Increased Cardiorespiratory Coordination in Preeclampsia

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Abstract

Preeclampsia is one of the main sources of morbidity in pregnancy with a high mortality rate without a known ultimate cause. Using a corpus including 927 measurements of pregnant women with and without different hypertonic diseases at multiple stages of pregnancy, we utilised a new approach to analyse cardiorespiratory coordination. Since the recording quality of respiratory effort was limited due to a high signal to noise ratio, we applied an ECG derived respiration approach to create an ersatz respiratory signal. After applying the few available recordings with a sufficiently high quality of the respiratory signal to validate the substitute, coordigrams were calculated and quantified by utilising the epsilon method. We showed significant ($p < 0.05$) differences in the coordination between healthy and preeclampsia subjects in a matched (BMI, age, gestational week) comparison of preeclampsia and healthy subjects. Hopefully future applications of and improvements on these methods are able to create a fast and convenient prediction methodology to reduce the impact of this disease as well as help in the determination of its underlying cause.

1 Introduction

Preeclampsia is a serious disorder of the cardiovascular system during pregnancy and is the main cause of maternal and neonatal morbidity (around 2-5%) (Lo et al., 2013). It is characterised by a systolic and diastolic blood pressure greater than 140/90 mmHg and a proteinuria (serum proteins in the urine greater 300 mg in 24 h) without a known cause. Early detection has not been available in clinical practice until recently (Stepan et al., 2008) and the only

treatment option is premature induction of labour (Weyerstahl and Stauber, 2013).
Cardiorespiratory coordination (CRC) lends itself to study this phenomenon by taking a more integrative view on the cardiovascular system as it relates to other physiological features especially respiration. This new approach, for investigating the aetiology, extends on previous ones that only took heart rate, blood pressure dynamics and baroreflex into account. Earlier results showed a changed variability in diastolic blood pressure in preeclampsious subjects compared to controls (Riedl et al., 2010). Investigating the assumption that respiration is either strongly affected or even causally linked, we applied cardiorespiratory coupling analysis using the CRC method. In a previous study sleep apnoea was found to be correlated with an increase in CRC Riedl et al. (2014) and sympathicotonia (Somers et al., 1993). Therefore an increased sympathicotonus linked to hypertension in preeclampsia (Intensivmedizin, 2011) should also increase CRC.

2 Data and preprocessing

2.1 Cohort

The data set includes 69 measurements of subjects suffering from preeclampsia and a control set matched to age and body mass index (BMI) of the subject and week of gestation (WOG) at time of measurement. To analyse heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS), synchronously high resolution electrocardiogram (ECG) (Frank-(Z-) lead, 1600 Hz, Porti system by TMSI, The Netherlands or Frank-(Z-) lead, 1000 Hz, Powerlab system, ADInstruments, Australia), noninvasive continuous blood pressure were recorded via finger cuff (100 Hz, PORTAPRES device Model 2, BMI-TNO, Amsterdam, Netherlands) and a concurrent measurement of respiratory effort using a piezzo electric belt (10 Hz). From the ECG recordings, time series of beat-to-beat intervals (BBI) were extracted to analyse HRV.
From the PORTAPRES recordings, time series of systolic beat-to-beat pressure values were extracted to analyse BPV and BRS. All time series were filtered to exclude ventricular premature beats and artefacts. All measurements were performed over 30 min under standardized resting conditions between 08:00 and 12:00 hours. Subjects were in supine resting position during recording. Demographic data such as age, WOG, BMI, mean normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarisations) (meanNN), the standard deviation of the NN interval (SDNN), the mean of Breath to Breath intervals (meanBB) and the standard deviation of the BB interval (SDBB) is shown in Tab 1. There was no significant difference between the meanBB but in meanNN of healthy subjects and those suffering of Preeclampsia. A significant difference between those groups indicates, that the heart rate of the control group was significantly higher than those of preeclamptic subjects. The study was approved by the local ethics committee

and informed consent was obtained from all subjects. All measurements were performed in the Universittsklinikum in Leipzig.

