Herzschr Elektrophys 11:179–183 (2000)

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Irregularities and nonlinearities in fetal heart period time series in the course of pregnancy

Received: 20 May 2000
Accepted: 20 July 2000

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Summary Fetal heart rate variability reflects fetal development and is affected by pathological conditions. The aim of this study was to examine fetal heart period irregularity by focussing on nonlinear dynamical components. We recorded 165 fetal magnetocardiograms in 39 healthy pregnancies between the 16th and 41st week. The irregularity of the RR time series of each recording was quantified on the basis of the approximate entropy (ApEn). In order to estimate the nonlinear component, a surrogate time series was generated for each time series and ApEn was again calculated. Next, the purely dynamical aspect of the series was examined using a binary representation reflecting increase or decrease in RR interval of the original time series. ApEn of the original time series increased during pregnancy with a significant dependence on gestational age ($p < 0.0005$). The ApEn values of the surrogate data increased similarly although the power of the relationship to week of gestation was weaker ($r_{original} = 0.68$, $r_{surrogate} = 0.46$). Also the values of the surrogate series were generally higher, the mean difference being 0.24±0.24 ($p < 0.0005$). ApEn of the binary series revealed no dependency on gestational age but again the values for the surrogate series were higher than those for the original series. The increase in irregularity of RR interval time series during pregnancy can be attributed in part to an irregular, nonlinear temporal structure and is not solely due to linear autocorrelations. Reducing information by constructing time series using binary symbolization which ignores the absolute beat durations resulted in a loss of dependency on gestational age but a retention of nonlinearity. The ability to quantify these processes promises to aid in prenatal risk stratification.

Key words Approximate entropy – fetal heart rate variability – irregularity – gestational age – magnetocardiography

Introduction

Assessment of the fetal condition on the basis of heart rate is central to prenatal and perinatal surveillance. In the clinical routine, the fetal heart beat is recorded using cardiotocography which delivers a tachogram in the form of momentary heart rate. As the temporal resolution is limited, only semi-quantitative, visual estimation and classification of fetal heart rate variability is often performed. Although fetal heart rate monitoring based on ultrasound can be used to quantify heart rate variability (3, 6), it does have its drawbacks (5, 6). On the other hand, fetal magnetocardiography (FMCG) permits precise non invasive registration of cardiac activity, as QRS complexes can be identified as early as the beginning of the second trimester (17). In contrast to fetal ECG, there is minimal influence of the vernix caseosa and the maternal signal. This allows for an estimation of fetal heart rate variability (HRV) using standard measures (10) and, beyond enabling comparison with

postnatal and adult data, it may well lead to more discriminating diagnostics for fetal surveillance.

Using FMCG, we have been able to show that such standard time domain estimates of fetal HRV increase in the course of normal pregnancy (18). Furthermore, the data also demonstrated an increase of complexity, suggesting the presence of a nonlinear component in the HRV. In this study, we wished to determine whether the complexity found in fetal heart period time series is due to linear or nonlinear processes by comparing the estimation of complexity found in the original data to that in surrogate data. The surrogate data used in this study retained the distribution and the power spectrum of the original time series while nonlinear properties were randomized. Furthermore, using a binary representation reflecting increase or decrease in momentary heart rate of the original time series, we sought to gain a better understanding of the origins of increasing complexity.

Materials and methods

We examined 39 women between 26 and 38 years of age (mean ± standard deviation: 32 ± 3) who presented with healthy singleton pregnancies in the second trimester or later. Fetal magnetocardiograms were obtained at regular intervals of roughly four weeks up to the time of birth, between 1 and 14 per fetus (4 ± 3). Altogether, 165 recordings were acquired between the 16th and 41st week of gestation. Using either a 37-channel biomagnetometer (Siemens Krenikon, Erlangen) or a 67-channel biomagnetometer (BTi 1300C, San Diego) in a magnetically shielded environment, data were acquired for five minutes with a bandpass of 1–200 Hz at a sampling rate of 1 kHz. In post-processing, the maternal cardiac artifact was identified on the basis of a QRS signal template and the maternal PQRST signal was digitally subtracted. Next, the fetal QRS complexes were marked using a fetal QRS template and the RR intervals were determined to an accuracy of 1 ms as the time between consecutive QRS complexes.

