



Multiscale entropy and detrended fluctuation analysis of QT interval and heart rate variability during normal pregnancy

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ARTICLE INFO

Keywords:

Pregnancy

QT variability

Heart rate variability

Multiscale analysis

Detrended fluctuation analysis

ABSTRACT

Pregnancy leads to physiological changes in various parameters of the cardiovascular system. The aim of this study was to investigate longitudinal changes in the structure and complexity of heart rate variability (HRV) and QT interval variability during the second half of normal gestation. We analysed 30-min high-resolution ECGs recorded monthly in 32 pregnant women, starting from the 20th week of gestation. Heart rate and QT variability were quantified using multiscale entropy (MSE) and detrended fluctuation analyses (DFA). DFA of HRV showed significantly higher scaling exponents towards the end of gestation ($p < 0.0001$). MSE analysis showed a significant decrease in sample entropy of HRV with progressing gestation on scales 1–4 ($p < 0.05$). MSE analysis and DFA of QT interval time series revealed structures significantly different from those of HRV with no significant alteration during the second half of gestation.

In conclusion, pregnancy is associated with increases in long-term correlations and regularity of HRV, but it does not affect QT variability. The structure of QT time series is significantly different from that of RR time series, despite its close physiological dependence.

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1. Introduction

Pregnancy leads to changes in the cardiovascular system. These include the decrease in mean arterial pressure, peripheral vascular resistance as well as the increase in circulating volume, heart rate and cardiac output. Heart rate variability (HRV), which refers to variability in the RR interval of body surface ECG, has been shown to alter during pregnancy [1–3]. As HRV is modulated by vagal and sympathetic efferents of the autonomic nervous system [4], it provides indirect evidence of altered neural outflow to the sino-atrial node of the heart during pregnancy. In particular, the magnitude of beat-to-beat changes and high frequency oscillations, which are both associated with vagal heart rate modulation, have been shown to reduce during normal pregnancy [5–7]. Little is known, however, whether nonlinear characteristics of heart rate fluctuations, such as long-term temporal correlations

and complexity over multiple time scales, are altered during pregnancy.

Repolarization of the ventricular myocardium might also be affected by pregnancy due to changes in circulating hormones, electrolyte levels [8] and increased sympathetic neural outflow [9]. The duration of ventricular repolarisation can be estimated from the QT interval of the body-surface ECG. Elevated beat-to-beat variability of the QT interval is a marker of temporal repolarisation lability as well as increased arrhythmic risk and has been observed in patients with cardiovascular disease [10,11], obstructive sleep apnoea [12] and psychological disorders [13,14]. It has been debated whether increased QT variability is a marker of sympathetic cardiac activation [15–17]. The structure and complexity of beat-to-beat QT variability in general is poorly understood, in particular during pregnancy.

From a clinical point of view, assessment of heart rate and QT interval variability during pregnancy may be important, because hypertensive pregnancy disorders, such as pre-eclampsia, affect around 10 percent of women and have been linked to elevated sympathetic nerve activity [18]. Further, there is evidence suggesting that pregnancy can exacerbate pre-existing underlying ventricular arrhythmias or even cause de novo arrhythmias [19].

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We hypothesised that physiological adaptation of the cardiovascular system to pregnancy affects nonlinear characteristics of heart rate and QT interval fluctuations. The aim of this study was to investigate longitudinal changes in temporal correlation patterns and complexity of heart rate and QT interval variability during normal gestation.

2. Methods

2.1. Subjects

In this longitudinal study, data from 32 healthy pregnant women with normal uterine perfusion (CON, age: 28 ± 4 years) and normal pregnancy outcomes were retrospectively analysed. Maternal age, gravidity, parity, week of delivery and birth weight are summarised in Table 1. Linear heart rate and QT interval variability analyses of this data set have been reported previously [2,5,20]. The investigation conforms to the principles outlined in the Declaration of Helsinki. The University of Leipzig ethics committees' approval and written informed consent of all subjects have been provided.

2.2. Data acquisition and pre-processing

High resolution ECG (1600 Hz, modified orthogonal Frank lead system) was recorded monthly until delivery, starting at the 20th week of gestation. ECGs were measured over 30 min in the supine position under standardized resting conditions between 8 am and 12 pm as described before [2]. For this study we used the x-lead, because it showed the largest T waves. A modified version of the algorithm proposed by Pan and Tompkins [21] was used for RR interval extraction. For beat-to-beat QT interval measurement the algorithm proposed by Berger et al. [11] was applied. Here, the operator defines a template QT interval by selecting the beginning of the QRS complex, the start and the end of the T wave of one beat. The algorithm then finds the QT intervals of all other beats by determining how much each T wave must be stretched or compressed in time to best match the template. Thus, the QT interval measurement is relatively robust and insensitive to noise, as it does not rely exclusively on the exact determination of the T wave terminus.

