Unobtrusive assessment of neonatal sleep state based on heart rate variability retrieved from electrocardiography used for regular patient monitoring

Early Human Development 113 (2017) 104–113

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

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ARTICLE INFO

Keywords:
Active sleep
Quiet sleep
Heart rate variability
Support vector machine
Automated
Separation

ABSTRACT

As an approach of unobtrusive assessment of neonatal sleep state we aimed at an automated sleep state coding based only on heart rate variability obtained from electrocardiography used for regular patient monitoring. We analyzed active and quiet sleep states of preterm infants between 30 and 37 weeks postmenstrual age. To determine the sleep states we used a nonlinear kernel support vector machine for sleep state separation based on known heart rate variability features. We used unweighted and weighted misclassification penalties for the imbalanced distribution between sleep states. The validation was performed with leave-one-out-cross-validation based on the annotations of three independent observers. We analyzed the classifier performance with receiver operating curves leading to a maximum mean value for the area under the curve of 0.87. Using this sleep state separation methods, we show that automated active and quiet sleep state separation based on heart rate variability in preterm infants is feasible.

1. Introduction

Newborn infants show two distinct sleep states defined as active sleep (AS) and quiet sleep (QS) [1]. In full-term infants AS is traditionally associated with rapid eye movements (REM), increased variability in cardiorespiratory rates, low muscle tone, and body movements in combination with specific continuous patterns of the electroencephalography (EEG). In contrast, QS is associated with absence of REM, decreased variability in respiratory rates and fewer body movements in combination with a discontinuous EEG pattern. Even in very preterm infants, rudimentary sleep states can be identified from 26 weeks postmenstrual age (PMA) [2].

The important role of sleep states on brain development is only beginning to be understood. It has been shown that sleep cycles are necessary for normal sensory and cortical development of the fetus and newborn [3,4]. AS is important in providing the early stimulation and activity requirements of the growing brain. During AS several organizational events take place such as the topographic alignment of the somatosensory, auditory and the visual system and their connection to the cortex structures [3,4].

The time spend in AS and QS has been shown to be associated with maturation [4–6]. The distribution changes from 80% AS and 18% QS at early gestational age (GA) to around 60% AS and 30% QS at term age (see Fig. 1) [7]. The neonatal intensive care unit (NICU) environment has a profound detrimental effect on sleep pattern development. Significant differences are found in sleep behavior between fetuses and preterm infants at the same postmenstrual age. It has been shown that preterm infants spend less time in AS and more in QS compared to fetuses at comparable age [3,8,9] The difference can be related to the clinical condition of the preterm infant or to the interaction with the “hostile” NICU environment with a variety of noxious stimuli and painful procedures [9,10].

Therefore, investigation of sleep states in preterm infants provides the opportunity to gain more insight in preterm brain development and identify which factors support or disrupt preterm brain development. Currently, polysomnography (PSG) is considered to be the standard for sleep assessment. PSG employs audio and video recording of the infant as well as the typical recordings of respiration, heart rate (HR), electromyography, electro-oculography and EEG. However, the instrumentation required for these studies is only found in sleep laboratories and not in a typical NICU setting. Furthermore, PSG requires placement of multiple electrodes and sensors which are not tolerated by the skin of the vulnerable preterm infant.

Recent advances in technology allow to collect a variety of physiological data in the clinical setting and to process and analyze these in an

Abbreviations: AM, Antedependence models; AS, Active sleep; AUC, Area under the curve; CFS, Correlation based feature selection; ECG, Electrocardiogram; EEG, Electroencephalogram; FSMC, Minority class based feature selection; GA, Gestational age; HR, Heart rate; HRV, Heart rate variability; LDA, Linear Discriminant Analysis; LVQ, Learning Vector Quantization; LOOCV, Leave one out cross validation; MLP, Multi Layer Perceptron; NREM, Non rapid eye movement (sleep); PMA, Postmenstrual age; PSG, Polysomnography; QS, Quiet sleep; REM, Rapid eye movement (sleep); ROC, Receiver Operating Characteristic; SVM, Support vector machine

http://dx.doi.org/10.1016/j.earlhumdev.2017.07.004

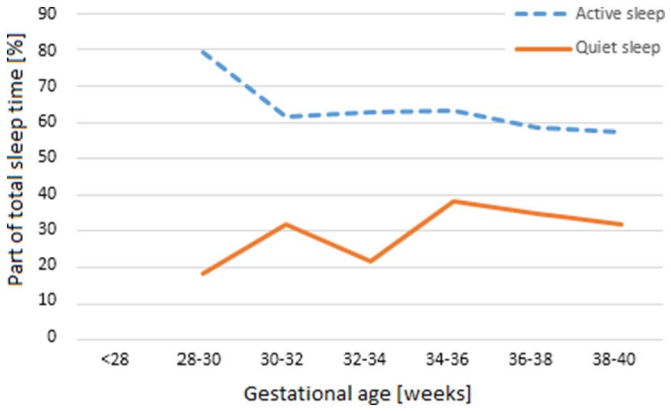

Fig. 1. Percentage of active and quiet sleep of the total sleep time over the gestational age. Active sleep at low gestational age is dominant with around 80% it lowers to around 58% until term age. Vice versa, at low gestational age quiet sleep is less strong represented with around 18%. It increases over the course of development to around 32% at term age. The data is accumulated from several publications, published in [7].

