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Citation/Reference	M. Lavanga *et al.*, "**The implementation of an apnea-based perinatal stress calculator**," in *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2019, pp. 6000–6003.
Archived version	Author manuscript: the content is identical to the content of the published paper, but without the final typesetting by the publisher
Published version	https://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=8856955
Journal homepage	https://ieeexplore.ieee.org/document/8856955
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Abstract	Early life stress in the neonatal intensive care unit (NICU) predisposes premature infants to adverse health outcomes. Although those patients experience frequent apneas and sleep-wake disturbances during their hospital stay, clinicians still rely on clinical scales to assess pain and stress burden. This study addresses the relationship between stress and apneic spells in NICU patients to implement an automatic stress detector. EEG, ECG and SpO_2 were recorded from 40 patients for at least 3 hours and the stress burden was assessed using the Leuven Pain Scale. Different logistic regression models were designed to detect the presence or the absence of stress based on the signals reactivity to each apneic spell. The classification shows that stress can be detected with an area under the curve of 0.94 and a misclassification error of 19.23%. These results were obtained via SpO_2 dips and EEG regularity. These findings suggest that stress deepens the physiological reaction to apneas, which could ultimately impact the neurological and behavioral development
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The implementation of an apnea-based perinatal stress calculator

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***Abstract*— Early life stress in the *neonatal intensive care unit* (NICU) predisposes premature infants to adverse health outcomes. Although those patients experience frequent apneas and sleep-wake disturbances during their hospital stay, clinicians still rely on clinical scales to assess pain and stress burden. This study addresses the relationship between stress and apneic spells in NICU patients to implement an automatic stress detector. EEG, ECG and SpO_2 were recorded from 40 patients for at least 3 hours and the stress burden was assessed using the Leuven Pain Scale. Different logistic regression models were designed to detect the presence or the absence of stress based on the signals reactivity to each apneic spell. The classification shows that stress can be detected with an *area under the curve* of 0.94 and a misclassification error of 19.23%. These results were obtained via SpO_2 dips and EEG regularity. These findings suggest that stress deepens the physiological reaction to apneas, which could ultimately impact the neurological and behavioral development.**

I. INTRODUCTION

Premature infants are at risk of adverse health outcomes, neurodevelopmental delays and behavioral problems. One of the causes of this maladaptive outcomes can be the early experience of stress in the *neonatal intensive care unit* (NICU) [1]. The current stress experience in the NICU consists of multiple noxious stressors (light, sound, etc.) and invasive care-giving procedures which lead to a cascade of physiological reactions. There have already been multiple attempts to automatically detect stress using biomedical signals in adults, but neonatologists tend to assess the level of stress via clinical scales or using the number of painful procedures. However, Barbeau [2] reported that NICU patients present sleep-wake cycles (SWC) disturbances after care-giving contact and most of those events are likely to be accompanied by apneas, long bradycardias and deep desaturations. As reported in [3] and [4], apneas are common in the premature population and can have an effect on developmental outcome. A recent study proposed a model to explain how apneas can induce prefrontal cortex dysfunction in the adults and children due to the disruption of sleep and chemical homeostasis [5]. Furthermore, children with Obstructive Sleep Apneas (OSA) are prone to attention disorders and hyperreactivity as a consequence of the reduced cerebral blood flow and the intermittent gas abnormalities [5]. In contrast, sensorial procedures (like nurturing and Skin-to-skin contact) will have a positive influence on development and cerebral oxygenation [6]. It seems reasonable to hypothesize that one of the pathways of the relation between stress in NICU and maladaptive outcomes is represented by apneas. Therefore, the prevention of their onset can be the first step to guarantee a normal development trajectory. A consistent body of literature proved the reduction of cerebral oxygenation in case of apneas with severe bradycardias as well as the relationship between apnea-hypopnea index (AHI) and the synchrony among different physiological signals [3], [7], [8]. Specifically, increases in EEG frequency showed significant correlation with SpO_2 dips during sleep disturbances caused by apneas. Similarly, sleep disturbances due to apnea are correlated with heart-rate arousals as well as with the AHI. Given the intertwined nature of apneas, sleep disturbances, noxious events and stress, the aim of this study is to detect stress load in premature infants assessing the reaction of physiological signals to apneas. This paper is organized as follows: in section (II), the data collection and the stress classification model are outlined. In section (III), the results of the study are presented, while the last section (IV) focuses on the discussion.

