Assessment of Left Ventricular Pre-Ejection Period in the Fetus Using Simultaneous Magnetocardiography and Echocardiography

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Key Words

Pre-ejection period • Fetal magnetocardiography • Fetal echocardiography • Electromechanical coupling • Systolic time intervals

Abstract

Introduction: Fetal magnetocardiography (fMCG) is a promising new technique for assessing fetal rhythm; however, no prior studies have utilized fMCG to evaluate human fetal electromechanical physiology. Pre-ejection period (PEP) is an important measure of the electromechanical activation of the heart, and is altered by disease states and arrhythmias.

Materials and Methods: A novel technique was used to assess fetal PEP and its relationship to other fetal systolic time intervals, RR interval, and gestational age (GA). 25 normal human fetuses between 19 and 38 weeks' gestation were studied using simultaneous pulsed Doppler ultrasound and fMCG. Correlations among PEP, ejection time, QRS width and RR interval were assessed using linear regression. **Results:** Across all subjects, PEP was found to correlate with GA ($R = 0.57$, $p < 0.0001$), QRS width ($R = 0.35$, $p = 0.026$), and RR interval ($R = 0.37$, $p = 0.018$). In individual sessions, PEP nega-

tively correlated beat-to-beat with the preceding RR interval.

Conclusion: PEP exhibits developmental trends that provide a better understanding of the normal development of the human fetal heart.

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Introduction

Electromechanical coupling is a fundamental and clinically important aspect of cardiac physiology. Electromechanical indices are altered by disease states, and provide a reliable, noninvasive means of assessing cardiac function [1, 2]. One of the most commonly investigated electromechanical indices is the pre-ejection period (PEP), which corresponds to the time from the onset of the QRS complex to the onset of systole, and is altered during cardiac remodeling. Assessment of PEP is often performed in conjunction with measurement of other systolic time intervals for detection of intra- and inter-ventricular conduction abnormalities. In particular, the ratio of PEP to ejection time (PEP/ET) has been proposed as a useful index of myocardial contractility [3].

Although electromechanical parameters are routinely evaluated in the neonate, child, and adult, electromechanics in the fetus, despite significant technological advances, is more challenging to assess. Nii et al. [4] evaluated tissue Doppler systolic parameters and found that the time from onset of atrial contraction to onset of isovolumic contraction correlated significantly better with fetal signal-averaged electrocardiogram (ECG) PR interval than did measures that incorporated the isovolumic contraction time. However, adequate fetal ECG could be obtained only 61% of the time.

The fetal PEP was studied in the 1970s and 1980s as a possible parameter of fetal condition [5–10]. It was suggested that PEP reflects both myocardial contractility and the loading conditions of the heart, and may be a useful indicator of fetal cardiac performance and hence of the condition of the fetus as a whole [5]. Organ et al. [9] found that PEP shortens with acute hypoxemia. However, during sustained and severe hypoxemia, PEP becomes prolonged. Murata et al. [10] showed a strong correlation between PEP prolongation and abnormalities in the perinatal course such as growth retardation, hypoglycemia, hypoxemia, and fetal death.

At the time of these studies, electromechanical assessment was based on the use of fetal ECG to register the onset of the QRS complex, and the fetal phonocardiogram or continuous-wave Doppler ultrasound to register valve motion; however, these techniques have since been surpassed. Fetal magnetocardiography (fMCG) provides higher signal quality than fetal electrocardiography, and more reliable beat-to-beat rhythm assessments at gestational ages over 20 weeks [11]. Pulsed Doppler has largely displaced continuous-wave Doppler for cardiac evaluation, and provides lower energy exposure and spatial selectivity. It is also notable that flow onset, rather than valve motion, is now the most commonly used means of defining the onset of ventricular ejection. While tissue Doppler has been used to measure fetal cardiac function, the technique has not been reliably validated in the human fetus against cardiac rhythm recordings, especially beat-to-beat recordings, and most echocardiographic equipment has only recently been adapted to provide high-resolution tissue Doppler tracings of the tiny fetal myocardial wall.

