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FETAL MAGNETOCARDIOGRAM WAVEFORM CHARACTERISTICS

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Abstract

Background: Fetal magnetocardiography (fMCG) is the most direct and precise method of assessing fetal rhythm and conduction. Although the utility of fMCG for evaluation of fetuses with serious arrhythmia is generally acknowledged, many aspects fetal rhythm and conduction are relatively unstudied.

Objective: To record fMCG in a large group of normal fetuses in order to provide a more comprehensive evaluation of fMCG waveform characteristics, including waveform intervals, amplitudes, and morphology.

Approach: The subjects were 132 healthy women with uncomplicated singleton pregnancies, studied at 15.7–39.9 (mean 28.9) weeks' gestation in 259 sessions. The P, PR, QRS, QT, QTc, and RR intervals and the P/QRS and T/QRS amplitude ratios were measured.

Main Results: The P, PR, QRS, and RR intervals increased with gestational age, but QT and QTc did not. U-waves were seen in 11% of fetuses. The T-waves were often flat with low T/QRS amplitude ratios. Equiphasic QRS complexes were associated with tall P-waves. The PR, QRS, and QT intervals showed a power law dependence on RR interval with power law exponents 0.445, 0.363, and 0.381, respectively.

Significance: The data establish prediction intervals for fMCG waveform intervals and amplitudes in normal fetuses. This is critical for identification of fetuses with abnormal rhythm. Our study is the first to document the incidence of U-waves and flat T-waves in the fetus, both of which are uncommon postnatally. The association of tall P-waves with equiphasic QRS complexes provides a useful means of improving the resolution of fetal P-waves.

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AUTHOR CONTRIBUTIONS

Sarah Strand performed the data analysis and much of the data collection.

Janette Strasburger performed the clinical interpretation of the data.

Ronald Wakai is the principal investigator and supervised all aspects of the research.

STATEMENT OF ETHICS

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

Keywords

fetal magnetocardiography; fetal monitoring; fetal rhythm; cardiac intervals; repolarization; U-wave

OBJECTIVE

Fetal magnetocardiography (fMCG), the magnetic analog of fetal electrocardiography (ECG), is the most direct and precise method of assessing fetal rhythm and conduction. In recent years, the efficacy of fMCG for diagnosis and prognosis of serious fetal arrhythmia has become widely recognized (Donofrio et al., 2014, DeMaria et al., 2009).

A critical capability of fMCG is measurement of waveform intervals, which are fundamental parameters of cardiac rhythm. While echocardiography can also infer cardiac time intervals from the mechanical activity of the heart (Pasquini et al., 2007), the corresponding intervals are imprecise and do not always accurately reflect the underlying electrical activity (Van Hare). Furthermore, echocardiography cannot assess repolarization.

Although the utility of fMCG for evaluation of fetuses with arrhythmia is generally acknowledged, conduction in normal fetuses has not been comprehensively characterized, despite a substantial literature (Horigome et al., 2000, Stinstra et al., 2002, Kahler et al., 2002, Lowery et al., 2003, Van Leeuwen et al., 2004, Comani et al., 2005, Kiefer-Schmidt et al., 2012, Stingl et al., 2013). Many of these studies were performed in the early 2000s, when the field was relatively new, and show some discrepancies. The largest and most widely cited study, performed by Stinstra and co-workers (Stinstra et al., 2002), involved five centers and 582 normal fetuses. Although the overall results were largely consistent with other studies, the data showed a considerable amount of scatter. A substantial number of subjects had extreme interval measurements, such as $PR > 140$ ms or $QRS < 30$ ms, resulting in wide prediction intervals. The upper levels of the 95% prediction intervals are of particular importance because they are used as the thresholds for detection of the most common serious fetal arrhythmias. For example, AV block, ventricular tachycardia, and long QT syndrome, are associated with prolongation of PR, QRS, QTc, respectively.