automated fashion. Various methods have been explored to develop sleep state separation techniques that require only a subset of standard PSG measures [11–13]. Automated sleep staging (or sleep state classification) based on e.g. heart rate variability (HRV) is already successfully implemented in adults [14–17]. For newborns, however, automated sleep scoring is still in the exploration phase, while the development of stable EEG based algorithms is only recently emerging (see Table 1). The first research was introduced in the late eighties by Harper et al. [18] and Haddad et al. [19]. Harper et al. used cardiorespiratory signals with a discriminant analysis on 25 term infants over a period of 6 month to separate AS, QS and wake. They created different models depending on age and achieved an overall agreement with the manual observations of 85%. Haddad et al. [19] exceeded the results of Harper et al. classifying only AS from QS based on respiratory variability with an accuracy of 99% on detecting AS and of 93% on detecting QS using Kolmogorov Smirnov distances. These good results might be explained by the age of the subjects, varying from 44 to 56 weeks PMA. Sleep state separation becomes easier with increasing maturation as each sleep state becomes more pronounced and can be separated more clearly. This was also found by Sadeh et al. [20] who separated AS, QS and wake only using actigraphy. They created several movement-based features which were analyzed with an linear discriminant analysis (LDA) for 41 term infants with age ranging from birth (term) to one year of age. The classification accuracy increased over the curse of development from 89 to 97% for sleep and wake distinction. Nason et al. [21] confirmed this observation when they used wavelet analysis in combination with LDA and antedependence models (AM) to separate sleep and wake on one subject over a duration of 4 month. Performance increased over age from 75 to 90% with an LDA and 90–96% with AM.

In 2004, the group of Lewicke and Schuckers used the CHIME study for sleep staging in term infants based on HRV. Lewicke et al. [22] first compared the use of HRV against actigraphy for sleep staging with a learning vector quantization (LVQ) neural network. They reported that the use of HRV resulted in a correct detection of sleep in 90% and wake in 57%, respectively. The use of accelerometer measurements led to 92% for sleep and 42% for wake detection, respectively. The lower agreement for wake could be explained with the use of accelerometer measurements which might not detect wake episodes with less or no movement. In addition, the generally lesser amount of data on wake episodes in term infants can reduce neural network performance as it is directly linked to the quantity of training data. In a second study [23], they applied two additional classification methods together with the LVQ on an extended data set of 190 early term infants. In that study, they used only HRV as input for the LVQ, Multilayer perceptron neural network and a support vector machine (SVM). With a huge amount of 57,000 30s epoch for each training, test and validation set, they were able to increase the correct prediction for wake to 80%. The SVM created the highest scores with a detection accuracy of 90% for sleep and 79% for wake. This was the first time that such amount data was analyzed for automated sleep staging for early term infants. It could be postulate that this was the first stable sleep staging algorithm for early term infants. Automated analysis of preterm infant sleep using cardiorespiratory signals has been published in 2016. Similar to Haddad et al., Isler et al. [12] created a threshold-based algorithm where the threshold was derived from the normalized instantaneous breathing rate variance and respiration variability. By replicating the manual scoring process and tailoring the analysis specifically to the dataset they reached a 100% agreement with the observer annotations. The more general performance of their method ranges from 78% to 92% agreement with the observer annotations.

In 2017, Dereymaeker et al. [25] and Koolen et al. [26] published a classification algorithm of preterm infant sleep states using EEG signals. Dereymaeker et al. focused mainly on identifying QS, where they based their analysis on the heightened discontinuity of the EEG during QS. Using a cluster-based adaptive sleep staging method they achieved very high results from the “Receiver Operating Characteristic” (ROC) with an area under the curve (AUC) of 0.97 for detecting QS from other sleep states out of preterm infant data stream. Koolen et al. used six features on a nonlinear SVM classifier, resulting in an AUC of 0.83 for preterm infants $<$ 32 weeks PMA and 0.87 for infants $>$ 32 weeks. PMA. A more complete overview on sleep state classification based on EEG is given in another article of this special issue by Dereymaeker et al.

As most previous studies were based on term newborns, in this paper we aimed to investigate the feasibility of classifying AS and QS based on HRV only for preterm infants. This would be complementary to the studies by Koolen et al. and Dereymaekers et al. (focusing on EEG analysis) as well as the work by Isler et al. (focusing on respiratory analysis).

2. Material and methods

2.1. Population

In this retrospective study we analyzed eight healthy and stable preterm infants born at a mean gestational age of 30 $\pm$ 2.6 weeks, who were studied at a mean postmenstrual age of 34 $\pm$ 2.8 weeks. The mean birth weight was 1646 $\pm$ 309 g. The infants were admitted to the neonatal department at Máxima Medical Center Veldhoven, the Netherlands. Ethical approval was given by the medical ethical committee of the hospital and written consent was given by the patient's parents.

Table 1
Review of literature on automated sleep staging.