Although it is generally difficult to record the fMCG in conjunction with other techniques due to its susceptibility to electronic interference, the advent of portable, battery-operated ultrasound machines has recently allowed the fMCG and echo/Doppler ultrasound to be recorded simultaneously [12]. This study demonstrates the

application of this new methodology to the study of PEP and other systolic time intervals in normal human fetuses.

Materials and Methods

Twenty-five normal fetuses between 19 and 38 weeks' gestation (mean gestation = 29.8 ± 0.8 weeks) were studied in 45 sessions. Ten of the 25 fetuses were studied serially. All showed normal heart rate tracings and echocardiograms during their visits. Simultaneous fMCG and ultrasound could be acquired successfully in 41 of 45 sessions (91%). The other 4 sessions were excluded due to poor signal or technical complications (2 of these sessions were part of serial studies). The University of Wisconsin Institutional Review Board approved the protocol to study the patients and informed consent was obtained from each subject prior to the procedure.

A SonoSite TITAN (Bothwell, Wash., USA) portable ultrasound scanner equipped with a 60-mm broadband (2–5 MHz) curved array transducer was used by board-certified pediatric cardiologists (J.F.S., S.S.) for the acquisition of pulsed Doppler ultrasound. A 37-channel superconducting quantum interference device (SQUID-Magnes, 4D Neuroimaging, Inc., San Diego, Calif., USA) in a magnetically shielded room was used to record the fMCG. Sequences of pulsed Doppler ultrasound frames were captured and saved using a videotape recorder (Sony GV-D800 National Television System Committee, Japan). During each scan, the ultrasound transducer and SQUID (superconducting quantum interference device) were positioned on the maternal abdomen to optimize the detection of the fMCG while enabling echo/Doppler assessment of fetal cardiac function. In pulsed Doppler mode, the gate was positioned between the mitral valve and the aortic valve for inflow-outflow analysis and at the level of the aortic valve for valve clicks at an angle of $<30^\circ$. Time alignment of the Doppler and fMCG tracings was achieved by inputting a square-wave timing pulse into the ECG input of the ultrasound scanner and the fMCG data acquisition system, as described by Zhao et al. [12].

Due to interference from the ultrasound scanner, signal processing of the resulting fetal heart signals was essential. Interference from the ultrasound scanner was mainly due to large periodic interference at several discrete frequencies and large low frequency interference arising from the permanent magnetic moment of the transducer. We applied a mean square error filter technique $W = C_s C_n^{-1}$, where C_s is the covariance of the clean signal and C_n is the covariance in the presence of scanner interference. The clean signal was obtained by powering off the ultrasound machine during the last 30 s of data acquisition.

Measurements and Reproducibility

PEP was defined to be the interval from the beginning of the QRS complex to the time of flow onset and/or aortic valve opening (fig. 1). PEP could be precisely assessed using flow onset in 13 of 41 (32%) sessions and using valve clicks in 38 of 41 (93%) sessions. The PEP measurement method of Fleming et al. [13], which employs waveform averaging, was used for further precision of QRS onset (fig. 1). The average waveform of QRS beats was obtained from the fMCG during the final quiet 30 s of data acquisition. The QR interval was measured from the onset to the peak of

Fig. 1. **a** Simultaneous fMCG and ultrasound in subject 2 at 34 weeks. **b** Top: tracings of subject 4 at 31 weeks. Interval 1 is shown. Bottom: averaged waveform showing QR interval. PEP (per beat) = interval 1 + QR interval.

the averaged QRS complex. The intervals from the peaks of each QRS to the corresponding flow onsets and/or aortic valve openings are labeled in figure 1 as '1'. The QR interval was added to each of the intervals labeled '1', to obtain the PEP associated with each QRS. The mean PEP was computed for each session. This technique was less subjective since QRS peaks are more easily discerned, and signal averaging further reduces noise which may obscure QRS onset.

Ejection time was measured from flow onset or aortic valve opening to the end of the Doppler systolic velocity waveform or aortic valve closure. The RR interval was measured as the interval between the peaks of the QRS complexes.

Reproducibility

To assess interobserver variability, two different observers (N.A.M.B., J.F.S.) performed the same 50 PEP measurements using data from 10 sessions. The differences were analyzed using plots suggested by Bland and Altman [14]. To assess differences between PEP measurements derived from flow onsets versus aortic valve clicks, the same observer (J.F.S.) performed PEP measurements from 12 sessions in which both flow onsets and valve clicks were recorded. The differences were analyzed using a paired t test.