II. METHODS

A. Dataset

The study included 40 neonates, who are a subset of a larger study on perinatal stress and its impact on neonatal development (the Leuven Resilience study). All the infants were born below 34 weeks of gestation, with *Post-Menstrual Age* (PMA) ranging from 33 to 35 weeks at the moment of data recording. Most of the participants had PMA of 34 weeks to reduce the effect of age covariate. According to the clinical protocol, full-channel EEG was recorded synchronously with ECG and SpO_2 for at least 3 hours. The EEG set-up included 9 monopolar electrodes (F_1,F_2,C_3,C_4,T_3,T_4,O_1,O_2,C_z), whose reference C_z was excluded from further analysis. The sampling frequencies for EEG, ECG and SpO_2 were 256, 500 and 1 Hz respectively. The EEG was resampled at 250 Hz. The tachogram or *Heart-Rate Variability* (*HRV*) was derived via R-peak detection of the ECG according to the methodology described by [9]. Subsequently, the tachogram (RR_i) was resampled at 8 Hz. During the NICU stay, the Leuven Pain score was collected by trained nurses every hour [10]. In order to define a chronic stress burden for each patient, the maximum pain score of the previous day was considered as accumulated stress by each

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patient. None of the infants had poor clinical outcome at the moment of the recording. 18 infants underwent *Kangaroo Care* (KC) sessions during the signal recording, with a skin-to-skin contact duration up to 3 hours.

B. Bradycardia detection and preprocessing

In [3], [7], it was shown that the most severe type of apneas are associated with *bradycardias*, i.e. sudden and persistent drops in Heart-Rate (HR). Based on these results, this study takes the bradycardic events as the starting points of the apnea-based stress calculator. Clinically relevant apneas are characterized by RR_i elongations above $1.5 * \overline{RR_i}$, where $\overline{RR_i}$ is the average of the entire tachogram, with variation of SpO_2 greater than 10% with respect to the baseline, as argued in [4]. Therefore, apneic events were defined as bradycardic event with concomitant variations of RR_i and SpO_2, whose thresholds were respectively set at $1.5 * \overline{RR_i}$ (which means drops in HR ≤ 100 *bpm* from an average of 160 *bpm* in case of premature infants) and at 3%, 5% or 10% drops in SpO_2. The three different thresholds were used to test the severity of the apnea in the stress detection. SpO_2 dips were detected according to [11]. The reaction to the apneic event in the other physiological signals was investigated around each bradycardia, considering 3 minutes before and after each event peak. During this apneic frame, the EEG reactivity was described in terms of morphology, temporal and spectral attributes, and its interaction with other signal modalities (RR_i, SpO_2). EEG artifacts were filtered with *indipendent component analysis* and bandpass filtering between [1-40] Hz. In order to perform the stress classification, the pain score of the related patient was assigned to each apneic event.

C. Univariate and multivariate analysis

The stress calculator was built as a classifier able to discriminate whether an apneic event belonged to patients with or without stress load. The first step of the implementation consisted of features computation from EEG, HRV and SpO_2 in both a univariate and multivariate sense. The features were usually derived at least in 2 epochs, *before* and *after* each apneic spell, but also during the braydcardia if possible or during the entire apneic window. For example, indices like fractality could require a higher number of samples, which were not available within the bradycardia window. Furthermore, the epoch durations before and after the bradycardia were variable according to the intensity of the apnea. The extracted features are described in the next paragraphs.