Two time series were examined per recording: the series of about 600–800 RR intervals and the symbolic binary sequence reflecting the increase or decrease in RR interval duration of successive beats. For the latter the following symbolization was used: positive differences between successive RR intervals were set to 1 and negative differences or equal successive RR intervals to 0. This representation only retains the dynamical aspects of the fetal heart beat disregarding the absolute values of the increase or decrease of the RR interval.

Heart period irregularity was assessed for both series on the basis of the approximate entropy (ApEn). ApEn was introduced by S. Pincus (11) to quantify serial irregularity, i.e., the 'extent of randomness' in sequences or time series (see also (15), this issue). One important feature of ApEn is that it is model-independent and no constraint delimits the length of the series under consideration. Although the theoretical basis of the method is broad and mathematical details are complicated, the central idea of the method is straightforward and can be verbalized in only one sentence: *ApEn(m,r)* measures 'the negative logarithmic likelihood that runs of patterns that are close (within tolerance *r*) for *k–1* observations remain close on the next incremental comparison' (12).

Practically, when analyzing heart period sequences, for each *m*-dimensional vector (or pattern) of successive RR intervals, all vectors in the *r*-neighborhood (e.g., within an Euclidean state space distance $< r$) have to be found. Then, incremental comparison is done by increasing the number of vector components by one and comparing the distances of previously neighbored vectors. Finally, some trivial computations lead to the values of ApEn and to the associated quantification strategy of RR regularity: low values indicate serial regularity, and large values imply irregularity or randomness in RR tachograms. For further details and computing algorithms the reader is referred to the relevant literature (2, 11).

For binary sequences a notion of irregularity can be introduced as follows. Considering the binary sequences 000000, 101010 and 111001, the first two can be easily identified as regular. The third example does not reveal an easy rule for its generation. Hence, this sequence can be called more irregular (14). The application of ApEn to symbolic sequences quantifies this kind of irregularity. ApEn of the symbolic binary sequence was calculated in a similar fashion with the following differences. Because the number of possible binary patterns is considerably lower than the number of possible patterns of consecutive absolute RR intervals, the length *N*, for which ApEn was calculated, could be restricted to $N = 6$. Also, the binary nature of the sequences resulted automatically in a tolerance $r > 1$. A window of length 6 was moved over the entire binary series and ApEn was calculated for each window. The average binary ApEn (BinApEn) over all windows was used to quantify the binary sequence [for further details see (4)].

Surrogate data were generated for each RR interval series by phase randomization of the Fourier transformation of the RR interval series followed by an iterative scheme which retains the power spectrum (i.e., the autocorrelations) and the distribution of the original data within sufficient accuracy (16). Subsequently, the surrogate data were analyzed in the same manner as the original data.

Statistics

Values are generally expressed as means ± standard deviation. For the small number of results before the 21st and after the 37th week of pregnancy, medians were deemed more appropriate. Linear regression analysis was used to determine the dependency of ApEn and BinApEn on gestational age. The two-sided Wilcoxon test for paired data was used to examine the difference between the results for original and surrogate data. Values of $p < 0.05$ were considered statistically significant. In the results section, r refers to the correlation coefficient, not to be confused with the tolerance *r* in ApEn (see methods), which is printed in italics.

Results

The ApEn values of the RR interval time series increased during the course of pregnancy from a median value of 0.15 before the 21st week of gestation to 0.67 after the 37th week (Fig. 1). Linear regression analysis revealed a clear dependency on gestational age ($y = 0.030 \times x - 0.384$, $r = 0.68$, $p_{slope} < 0.0005$). The ApEn values of the surrogate data also increased, although the values were generally higher, from 0.21 before the 21st week to 0.96 after the 37th week ($y = 0.028 \times x - 0.100$, $r = 0.46$, $p_{slope} < 0.0005$). Also, the spread of the values was greater (Fig. 1) as reflected in the lower correlation coefficient in combination with wider 95% confidence intervals for the slopes (original: 0.025–0.034 vs. surrogate data: 0.020–0.036). The left panel in Fig. 3 shows the differences between the original and surrogate ApEn values. The mean of these differences was 0.24 ± 0.24 ($p < 0.0005$).