2.3. Detrended fluctuation analysis

Detrended fluctuation analysis (DFA) has been developed to analyse long-range correlations (long-memory dependence) in

non-stationary data, where conventional fluctuation analyses such as power spectra and Hurst analysis cannot be reliably used [22]. The DFA algorithm involves four steps: Firstly, the cumulative sum $c(k) = \sum_{i=1}^k [s(i) - \bar{s}]$ of the time series s is computed, where $\bar{s}$ is the mean value. Secondly, local linear trends $c_n(k)$ within boxes of varying size n are calculated. Thirdly, the root-mean-square of the linearly detrended time series is computed as a function of box size n as $F(n) = \sqrt{(1/N) \sum_{k=1}^N [c(k) - c_n(k)]^2}$, where N denotes the size of s . Lastly, $\log[F(n)]$ is plotted against $\log[n]$.

If data contain long-range dependence, then $F(n) \sim n^\alpha$, where α is the scaling exponent. Values of $0 < \alpha < 0.5$ are associated with anti-correlation (i.e. large and small values of the time series are likely to alternate). For Gaussian white noise $\alpha=0.5$. Values in the range $0.5 < \alpha \leq 1$ indicate long-range power-law correlations (i.e. large values of the time series are likely to be followed by large values). Values in the range $1 < \alpha \leq 1.5$ represent stronger long-range correlations that are different from power-law, where $\alpha=1.5$ for Brownian motion [22].

In the case of RR time series, DFA shows typically two ranges of scale invariance, which are quantified by two separate scaling exponents, α_1 and α_2 , reflecting the short-term and long-term correlations, respectively. To obtain more comprehensive insight into the scaling characteristics of RR and QT interval time series, we computed a spectrum of α values by differentiating $\log[F(n)]$ with respect to $\log[n]$ as proposed by Castiglioni et al. [23], following equation $\alpha(n) = (\log[F(n+1)] - \log[F(n-1)]) / (\log[n+1] - \log[n-1])$. Considering the short recording duration (30 min) we calculated scaling exponents up to $n=40$.

2.4. Multiscale entropy analysis

Multiscale entropy (MSE) was computed according to the procedure published by Costa [24]. Firstly, we constructed consecutive coarse-grained time series $\{y^{(\tau)}\}$ from one-dimensional discrete time series $\{x_1, \dots, x_i, \dots, x_N\}$ following equation $y_j^{(\tau)} = (1/\tau) \sum_{i=(j-1)\tau+1}^{j\tau} x_i$, where τ is the scaling factor and $1 \leq j \leq N/\tau$. The length of each coarse-grained time series is given by the ratio N/τ (Fig. 1). Secondly, we calculated sample entropy (SampEn) values [25] of the coarse-grained time series as a function of τ .

Sample Entropy quantifies the irregularity of a time series and estimates the conditional probability that two sequences of m consecutive data points, which are similar to each other (within given tolerance r), will remain similar when one consecutive point is included. The SampEn algorithm considers two parameters: tolerance level r and pattern length m . According to

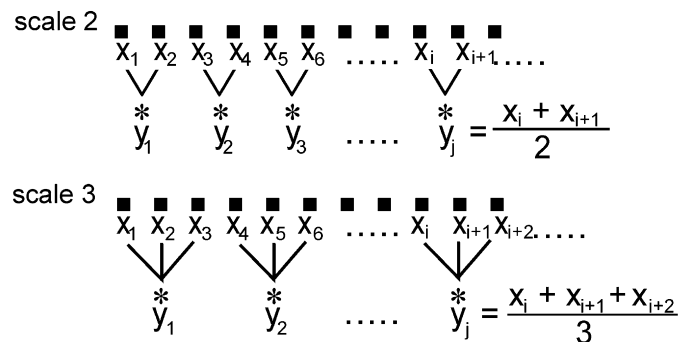


Fig. 1. Schematic illustration of the coarse-graining procedure of a time series for scales $\tau=2$ and 3 . Original beat-to-beat values, represented as squares, are coarse-grained by computing of arithmetic mean of two successive values for scale two and three successive values for scale three, respectively, without overlap (represented by asterisks).