Author year	Population, PMA [wk]	Gold standard annotations	Sleep states of interest	Used signals for analysis	Method	Results
Harper 1987 [18]	39–41 PMA	Manual scoring based on PSG	AS, QS, W	HR, RR	LDA	Agreement for separation of AS-QS-W HR: 82%; RR: 80%; HR + RR 85%
Haddad 1987 [19]	44–56 PMA	Manual scoring EEG, EOG, chin EMG and behavior	AS, QS	HR, RR	Kolmogorov Smirnov distances	Agreement for separation of AS and QS AS 99% and for QS 93%
Sadeh 1995 [20]	40–84 PMA	Manual scoring respiration and behavior	AS, QS, W	Actigraphy	LDA	Agreement for separation of AS-QS-W 75–87% depending on PMA, and for S−W 89–98% depending on PMA
Nason 2001 [21]	48–60 PMA	Manual scoring EEG, EOG, ECG, chest and abdominal movement	S, W	HR	LDA; AM	Agreement for separation of S and W LDA, 75%–90% depending on PMA AM: 89%–96%
Lewicke 2004 [22]	33–58 PMA	Manual scoring EEG, EOG, EMG	S, W	HR Actigraphy	Neural network (LVQ)	Agreement for separation of S and W HRV: Sleep: 90% Wake: 57% Actigraphy: S 92%, W 42%
Lewicke 2008 [23]	39–53 PMA	Manual scoring EEG, EOG, EMG	S, W	HR	Neural network (MLP; LVQ); Non linear SVM	Agreement for separation of S and W MLP, S 86% and W 85% LVQNN, S 89% and W 80% SVM, S 90% and W 79%
Fraiwan 2011 [13]	40 PMA	Manual scoring based on PSG	AS, QS, W	EEG	Time frequency analysis	Agreement for separation of AS-QS-W 63%–75%
Terril 2012 [52]	48–84 PMA	Manual scoring based on PSG	AS, QS, W	RR	Time frequency analysis	Agreement for separation of AS-QS-W 80%–85%
Palmu 2013 [24]	25–32 PMA	Manual scoring EEG, EOG, chin EMG	S-W	EEG	Time frequency analysis	Agreement for separation of S-W, extracted from table 90%
Isler 2016 [12]	37–44 PMA	Manual scoring EEG, EOG, chin EMG, respiration, behavior	AS, QS	RR variability	Time frequency analysis	Agreement for separation of AS-QS AS 78%–90%, QS 87–100%
Dereymaeker 2017 [25]	27–42 PMA	Manual scoring EEG and video	QS	EEG	Time frequency analysis	AUC 0.97 for detecting QS
Koolen 2017 [26]	24–45 PMA	Manual scoring EEG	AS, QS	EEG	Non linear SVM	Accuracy for separation of AS and QS: 85%, sensitivity 83%, specificity 87%

This table gives an overview of the literature on automated sleep staging, from 1987 until 2017 (with citations indicated). Abbreviations: postmenstrual age (PMA) [gestational age + postnatal age], polysomnography (PSG), electroencephalography (EEG), electro oculography (EOG), electromyography (EMG), active sleep (AS), quiet sleep (QS), wake (W), sleep (S), heart rate (HR), heart rate variability (HRV), respiratory rate (RR), linear discriminant analysis (LDA), antedependence models (AM), learning vector quantization (LVQ), multi layer perceptron (MLP), support vector machine (SVM), area under the curve (AUC).

Table 2
Heart rate variability features.

Feature [unit]	Description	Connotation
BpE	Beats per Epoch	ECG R-R intervals detection due to noise is reflected. If ECG is noise distorted, BpE decrease. This mostly appears during AS and wake. Longer heart rate is reflected when long term windowed.
TotPow [ms^2]	Total power or variance of NN intervals of a defined window size.	Reflects overall heart rate variability [30,49]
VLF [ms^2]	The power of the very low frequency band between 0.003 and 0.04 Hz of a defined window size.	Oscillations in VLF are attributed to peripheral resistance fluctuations caused by thermoregulation [44].
LF [ms^2]	The power of the low frequency band between 0.04 and 0.15 Hz of a defined window size.	LF fluctuations are assumed to be related to baroreflex activity and under parasympathetic and sympathetic influence [40,44]. Fluctuations in the neonatal baroreceptor loop are at approximately 0.07 Hz [40,45,46].
LFnorm [%]	LF power in normalized units LF / (Total Power-VLF) × 100	Normalization, to correct for total power variability.
HF [ms^2]	The power of the high frequency band between 0.15 and 0.4 Hz of a defined window size.	HF fluctuations are associated with activities of the parasympathetic system and respiratory activity [42,44,45]. Respiratory activity is closely linked to preterm sleep states [7,12] and seems more prominent during quiet sleep [42].
HFnorm [%]	HF power in normalized units HF / (Total Power-VLF) × 100	Normalization, to correct for total power variability.
pHF1 [ms^2]	The power of the high frequency band between 0.4 and 0.7 Hz	pHF1 fluctuations are associated with activities of the parasympathetic system and respiratory activity especially in reterm infants [31].
pHF2 [ms^2]	The power of the high frequency band between 0.7 and 1.5 Hz	pHF2 fluctuations are associated with activities of the parasympathetic system and respiratory activity especially in reterm infants [31].
LF/HF [n.u.]	Ratio LF/HF	This estimate claims to reflect the sympathovagal balance in adults, although the value has to be established in newborns [45]. Increased values may indicate greater sympathetic and/or lesser vagal modulation [40].
SDNN [ms]	The standard deviation of normal to normal R-R intervals of a defined window length.	Reflects the overall heart rate variability influenced by both the para- and sympathetic nervous system [30,49].
RMSSD [ms]	Root mean square of successive differences between adjacent R-R intervals of a defined window length.	Influenced mainly by parasympathetic activity and respiratory activity.
NNx [count]	The number of pairs of successive R-R intervals that differ by > 10, 20, 30 or 50 ms of a defined window length.	NNx reflects parasympathetic activity. While NN10 covers more overall changes, NN50 represents high frequency variations with influence from respiratory activity [54].
pNNx [%]	The proportion of NNx divided by total number of R-R intervals of a defined window length.	pNNx are directly linked to the NNx features. pNNx for values of x < 50 ms may provide more robust estimates of cardiac vagal tone modulation even in the presence of outliers [54,67].