Table 1: Overview of the cohort (mean ± SD; p-value with U-test)

group	control group	preeclampsia	p - value
group size	69	69	
age [a]	27.93 ± 4.80	28.45 ± 4.94	n.s.
WOG [w]	29.32 ± 5.10	29.32 ± 5.10	n.s.
BMI [kg/m^2]	28.67 ± 6.07	28.23 ± 6.07	n.s.
meanNN [ms]	685.54 ± 96.88	733.28 ± 135.65	n.s.
SDNN [ms]	43.11 ± 15.26	45.83 ± 18.68	n.s.
chest meanBB [s]	3.35 ± 0.67	3.19 ± 0.46	n.s.
chest SDBB [s]	1.04 ± 0.30	0.88 ± 0.33	n.s.
EDR meanBB [s]	3.20 ± 0.43	3.15 ± 0.50	n.s.
EDR SDBB [s]	1.13 ± 0.31	1.43 ± 2.08	n.s.

2.2 Preprocessing

The respiratory effort signal was oversampled at the ECG-sample rate and quantisation problems led to a mean signal to noise ratios approaching -10 dB, which is visualised in Fig. 1.

To work around this limitation we created an ersatz respiration signal using a method based on ECG-derived respiration as presented by Moody et al. (1986, 1985), using the respiration induced fluctuation of the R-peak hight. Readers interested in the validation are also advised to look at the work of Malacarne et al. (2007). To calculate the required R-peak amplitudes the raw ECG-signal was freed from power line interference and baseline wander before using a R-peak detector based on Benitez et al. (2001). The validity of this signal was checked by comparing the Kullback-Leibler divergence (KLD) of the power spectra, the Shannon entropy of the first derivative of the EDR-signal and the signal of the respiratory belt. When manually selecting those respiratory signals that were deemed of sufficient quality, the KLD was $\ll 1$, indicating nearly identical spectra and providing high confidence in the generated ersatz signal. Cases with a high KLD differ in phase, time shift and the number of identified onsets (Fig. 2) while a low KLD assures overall related signals (Fig. 3). The considered Shannon entropy will be high for the signals without a quantisation error. Note that it is hard to find a proper onset from the chest strap respiration, since it is not clear where exactly one should locate a feature in the time series (cf. Fig. 1). To visualise the difference of the respiration signals we created a filtered dummy to give a rough estimate of the characteristics. Calculating a complete quantification would require a usable chest strap respiration to receive all the required information e.g. whether to use an extrema or other onset of the curve

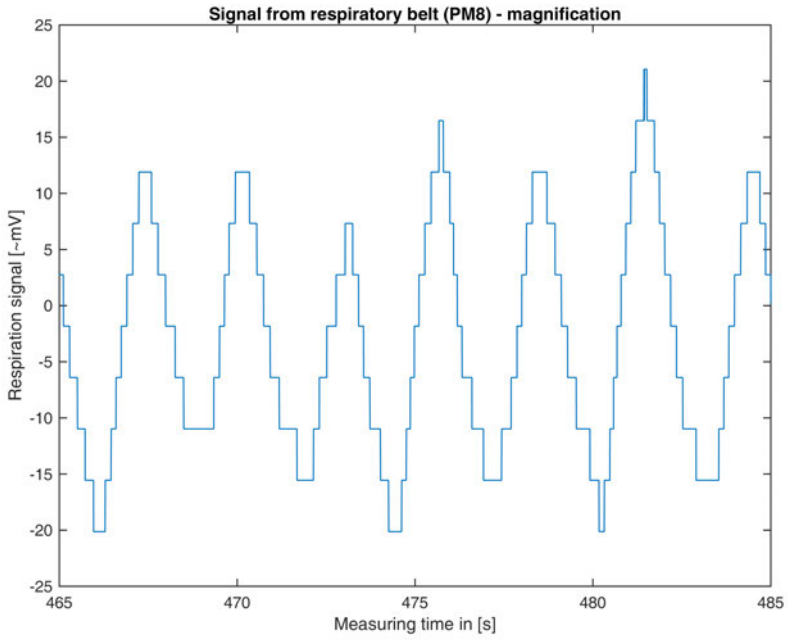

Figure 1: Signal from respiratory belt (PM8) - magnification. There is a visible formation of steps due to a wrong amplitude quantisation (too little amplification of the signal for given resolution).

or the explicit errors of the time series in contrast to the EDR, which is out of the scope of this study. There was no trend for KLD in healthy or diseased subjects.

