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Magnetocardiography for Fetal Arrhythmias

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The failing adult heart is known to revert to fetal patterns of contractile protein expression during pathologic remodeling, yet very little is known about the electrophysiology or electromechanics of the living human fetal heart during normal prenatal development or during stress. This owes largely to the inability to easily record the fetal electrocardiogram (fECG). While fetal echocardiography provides mechanical assessment of heart rhythm, it does not provide details of the electrophysiology of the fetal heart. These details, along with the genetics of fetal and neonatal demise, are emerging as potential leading factors in defining prenatal sudden death risk. While echocardiography has been utilized extensively for 20 years in prenatal high risk screening, it has not had the desired outcome in reducing overall fetal sudden death to the extent that sudden death has been reduced in the infant, child, and adult. Late gestation unexplained fetal death costs 26,000 fetal lives yearly in the United States and over 4 million fetal lives each year worldwide. Fetal Magnetocardiography (fMCG) opens a new window in fetal healthcare assessment. Fetal cardiac deaths may be preventable because the diseases that lead to these deaths are often treatable, especially if the sophisticated modern ICU monitoring and management techniques could be translated to the field of prenatal care.

Fetal Magnetocardiography

Fetal magnetocardiography (fMCG) is a noninvasive technique for recording magnetic fields generated by the electrical activity of the fetal heart. Unlike fetal MRI, fMCG does not emit magnetic fields or energy. It is a passive and safe recording technique, analogous to the ECG, utilizing the extremely high sensitivity Superconducting Quantum Interference Device (SQUID) sensors. These sensors amplify signals that are naturally occurring and extremely weak—on the order of 10^{-12} tesla, much smaller than environmental magnetic interference.

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Enhancing the signal-to-noise ratio is best achieved using a magnetically shielded room. These rooms are constructed from a nickel alloy and cost in excess of \$350,000. As a result, this promising technology has been largely confined to physics labs around the world. A Catch 22 situation exists, in which hospitals fail to invest in this promising technology because of the inability to recoup their investment through billings, and laboratories investigating fMCG can not meet the “multi-institutional” requirement to establish a CPT code. Thus, the vast field of Fetal Electrophysiology remains hidden at the present time.

While we have begun to understand the fetal cardiac conditions associated with fetal heart rates outside the normal range, the majority of electrophysiologic disease at all ages is seen primarily when the heart rate does not deviate substantially or frequently from normal. This group of fetal patients has not been studied extensively during sinus rhythm because obstetricians do not often suspect electrophysiologic disease in the absence of arrhythmia. Hidden electrophysiologic disease leaves markers such as QT prolongation or bundle branch block - abnormalities in depolarization or repolarization - evident only through non-invasive electrophysiologic assessment. To understand the magnitude of electrophysiologic disease in the fetus, it will be necessary to evaluate not just those fetuses with arrhythmias, but also those fetuses with conditions that in the infant, child, or adult, would be likely to cause electrophysiologic changes. Such conditions would include drug or medication exposure, myocarditis, ischemia, cardiomyopathy, congestive heart failure (hydrops fetalis), structural cardiac defects, and many more.

Simultaneous fMCG and Echo/Doppler can provide in-utero assessment of electromechanical as well as cardiac functioning; complementing the ability of fMCG to assess beat-to-beat variability and waveform information.⁽¹⁾ We are utilizing this novel technique to serially evaluate high risk fetuses transitioning into infancy and have developed new methods of cardiac assessment based on the ventricular pre-ejection period (time from onset of QRS to onset of aortic systolic Doppler velocity).

Fetal Electrocardiography

Fetal ECG, while less expensive than fMCG, has failed to become widely adopted because the recording techniques are not widely appreciated by Obstetricians as contributing to prenatal care over echocardiography, and because manufactures of such equipment have not submitted or attained FDA approval in this country for their custom equipment. In addition, the vernix caseosa surrounds the fetus during the latter second trimester and most of the third trimester. The poor electrical conductivity of the vernix is believed to account for the typically low fECG amplitude, resulting in the need to perform signal averaging and precluding beat-to-beat analysis of many arrhythmias. This makes real-time assessment of arrhythmias difficult at a time when fetal arrhythmias are most prevalent.

Fetal Sudden Death and Long QT Syndrome

A number of recent excellent reviews have documented the potential that 10% or more of fetal and neonatal sudden death may be the result of genetic or acquired ion channelopathies. If indeed this is the case, accurate prenatal diagnostic techniques, in addition to universal newborn ECG screening, may help identify the large pool of potentially at-risk fetuses and infants with these conditions. If treatments can be found to be effective in prolonging the lives of such fetuses and infants, then public health measures to promote detection of electrophysiologic diseases are in order. This will likely require that the pharmaceutical industry develop more reliable time-released formulations of beta blocker medications for infants, and that they support pharmacokinetics studies of new more sustained formulations of the beta blocker medications used in infants and children. Since many of these drugs are no longer under patent protection, this would be best achieved through drug industry funding of clinical trials lead by

industry-neutral research advocates such as the National Institutes of Health, American Heart Association, or the Pediatrics and Congenital Electrophysiology (PACES) section of the Heart Rhythm Society.

Fetal MCG has been used to detect repolarization abnormalities in normal and high risk fetuses. (2) T-wave alternans and prolonged QT-intervals were demonstrated in association with adverse outcomes. Conditions associated with T wave alternans in utero were ventricular tachycardia, congenital AV block, Long QT Syndrome, and cardiomyopathy. Examples of fetal repolarization abnormalities are shown in Figure 1.