Table 1
Characteristics of study participants at enrolment (20th week of gestation) and pregnancy outcomes.

Parameter	CON (N=32)
Maternal age (years)	28 ± 4
Obesity (%)	0
Hypercoagulability (%)	0
Initial systolic BP (mmHg)	123 ± 18
Initial diastolic BP (mmHg)	72 ± 9
Primipara (%)	59
Week of delivery	39 ± 1
Pregnancy-induced hypertension (%)	0
Birth weight (g)	3450 ± 427
Rate of caesarean section (%)	28
Rate of small-for-gestational-age infants (%)	0

Data presented as group means and standard deviations or percentage, respectively.

previous studies, we chose a tolerance level of $r=0.15$ times standard deviation of the time series to account for differences in signal magnitude. Due to the relatively short recording duration (approximately 2000 beats), we computed SampEn values for $m=2$ in the range $1 \leq \tau \leq 10$.

2.5. Statistics

For statistical analysis monthly ECG measurements were binned according to the following classes: week 20: 18th–22nd week of gestation; week 24: 23rd–26th week of gestation; week 28: 27th–30th week of gestation; week 32: 31st–34th week of gestation; and week 36: 35th week of gestation until delivery. One-way ANOVA was conducted to test for time effects of pregnancy. Post-hoc analyses were performed based on Dunnett's multiple comparison tests with regard to week 20.

To assess whether DFA and MSE analyses reveal structures in RR and QT time series that are different from those of random processes we generated a surrogate for each time series based on random permutation. The average DFA and MSE functions of surrogate data were then compared to those of the original time series.

3. Results

Average RR (ANOVA: $p=0.0002$) and QT intervals (ANOVA: $p=0.01$) shortened significantly during the second half of pregnancy as reported previously (Table 2). Overall beat-to-beat variability of RR intervals (sdRR) and QT intervals (sdQT) was not significantly altered during the second half of gestation.

Detrended fluctuation analysis of RR interval time series revealed α spectra as displayed in Fig. 2A. After an initial decay, α coefficients asymptotically levelled out. Comparing spectra obtained during different weeks of gestation, α appeared to be higher towards the end of gestation. For further statistical comparison, we computed average values of α over scales 4–11 and 12–32, analogous to the short-term scaling exponent α_1 and the long-term scaling exponent α_2 , which are used commonly. Both, α_1 and α_2 increased significantly during the second half of gestation (Fig. 3A and B; ANOVA: $p < 0.0001$).

The DFA α spectra of QT interval time series were markedly different from those of RR interval time series (Fig. 2B). Initial α values of QT time series were significantly lower than those of RR time series and continuously increased after a small drop around $n=8$. Overall, visual inspection of the DFA results of QT variability suggests a lack of scale invariance (i.e. no stable values of α). The α spectra of QT time series were similar throughout the second half of gestation.

DFA spectra of the randomized RR and QT interval time series showed α values lower than those of the original time series and