Little has been published regarding signal amplitude, which is often used in ECG to predict hypertrophy or cardiac chamber enlargement. It is commonly thought that fMCG signal amplitude has little value because it can vary due to fetal lie; however, Li and coworkers (Li et al., 2004) showed that P/QRS ratio is markedly increased in fetuses with bradycardia and may be an indicator of atrial hypertrophy.

One of the main goals of this study is to measure fMCG waveform intervals and amplitudes in a large group of normal subjects in order to establish the range of normative data from a single center with substantial volume of cases. This is critically important given the increased use of fMCG for clinical application. The correlation of the intervals with gestational age and their dependence on heart rate is assessed. We also document the incidence of U-waves and flat T-waves, which have not been systematically studied and are

not well understood. Lastly, we demonstrate an association between the amplitude of the P-wave and QRS morphology.

APPROACH

Subjects

The subjects were 132 healthy women with uncomplicated singleton pregnancies, studied at 15.7–39.9 (mean 28.9) weeks' gestation. Forty-five subjects were studied serially in 2 to 6 sessions. The total number of sessions was 259. Medications such as prenatal vitamins were noted, and subjects taking drugs known to affect cardiac intervals were excluded. Informed consent was obtained from each subject.

Data Acquisition

The fMCG was recorded using a 37-channel (Magnes, 4D Neuroimaging, Inc., San Diego, CA) or 21-channel (Model 624, Tristan Technologies, San Diego, CA) superconducting quantum interference device (SQUID) biomagnetometer, housed in a magnetically-shielded room. The magnetic field resolution per channel was 4–8 fT/(Hz)^{1/2}. Both devices have FDA 510(k) clearance.

The mother changed into nonmagnetic clothing and lay supine or slightly on her side if she experienced discomfort lying supine. A brief ultrasound exam was performed to locate the fetal heart to guide probe placement. At least 10 minutes of data was recorded during each session, using a sampling rate of at least 500 Hz.

Signal Processing and Averaging

A digital filter with a 1–80 Hz passband was applied to band-limit the data. Signal processing was used to remove the maternal MCG and other interferences (Yu and Wakai, 2011).

Averaging was used to increase the signal-to-noise ratio (SNR). Using the QRS complexes as triggers, averaged waveforms were computed during periods when the fetal heart rate was at or near baseline. The heart rate was considered to be at baseline when the fetus was quiescent and the heart rate was within 5 bpm of a stable minimum seen over the duration of the recording, excluding periods of marked variability or episodic changes. Fetal quiescence was inferred from an absence of fetal movement, as determined by fMCG actography (Lutter and Wakai, 2011). Typically, 50–100 consecutive complexes were averaged, depending on the SNR of the raw recording.

Waveform Interval and Amplitude Measurements

Waveform intervals—P, PR, QRS, QT, QTc, and RR—were measured by a trained technician and confirmed by a board-certified pediatric cardiologist (JFS) from “butterfly” plots, which superimposed the signals from all channels (Fig. 1). The measurements were made on a computer display with the aid of screen calipers. The P interval was measured from the beginning to the end of the P-wave and corresponds to the duration of atrial depolarization. The PR interval was measured from the beginning of the P-wave to the

beginning of the QRS complex and corresponds to the time from the onset of atrial depolarization to the onset of ventricular depolarization. The QRS interval was measured from the beginning to the end of the QRS complex and corresponds to the duration of ventricular depolarization. The QT interval was measured from the beginning of the QRS complex to the end of the T-wave and corresponds to the time from the beginning of ventricular depolarization to the end of ventricular repolarization. The RR interval was measured from the peak of the QRS complex to the peak of the next QRS complex and corresponds to the time between ventricular beats (Fig. 1a). QTc was computed using Bazett's formula: $QTc = QT/RR^{1/2}$. The peak-to-peak amplitudes of the P, QRS, and T components were measured using a computer program that detected the maxima and minima of the waveform components, following determination of the onset and termination of each waveform component by the user.