a) HRV analysis: The tachogram's reaction to apneas was investigated via the classical temporal and spectral attributes, namely the mean (μ_{RR}) and standard deviation (σ_{RR}), as well as the normalized spectral indices such as the $\frac{LF}{HF}$ ratio and normalized $HF_{nu} = \frac{HF}{(LF+HF)}$. LF stands for the RR_i spectral power in the band $[0.08-0.2)$ Hz, while the HF corresponds to the power in the band $[0.2-4]$ Hz. Due to the nonstationarity of the HR drops, the power of HRV signal was derived via *continuous wavelet transform* (CWT) using as mother wavelet *analytic morlet* (AM). In addition, each tachogram was described via the *Poincaré − Plot* (PP), which studies the relationship between each $RR(t)$ sample and its delayed version $RR(t+\tau)$, where τ = 750 ms, corresponding to a sample 2 heartbeats later. The variances along the main axis and the perpendicular axis SD_1 and SD_2 were extracted as the first two singular values of the matrix $\mathbf{X} = [\mathbf{RR}(t), \mathbf{RR}(t+\tau)]$, together with centroid coordinates C_x and C_y of the PP. $\mathbf{RR}(t)$ is a vectorial representation of RR_i time series of dimension $\mathbb{R}^{(N-1)\times 1}$, where N is the number of samples. Therefore, C_x, C_y, SD_1 and SD_2 were the features used in the stress model and were computed for the entire apneic frame.

b) SpO_2 analysis: Similarly to HRV, temporal features such as mean (μ_{SpO_2}) and standard deviation (σ_{SpO_2}) of the oxygen saturation were derived. The slight difference was to consider the periods before and after the SpO_2 dips, since they are delayed compared to the bradycardias. The *Poincaré − Plot* analysis was also performed considering $\mathbf{X_{sp}} = [\mathbf{SPO}(t), \mathbf{SPO}(t+\tau_{Sp})]$ to obtain SD_1, SD_2, C_x and C_y. The delay τ_{Sp} was set equal to 1 sec, which represents exactly 1 sample of SpO_2 and follows the classical definition of PP.

c) EEG analysis: The cortical activity was described on a spectral, temporal and fractal level. Besides the mean and the standard deviation, the power in the most common frequency bands δ = $[0-4)$ Hz, θ = $[4-8)$ Hz, α= $[8-12)$ Hz, β = $[12-21)$ Hz was computed using Welch's method with overlap of $ov = 70\%$ and with subwindow of 4 sec. In parallel, EEG δ oscillations (P_δ) via CWT using AM as wavelet were derived in the restricted band $[0.5-3]$ Hz. This frequency band is known to represent subcortical areas, such as the thalamus,which are involved in the stress management. Along with the first and the second order statistical moments (μ_δ, σ_δ) for the time series P_δ, the fractal *Hurst* exponent H and the width coefficient c_2 of the *singularity spectrum* (which represent the variation of H in the time course of the signal) were derived according to *multifractal formalism* presented in [12].

d) The EEG - HRV - SpO_2 connectivity: Once the EEG δ oscillations were extracted for each bradycardias, both P_δ and SpO_2 were resampled at fs_{RR} = 8 Hz. As explained in [13], the level of synchrony and entrainment along the brain-heart axis was assessed via time-variant coherence in the *very-low frequency* band [0.01 - 0.08] Hz. Due to the large number of channels (8 EEGs, 1 SpO_2, 1 RR_i) and the exponential number of associated interactions, graph theory was used to give a compact representation of the connectivity framework as a network. Considering each signal as a node, the *path length* (PL) was derived. This index represents the average distance to reach a node from any another node in the network, as shown in [14]. Due to the time-variant nature of the considered coherence, the PL was consequently time-variant and the statistical descriptors such as μ_{PL} and σ_{PL} were derived. Moreover, the variances SD_1, SD_2 and the centroids C_x, C_y were derived with the *Poincaré − plot*, using τ_{PL} = 750 ms, which relates each sample with the two heartbeats that follow.

e) EEG connectivity: Together with PL_{EEG}, the absolute *imaginary coherence* (*ImCoh*) among EEG channels in the frequency bands δ, θ, α, β was computed, as reported in [14]. The complex coherency was computed using Welch's method (4 sec subwindow, 70% overlap) and the PL based on *ImCoh* was derived before and after each bradycardic event.