3 Methods

The aim of this study on preeclamptic subjects is to find differences in the CRC from spontaneous fluctuations. This a classical topic in cardiovascular control analysis (cf. (Bahraminasab et al., 2008), (Kenwright et al., 2015), (Bari et al., 2016), (Porta et al., 2014), (Galletly and Larsen, 1997), (O'Keeffe, 2012), ...). The quantification of synchronisation via synchrogram and the coordination via coordigram are two viable tools utilised for the characterisation of cardiorespiratory coupling.

3.1 Cardiorespiratory Coordination

In contrast to cardiorespiratory synchronisation (CRS) (Schäfer et al., 1998) which is studied in the phase domain, the CRC is based on analysis in the time

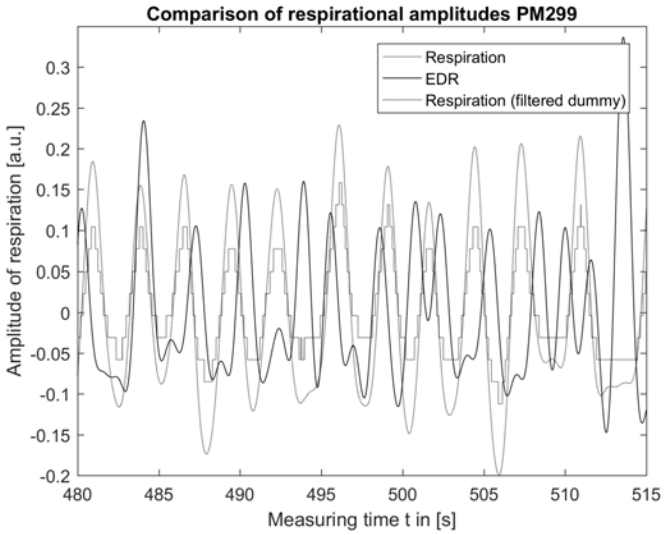

Figure 2: Comparison between the signals from the respirational belt and EDR of PM299 (KLD= 0.911) with a normalised amplitude. The signals differ in phase, time shift and the number of identified onsets (grey - 10, black - 13), which results in a different number of respiration cycles of both methods.

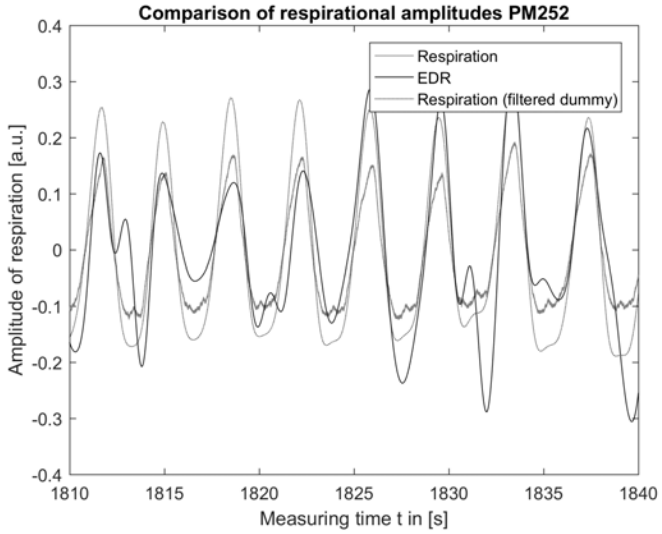

Figure 3: Comparison between the signals from the respirational belt and EDR of PM252 (KLD= 0.044) with a normalised amplitude. The time series shows qualitatively the same behaviour (mean $\pm$ SD difference between onsets is -0.04 $\pm$0.107 s).