Statistical Analysis

The correlation of the waveform intervals and amplitudes with gestational age was assessed using linear regression. Because some subjects participated in multiple sessions, the data were analyzed 3 ways. The first used data from all sessions. The second used data from just the first session for subjects with multiple sessions and the third used data from just the last session.

The power-law dependence of the waveform intervals on heart rate was investigated by plotting the waveform intervals versus RR on a log-log plot and performing linear regression. For log-log data the correlation coefficient is equal to the slope of the regression line and yields the power-law exponent.

MAIN RESULTS

The signal quality was inadequate for analysis in 24 subject sessions, 19 of which occurred prior to 20 weeks' gestational age. The SNR in these subjects was less than one, and QRS detection was not sufficiently reliable for computation of averaged waveforms. The number of sessions used in the analysis was 235.

Waveform Intervals

Scatter plots of cardiac waveform intervals versus gestational age are shown in Fig. 2. These data are presented in tabular form in Table 1. Using data from all sessions, P ($R^2 = 0.17$, $P < 0.001$), PR ($R^2 = 0.07$, $P < 0.001$), QRS ($R^2 = 0.16$, $P < 0.001$), and RR ($R^2 = 0.16$, $P < 0.001$) increased significantly with gestational age, but QT and QTc did not. The results were essentially the same if serial data were excluded. Using data from just the first session of each subject, the correlations with gestational age were significant for P ($R^2 = 0.10$, $P < 0.001$), PR ($R^2 = 0.07$, $P = 0.0016$), QRS ($R^2 = 0.12$, $P < 0.001$), and RR ($R^2 = 0.14$, $P < 0.001$), but not for QT and QTc. Using data from just the last session of each subject, the correlations with gestational age were significant for P ($R^2 = 0.17$, $P < 0.001$), PR ($R^2 = 0.07$, $P = 0.0025$), QRS ($R^2 = 0.10$, $P < 0.001$), and RR ($R^2 = 0.13$, $P < 0.001$), but not for QT and QTc.

From 20 to 40 weeks' the upper bounds of the 95% prediction intervals increased from 114 to 126 ms for PR and from 56 to 66 ms for QRS. The upper bound of the 95% prediction interval for QTc, which did not show a statistically significant correlation with gestational age, was approximately 495 ms.

U-waves were visible in 26 sessions (11%) (Fig. 1b). The height of the U-wave exceeded half the height of the T-wave in 14 sessions (6%) and exceeded the height of the T-wave in 7 (3%). Thirteen subjects had QTUc > 500 ms, with QTUc ranging from 503–569 ms.

Waveform Component Amplitudes

An adventitious finding was that the waveforms with equiphasic (isoelectric) QRS complexes showed tall P-waves (Fig. 1c). The QRS complex was considered equiphasic if the positive and negative peak amplitudes were equal to within 50% in the channel with largest peak-to-peak QRS amplitude. Compared to monophasic QRS complexes, equiphasic complexes showed higher P-wave amplitude ($1.47 \times 10^{-13} \pm 1.0 \times 10^{-13}$ versus $0.96 \times 10^{-13} \pm 0.77 \times 10^{-13}$; $p < 0.001$) and higher P-to-QRS (peak-to-peak) amplitude ratio (0.10 ± 0.05 versus 0.08 ± 0.05 ; $p = 0.002$ (Fig. 3a)), but the QRS amplitude was not significantly different. This implies that the tall P-waves were not due to a large QRS amplitude.

Many subjects showed flat, low amplitude T-waves (Fig. 1d). The mean T-to-QRS amplitude ratio was 0.04 ± 0.02 (Fig. 3b). Linear regression showed a weak, but statistically significant, association with gestational age ($p = 0.048$).

Cycle Length Dependence

Log-log scatter plots of the waveform intervals versus RR (Fig. 4) showed statistically significant correlation coefficients, r , for PR ($r = 0.4453$, $p = 0.0003$), QRS ($r = 0.3627$, $p = 0.0126$), and QT ($r = 0.3809$, $p = 0.0042$).