As can be seen in Fig. 2, the ApEn values of both the original and surrogate symbolic binary series (BinApEn) showed no dependency on gestational age (original: $y = 0.0004 \times x + 0.375$, $r = 0.10$, $p_{slope} = 0.19$; surrogate: $y = 0.0001 \times x + 0.40$, $r = 0.02$, $p_{slope} = 0.82$). However, the original values were lower than the surrogate (0.39 ± 0.03 vs. 0.41 ± 0.03) and the mean difference between the original and surrogate values was different from zero (0.02 ± 0.03, $p < 0.0005$, see Fig. 3).

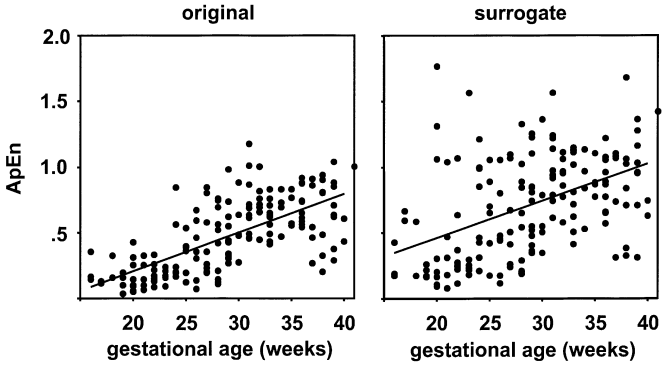

Fig. 1 ApEn of original data and surrogate data vs. gestational age with the corresponding regression lines

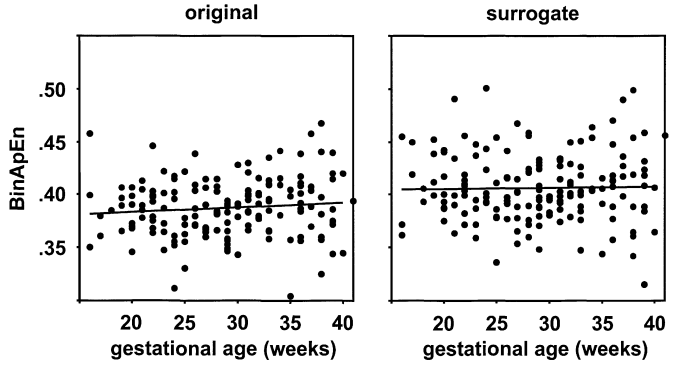

Fig. 2 BinApEn of original data and surrogate data vs. gestational age with the corresponding regression lines

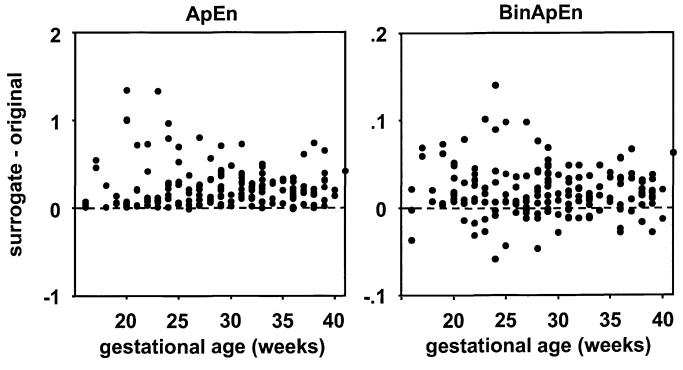

Fig. 3 Differences between surrogate data and original data for ApEn and BinApEn

Discussion

It is known that in the course of pregnancy, fetal heart rate variability increases concurrent with a tendency towards lower fetal heart rates. This increase in variability is confirmed by the results presented here with

respect to ApEn, a statistical measure for irregularity. We may also conclude that the irregularity quantified by ApEn contains a nonlinear component since the ApEn values of the surrogate data sets were significantly higher than those of the original data. In the generation of the surrogate data the nonlinear component of the original data was interchanged with a randomized component. The surrogate data retained the distribution and spectral properties of the original data while randomizing their order. Thus, in the original data, the changes of ApEn reflect changes in their temporal structure which cannot be attributed to linear properties. This is in agreement with a study by Groome et al. (9) in which ApEn was determined in the RR tachograms of 12 fetuses between the 38th and 40th week of pregnancy. The results were compared to model data containing uncorrelated noise, linearly correlated noise or linearly correlated noise with linear distortion but having the same mean and standard deviation of the heart rate as the original series. The authors found that ApEn of the original series differed significantly from ApEn of the model data, suggesting that fetal heart rate time series contain nonlinear components. The results found in the present study confirm this over a 25-week range of gestational age.