The HRV features are derived from the Task Force [31] and comments are added from neonatal studies.

2.2. Annotation

Data were annotated by three independent observers for the following neonatal sleep states adhering the Prechtl system [27]: AS, QS, active and quiet wake, vocalization and body positions. The mean annotation time per infant was 334 ± 54 min with simultaneous video recording, ECG and thorax impedance. After removal of caretaking episodes, the recordings were divided into 30-s epochs and sleep states were assumed to be coded correctly if at least two annotators agreed. The total number of annotations were 4057 30-s epochs, of which 845 were discarded because of signal corruptions or disagreement between observers. Of the remaining 3212 annotated 30-s epochs, 283 had other sleep states than AS or QS. For the analysis a total of 2929 30-s epochs remained with AS (n = 2617) or QS epochs (n = 312). The Cohen's kappa (κ) coefficient of agreement representing interrater variability ranged between 0.61 and 0.80 for AS (substantial) and between 0.41 and 0.60 for QS (moderate) [28].

2.3. Data acquisition

The ECG was recorded with three standard leads. The recording device was a Philips monitor (IntelliVue MX 800, Germany) using 250 Hz (n = 2) and 500 Hz (n = 6) sample frequency for the ECG. Sample frequencies of 250 Hz and higher are sufficient for linear HRV analysis [29]. From the ECG signal the R peaks were detected with an in-house developed algorithm [30]. Subsequently, the R-R intervals were used for HRV feature analysis.

2.4. HRV features

We selected 20 HRV features using 18 commonly used features in adult sleep analysis [14,16,31] and two preterm infant specific frequency domain features. The adult frequencies are divided into very low frequency (VLF), low frequency (LF) and high frequency (HF). We refer to Table 2 for details. To create the two additional premature frequency ranges we extended the HF feature to three HF features: HF, pHF1 and pHF2 with a standard adult frequency range from 0.15 to 0.4 Hz for HF, and additional ranges of 0.4–0.7 Hz for pHF1 and 0.7–1.5 Hz for pHF2 [32] to accommodate the increased cardiorespiratory rates in preterm infants. A sliding window of different length (1; 2.5; 5 min) centered on each 30-s epoch was used to evaluate if different windowing gives additional information for separating sleep states in preterm infants.

R-peaks in ECG, needed for the HRV, appear inherently non-equidistant in time. To avoid introducing extra parameters in resampling the signal, the Lomb-Scargle algorithm for spectral analysis was applied [33].

2.5. Feature selection

Supervised learning for classification with a SVM needs a selection of normalized input features to avoid overfitting resulting in a decrease of performance. We implemented a linear and non-linear classification approach, including three feature selection methods (two filtering methods and a wrapper method) which were used to find the top feature subset separating AS from QS. First, the correlation based feature selection (CFS) was applied and second, because the classes are imbalanced, the minority based feature selection method (FSMC). For both filtering feature selection methods, a greedy forward search was used to find the optimal feature subset. The CFS is sorting the features by the highest correlation between

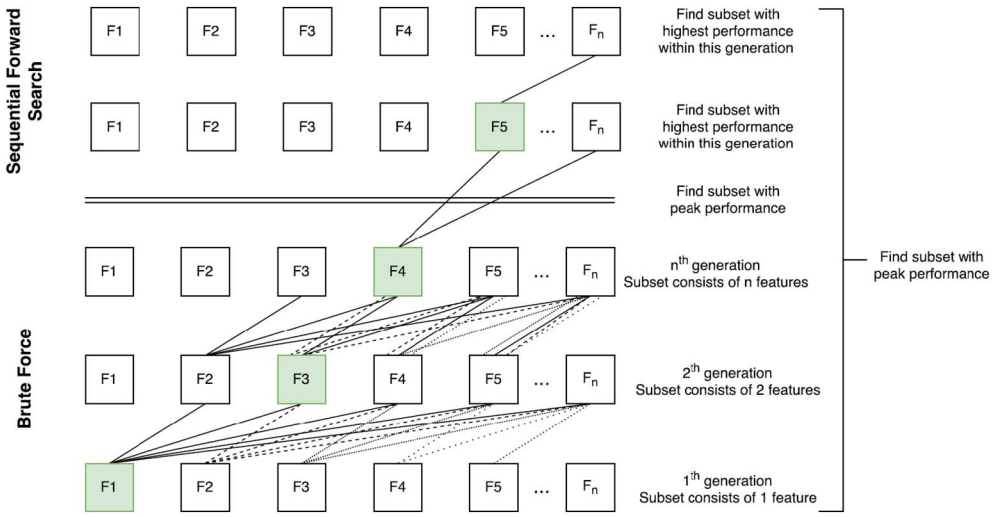

Fig. 2. The brute force method creates subsets with feature combinations of only one feature (1th generation) up to combinations of n features (nth generation). Thereby, features in each subset are not repeated (e.g. F1, F2) and the order is ignored (F1,F2 = F2,F1). Afterwards, all created features are evaluated for their perfomrance and the feature set with highest performance is chosen. The sequential forward search adds in each iteration one feature to the chosen subset, finds the highest performance in this iteration and continues to the next iteration. Finally, the subset with the overall highest performance is chosen to proceed.