D. Classification

The features were extracted before, during and after each bradycardia and they were plugged into a *logistic regression* model (LOGIT) to discriminate whether the associated apneic spell belongs to a patient with or without stress burden. The presence of stress was defined in case of pain score greater than zero, otherwise the absence of stress label was used. However, the large number of extracted features would risk to overfit the data. Therefore, the features were firstly grouped into 5 categories based on the signal modality or way of data processing, namely: HRV, SpO_2, EEG, EEG-connectivity ($EEG-Conn$), EEG - HRV - SpO_2 connectivity (EHS), all features together (All). For each group, each feature was tested separately via logistic regression and ranked based on the classification error. Subsequently, the subset of the 5 features with lowest errors was selected. Since other design parameters of the classification could potentially influence the LOGIT models, three parameters were tested for the All features group: the number of features, the SpO_2 dips threshold to define apneas and the KC correction, which states whether the patient underwent KC. Specifically, the tested number of subset features were 3, 5, 10. In case of SpO_2 dips, the tested thresholds were 3 %, 5 %, 10 %. The KC correction was implemented with inclusion of a dummy binary variable to discriminate apneic spells belonging to a patient who underwent KC or not. In more detail, the model with All features group, SpO_2 threshold of 10%, 5 features and KC correction was considered the reference model. The effect of one parameter was investigated by freezing the reference values of the other parameters. The KC correction was also implemented for the EEG feature group. Each LOGIT model was tested with a cross-patient approach with 70% of the patients in the training set and 30% in the test set. The division of patients was repeated 1000 times at random. The results are reported as median(25%-75% quantiles, q_{25} - q_{75}) of all repetitions in terms of error and AUC

III. Results

The changes in the physiological modalities were different according to the stress burden, which in general deepen the apneic spell, as shown in fig 1. It can be seen that the oxygen saturation does not only decrease more in case of stress, but it has also a greater transient before going back to baseline level. In the period around each bradycardic event, the slow-wave EEG (P_δ) presents higher amplitude and an increased regularity with a higher Hurst exponent in the post-bradycardia period, as reported in fig 2. Both results of SpO_2 and EEG are in line with the sleep fragmentation in OSA patient reported in [8]. Furthermore, fig. 3 shows the path-length of EEG-SpO_2 network estimated using wavelet coherence. The results are twofold: the PL is not only reduced during the apneic spell (which means a higher connectivity), but the reduction is even higher in case of stress. As expected, the visual display is further supported by the logistic regression results in table I. All the investigated modalities have a certain classification power to discriminate the presence or the absence of stress. However, both EEG and the SpO_2 analysis outperform the other modalities as stress discriminator. Table I also reports the influence of the number of features, KC correction and SpO_2 thresholds on the stress calculator. The threshold for SpO_2 is negatively correlated with the classification error. A similar trend can be retrieved with the number of features ($\#_{features}$). The KC has also a beneficial effect in stress detection, since the inclusion of the dummy variable decreases the classification error. The results in bold represent the reference model.

TABLE I: The classification results for the different logistic regression models. The results in bold are the reference model.

LOGIT	Median(q_{25} - q_{75})	
Features	Error (%)	AUC (.)
All	**19.23(11.65-27.27)**	**0.94(0.84-0.99)**
SPO_2	23.08(16.67-31.58)	0.86(0.77-0.94)
EEG	28.57(15.38-40.82)	0.89(0.74-0.96)
$EEG-Conn$	30.43(22.22-41.18)	0.81(0.69-0.88)
EHS	31.25(22.73-43.10)	0.77(0.66-0.87)
HRV	35.48(26.67-46.67)	0.74(0.61-0.84)
SpO_2 THR	Error	AUC
10%	**19.23(11.65-27.27)**	**0.94(0.84-0.99)**
5%	28.57(21.05-36.00)	0.80(0.71-0.88)
3%	34.48(26.67-43.53)	0.79(0.66-0.87)
$\#_{features}$	Error	AUC
5	**19.23(11.65-27.27)**	**0.94(0.84-0.99)**
3	19.14(12.00-26.09)	0.94(0.84-0.98)
10	24.14(14.29-34.62)	0.88(0.78-0.97)
KC Correction	Error	AUC
Yes - All	**19.23(11.65-27.27)**	**0.94(0.84-0.99)**
No - All	25.00(17.24-34.29)	0.87(0.78-0.96)
Yes -*EEG*	28.57(15.38-40.82)	0.89(0.74-0.96)
No - *EEG*	33.33(26.20-40.91)	0.78(0.70-0.87)