domain. Earlier results showed that coordination maybe apparent were CRS does or even cannot occur (Riedl et al., 2014). In order to investigate CRC we apply the coordigram. Its construction is similar to that of the synchrogram; the point in time of each R-peak t_{r_k} where $k = 1 \dots N_r$ and the onsets (negative zero-crossing of the second derivative) of respiration t_{a_i} where $i = 1 \dots N_a$, were N_r and N_a representing the last heart beat and respiration onset, are identified, before taking the 2 adjacent onsets $a_{i\pm1}$ from each t_{a_i} to limit the R-peaks. A column like point distribution for each respiratory onset i at time offsets $-6\,s < \Delta t < 6\,s$ is created:

$$f_i(\Delta t) = \frac{2\pi}{w} \sum_{t_{\Delta k} \in a_i} K\left(\frac{\Delta t - t_{\Delta k}}{b}\right), \tag{1}$$

where b is the bandwidth of the Gaussian kernel estimator K

$$K(x) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{x^2}{2}\right) \tag{2}$$

and w is the chosen window length in effect a bandwidth over respiratory indices. The sum is performed over all elements of respiratory onsets $a_i = \bigcup_{k=i-w,\dots,i+w} t_{\Delta k}$ and $t_{\Delta k} = \left\{t_{r_k} - t_{a_j}\right\}_{j=1,\dots,N_a}$. The chosen window length w of 2 respiration cycles ensures a high sensibility for a fast changing CRC while still providing smoothness while b, is typically set around twice the sample rate. The resulting distribution is normalised to generate a maxima of 1 in the case of stacked lines, which might be indicated as yellow in colour coding's such as in Fig. 4 (F) (Riedl et al., 2014).

Large values (appearing as lines in the plotted coordigram) located in the negative area of Δt indicates cardiac influence on the respiration and those in the positive range point to influence from the respiration on the cardiac system.

3.2 Quantification

The method as described above can only be used in qualitative sense as it relies on an observer to judge the existence of coordination. To compare different measurements, a method for quantisation of coordination is needed. Out of 3 methods (Müller et al., 2012), Fourier, Shannon-Entropy, and ε, we chose the ε-method, that does not rely on interpretation and is relatively simple to implement correctly. The ε-method utilises 2 parameters, the width of the eponymous epsilon of the ε neighbourhood (a length of time) and its length l (the number of considered respiratory cycles). A heart beat is said to be coordinated if there are $l - 1$ other heart beats inside of the ε-neighbourhood. These values are closely related but as of yet empirically selected. For this work we calculate using ε equal to 0.1 s as well as 0.2 s to show its influence and set l as 2. ε can therefore be seen as a radius. Further information about the ε method, e.g. how to take CRS into account can be found in publications of Porta et al. (2004).