feature and class as well as the lowest correlation in-between features [34]. The FSMC is determining the difference between feature values for majority and minority class. It sorts the features by the highest difference between the values for majority and minority class [35]. Third, a mixed wrapper method was implemented (Fig. 2). Starting the wrapper, a brute force forward search was used where all possible subset combinations of all features (without repetition) were generated and for each subset sleep state separation performance was validated. With a search for highest performance the optimal subset was determined. Due to exponential increase of computation time per subset combination length (generation), subsets combinations of all features were limited to the seventh generation (137,979 combinations/iterations in total). The remaining 10 generation of subset combinations were analyzed with a sequential forward search (best first), where only the next single best feature was added to the previous subset combination (105 iterations). The final subset with maximum performance was determined.

2.6. Classifier

After the feature selection and within the wrapper method, a SVM classifier, embedded in Python's Scikit-learn library [36], was used to train and test on the dataset. SVM is a widely used classifier [37] which is searching for hyperplanes separating the different classes with a maximum margin under the condition that misclassifications are minimized. Thereby, misclassification is penalized with a constant C which is multiplied with the amount of misclassifications. A large C value will increase the misclassification penalty (decreasing the misclassification), leading to a decrease of the minimum margin around the hyperplane separating the classes and vice versa. If the C value is chosen to be large, the generalization of the SVM model can get weakened. For this study the C value was set to value 3.6 after a parameter search as a good balance between speed, accuracy and generalization.

As the data is unbalanced for AS and QS states the C value can additionally be multiplied with value pairs representing the distribution of a dataset to compensate for the class imbalance. In preterm infants the class distribution change over time and development, therefore, we clustered the participants into four different GA ranges and computed the class weight pair for each cluster not on the actual data distribution per cluster, but on the gross expected distribution known from literature [7] as seen in Fig. 1. The subjects were ranked into the following clusters in GA: 31–32 weeks (n = 2), 33–34 weeks (n = 1), 35–36 weeks (n = 2) and 37–39 weeks (n = 3). This clustering should not be mistaken for an age clustering to create different feature/training sets which is not feasible due to the limited population size.

Within the wrapper feature selection method a nonlinear SVM classification was used. The SVM is optimal extendible for nonlinear tasks using the “kernalisation” or “kernel trick” where the training data are transformed into a higher dimensional feature space where the problem then becomes linear again [38]. The applied SVM used the radial basis function (RBF) kernel for non-linear approximation. The RBF kernel also uses a free parameter γ which determines the inverse influence of the support vectors. We used a γ value of 0.2.

A leave one out cross validation (LOOCV) was applied to attest the classifier performance. Cross validation methods separate the total data into different parts of which one is used to validate the classifier and the remaining parts to train. Nevertheless, for small datasets these methods can become biased as it is highly probable that training and testing sets are created from the same patients. To avoid a biased validation the LOOCV uses the patients itself as separation. All but one patient are chosen for training and the remaining patient for testing. For more detailed description we refer to the literature [37].

2.7. Statistical analysis

For continuous distributed data median and inter quartile range (IQR) were calculated. Data were analyzed with Matlab 2014b software program (MathWorks, Natick, Massachusetts, US). The performance of sleep state separation was calculated with the receiver operating curve (ROC) and corresponding area under the curve (AUC).

3. Results

In Table 3 the median of all 20 HRV features for AS and QS are presented together with inter quartile range with 25 and 75 percentiles for comparability with the literature.

We used 1, 2.5 and 5 min windows to investigate effects of window length effects in preterm infant sleep staging. The combination of different window sized did not increase the classifier performance. In contrary, the analysis of only 30s epoch based HRV features lead to a lowered sleep

Table 3
HRV feature values for preterm infant sleep states.

Features	Units	AS				QS			
		Median	IQR	Percentile		Median	IQR	Percentile	
				25	75			25	75
BpE	counts	770	49	749	798	745	72	704	776
NN10	counts	118	159	44	203	90	178	8	186
NN20	counts	37	95	11	106	10	35	0	35
NN30	counts	21	64	3	67	2	10	0	10
NN50	counts	10	33	0	33	0	5	0	5
RMSSD	ms^2	18	30	8	38	12	16	6	22
SDNN	ms^2	24	16	16	32	13	11	8	19
pNN10	%	16	21	7	27	13	25	1	26
PNN20	%	5	13	2	15	1	5	0	5
pNN30	%	3	8	1	9	0	1	0	1
PNN50	%	1	4	0	4	0	1	0	1
HF	ms^2/Hz	38,962	63,774	16,817	80,591	15,898	28,401	3	31,289
Hfnorm	%	12	8	8	16	10	6	7	13
LF	ms^2/Hz	117,274	148,547	59,518	208,065	49,878	125,967	22	147,946
Lfnorm	%	39	41	21	62	55	38	32	70
VLF	ms^2/Hz	258,488	380,003	114,717	494,720	57,558	87,281	31	118,391
ratioLFHF	n.u.	3	4	2	6	5	5	2	7
pHF1	ms^2/Hz	26,039	80,965	6262	87,227	9764	24,230	1	25,335
totpower	ms^2/Hz	687,347	897,832	303,403	1,201,235	204,300	364,824	76	441,208
pHF2	ms^2/Hz	59,147	271,635	10,071	281,707	8087	25,003	2	27,097

This table presents the unscaled HRV features for active sleep (AS) and quiet sleep (QS) as median, inter quartile range (IQR) and [25th, 75th] percentiles.

staging performance of 0.71. Hence, we used the 5-min window length for sleep state separation and classifier methodology recommended by the Task Force [31].