Furthermore, the results suggest that the nonlinear components do not change greatly with increasing gestational age. The difference between the ApEn values of the original and the surrogate data was almost constant in the course of pregnancy suggesting an unchanging nonlinear influence. Hence, mainly linear properties were responsible for the increase of irregularity as indicated by ApEn. The dependency of ApEn in the surrogate data on gestational age is in agreement with the fact that linear measures of HRV also increase in the course of pregnancy. In a previous study (18), we showed that both the standard deviation as well as the root mean square of successive differences of the RR intervals also correlate with gestational age. In the data evaluated here, the strength of the relationship as estimated by the correlation coefficient r was much lower for the surrogate data. This indicates that, in the original data, there is an additional component which contributes to the explanatory power of the relationship to gestational age.

One may question whether increases in HRV, linear or nonlinear, are simply due to the physiological increase in heart rate variability associated with decreases in heart rate or whether they reflect the maturation of the fetal cardiac system. In this vein, other work suggests that the different measures reflect complementary and noncoincident information which may result from underlying developmental processes (8). These authors observed differences in the course of ApEn between male and female fetuses not apparent in their standard deviation. They postulated that ApEn may be more sensitive to gender differences in the development of parasympathetic innervation.

In order to examine the effect of the absolute beat period durations on ApEn, the information content of the original time series was reduced by converting them into binary sequences – which indicate solely the increment or decrement of the beat period duration – and then calculating the approximate entropy of the resulting sequences (BinApEn). In contrast to the results for the time series of absolute RR intervals, the analysis of the binary sequences led to results which no longer displayed the dependency on gestational age, i.e., the pure dynamics of fetal heart rate did not change in the course of pregnancy. This seems to indicate that the dependency of the original time series is related to the absolute values of the beat period. On the other hand, the results for BinApEn may be influenced by a scaling effect. The dynamics present in shorter RR intervals earlier in pregnancy (corresponding to higher heart rates) might be masked by the limits placed on the temporal resolution resulting from the data sampling rate. In other words, should there be a significant beat to beat dynamic below 1 ms, recording with a higher temporal resolution would lead to time series with different BinApEn values. Be that as it may, the fact that the analysis of the surrogate binary sequences led to higher ApEn values suggests that, although a relation to age could no longer be identified, the binary sequences did retain a nonlinear component.

If the nonlinear component can be shown to be stable and reproducible in normal pregnancies, the calculation of the strength of this component may be useful in the identification of pathological conditions. It has been shown that lower ApEn values during labor may be associated with a higher likelihood of fetal acidosis (13) and with poorer outcome (7). Arduini et al. (1) have demonstrated that ApEn in growth retarded fetuses, determined directly prior to elective caesarian section, was significantly lower than that for healthy fetuses at comparable gestational age. In particular, the sensitivity and specificity of ApEn with respect to acidosis at birth were higher than in other commonly used indices for fetal heart rate variation. It is important to note that the results in these studies were obtained using standard ultrasound fetal heart rate monitors which generally only resolve heart rate over a number of seconds. Thus such results are very encouraging: one could expect that data acquisition methods such as magnetocardiography, which allow for high temporal beat to beat accuracy, will lead to even better discrimination between groups of subjects because of the possibility of including short term dynamics in the evaluation.

Conclusions

The increase in irregularity of fetal heart period time series during pregnancy can be attributed in part to an irregular, nonlinear temporal structure and is not solely due to linear autocorrelations. Reducing information by constructing time series using binary symbolization which ignores the absolute beat durations resulted in a loss of dependency on gestational age but a retention of nonlinearity. Taken together, we may conclude that the irregularity found in fetal heart period time series is due to nonlinear processes. Measures which take only linear aspects of variability into account will not reflect the time structure of the data completely and may, therefore, be less discriminant of different physiological or pathological conditions.

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