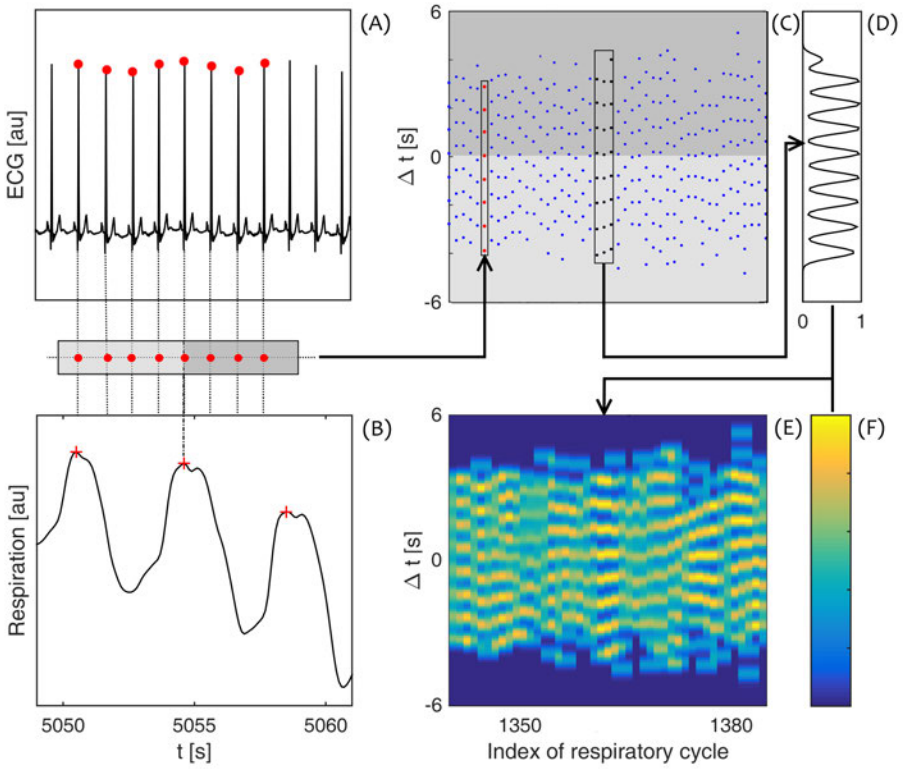

Figure 4: Schematic creation of CRC: (A) Time of R-peaks t_R. (B) Maxima of respiration (We used the negative zero-crossing of the second derivative in contrast to the here shown maxima). (C) Each column in the coordigram reflects the time dependence between cardiac and respiration onsets in a range of 2 respiration cycles. (D) Estimation of the point distribution of the moving window over 3 respiration onsets from Eq. 1 and Eq. 2. (E) Amplitude of each distribution is coded through (F) with coordination pattern from (C) (Δt positiv: heart beat triggered by respiration; Δt negativ: heart beat influences respiration) (after (Riedl et al., 2014)).

3.3 Matching

In order to allow causal inference on the effects of preeclampsia we would need to compare two identical individuals or groups only differing in this characteristic. As this is impossible and there is no possibility to do random trails we need to create a control group artificially. For this we postulate that a group consisting of measurements pairwise matched on WOG at time of measurement, age and BMI of the subject will on average be sufficiently similar to our hypothetical group. A detailed description of matching can be found in Sachs and Hedderich (2006). Matching is a qualitative equivalent alternative to the repetition of an

experiment. As statistical test we used the U-Test from Mann and Whitney of the statistical programming language *R* (wilcox.test), because the Shapiro-Wilk normality test revealed that some variables are not normally distributed. A comparison of properties of the original and matched measurements are shown in Tab. 1. There is no statistical difference between the measurements in our matched properties as well as in simple features of heart rate variability allowing us to be highly confident in the suitability of our matching.

4 Results

Comparing results of the quantification of CRC between groups using the U-Test we found a significant higher total amount of coordination in subjects with preeclampsia compared with the control groups for $\varepsilon = 0.1\,\mathrm{s}$. No difference was found for $\varepsilon = 0.2\,\mathrm{s}$. Giving a total overview we performed our calculation for the chest strap dummy data but found no differences between the control group and the preeclamptic subjects. See Tab. 2. Although some coordigrams are hard to distinguish by eye, we can see a clear difference between the two groups. The pre-eclamptic subjects show explicit yellow lines of coordination in Fig. 5, where