To evaluate the linear approach of sleep state separation, we implemented the CFS and FSMC filter methodologies. The performance of the optimal subset was evaluated with a linear SVM classifier and resulted in a mean AUC of 0.32 ± 0.16 for CSF. The FSMC method could not identify any suitable features for a subset conformable with its selection rules. These results showed that sleep state separation with a linear kernel is not feasible for this set of features.

After exclusion of sleep state separation with a linear kernel we implemented a wrapper solution with a nonlinear kernel SVM. The optimal subset was obtained by training the SVM on seven preterm infants while one is left out for cross validation (Figs. 3 and 4). The performance analysis of sleep state separation was calculated with the ROC and AUC for each iteration of the wrapper and the following sequential forward search. The ROCs per patient and mean ROC of the chosen subset is shown in Fig. 3 with a mean AUC value of 0.85 ± 0.46.

As the sleep states were unbalanced we adapted the classifier parameter C with weighting factors pairs calculated from the expected distribution which grossly correspond with the four age cluster (see Material and Methods). Using the different class weights we achieved a better performance of the sleep staging with an AUC of up to 0.87 ± 0.42 (Fig. 4). The optimal subset features resulted from the wrapper analysis for both classification types were BpE, NN20, SDNN, pNN20 and total power.

4. Discussion

HR is an important physiological parameter for sleep monitoring in newborn infants, children and adults. In this study we explored the feasibility of sleep state separation by automated analysis of HRV features obtained from standard patient monitoring. A nonlinear kernel support vector machine for sleep state separation between AS and QS was used. The classifier performance with receiver operating curves resulted in a mean value

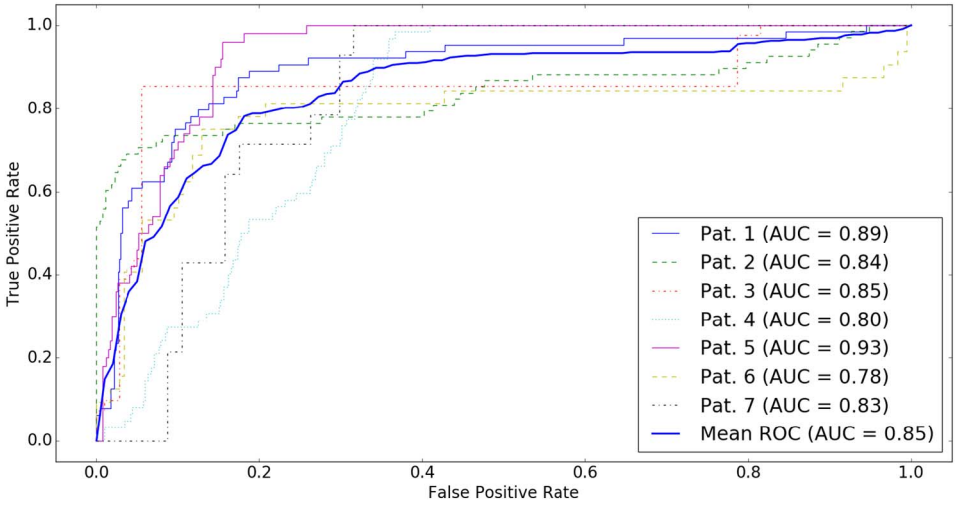

Fig. 3. The "Receiver-Operating-Characteristic" for the eight fold leave one out cross validation of SVM sleep state separation. Patient 8 showed only active sleep and therefore this data was included in testing and training, but the ROC could not be calculated.

