association between RF and sleep states [15,65,69,70]. The pooled data of these studies show support for a development-related pattern: RF is higher in QS than in AS for 27–32 wk PMA [15]; RF does not differ between QS and AS for 31–34 wk PMA [65]; and RF is higher in AS than QS for late preterm infants (>35 wk PMA) [69,70]. However, the studies contributing to this pattern are of varying methodological quality: one of low quality [65], one of moderate quality [70] and two of high quality [15,69].

Three studies assessed variability of RF [12,65,66]. All studies show that RF variability is higher in AS than QS, which applied to infants between 27 and 37 wk PMA. Three studies assessed apneas

in relation to preterm sleep [12,70,73]. Two studies found that apneas are more intense and occur more frequently during AS compared to QS [12,70]. However, one study [73] found no effect of sleep state on apnea-related parameters, although they did find a decrease of desaturation during QS (only in supine position). Finally, two studies by Curzi-Dascalova et al. [69,70] concluded that RF in general seems to differ highly between infants.

In sum, all studies found that RF is more stable in QS than in AS. Two of three studies found that apneas are less apparent in QS than in AS. Finally, the relation between RF and sleep states appears to be influenced by PMA.

Cardiorespiratory coupling

Three studies assessed the coupling between respiration and heart function in relation to preterm sleep [67,72,74]. Yet the study by Äärimaa et al. [74] was of low methodological quality and thus not included in the analysis. The two remaining studies assessed cardiorespiratory coherence in patient groups with collective ages ranging from 27 to 32 wk PMA [67] and from 35 to 37 wk PMA [72].

Reulecke et al. [67] used nonlinear dynamics for the assessment of cardiorespiratory coupling: cross conditional entropy (CCEn), cross correlation, mutual information, and joint symbol dynamics (JSD). Bivariate analysis of cardiorespiratory coupling (CCEn, cross correlation and mutual information analysis) and analysis of short-term cardiorespiratory coupling (JSD) showed no differences in cardiorespiratory coupling between AS and QS. However, low synchronization values were found in their patient group, suggesting that cardiorespiratory coupling is (nearly) absent in preterm infants of 27–32 wk PMA.

Lucchini et al. [72] analyzed cardiorespiratory coupling in late preterm infants (34–36 wk PMA) from a phase relationship perspective, in terms of phase coupling and changes in coupling degree. They found that cardiorespiratory synchronization occurs more often and longer in QS. Furthermore, a dominant influence of breathing on HR was found during QS. During AS, the coupling between HR and RF was more balanced and did not show a clear directionality.

Taken together, cardiorespiratory phase coupling shows an influence with preterm sleep states, but this is only found in late preterm infants. Thus, cardiorespiratory phase synchronization during preterm sleep appears influenced by PMA.

Blood pressure

Two studies assessed BP in relation to preterm sleep [14,64], with patients' ages ranging from 28 to 36 wk PMA. Andriessen et al. [64] found higher LF power of systolic BP during QS compared to AS. This was accompanied by a high LF/HF ratio for systolic BP during QS. They also found more coupling between the RR interval and systolic BP in the LF area, in which BP precedes fluctuations in RR intervals. Van Ravenswaaij-Arts et al. [14] found a higher variability in BP during wake than during sleep. None of the included studies assessed BP differences between AS and QS. Therefore, no conclusions can be drawn regarding the value of BP for classification of AS versus QS in preterm infants.

Potential confounding factors

To identify potential confounding factors for the assessment of cardio-respiration in relation to sleep in preterm infants, we assessed the influence of other factors on cardiorespiratory parameters in the included studies.

Gestational age at birth

Three studies assessed the relation between GA at birth and respiration. Unlike the influence of PMA at classification on the relationship between RF characteristics and sleep states (see results: RF), all three studies found that overall RF and RF variability are not influenced by GA at birth [12,69,77]. This applies to a GA range of 27–36 wk, in both QS and AS. Siassi et al. [12] reported decreased apnea frequency during QS with increasing GA.