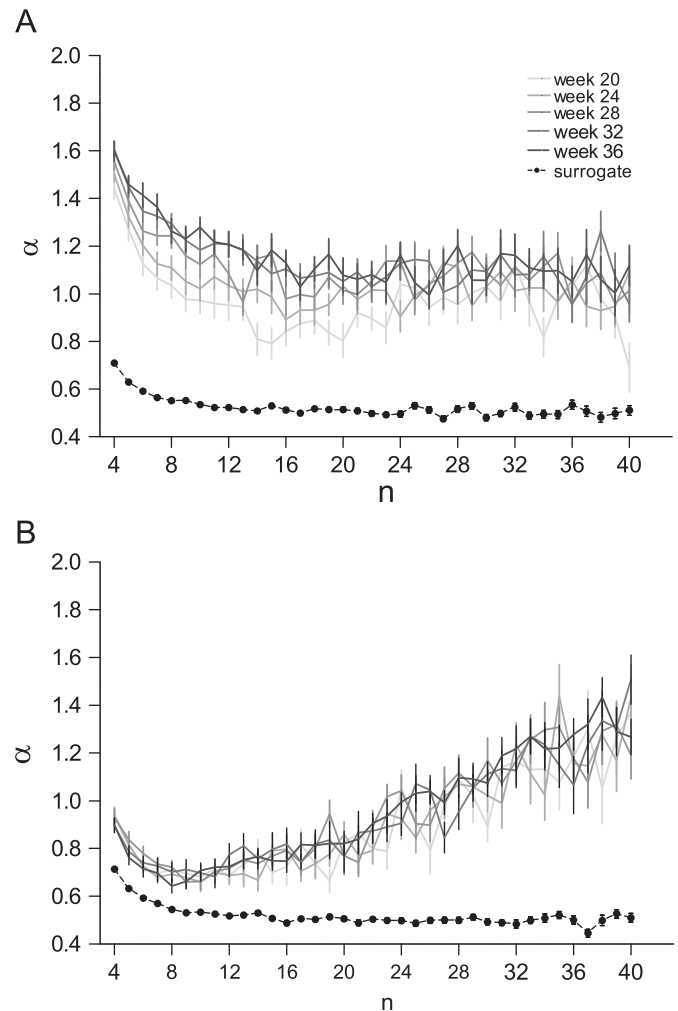


Fig. 2. Local scaling exponents obtained by detrended fluctuation analysis of RR interval (A) and QT interval (B) time series during the second half of normal pregnancy. Lines indicate group mean values and SEM for different weeks of gestation and for randomized surrogate data.

close to that of white noise (i.e. $\alpha=0.5$) for $n > 8$. For smaller n , the DFA method overestimated theoretical α values, which is a known shortcoming of the algorithm [22].

MSE functions of the randomized RR interval time series were also significantly different from those of the original RR time series (Fig. 4A). Surrogate time series showed a decay in SampEn with increasing scales, similar to that of white noise [24]. For $\tau < 5$, SampEn values of surrogates were higher than those or original time series. For $\tau > 6$, SampEn values of original time series were higher than those of surrogates.

Multiscale entropy analysis of RR time series showed an initial steep increase in SampEn from scale one to scale two (on average: 1.3 ± 0.4 vs. 1.6 ± 0.4 ; $p < 0.0001$; Fig. 4A). Subsequent changes in SampEn were less pronounced and SampEn gradually approached average values of 1.7 ± 0.2 (scale ten). Comparing MSE functions throughout the second half of gestations, SampEn values on scales one and two significantly decreased (weeks 28–36 compared to week 20). On scale three, SampEn was also significantly lower in weeks 32 and 36 compared to week 20. On scale four, SampEn was significantly lower in week 36 compared to week 20.

The MSE functions of QT interval time series were significantly different from those of RR interval time series and smaller than those of randomized data (Fig. 4B). Initial SampEn values of QT time series were significantly higher than those of RR time series

Table 2

Mean RR and QT intervals as well as standard deviations during the second half of gestation.

	Week 20	Week 24	Week 28	Week 32	Week 36
meanRR	722 $\pm$ 72	689 $\pm$ 83	664 $\pm$ 80*	635 $\pm$ 71***	635 $\pm$ 74***
sdRR	37 $\pm$ 12	36 $\pm$ 14	38 $\pm$ 13	37 $\pm$ 10	41 $\pm$ 14
meanQT	367 $\pm$ 27	359 $\pm$ 26	353 $\pm$ 27	347 $\pm$ 23*	342 $\pm$ 31**
sdQT	4.30 $\pm$ 0.38	4.39 $\pm$ 0.44	4.52 $\pm$ 0.38	4.47 $\pm$ 0.37	4.51 $\pm$ 0.34

Data presented as group means and standard deviations.

* $-p < 0.05$.

** $-p < 0.01$.

*** $p < 0.001$.

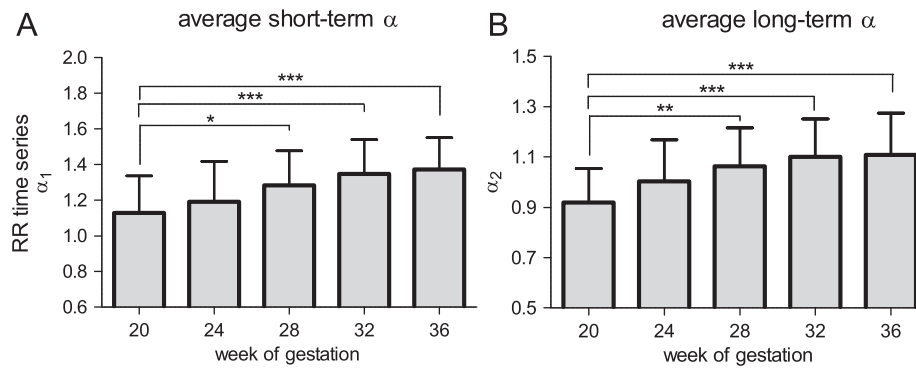


Fig. 3. Short-term (A) and long-term (B) fractal scaling exponents of RR time series obtained during different weeks of gestation. Bar plots represent means and standard deviations. * Indicates $p < 0.05$; *** indicates $p < 0.001$.

