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Change in Complexity of Fetal Heart Rate Variability

Nikhil S. Padhye, *Member, IEEE,* Audrius Brazdeikis, *Member, IEEE,* and M. Terese Verklan

***Abstract*—In a pilot study of fetal heart rate variability using magnetocardiograms it was found that substantial changes occur in complexity as the fetus matures. The self-similarity parameter increased sharply from 26 weeks to 30 weeks gestational age, while the relationship of entropy to timescale reversed during the same period. This suggests that there is distinct maturation of the autonomic nervous system during this period.**

I. Introduction

SUPERCONDUCTING quantum interference device (SQUID) technology has made it possible to routinely measure the minute magnetic fields that arise from the electrodynamics of the fetal heart [1]. This has opened up the promising new vista of fetal magnetocardiography (FMCG) for noninvasive monitoring of the developing autonomic nervous system of the fetus. A limitation of the FMCG technique is that it requires a magnetically shielded environment to obtain best signal-to-noise ratio. It has been shown that FMCG can be obtained in noisy environments [2], however it is largely untested and unknown whether parameters of fetal heart rate variability (FHRV) can be obtained of sufficiently good quality for clinical purposes based on FMCG signals recorded in noisy, unshielded environments. One motivation of this study has been to compare successive FMCG recordings conducted in a magnetically shielded and a high-frequency noise (unshielded) environment to examine the feasibility of future measurements in unshielded clinical settings. Previously [3], we have reported findings from spectral analysis of FHRV. Here we present results of a retrospective study of the complexity properties of FHRV.

Our interest in studying measures of complexity stems from the success achieved by the use of multiscale entropy (MSEn) to distinguish between beat-to-beat series in normal adults and those with congestive heart failure and atrial fibrillation [4]. Van Leeuwen *et al.* [5] reported a closely related quantity, approximate entropy, in fetuses ranging from 16 to 40 weeks and found an increasing trend with age of the fetus. Kikuchi *et al.* [6] studied FHRV in fetuses ranging from 22 to 41 weeks GA using ultrasound recordings and reported that the fractal dimension at fast time scales (500 ms to 5 s) is higher after 30 weeks.

The measures of complexity presented in this paper include MSEn and the self-similarity parameter of the RR-series. Fractal properties of signals include self-similarity, a property by virtue of which signals appear similar when viewed on different timescales. Self-similarity can be quantified by means of detrended fluctuation analysis (DFA) [7, 8]. The irregularity of a signal can be measured by the sample entropy [9], or an extension of that idea, the multiscale entropy [4]. Multiscale entropy is the sample entropy at different timescales of the original series, with each scale representing a coarse-graining of the series by that factor. The sample entropy is an inverse measure of the fraction of matching pairs of observations. Recently, lowered levels of MSEn have been found to be an indicator of fetal distress [10, 11].

II. Methodology

A. Data Collection

Data were collected at the MSI Center at the Hermann Memorial Hospital in the Texas Medical Center. We report here on observations from 17 fMCG recordings obtained from 6 fetuses with GA $\geq$ 26. Two fetuses were studied on more than one occasion and the rest were one-time observations. All but one of the recordings were in pairs of consecutive data collection sessions in magnetically shielded and unshielded environments.

The magnetic signals are largely unaffected by tissue density or conductance variation but fall rapidly with the distance away from the source. This can be used advantageously to filter out interferences arising from the maternal heart, muscle noise, and distant environmental noise sources. We employed a 9-channel SQUID biomagnetometer with second order gradiometer pick-up coils that effectively suppress noise from distant sources while enabling the detection of signals from near sources that generally have stronger gradients at the location of the detector [12]. After careful placement of the sensor array over the maternal abdomen it was possible to record fetal magnetocardiograms at several spatial locations largely unaffected by the maternal signal.

B. Signal Processing

The fMCG signal was digitized at 1 kHz in each of 9 SQUID channels and signal from the best channel was selected for further analysis. High-frequency noise, baseline drifts, artifacts, and occasionally maternal-MCG were removed using standard techniques of biomagnetic signal processing. The RR-series for fHRV analysis was obtained after implementing a QRS detector using a modified Pan-Tompkins algorithm [13].

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N. S. Padhye is with The University of Texas Health Science Center at Houston, Houston, TX 77030 USA (phone: 713-500-2035; fax: 713-500-2033; e-mail: nikhil.s.padhye@uth.tmc.edu).

A. Brazdeikis is with The University of Houston, Houston, TX 77004 USA. (e-mail: audrius@uh.edu).

M. T. Verklan is with The University of Texas Health Science Center at Houston, Houston, TX 77030 USA (e-mail: m.t.verklan@uth.tmc.edu).

A self-similar signal must necessarily be nonstationary. In first-order DFA, the signal at any time is transformed into a signal that has been integrated up to that time instant, ensuring nonstationarity. Fluctuations around linear trends are then computed for varying box sizes. If the resulting logarithm of fluctuations varies linearly with the logarithm of box size, there is evidence of self-similarity. The self-similarity parameter α represents the slope of the linear relationship. It is closely related to the asymptotic spectral exponent and to the Hurst exponent.

Since it is important to have precision in the timescales or box sizes in the computation of α, the RR-series was uniformly resampled on a grid with 400 ms spacing between points. The grid spacing corresponds closely to the average RR interval of 420 ms for our sample. Far outliers were removed using interquartile range boxes with asymmetric tolerance factors of 3 and 6 on the lower and upper side, respectively, to accommodate strong, natural variability. Less than 0.25% of data points were deemed far outliers in any data set, while most sets were not affected by far outliers at all.