Average HR seems to increase with GA [12]. For the relationship between HRV and GA, most features regard the frequency domain. No convincing relationship between LF and VLF HR with GA is found [46,70]. Furthermore, development in LF and VLF HR is mainly related to AS, as both a trending increase in these measures [68] and a decrease in oscillations [15] occur most strongly in AS, compared to QS. For both sleep states, HF HR increases have been found related to GA [45,68,77] and PMA [15]. Overall, LF HR is more pronounced than HF HR in preterm infants [65], but this distinction seems to shift during maturation. HF HR clearly increases with GA, while LF HR features do not change much. Interestingly, Werth et al. [45] found no interaction between GA and sleep states on HRV values. Furthermore, Andriessen et al. [64] did not find an influence of GA HRV frequency domain measures. However, the latter study only considered QS, while the other results were either found when looking at both sleep states [14,15,45,65,66,68] or at an older patient group (GA: 35–37 wk [77] as opposed to GA: 27–34 wk [64]).

Two studies assessed GA at birth in relation to cardiorespiratory coupling [67,72], and for GA between 27 and 32 wk, no coupling was found. Bivariate frequency domain analysis of HR and RF showed an increase in linear cardiorespiratory coupling with GA (late preterm versus full term infants) [72].

Summarized, GA does not appear to influence RF or RF variability in preterm infants. There is support that HR decreases with GA, while HRV increases. This increase is mainly related to AS.

Postnatal age at time of classification

Five studies agreed that HR, frequency domain related HRV and BP (although slightly) increase with PNA (between 3 and 5 d) [14,15,63,65,66]. More specifically, a higher PNA is related to higher HF HR in both sleep states [14,15,65,66]. LF and VLF HR seem to increase with PNA [66]. In contradiction, Andriessen et al. [64] did not find an influence of PNA on HRV frequency domain measures. This might be related to sleep state, as Andriessen et al. only looked at QS, whereas the others included data from both QS and AS.

One study looked at RF in relation to PNA (between 2 and 10 d) and found a positive correlation, in both sleep states [69]. One study found that the frequency and duration of bradycardias is not influenced by PNA [73]. Finally, increased PNA in very preterm infants was related to lower cerebral oxygenation measures (tissue oxygenation and cerebral fractional tissue extraction) and higher SaO_2 in both sleep states [63], whereas no differences were found in SpO 2 during AS [62]. This could be related to PMA.

Taken together, PNA influences cardiorespiratory values during preterm sleep, showing positive correlations with HR, frequency-domain measures of HRV, RF and BP. A sleep state-specific effect on the relation between PNA and HRV cannot be excluded.

Birth weight

Only two studies assessed birth weight (BW) in relation to HR and RF during preterm sleep. Andriessen et al. [64] found no clear influence of BW on RR interval and systolic BP values. Curzi-Dascalova et al. [70] assessed the effect of intrauterine growth retardation on RF and found a higher incidence of respiratory pauses, and absence of age-related decrease of respiratory pauses, and increase of RF in the patient group with lower BW. These effects apply to both QS and AS.

Sleep position

Research by Shepherd et al. [73] showed that prone, as opposed to supine, sleep increased cardiorespiratory stability, independent

of PMA. More specifically, in extremely preterm infants (24–28 wks GA) the prone position was associated with lower frequency of bradycardias and desaturation duration and lower FiO2 requirement. In both extremely and very preterm infants (29–34 wks GA) prone position was related to lower desaturation frequency in AS. Elder et al. [62] did not find differences in SpO_2 or oxygen requirement related to sleep position, whereas another study by Shepherd et al. [63] found that prone position, as opposed to supine position, was related to higher tissue oxygenation, cerebral fractional tissue extraction, SaO_2 and HR, but not higher mean arterial blood pressure in extremely and very preterm infants.