SIGNIFICANCE

The main result of this study is the determination of ranges for fMCG waveform intervals in normal fetuses. As mentioned above, the upper bounds of the 95% prediction intervals for PR, QRS, and QTc, are of greatest clinical importance because the most common serious fetal shortening as well as QRS prolongation. Short QT syndrome is seen postnatally, but has not been reported in fetuses. The ability to directly and precisely measure waveform intervals, including those due to repolarization, is a critical advantage of fMCG versus Doppler ultrasound and allows for a more accurate differential diagnosis of fetal arrhythmia.

Discrepancies between our data and those of other investigators can result from such factors as instrumentation, methodology, data quality and quantity, and subjective assessment. As mentioned above, many older studies show some discrepancies. For example, Stinstra and co-workers reported higher PR intervals at late gestational ages and lower QRS intervals at early gestational ages (Stinstra et al., 2002). In addition, they reported lower values for QTc. Their study involved the use of several fMCG systems, ranging from a 1-channel vector magnetometer to a 67-channel magnetometer. Thus, their results likely reflect increased

methodological variation inherent in multi-center studies. On the other hand, nearly all other studies, including ours, were performed at a single center and were limited by smaller subject numbers. Fewer studies have been performed in recent years, but our results show good agreement with those of Kiefer-Schmidt and co-workers (Kiefer-Schmidt et al., 2012), who studied 103 subjects. Although they do not plot confidence intervals, the confidence intervals can be inferred from the means and standard deviations and appear to be in reasonable agreement with ours. Our results are also compatible with studies of serious fetal arrhythmia. For example, the great majority of fetuses with AV block (Menendez et al., 2001, Zhao et al., 2008), ventricular tachycardia (Das et al., 2008, Strasburger and Wakai, 2010), and long QT syndrome (Hamada et al., 1999, Hosono et al., 2002, Cuneo et al., 2013), respectively, have PR, QRS, and QTc intervals that exceed the upper limit of the 95% prediction intervals seen here.

We found that PR and QRS duration increased significantly with gestational age, but QTc did not. Some prior studies found the same results (Stingl et al., 2013), but several found that QTc, in addition to PR and QRS, increased with gestational age (Stinstra et al., 2002, Van Leeuwen et al., 2004, Kiefer-Schmidt et al., 2012). Overall, these findings confirm the importance of taking gestational age into account and underscores the need to study enough subjects to accurately characterize the data over a wide range of gestational ages. Although low signal amplitude at early gestational ages is a limitation of fMCG, the success rate after 20 weeks' gestation is high.

Log-log plots of PR, QRS, and QT versus RR showed a significant dependence on log RR with correlation coefficients, 0.445, 0.363, and 0.381, respectively. These correspond to the exponents of the power-law dependences. The fact that they were similar for PR, QRS, and QT implies that the timing of the individual events in the cardiac cycle scale with cycle length in a similar way. The exponents were all less than 0.5; however, the confidence intervals encompassed 0.5, implying that the power-law dependence for QT is roughly compatible with Bazett's formula. Given that PR, QRS, and QT increase with RR interval and that RR increases with gestational age, it is somewhat surprising that QT does not increase with gestational age. There are many possible explanations. It could, for example, reflect important fundamental differences that result because PR and QRS are due to depolarization while QT is due to repolarization. It should be noted, however, that the variance of the data is greater for QT than for PR or QRS, which, given the limited subject numbers, increases the difficulty of demonstrating correlations between QT and other variables.