Congenital Atrioventricular Block (CAVB)

Recently, we reported that isolated CAVB is electrophysiologically intricate and dynamic. Heart rate variability and ventricular reactivity can be lost over the course of prenatal development. Thirty percent of fetuses in the early stages of isoimmune-mediated AV block demonstrated junctional or ventricular tachycardia and frequent ventricular ectopy. (Figure 2) These findings portended a worse outcome, likely reflecting the severity of the inflammatory response. (3) Further, echocardiography did not generally detect such severe findings prior to fMCG. Added to this limitation of fetal echocardiography were the recent results of the PRIDE Study. According to Friedman and colleagues, prolongation of mechanical Doppler PR interval did not precede more advanced congenital AV Block and cannot be considered as a predictor of early signs of heart block in SSA or SSB positive pregnancies. However, atrial echo density and moderate to severe tricuspid regurgitation were signs of injury leading to advanced AV block. (4) These findings thus demonstrate the need to have advanced and integrated imaging modalities for fetuses at risk of developing congenital AV block.

Fetal Supraventricular Tachycardia (SVT)

Patterns of initiation and termination of SVT are more complex than previously appreciated. Understanding the electrophysiologic mechanisms of SVT can guide antiarrhythmic drug therapy. (5) FMCG has been underutilized to date in the ongoing monitoring of SVT treatments, where antiarrhythmic therapies have been shown to create significant electro-magnetocardiographic abnormalities related to prolonged drug accumulation, amniotic fluid re-absorption, and adverse placental findings in association with fetal interventions and high-risk pregnancy.

Fetal Well-being

Fetal magnetocardiography has the potential to provide detailed beat-to-beat fetal heart rate analysis both in normal rhythm as well as in fetal arrhythmias. This has been useful to elucidate mechanisms of arrhythmias, and can be a useful adjunct to electrophysiologic diagnosis. Fetal movement is assessed by amplitude changes in the fMCG, via a technique known as actocardiography. While actocardiography and fetal heart rate monitoring have not been widely utilized by electrophysiologists, fetal heart rate variability reflects the developmental state of the fetus and the heart-CNS interactions. These interactions appear to change in response to stress.

The Future of Fetal Electrophysiology

The means by which biomedical technologies such as fMCG and fECG unfold for the pregnant female and the human fetus warrants comment. Efforts to bridge the critical care continuum from the fetal period into infancy for pregnant women nearing delivery must be studied. In conjunction with bringing forward new technologies for fetal rhythm diagnosis, advanced care strategies are essential. This will likely entail a new field of high-risk obstetrical

electrophysiology. Just as primary care medical fields have given rise to subspecialty fields, where expertise exists for specialized cardiac bioinstrumentation, cardiac procedures, and complex cardiac care, the same will need to happen as Fetal Electrophysiology expands beyond its present state of infancy. A question remains as to whether high-risk obstetricians with training in advanced cardiology and electrophysiology will be able to acquire the skills needed to manage arrhythmia patients independently, or whether perinatal pediatric electrophysiologists with comprehensive training in fetal and neonatal electrophysiology will emerge to be an integral part of the care of these pregnant patients and their fetuses. Enhancing clinical research in the area of fetal and neonatal electrophysiology and intensive care will be an essential part of developing these strategies.

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Abbreviations

AV, Atrioventricular Block
 CAVB, Congenital Atrioventricular Block
 CNS, Central Nervous System
 CPT, Current Procedural Technology
 ECG, Electrocardiogram
 fECG, Fetal Electrocardiogram
 fMCG, Fetal Magnetocardiogram
 ICU, Intensive Care Unit
 LQTS, Long QT Syndrome
 MRI, Magnetic Resonance Imaging
 PRIDE, PR Interval and Dexamethasone Evaluation
 SQUID, Superconducting Quantum Interference Device

Figure 1. Fetal Cardiac Conduction and Repolarization by fMCG

Representative averaged fetal magnetocardiographic waveforms depicting variation of QTc with heart rate. (a) Normal subject at 39 weeks' gestation, (b) normal subject at 37 weeks' gestation, (c) subject at 27 weeks' gestation who had VT at 25 weeks' gestation, (d) subject with SVT at 27 weeks' gestation, (e) subject with SVT at 31 weeks' gestation, (f) same subject as in (c) during VT at 25 weeks' gestation, (g) subject with complete AVB (CAVB) at 30 weeks' gestation, (h) subject with complete AVB (CAVB) at 25 weeks' gestation and (i) subject with blocked premature atrial contractions (PACs) at 20 weeks' gestation. Waveforms taken from channel with largest signal amplitude. Amplitudes given in units of femtotesla (femtotesla = 10^{-15} tesla). Used with permission, American Journal of Cardiology. (2)

Figure 2. Ectopy and Tachycardia in 3° Fetal AVB

Rhythm strips from third-degree (3°) atrioventricular block (AVB) fetuses showing: (a) ventricular bigeminy with wide ectopic complexes; (b and c) episodes of nonsustained VT in fetuses #4 and #3, respectively; and (d) junctional ectopic tachycardia in fetus #14 with highly irregular ventricular rhythm at 19 weeks' gestation. Used with permission, *Journal of the American College of Cardiology*. (3)