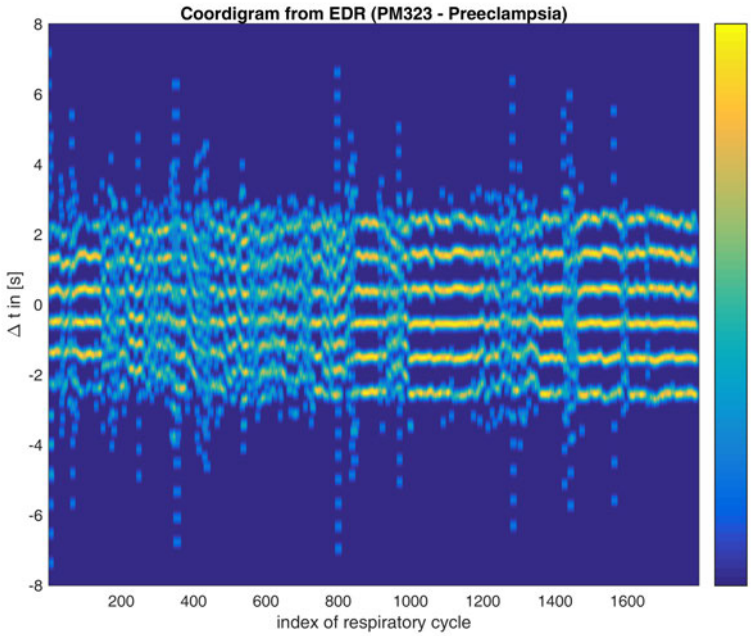

Figure 5: Coordigram for PM323 (Coordination $\approx 51\,\%$) with explicit areas of coordination indicated by yellow horizontal lines.

the control group shows only small separated yellow zones (Fig. 6).

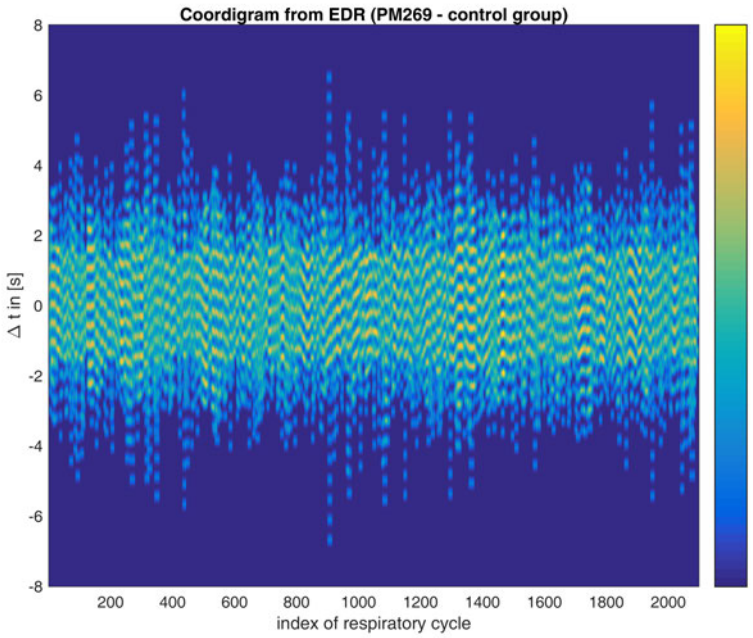

Figure 6: Coordigram for PM323 (Coordination $\approx 34\,\%$) with few coordinated zones indicated by yellow lines.

Table 2: U-Test of CRC between preeclampsia and a matched control group (mean $\pm$ SD).

		control group		preeclampsia		
group size		69		69		
	ε in [s]	mean	SD	mean	SD	p-value
CRC	0.1	30.66	$\pm$ 4.62	34.38	$\pm$ 8.91	< 0.05
(EDR)	0.2	55.28	$\pm$ 6.36	57.70	$\pm$ 8.13	n.s.
CRC	0.1	28.64	$\pm$ 4.32	28.81	$\pm$ 5.82	n.s.
(chest strap)	0.2	54.09	$\pm$ 7.62	53.56	$\pm$ 8.90	n.s.

Trying to discern a more detailed view of the effects of preeclampsia on CRC we compared the results of the ε-method limiting ourself to $\varepsilon = 0.1\,\mathrm{s}$ in different subgroups that we deemed relevant. These were age (below 20 y; 20 - 24 y; 25 -

29 y; 30 - 34 y; greater 35 y) (Fig. 7), BMI (underweight, below 18.5; normal, 18.5 - 24.9; overweight, 25 - 29.9; obese, 30 and higher)(Fig. 8), and WOG at time of measurement (18 - 22; 23 - 26; 27 - 30; 31 - 34; greater 34th week)(Fig. 9).

While a tendency seems to appear to be visible no statistically significant differences are found.