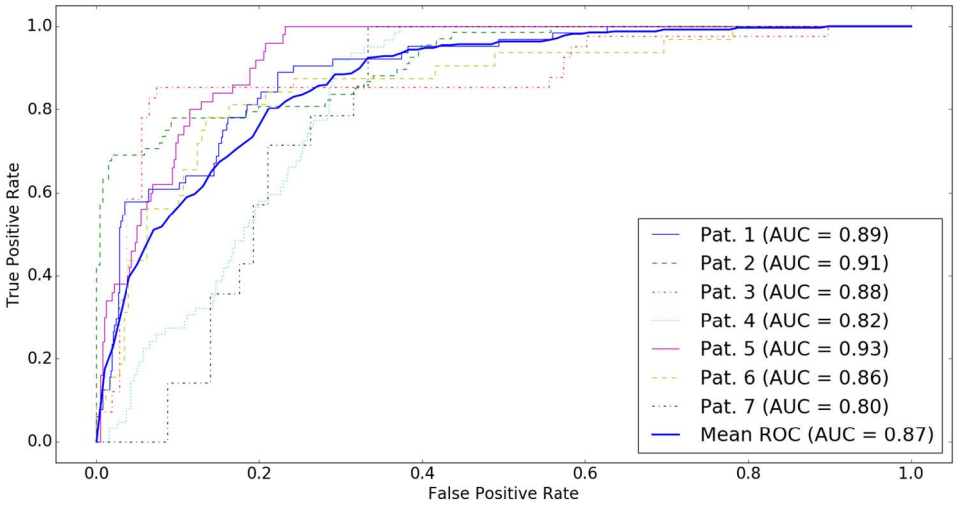

Fig. 4. The "Receiver-Operating-Characteristic" for the eight fold leave one out cross validation of SVM sleep state separation. Here we use used adapted missclassification penalty value pairs for parameter C to counter class imbalance. Patient 8 showed only active sleep and therefore this data was included in testing and training, but the ROC could not be calculated.

for the AUC of 0.85 (Fig. 3) and under consideration of sleep state distribution an AUC of 0.87 (Fig. 4), indicating that HRV features are valuable for automated sleep state separation in preterm infants.

The early postnatal period for preterm infants is characterized by fluctuating periods of active sleep (AS) and quiet sleep (QS) states, with intermediate/undetermined sleep phases. These fluctuating states are associated with characteristic cardiorespiratory variability [6]. Although cardiorespiratory coupling is weak in very preterm infants, studies conducted in more mature infants show the presence of cardiorespiratory coupling [39]. In Table 3 the different HRV values for AS and QS per feature are presented. Overall, the high IQR of the various HRV values may reflect an immature autonomic nervous regulation. Also, recovery to a stable state of autonomous control after any disturbance is reflected by a relative long time constant of approximately 10 min [40]. Our findings are comparable with other preterm infant HRV studies [41–43] and the time domain features shows less complexity in HR regulation during QS, reflected in lower median values and IQR. As the respiratory sinus arrhythmia in preterm infants is less dominant than in term babies [43], the median increase with AS in the time domain can probably be linked to the dominance of the sympathetic nervous system in preterm infants [31,44]. This might originate from the not fully developed adrenergic receptors in the sinus node [43]. It has been suggested that the limited cardiorespiratory coupling is stronger during QS than during AS [43]. This enhances the difference in median and IQR as more regular breathing patterns during QS reduce the signal complexity while the irregular breathing during AS does show only limited influence. The predominance of the sympathetic nervous system is associated with an increase in LF power [45], increasing the feature values for LF and LFnorm compared to HF and HFnorm. However, also vagal modulation of baroreflex response to blood pressure disturbances is important [46]. In addition, the baroreceptor reflex sensitivity increases during maturation [47] with reduced high frequency contribution to HRV in preterm infants. Like other studies the LF/HF ratio showed slightly higher values for QS, probably indicating a greater sympathetic or less vagal modulation [41]. In general, the spectral power values were decreased in QS compared to AS suggesting that the autonomic modulation is lower during QS [42]. This could be explained as the AS state is seen as the most basic state which is regulated by a network of several forebrain areas and the controlling brainstem [48] and therefore, earlier developed and more pronounced than the QS [49].

4.1. Features

In general, the approach to automatically separate sleep states using a cardiorespiratory signal consists of a feature extraction approach (i.e. HRV features), followed by a classification step (i.e. SVM). The features we chose are derived from adult sleep analysis [50,51] as the main objective was to proof the feasibility of separating sleep states in preterm infants based on HRV. We also added two additional features with increased frequency ranges to accommodate the general higher cardiorespiratory rates in preterm infants. The new used frequency ranges for preterm infants (see Table 1) were proposed in 2008 by Indic et al. [32]. The new feature pHF1 consistently appeared in the top feature subsets underlining the importance and influence on sleep state separation and also the assumption of Indic et al. that higher cardiorespiratory rates in preterm infants need adapted frequency ranges seems to be valid. This is not surprising as other groups already explained [6] and demonstrate [12,52] the benefit of respiration analysis for sleep staging. In the top feature five feature subsets, which all resulted in comparable performance (AUC: 0.85–0.87), total power and SDNN were always present. pHF1, NN20, NN30 and pNN20 were present three out of five times. The time domain feature BpE appeared only in the top feature subset.

To further increase classification performance and stability, recently published novel term [53] or preterm infant HRV features [54] can be implemented in future research. In addition, the preterm infant desaturation features presented by Kommers et al. [55] can be used to eliminate episodes of tachycardia avoiding misinterpretation of autonomous activity due to, non-sleep-related, altered HRV. Also, instead of eliminating noise from the signal it could rather be used as additional information source supporting sleep state separation [56].

4.2. Sleep states separation

The nonlinear SVM kernel was chosen based on a good separation performance with a mean AUC of 0.85 to 0.87 (Figs. 3 and 4). The SVM classifier was selected as it is robust against outliers, while showing high performance for single and multiclass classification problems [57]. Outliers have to be expected as the sleep state annotation is challenging by various covariates.

The age clustering for compensating changing state distributions increased the performance. Nevertheless, while the performance improved for most subjects (4) some did not change (2) and one patient actually decreased. This could be interpreted as hitting the right cluster improves the classification while a false clustering can lead to a decrease of performance. In our opinion, only clustering on age is the reason for the possibility of a

decrease in performance. Commonly, it is postulated that sleep state change over gestational age [7]. This is certainly correct, but age is only one indicator for neural development. The coupling between age and development (sleep state distribution) can change with neural miss-development. Therefore, we suggest that the correct clustering has to be determined and based not only on age but rather overall condition including weight and size and other biomarkers.