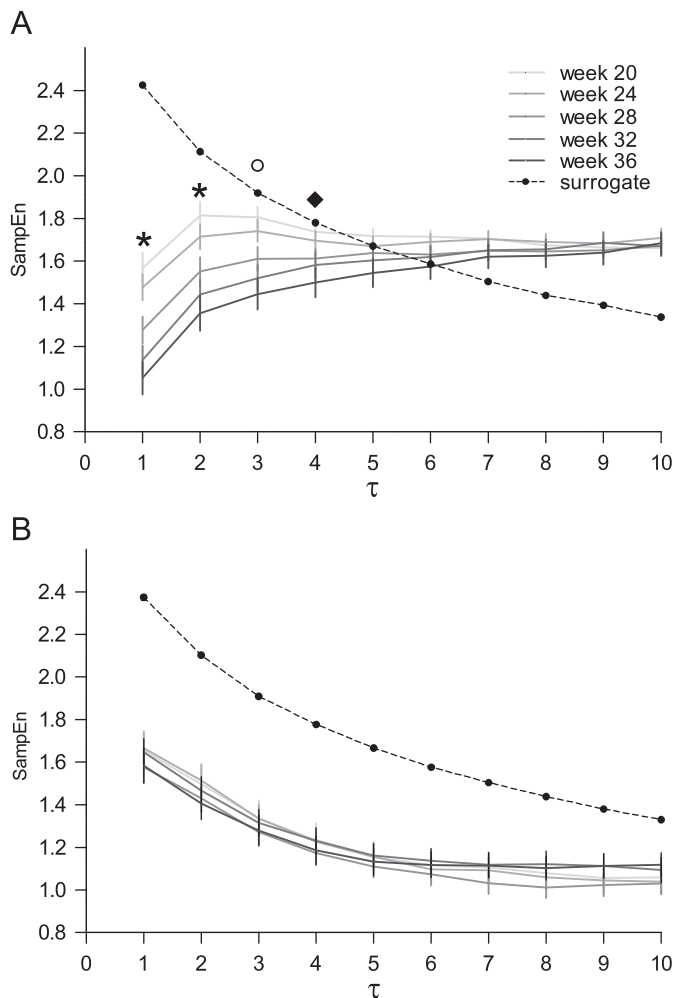


Fig. 4. Multiscale entropy analysis of RR interval (A) and QT interval (B) time series during the second half of normal pregnancy. Lines indicate group mean values and SEM for different weeks of gestation and for randomized surrogate data. The asterisk indicates significant differences in weeks 20–36 vs. week 20. The circle indicates significant differences in weeks 32 and 36 vs. week 20. The diamond indicates significant differences in week 36 vs. week 20.

(scale one: 1.6 ± 0.4 vs. 1.3 ± 0.4 ; $p < 0.0001$). In contrast to RR time series and similar to surrogates, MSE functions decreased asymptotically (scale ten: 1.1 ± 0.3). There were no significant differences in the MSE functions of QT variability with respect to the week of gestation.

4. Discussion

The major findings of this study are as follows: (1) temporal correlations and complexity of RR time series change during the second half of normal gestation, whereas (2) temporal correlations and complexity of QT interval time series do not change; and (3) the complexity of QT interval time series is significantly different from that of RR interval time series.

4.1. Heart rate variability

Nonlinear analysis of HRV is gaining increasingly attention as several studies have demonstrated superior discriminative power of nonlinear HRV measures compared to traditional time and frequency domain measures [26,27]. Besides advantageous statistical properties, nonlinear measures are thought to provide additional insight into heart rate control. Detrended fluctuation analysis and MSE are two powerful techniques that provide information on temporal correlations and the complexity of time series over multiple time scales, respectively [24,28]. Both methods provide complementary information: while DFA describes the pattern of signal amplitude with changing time scale, MSE describes the pattern of signal complexity with changing time scale [24,28].