Statistical Analysis

For each session, the mean and the standard error of the mean of the systolic and cardiac intervals of interest were computed. Relationships among them were assessed using linear regression.

Fig. 2. A Bland-Altman plot for interobserver variability.

In addition, within each study, the beat-to-beat dependence of the parameters on the preceding RR interval, i.e. the RR interval preceding systole, was also assessed. A p value <0.05 was considered significant. All statistical analyses were performed using GraphPad Prism Version 3.02 for Windows (GraphPad Software, San Diego, Calif., USA).

Fig. 3. PEP (ms) vs. gestational age (weeks) – serial visits are connected. 95% prediction intervals are represented by dotted lines and trend lines predicted by Murata et al. [10] and Wolfson et al. [19] are shown.

Table 1. Parameters averaged across all 41 sessions

Parameter	Mean $\pm$ SEM	Correlation with PEP ¹	Correlation with gestation
Gestation, weeks	29.8 $\pm$ 0.8	n = 41, R = 0.57, p < 0.0001	–
PEP, ms	60.1 $\pm$ 1.1	–	n = 41, R = 0.57, p < 0.0001
PEP/ET	0.36 $\pm$ 0.01	n = 41, R = 0.9, p < 0.0001	n = 41, R = 0.63, p < 0.0001
QRS width, ms	44.6 $\pm$ 1.0	n = 41, R = 0.35, p = 0.026	n = 41, R = 0.39, p = 0.01
RR, ms	432 $\pm$ 3.7	n = 41, R = 0.37, p = 0.018	n = 41, R = 0.30, p = 0.055
Ejection time, ms	166 $\pm$ 1.5	n = 41, R = -0.04, p = 0.8 (NS)	n = 41, R = -0.24, p = 0.13 (NS)

¹ All correlations obtained using linear regression. NS = Correlation not significant.

Results

Reproducibility

The Bland-Altman plot is shown in figure 2 (2 SD = 8.4 ms). The bias (average difference between the PEP measurements of both observers) was -0.31 ms with a 95% confidence interval from -1.5 to 0.9 ms. These results show that the means between both observers did not differ significantly. The PEP measurements determined from valve clicks and from outflow onsets also were not significantly different. The mean PEPs obtained using

flow onsets versus valve clicks were 58.3 ± 1.9 and 58.6 ± 1.7 ms, respectively, and the standard deviations were ± 6.3 and ± 4.5 ms, respectively. (The standard error of mean is reported for mean values obtained across patients. The standard deviation is reported for beat-to-beat within-subject measurements.)

Correlations

Statistically significant correlations among the parameters in table 1 are plotted in figures 3–6. PEP values are reported for measurements involving valve

Fig. 4. a PEP/ET vs. gestational age. **b** Ejection time vs. gestation in 41 sessions of normal human fetuses.

clicks, except in three studies where outflow was obtained without clicks. PEP increased in 13 of 16 serial sessions.

On a beat-to-beat level, PEP correlated inversely with the preceding RR interval in 10 of 41 sessions (24%). The correlations were significant ($p < 0.05$) and the R values were -0.63 , -0.78 , -0.66 , -0.49 , -0.22 , -0.37 , -0.75 , -0.57 , -0.39 and -0.43 . PEP correlated positively with the pre-

ceding RR interval in 2 of 41 sessions (5%), where the subjects showed higher heart rates and/or reduced ejection time. The correlations were significant and the R values were 0.49 and 0.5 . A positive correlation between beat-to-beat ejection time and RR was also seen in 11 of 41 sessions (27%). The R values were 0.65 , 0.53 , 0.73 , 0.58 , 0.4 , 0.6 , 0.76 , 0.48 , 0.77 , 0.45 and 0.8 .

Fig. 5. **a** PEP (ms) vs. QRS (ms). **b** PEP (ms) vs. RR (ms). **c** QRS (ms) vs. gestational age (weeks). **d** RR (ms) vs. gestational age (weeks) in 41 sessions of normal human fetuses.