Other factors

HR and RF in relation to type of delivery was assessed by Andriessen et al. [64]. A clear influence of type of delivery (c-section versus vaginal delivery) on RR interval and systolic BP values was not found. Furthermore, Curzi-Dascalova et al. [69] found that RF rates during the second sleep cycle were higher than during the first sleep cycle, in both AS and QS.

Discussion

This systematic review aimed to determine the value of cardiorespiratory parameters for sleep classification in preterm infants, with the ultimate aim to improve future sleep classification in this population. Our findings make clear that RF and HR show distinguishable patterns between sleep states in preterm infants. Collectively, the included studies showed a more stable RF and a lower and less variable HR in QS, compared to AS. This applies to various linear and nonlinear HRV measures and is coherent with previous research [21]. No conclusions could be drawn with this review regarding the value of blood pressure (BP) for preterm sleep state classification.

We found a potential influence of PMA on the usefulness of beat-to-beat HRV features versus HRV features that reflect overall variability, for preterm sleep classification. This influence of PMA appeared the strongest for frequency-domain HRV features, rather than time-domain HRV features. HRV is regulated by the autonomic nervous system (ANS). Specifically, LF HR is thought to be modulated by both the sympathetic and parasympathetic branches of the ANS whereas HF HR is only influenced by the parasympathetic nervous system [78]. The sympathetic system develops and dominates early in development, whereas the parasympathetic system does not develop until 36–38 wk PMA, after which its influence increases throughout development [79]. This development fits our observations of an early distinctive ability of LF HR during preterm sleep, and later stabilization of HF HR as distinguishing factor in AS versus QS. The dominant presence and subsequent decrease of AS across the preterm period might also be related to this development of the ANS [79]. This positive association between the sympathetic nervous system and AS could be in line with studies in adults, which show a shift of the sympatho-vagal balance towards a sympathetic predominance during REM sleep compared to NREM sleep [80].

Regarding cardiorespiratory coupling we found increases during QS in very late preterm infants. This is in line with previous research, indicating that cardiorespiratory coupling is far from developed in preterm infants, and is sometimes even absent [81]. Previous studies in fetuses and (preterm) neonates have shown that the control systems for heart rate and respiration undergo major changes following birth, leading to improved synchronization between cardiorespiratory parameters and the circadian rhythm during the first six months of postnatal life [9,82]. As a result, sleep states become more pronounced with increasing development, making them easier to be classified. Additionally, we found a dominance of breathing on HR during QS in late preterm infants and a more balanced, bidirectional coupling during AS. Interestingly, this differential directionality of cardiorespiratory coupling seems indicative of the preterm period. With development, the directionality index decreases and ultimately evolves into a unidirectional interaction system dominated by respiration [83].

Our second aim was to identify factors that influence cardiorespiratory parameters during sleep in preterm infants. We found that both GA at birth and PNA at time of sleep classification influence HR and RF, yet in a different way. Moreover, variation in PNA is associated with more cardiorespiratory changes than variation in GA, which is in line with the differential influence of extrauterine life versus intra-uterine life on the development of heart rate and breathing in preterm infants [84]. Furthermore, we found support that maturation not only influences cardiorespiratory patterns but changes the respiratory parameters that define AS and QS. Specifically, RF is higher in QS than in AS for extreme to very preterm infants [15], but RF is lower in QS than in AS for late preterm infants [69,70]. Thus, it is important to consider the infant's (corrected) age when interpreting cardiorespiratory characteristics for sleep classification.

This systematic review has several strengths. First, applying the principles of the PRISMA statement guaranteed a systematic approach. Second, because the research designs of the included studies were very similar, it was easy to compare results and generalize the quality assessment. Third, the inclusion criteria were very strict on age selection. This is important since maturation showed to strongly influence cardiorespiratory parameters during preterm sleep.