Fetal T-waves are typically flatter and have lower T-to-QRS amplitude ratios, compared to what is seen postnatally. This has been noted anecdotally in several prior fMCG studies (Wakai et al., 1994, Horigome et al., 2000), but has not been explained. One possible explanation involves the direction of repolarization. QRS-T concordance is most often attributed to the direction of repolarization being largely opposite to the (base-to-apex) direction of repolarization. This reverses the intrinsic negativity of the repolarization current, resulting in a paradoxical positive T-wave. We speculate that flat T-waves can result when some areas of the heart repolarize base-to-apex and others repolarize apex-to-base so that the

currents cancel. Right-sided dominance of the fetal heart is another potential factor, as it would be expected to alter the direction of repolarization, as well as depolarization.

U-waves are relatively uncommon postnatally, but in this study they were seen in 11% of subjects. Some researchers, however, disregard U-waves unless they exceed half the height of the T-wave or the full height, which occurred in 6% and 3% of subjects, respectively. The ambiguous nature of the U-wave can be a significant confound because many subjects with U-waves show QTUc > 500 ms.

A potentially useful observation was that equiphasic QRS complexes were associated with tall P-waves. For fMCG, equiphasic QRS complexes result primarily from rotation of the heart vector during the QRS complex. The channels with equiphasic QRS complexes are those for which the direction of the heart vector rotates through the position of the channel, whereas monophasic complexes result when the direction of the heart vector remains on one side of the channel throughout depolarization. Thus, the channels with equiphasic QRS complexes lie approximately along the time-averaged direction of the rotating heart vector. By positioning the sensor to obtain equiphasic QRS complexes the resolution of the P-wave can be improved.

In summary, this study is the first to document the incidence of U-waves and flat T-waves in the fetus, both of which are uncommon postnatally and are not well understood. We demonstrate an association between tall P-waves and equiphasic QRS complexes, which provides a useful means of improving the resolution of fetal P-waves. The most clinically important result is the determination of normative ranges for fMCG waveform intervals and amplitudes. This is crucial for evaluation of fetuses with abnormal rhythm.

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a

b

c

d

Fig. 1.

Averaged waveforms of duration 1-second, showing examples of a) typical waveform with intervals indicated, b) U-wave, c) equiphasic QRS complex with tall P-wave, and d) flat T-wave.

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a

b

c

d

e

Fig. 2. Scatter plots of a) P, b) PR, c) QRS, d) QT, e) QTc, and f) RR interval versus gestational age. The solid lines and dashed lines, respectively, show the linear regression line and the 95% prediction interval, and are computed using data from all sessions.

a

Fig. 3. Scatter plots of a) P/QRS and b) T/QRS amplitude ratio versus gestational age. The P/QRS amplitude ratio was higher for equiphase versus monophasic QRS complexes.

a

b

c

Fig. 4.
Log-log scatter plots of a) PR, b) QRS, and c) QT versus RR.

Table 1.

Fetal waveform intervals versus gestational age.

Gestational Age (weeks)	N	RR (ms)	P (ms)	PR (ms)	QRS (ms)	QT (ms)	QTc (ms)
		Mean	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
15–24	53	408	39.5 $\pm$ 7.7	93.3 $\pm$ 10.1	44.4 $\pm$ 6.0	254.0 $\pm$ 30.5	398.4 $\pm$ 50.1
24–29	71	409	41.3 $\pm$ 7.1	95.3 $\pm$ 11.7	46.5 $\pm$ 6.7	250.5 $\pm$ 35.3	392.1 $\pm$ 55.1
29–35	63	432	45.7 $\pm$ 8.0	99.3 $\pm$ 12.1	49.2 $\pm$ 6.0	263.5 $\pm$ 31.5	401.5 $\pm$ 47.1
35–40	48	434	49.6 $\pm$ 9.3	101.5 $\pm$ 12.3	51.0 $\pm$ 7.5	249.8 $\pm$ 34.2	377.7 $\pm$ 46.9
15–40	235	420	43.8 $\pm$ 8.7	97.2 $\pm$ 11.9	47.6 $\pm$ 6.9	254.5 $\pm$ 33.5	393.0 $\pm$ 51.0