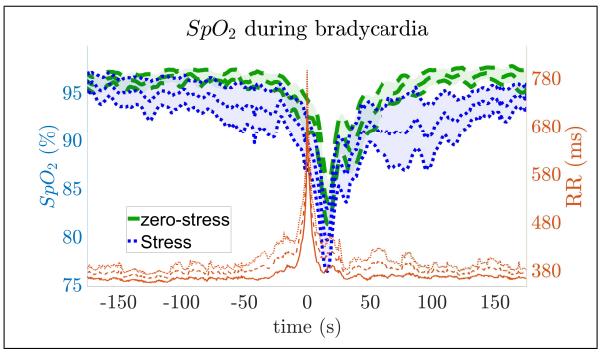
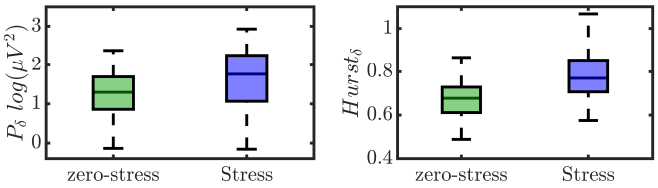


Fig. 1: The SpO_2 dips in presence (blue) and absence (green) of stress, which deepens the desaturation.

IV. Discussion

The present study examined the relationship between apneic spells and stress in premature infants. The findings



a) b)

Fig. 2: The amplitude and the Hurst regularity for the δ oscillations in channel F_1, which are enhanced by stress in the period after the bradycardia (*ranksum* test: $p_{value} \leq 0.01$).

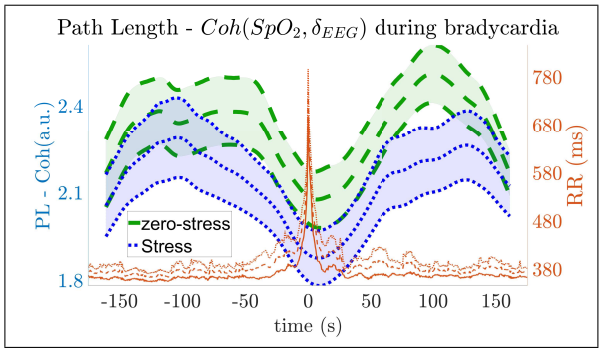


Fig. 3: The *path length* of EEG - SpO_2 network in presence (blue) and absence (green) of stress, which enhances the connectivity since the PL is lower.

suggest that apneas do not only threaten the health of the premature infants, but the stress load can enhance the associated bradycardia and oxygen desaturation (fig 1) as well as the autonomic and cortical connectivity, as shown by the PL reduction (fig 3). Similar results were obtained in other noxious states by [13] and [8]. Severe apneic events can have an impact on the development of the patient and the link between stress and development might be partly explained via cardiorespiratory events [4]. The continuous disruption of the cerebral blood flow in bradycardias could have an effect on the prefrontal cortex, which might result in behavioral and emotional problems. It is very interesting to note that the children with OSA can show hyperactivity that preemies can develop during growth [5]. This hypothesis can be further supported by the inclusion of KC: here, the skin-to-skin contact promotes cerebral oxygenation [6], unlike prolonged bradycardia [3]. The improvement of classification with inclusion of the KC variable confirmed the results by [6]. In accordance with [8], the best features to discriminate stress can be derived by SpO_2 and EEG, in particular the slow-wave oscillations and its regularity, that are related to the subcortical activity of the brain.

V. CONCLUSIONS

In this study, an approach to detect stress in premature infants was proposed, based on the information contained in the recorded apneic spells. The depth of desaturations and the EEG regularity contain relevant information to discriminate stress load, together with the administration of KC. Despite the usage of a binary regression model, promising results were achieved. However, further work should focus on the reactivity of the physiological signals in apnea-free period and the development of an ordinal regression model.

VI. ACKNOWLEDGMENT

Research supported by Bijzonder Onderzoeksfonds KU Leuven (BOF): The effect of perinatal stress on the later outcome in preterm babies (# C24/15/036); imec funds 2017; ERC Advanced Grant: (n° 339804)). M.L. and C.V. are respectively SB PhD fellow and postdoctoral fellow at Fonds voor Wetenschappelijk Onderzoek-Vlaanderen (FWO).

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