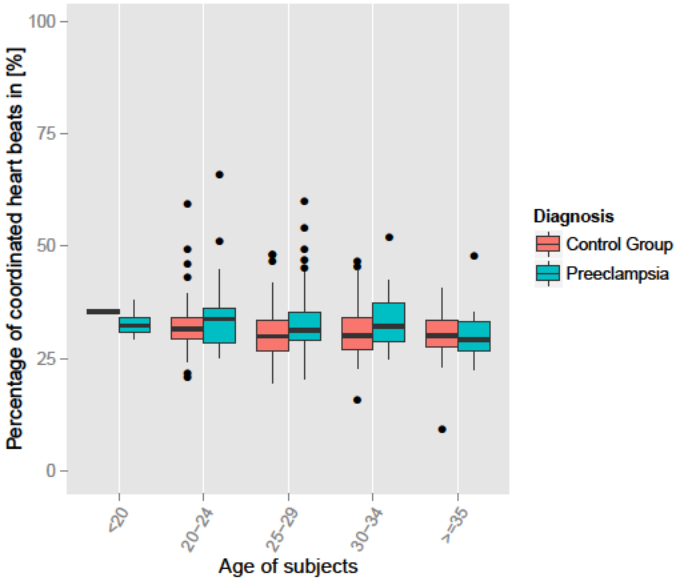

Figure 7: Boxplot ($\varepsilon = 0.1\,\mathrm{s}$) of age vs percentage of coordinated heart beats for subjects with and without preeclampsia.

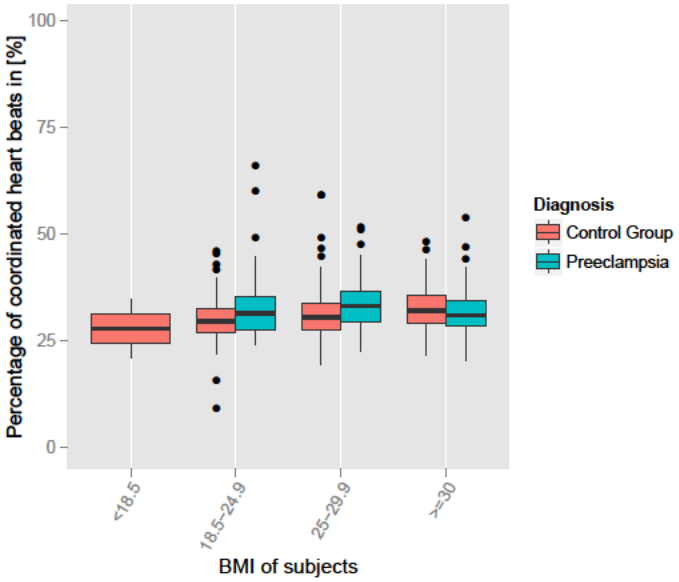

Figure 8: Boxplot ($\varepsilon = 0.1\,\mathrm{s}$) of BMI vs percentage of coordinated heart beats for subjects with and without preeclampsia.

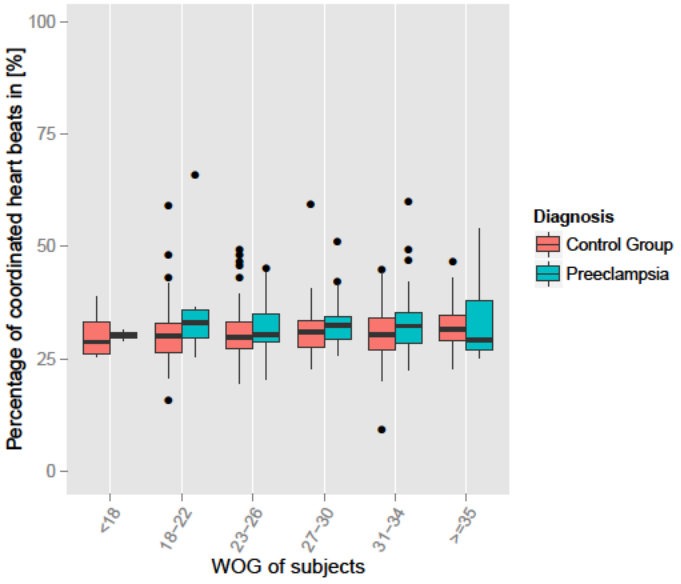

Figure 9: Boxplot ($\varepsilon = 0.1\,\mathrm{s}$) of WOG vs percentage of coordinated heart beats for subjects with and without preeclampsia.