In our study, DFA demonstrated that RR interval time series of pregnant women display long-range correlations that are similar to those of normal subjects [27,28]. Interestingly, our data indicate that the magnitude of long-range correlations increases with progressing gestation, i.e. HRV over a time scale of at least 32 heart beats is affected by pregnancy. Depending on the mean heart rate, this range covers typical high and low frequency oscillations of HRV [29], which are mediated by vagal and sympathetic efferents [4]. Previous time and frequency domain analyses of HRV suggest that vagal outflow is reduced during pregnancy [5–7]. Studies on muscle sympathetic nerve activity during pregnancy indicate activation of the sympathetic nervous system [9]. Possibly, this sympathetic activation extends to the cardiac nerves.

In contrast to long-range correlations, which were evidenced by similar values of α over multiple time scales, short-term correlations were not apparent, as α values varied substantially at small n . Part of this variation might be explained by the systematic error of the DFA algorithm when estimating α values at small n . The surrogate data, for which α should be 0.5 at all n , exemplifies this systematic offset of α , approaching only gradually 0.5 ($n > 8$). Additional variations in α might indicate that mono-fractal short-term correlation in HRV (i.e. a specific short-term scaling exponent α_1) does not exist. This argument has been put

forward by Castiglioni et al. [23] based on findings in normal healthy subjects. Due to its significance in clinical research and based on the notion that α can also be regarded as a measure of the time series' smoothness, we included α_1 in our analysis nevertheless. Similar to α_2 , α_1 values were increased at later stages of pregnancy, suggesting that short-term correlations or smoothness, respectively, were augmented. Our results are in contrast to a recent cross-sectional study of normal pregnancy, in which no significant changes in α_1 were reported, probably due to a lack in statistical power [30].

Multiscale entropy functions of our RR time series showed patterns similar to those observed in healthy volunteers [31]. The SampEn values on small scales continuously decreased with progressing gestation (i.e. the regularity of RR time series increased). Given that these scales predominantly reflect the part of HRV that is modulated by breathing, our data indicate that either breathing patterns became more regular during pregnancy or the influence of breathing on HRV attenuated, by a reduction in tidal volume and/or a reduction in vagal outflow. The latter is in line with previous observations of reduced high frequency power during the second half of gestation [7]. Sample entropy values of RR time series on higher scales were not altered during the second half of gestation, but higher than those of randomized data, suggesting that HRV contained deterministic structures that withstood the coarse-graining procedure.

4.2. QT variability

The structure of QT interval time series was markedly different from that of RR interval time series. Visual inspection of DFA α spectra showed no clear range of scale invariance in QT variability and no significant effect of the gestational week. To further explore whether scale invariance in QT variability was masked by nonlinear trends, we re-calculated DFA, using cubic trend removal [32]. No range of scale invariance was observed (data not presented), confirming the lack of scale invariance in QT variability.

The discrepancy between α spectra of QT and RR time series may appear initially surprising, given the close dependency of the QT interval on heart rate due to electrical restitution. The magnitude of beat-to-beat QT interval fluctuations (i.e. standard deviation), however, was much smaller than that of RR interval fluctuations, which might partly explain the lack of a *power-law* relationship within QT time series. Further, the rate-adaptation of the QT interval is complex and involves a rapid and slow component [33]. The latter takes more than 2 min and might thereby buffer the effect of rapid RR changes on QT variability.

Multiscale entropy analyses provide further evidence for the different structure of QT time series compared to RR time series. Interestingly, SampEn values of QT time series were higher than those of RR time series on scale one, despite lower standard deviations. This suggests that beat-to-beat QT variability is more irregular than RR variability. With subsequent coarse-graining, SampEn values continuously decreased and remained below that of randomized data, indicative of a deterministic component in QT variability.

4.3. Clinical perspective

Nonlinear HRV analysis is a simple, non-invasive tool for quantifying physiological changes in heart rate control during pregnancy. It could be useful for detecting abnormal autonomic cardiac control, which might precede clinical symptoms of hypertensive pregnancy disorders. Under normal circumstances, QT variability is not affected by pregnancy. Abnormal QT

variability observed during pregnancy might therefore be indicative of an increased arrhythmic risk.

4.4. Limitations

The ECG recordings were relatively short. This might have had a negative impact on the accuracy of MSE and DFA results on larger scales.

We conclude that normal pregnancy has a significant impact on temporal correlations and complexity of heart rate variability, but it does not affect QT interval variability. The structure of QT time series is significantly different from that of RR time series, despite its close physiological dependence.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was supported by grants from the German Research Council (VO505/4-2 and FA403-2) and the Australian Research Council (ARC DP110102049). M.B. holds an ARC Australian Research Fellowship. M.J. was supported by the Centre of Excellence for Perinatology project II (no. 26220120036) and by VEGA grant no. 1/0073/09.

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