At any given scale, the sample entropy is parameterized by the dimension of the vector that is being matched and the tolerance for matching. Pair-wise matching was chosen along with a tolerance that was set at 20% of the standard deviation. The RR-series was considered to be a point process for the computation of entropy.

III. Results

The linearly increasing spectral powers of fHRV from our study were previously reported [14]. The total power in decibels was given by $P = 22.33 + 1.48.t$, where t is the gestational age centered at 30 weeks (GA − 30).

A. Multiscale Entropy

The multiscale entropy of the 26 week old fetus showed high entropy at scale 1 and dropped thereafter. This is similar to the relationship of entropy to scale in adults with atrial fibrillation [4]. The relationship of entropy to scale is reversed in the fetuses 30 weeks GA or older. The multiscale entropy of older fetuses resembles that of normal adults [4].

Sample entropy is a robust statistic, not easily degraded by noise in the signal, however it is preferable to have about 100 data points or more in the series. Since there are approximately 700 RR intervals in each of our data sets, the multiscale entropy is reliable up to scale 7 and less reliable at higher scales. There was no apparent effect of the magnetic environment, shielded or unshielded, on the shape of the multiscale entropy curves, suggesting that fMCG recordings obtained in unshielded settings are suitable for FHRV studies.

B. Self-similarity

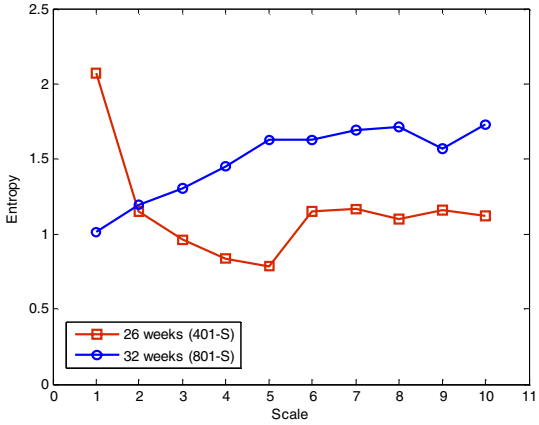

Fig.1. Multiscale entropy (MSEn) of the heart rate variability of a 26 week fetus and a 32-week fetus show a reversal of relationship between entropy and scale.

Detrended fluctuation analysis showed that there are often, but not always, two regimes of scaling. On a log-log scale, the fluctuations are linearly related to box size for time scales ranging from 400 ms to approximately 8 s. The slope of the line can change at higher time scales. In other words, there are often two power law scalings present in FHRV. This is in agreement with findings from studies of other fractal properties of FHRV [6, 15].

The self-similarity parameter α plotted against GA (Fig. 2) has been averaged across pairs of recordings in shielded and unshielded magnetic environments for each fetus. Recordings in unshielded settings did not introduce noticeable bias in estimation of the self-similarity parameter. A linear-fit to the data is also displayed although the change in α is unlikely to be linear. At 26 weeks, α was 0.17, while it more than doubled and ranged from 0.47 to 0.81 for fetuses 28 weeks and older.

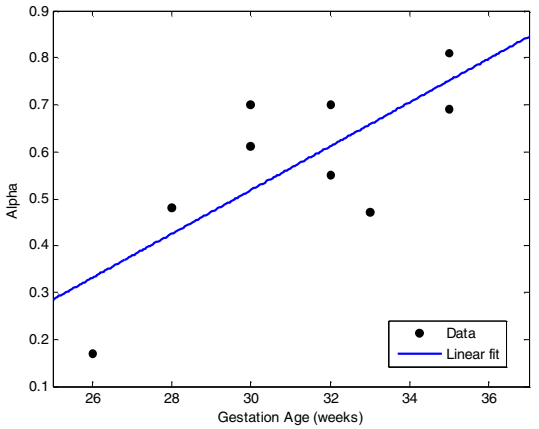

Fig. 2. Self-similarity parameter, α, increases with gestation age of the fetus.

DFA is generally done on series with a few thousand data points. The short RR-time series (5min) limits the accuracy of the resulting self-similarity parameter. There is some mitigation due to the fact that we are restricting results to the shortest time scales (< 8 s) since there appear to be two

scaling regimes. The lengths of our data recordings are a factor of 37 greater than the 8-second scale. Another mitigating factor is that DFA has been computed here with continuously sliding windows in order to improve the statistics.

IV. Discussion and Conclusion

Both measures of complexity that were computed indicate that fetuses likely undergo a substantial change from 26 weeks to 30 weeks gestation age in the autonomic nervous system that controls their heart rate variability. The relationship of entropy to scale reversed during that time period while the self-similarity increased substantially.

This pilot study is limited by the sample size. More data is required, especially for fetuses younger than 30 weeks GA, before a more confident conclusion can be drawn. However, the tendencies that were observed in the dependence of self-similarity of FHRV on age are similar to those reported for fractal dimension based on ultrasound recordings [6].

Fetal magnetocardiography offers potentially more accurate determination of beat-to-beat intervals than does fetal ultrasound or fetal ECG. At present its wide clinical use is limited since it requires expensive magnetically shielded rooms. The success of this pilot study in recording fetal magnetocardiograms outside the shielded environment is a promising development. Spectral as well as complexity measures were computed from recordings in the unshielded environment that did not differ appreciably from corresponding measures computed from recordings in magnetically shielded rooms.

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