As a limitation, we could not correct for biases or additional methodological flaws already present in the included studies. For example, the included studies used varying methods for sleep classification, 18 of which used behavioral scores for sleep classification [12–15,45,61–66,70–75,77], which cannot ensure accurate state classification. Still, this was in part compensated for by the careful quality assessment. Additionally, ten studies used cardiorespiratory patterns as a method of sleep classification [15,16,61,63,64,68,70,72,75,77], which could have biased the association with sleep states as the cardiorespiratory patterns reported in those studies were refined to a-priori defined patterns. Finally, we did not specifically include sleeping position in our search criteria, which has shown to be an important factor in preterm sleep [85–87].

The current research stresses the importance of age (PMA, GA, PNA) when classifying sleep states in preterm infants, as has been acknowledged before [88]. However, to our knowledge this review is the first to establish that maturation influences the link between cardiorespiratory regulation and sleep states in preterm infants (e.g., PMA determines whether low RF or high RF is indicative of QS). This moderating influence is notably absent from existing scores for behavioral sleep classification in preterm infants [8,23,46–51]. Furthermore, only one of these behavioral scores includes HR criteria for AS versus QS classification [23].

With the identification of sleep-state specific RF and HR patterns and the influences of GA and PNA, this review shows the importance of more refined guidelines for assessing sleep states of a preterm infant, both in behavioral and automated classification scores. Better behavioral classification can help steering elective care and interventions around AS, as this sleep state has been linked extensively to important processes of brain development during the preterm period [3–7,18]. Furthermore, application of this knowledge will likely contribute to a more accurate indication of the time spent in QS and AS. Knowing how much time an infant spends in QS and AS can give insight into the infant's development [89]. To reliably investigate the associations between sleep features and important developmental processes, automated sleep classification in the form of algorithms can be used. The field is invested in incorporating HR and

RF as parameters in these algorithms, as they have the advantage of being less intrusive and are often already available (compared to EEG). However, given that their autonomic nervous system is not fully developed, it is difficult to generate a sleep classification algorithm for young preterm infants. This review supports that nonlinear HRV techniques are valuable complementary measures to standard linear features, as they are better adjusted to the unpredictability of the underlying regulatory systems of HR and RF [90].

From our findings, we conclude that heart rate and respiration frequency are valuable parameters for sleep classification in preterm infants. Moreover, maturation is identified as a moderating factor that must be considered when classifying preterm sleep based on cardiorespiratory patterns. Incorporating the findings from this review into behavioral scores and automated sleep classification algorithms is likely to improve the validity of sleep state classification in preterm infants. This will not only contribute to a better understanding of preterm sleep and improved personalized care (i.e., health monitoring and protection of important sleep states for development), but also allows a better way to investigate the potential associations between sleep and important processes such as brain development in this vulnerable patient population.

Practice points

Preterm sleep is likely important for developmental processes such as brain maturation yet there are many different ways to classify preterm sleep. There is need for a uniform and valid classification system.

Heart rate and respiration frequency are non-intrusive parameters that show distinct patterns during preterm active sleep versus quiet sleep: active sleep is characterized by a higher and more variable heart rate and less stable respiration, compared to quiet sleep.

Maturation of the preterm infant potentially has an influence on the cardiorespiratory patterns during sleep states, as well as which respiratory patterns link to which sleep states. This influence of maturation seems different for gestational age at birth, and postnatal age at time of sleep classification.

Research agenda

The future of preterm sleep research will benefit highly from:

1. Implementing the characteristics of heart rate and respiration frequency for preterm active and quiet sleep in a novel behavioral classification score and improved automated classification algorithms.
2. Further investigating the influence of maturation on cardiorespiratory patterns during sleep and incorporating this in classification instruments.
3. Using the improved classification guidelines to investigate relations between preterm sleep and important developmental processes such as brain maturation to a more valid extent.

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Author contributions

EG and MK performed article screening, data analysis and wrote the manuscript.

JD, XL, XW, SP and MB edited the manuscript. AH designed the study, supervised article screening and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

Xi Long is partly employed at Philips research.

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Appendix A. Supplementary data

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