Comments

This study represents the first attempt to assess human fetal systolic electromechanics using simultaneous fMCG and pulsed Doppler ultrasound. fMCG is a promising new technique for assessing fetal rhythm [15, 16]; however, no prior studies have utilized fMCG to evaluate human fetal electromechanical physiology, despite the fact that these cardiac parameters are routinely evaluated in the neonate, child, and adult with heart disease. The high signal-to-noise ratio of fMCG allowed us to study subjects over a much wider range of gestational ages, compared to most prior studies. The high precision afforded by pulsed Doppler ultrasound in combination with fMCG allowed us to obtain serial measurements with good session-to-session consistency and in many cases to resolve beat-to-beat correlations.

Although the mean PEP obtained from flow onset and valve clicks were in excellent agreement, valve clicks can be detected with greater temporal precision than flow ve-

locity onset, evidenced by standard deviations of 4.5 and 6.3 ms, respectively. Valve clicks, therefore, may provide more precise estimates of mechanical, as well as electromechanical, intervals. This is notable because typically valve clicks are not utilized in routine clinical echocardiographic scanning nor in tissue Doppler.

Our measurement of PEP/ET (0.36 ± 0.01) in the fetus is in excellent agreement with that of the neonate and adult. In the adult, this ratio was found to be 0.345 by Garrard et al. [17], and in newborns a value of 0.350 has been calculated [18]. The correlation between this ratio and gestational age is also stronger than that of PEP and gestational age. According to Levy et al. [18], PEP/ET has been found to be an excellent index of function by virtue of its correlation with ejection fraction and its inherent characteristics of partially nullifying heart rate variability; thus it may have greater clinical utility than PEP alone.

Positive correlations between PEP and gestational age, and PEP and QRS width, were seen here, consistent with

Fig. 6. **a** Beat-to-beat PEP (ms) vs. beat-to-beat RR (ms) in subject 16 at 26 weeks. **b** Beat-to-beat ejection time (ms) vs. beat-to-beat RR (ms) in subject 4 at 28 weeks.

several earlier studies [9, 10, 19]. These trends were apparent within individual subjects, demonstrating the precision of our measurements. A proposed explanation for the increasing PEP with gestational age is the increase in myocardial mass and the concomitant prolongation of ventricular depolarization (fig. 5a, c) [9].

While most systolic time intervals increase with gestational age, it is notable that ejection time did not increase and in fact showed a decrease that was not statistically significant (fig. 4b). In particular, while onset of ventricular ejection is progressively delayed, reflected in the lengthening of PEP, ejection time stays the same or decreases, comprising a smaller fraction of the cardiac cycle, despite the fact that stroke volume continually increases during gestation.

Across sessions, PEP was found to correlate positively with RR [7, 9]. On a beat-to-beat basis, however, an inverse relationship between PEP and the preceding RR was seen. The observed beat-to-beat correlations between PEP and RR, and between ejection time and RR (fig. 6), are compatible with the influence of ventricular filling on stroke volume and contractility predicted by the Frank-Starling mechanism. Although stroke volume was not measured in this study, it has been shown to correlate positively with ejection time [20, 21]. Enhanced contractility also implies that ventricular pressure develops more rapidly, implying a negative correlation between PEP and RR interval, as observed here. The positive correlation between PEP and RR, seen in 2 subjects with higher heart rates and/or reduced ejection time, may have reflected a change in autonomic or blood flow state.

Study of fetuses with abnormal heart rates, arrhythmia, and ion-channel defects are currently underway. We are optimistic that assessment of fetal systolic electromechanical function via fMCG and echocardiography will provide a better understanding of the underlying processes that lead to poor systolic cardiac function and heart failure in the at-risk human fetus.

Acknowledgements

The authors would like to acknowledge Zhen Ji, PhD, William J. Lutter, PhD, Gretchen Eckstein, RN, Bettina F. Cuneo, MD, Suhong Yu, MS, and Carli Peters for their help with patient recruitment, coding, signal processing and data analysis. Research was supported by NIH R01HL63174, NIH R21HD049022 and a grant from the Advancing a Healthier Wisconsin Dean's Fund.

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