Nonetheless, also biomarkers which are not directly linked to neural development can give miss information and potentially create false sleep staging which consequently would lead to false results of development monitoring. Generally, it can be said that sleep state separation without additional background information should be aspired.

4.3. Unobtrusive HRV measurement

In this study adhesive ECG electrodes were used as part of standard care and patient monitoring. Recently, there have been innovative developments in obtaining unobtrusively cardiac signal measurements from which HRV can be derived [7]. In general, the unobtrusive HRV measurements can be classified as contact and non-contact methods. The contact methods include a variety of options, including a neonatal jacket embedded with smart textile electrodes for ECG measurements [58], a neonatal snuggle embedded with reflectance photoplethysmography based on near infrared spectroscopy technology for pulse oxygenation monitoring [59], and intelligent bed sheet embedded with polyvinylidenefluoride or electromechanical film sensors for ballistocardiography measurements [60]. These contact ECG sensors are suitable for sleeping scenario by integrating into a bed sheet or a mattress. The non-contact methods include HRV extracted from thermal imaging, video analysis, Doppler effect, and capacitively coupled ECG [7,61–63]. The imaging and Doppler methods could be embedded into a neonatal incubator for non-contact measurements. For example, the sensory neonatal jacket and snuggle provide natural platform for seamlessly embedding sensors for unobtrusive measurements. A major limitation of most unobtrusive methods are the sensitivity to motion artifacts deteriorating the signal quality. In general, the type of unobtrusive HRV method depend on various factors, such as the neonatal sleep monitoring scenario, the environments of incubator inside NICU, the reliability of measurements and the suitability for long term sleep monitoring.

4.4. Methodological limitations

The small sample size of analyzed preterm newborns is a limitation of our study. Also, this study included only AS and QS states. However, AS and QS are the dominant states in the early weeks after preterm birth and other states are less well defined in preterm infants. The objective of the study was the feasibility to separate AS and QS, which are most important for development monitoring, based on HRV measure alone. Future studies will have to attend the integrated problems of sleep staging. To increase the performance of sleep state separation, several demographic variables such as gestational and postnatal age could be taken into consideration as these variables influence the HRV [64]. Note that the methodology of gestational age clustering in this study was used only for consideration of the sleep state distribution, not for age determined feature creation and training sets. In our case age clustering for different classification was not feasible due to the small dataset. Clustering the data would have further decreased the training data. Finally, this study used mainly the (adult) recommendations from the Task Force as there is no consensus in newborns. The European and North American Task Force was formed in an attempt to set standards for future studies of HRV [31]. While important recommendations were made for the length of recordings and the required spectral indices, the conclusions were based on adult studies only. As the neonatal heart and breathing rate differs from adults the recommendations of the Task Force may not be applicable in preterm infants. However, until recommendations for neonatal standardized analytical methods are made, many fetal and neonatal studies uses the recommendations of the Task Force [65,66]. We followed this approach by using mainly the adult recommendations from the Task Force. Nevertheless, to account for the increased cardiorespiratory rates in preterm infants we used two additional frequency domain features, pHF1 and pHF2 [32].

5. Future recommendations

For a stable performance based on HRV features only and over a wide range in the preterm infant population, additional data is needed. For possible clinical application and a more holistic view on preterm infant sleep, classification between all states should be considered. As earlier research showed good performance of respiratory analysis for sleep staging we recommend to use cardio and respiratory features in combination to achieve higher or more stable performance. Finally, as the R peak detection is essential for correct classification with HRV, we suggest to investigate and validate R peak detection algorithms specifically for preterm infants.

6. Conclusion

This study shows that using a nonlinear SVM classifier approach for HRV features provides good results for preterm infant sleep state analyses of AS and QS. While our findings cannot yet be seen as robust due to the limited population size, the classifier performance can compete with the literature [23,26,52]. Merging the different vital sign approaches e.g. respiration [12] and activity [67] with HRV will most likely lead to a robust, unobtrusive automated methodology for continuous preterm infant sleep monitoring.

Declaration of interest

This work was performed within the framework of IMPULS Perinatology, a research collaboration between Philips Research, Eindhoven University of Technology and Máxima Medical Center. No financial assistance was received in support of this study. The authors report no conflict of interest.

Author's contribution

The authors meet the criteria for authorship as listed in the Early Human Development authors information pack. All authors approved of the final version to be published and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Jan Werth: contributed to the engineering part and programming; interpretation of data; wrote first draft.
Xi Long: supervising the engineering part and statistical analysis; revising the draft iterations for intellectual (technical) content.
Elly Zwartkruis-Pelgrim: responsible for sleep state annotation; revising the draft iterations for intellectual content.
Hendrik Niemarkt: revising the draft iterations for intellectual (medical) content.
Wei Chen: revising the draft iterations for intellectual (technical) content.
Ronald M. Aarts: contributed to design of the study; revising the draft iterations for intellectual (technical) content.
Peter Andriessen: contributed to design of the study; revising the draft iterations for intellectual (medical) content.

Acknowledgements

Special thanks to Ralph Wijshoff for providing the R peak detection algorithm.

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