5 Discussion

Identifying significantly higher coordination ($p < 0.05$) in preeclamptic subjects compared to a control group via the Mann-Whitney-U-Test, using $\varepsilon = 0.1\,\mathrm{s}$, shows that the CRC-method is potentially able to detect differences between normal and preeclamptic subjects. The drastic change in the results for different ε values indicates the need to more fully understand the relationship of ε and l and the effects that average heart and respiration rate have on this method. Future work should look into the use of random surrogates, destroying the inherent relationship of heart beat and respiration by using the respiratory onsets t_a from one subject and the R-peaks t_r of another. These could be used to optimise the parameters of the used method to avoid superfluous indications of coordination, a problem which is occurring in all current methods.

Validating the use of the EDR instead of a "good" respiration signal presents some problems. First, the different number of recognised onsets in the two signals which does not allow a proper comparison. Second, the EDR should ensure the conservation of the onset at least in the range of the ε-method. If one takes into account only the R-peak of the ECG to construct the EDR a conservation around 100 ms (respectively 200 ms for the ε-method since it relies on a radius of 100 ms) is needed. For the example in Fig. 3 with a mean deviation of -40 ± 107 ms this is assured, but for all other signals this has also to be taken into account. If this is not the case, than any relying results have to be marked

as unknown feature of the coordination analysis. This problem can possibly be overcome by the consideration of more features instead of taking only the fluctuating height of the R-peak into account.

Another problem is the non linear relationship between heart and respiration rate and the results of current quantification methods for coordination using a specific parameter set. For example we have seen an increase in the percentage of coordinated heart beats as calculated by the ε-method when increasing the heart and respiratory rate. From the definition of the ε-method it follows, that interpreting an ECG and respiratory time series as having twice the sampling rate is equivalent to doubling the ε value for the original. While this is not a major effect in practice due to the similarity of heart and respiratory rates, the effect should be studied and quantified to allow an improved quantification of CRC. The initial hypothesis that a sympathicotonia is linked with an increase in CRC could be confirmed. Future studies should therefore check for this relationship.

6 Outlook

The results of this study are promising and should be developed further. An aspect that should be a future focus is the ability to distinguish preeclampsia from other diseases evoking hypertension. Not only are those clinically hard to distinguish by definition (Bischofberger et al., 2012), they might also influence CRC through the same mechanisms. Key to such a study is a sufficient high number of subjects which degraded the ability to find statistical significant differences in the current study due to group size (Sachs and Hedderich, 2006). The resulting coding of health state should be extended to include any aberration that might be related to hypertension, as we encountered a subject coded as healthy but was missing a kidney which could be a cause of hypertension and thus is very relevant for our research topic.

Signal quality is an ever present problem that should be considered more deeply during the design phase of the study for example by including regular quality checks so that any problems can be fixed in with low delay.

Not only was there a significant higher coordination during apnoea, which is linked with a raised sympathetic nervous system activity (Riedl et al., 2014), but also preeclampsia shows significant higher action for regulation of this system (Faber et al., 2004). Our current hypothesis of a link between increased CRC and sympathicotonia is valid for a certain value of ε in this set of preeclampsia.

In order to improve the evidence we also plan to further investigate between CRC and other physiological parameters using tools such as the symbolic coupling traces (SCT) (Wessel et al., 2009). This method reduces a time series to indications of increasing and decreasing values and analyses the distribution of co-occurring words of a certain length over two time series. By including a time delay between the words this method can also analyse the coupling between non synchronous systems (Müller et al., 2012).

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