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Magnetocardiography in the evaluation of fetuses at risk for sudden cardiac death before birth

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Abstract

Background—We hypothesized that fetuses at risk for sudden death may have abnormal conduction or depolarization, ischemia, or abnormal heart rate variability (HRV) detectable by magnetocardiography.

Methods—Using a 37-channel biomagnetometer, we evaluated 3 groups of fetuses at risk for sudden death: group 1, critical aortic stenosis (AS); group 2, arrhythmias; and group 3, heart failure and in utero demise. Five to 10 recordings of 10-minute duration were recorded, and signal was averaged to determine rhythm, conduction intervals, HRV, and T-wave morphology.

Results—In group 1, 2 of 3 had atrial and ventricular strain patterns. In (n = 53) group 2, 15% had prolonged QTc and 17% had T-wave alternans (TWA). Of 23 group 2 fetuses with atrioventricular block, 74% had ventricular ectopy, 21% had junctional ectopic tachycardia, and 29% had ventricular tachycardia. Group 3 (n = 2) had abnormal HRV and TWA.

Conclusion—Repolarization abnormalities, unexpected arrhythmias, and abnormal HRV suggest an arrhythmogenic mechanism for “sudden cardiac death before birth.”

Keywords

Fetus; Arrhythmia; Echocardiography; Magnetocardiography; Congenital heart disease

Introduction

During a given lifetime, the highest likelihood of death is during the 40 weeks preceding birth. The mortality of human fetuses more than 20 weeks of gestation ranges from 6 per 1000 individuals per year for all races to 12/1000 per year for African Americans.¹ Fetal losses increase with advancing maternal age.² Whereas some fetal demise is attributable to uteroplacental insufficiency, fetal defects, or chromosomal anomalies, the deaths of many fetuses are unexplained.

Even the exact cause of death in fetuses at the greatest risk of sudden death before birth—those with arrhythmia, structural heart defects, and severe heart failure—is not known. Many of these fetuses have an abnormal electrophysiologic substrate, such as repolarization

abnormalities, or conduction system disease that is well known in newborn and infant. We speculate that many such fetuses succumb to the same arrhythmias that occur after birth. Thus, the fetus with complete atrioventricular (AV) block may die of ventricular tachycardia (VT) or ventricular arrest, the fetus with Wolff-Parkinson-White syndrome may succumb to atrial fibrillation that has degenerated to ventricular fibrillation, or in the fetus with severe heart failure and structural cardiac defects, the combination may lead to ischemia and ventricular fibrillation.³⁻⁶ Alternatively, the conditions unique to pregnancy, such as mild hypomagnesemia, or the hormonal effects may alter cardiac ion channels in these high-risk fetuses, adding to the a priori risk for abnormal conduction or repolarization.

Using magnetocardiography—a noninvasive technique that allows beat-to-beat analysis over many hours of fetal cardiac activity—it is possible to evaluate the electrophysiology of fetuses at the highest risk for sudden death. We hypothesized that the fetal magnetocardiography (fMCG) of such fetuses would manifest unsuspected conduction system disease or arrhythmia, repolarization abnormalities, or abnormal heart rate (HR) variability. This report summarizes our data, some of which have previously been published.⁷⁻⁹

Materials and methods

Patient population

We reviewed the clinical records, echocardiograms, and magnetocardiograms of all fetuses referred to the Biomagnetism Laboratory at the University of Wisconsin-Madison (Madison, WI) between 1996 and 2007. Subjects were divided into 3 groups, based on the indication for magnetocardiography (Table 1). Fetuses in group 1 had aortic stenosis; fetuses in group 2 had arrhythmias—1:1 reciprocating supraventricular tachycardia [SVT], ventricular tachycardia [VT], sinus bradycardia, nonconducted premature atrial contractions, or AV block. Group 3 fetuses were in severe heart failure and died within 2 weeks after magnetocardiography.

The initial diagnosis of structural cardiac defect, arrhythmia, or heart failure was made by the referring pediatric cardiologist using 2-dimensional, pulsed and color Doppler, and M-mode echocardiography, as previously described.¹⁰⁻¹² The severity of heart failure was graded by the cardiovascular profile score (CVPS), an echo Doppler assessment of heart size, venous and arterial flow patterns, hydrops, and AV valve insufficiency.¹³ The lower the CVPS, the more severe was the heart failure.

Fetuses were monitored by frequent, usually weekly, echocardiography and obstetrical ultrasound until delivery or in utero demise.

In utero treatment

Fetuses with isolated ectopy were merely observed closely and did not receive antiarrhythmic medications. The pharmacologic treatment given to those with sustained arrhythmias are summarized in Table 2. The 3 fetuses with critical aortic stenosis (group 1) underwent in utero balloon valvuloplasty, as previously described.¹⁴ Of the 3 fetuses, 2 were evaluated by fMCG both before and after the in utero procedure, and the third fetus was studied only afterward. Two were treated with transplacental digoxin from the time after the procedure until delivery.

Magnetocardiography

Recordings were made using a 37-channel biomagnetometer (MagneS 4D, Neuro-Imaging Inc, San Diego, CA) in a magnetically shielded room (Lindren RF Enclosures Inc, Glendale

Heights, IL), as previously described.¹⁵ Typically, 5 to 10 recordings each of 10-minute duration were obtained. Maternal interference was removed using previously published filtering methods.¹⁵ Averaged waveforms were computed from 20 to 50 consecutive QRS complexes.

Ventricular and atrial arrhythmias were diagnosed from the rhythm tracings. Ventricular tachycardia and junctional ectopic tachycardia (JET) were defined as paroxysms of a wide or narrow complex tachycardia exceeding baseline ventricular rate. The QRS duration was wide if it was more than the 95% confidence interval for gestation as previously defined.¹⁵ The QTc was computed using Bazett's formula: $QTc = QT/RR^{0.5}$. We examined the rhythm tracings for macroscopic T-wave alternans (TWA) and detected microscopic TWA by comparing waveforms derived from odd- and even-numbered beats.¹⁶ We assessed the minimum to maximum ventricular fetal heart rate (FHR) range and the presence or absence of atrial and ventricular FHR variability, defined as beat-to-beat FHR variations more than 2 beats per minute root-mean-square.

Statistical analysis

QTc duration in groups 1 and 2 was compared with the QTc in 93 normal fetuses.⁸ QT interval and QTc were plotted vs gestational age and HR and were analyzed using linear regression analysis.⁸

Results

Clinical outcome

Outcomes are presented in Table 3.

Fetuses in group 3 died shortly after the fMCG (at 34 and 23 weeks) in severe heart failure with CVPS of 5/10. One had severe dilated cardiomyopathy and the other critical aortic stenosis with tricuspid valve dysplasia and severe tricuspid valve insufficiency. All fetuses in groups 1 and 2 were born alive. After delivery, infants were observed in the neonatal intensive care unit and received treatment based on the recommendations of the referring cardiologist. Of group 1 patients, one infant with critical aortic stenosis underwent successful aortic balloon valvuloplasty in the cardiac catheterization laboratory within 48 hours after birth, one was evaluated for surgery, and one died before surgery from an intraventricular hemorrhage. Infants in group 2 received postnatal antiarrhythmic treatment; those with AV block were paced if they met class 1 indications, as outlined in the present pacing recommendations for children.¹⁷ The infant with congenital long QT syndrome (LQTS) was treated with high-dose propranolol and mexiletine, but despite multiple ambulatory electrocardiograms showing no VT or ventricular ectopy, died suddenly at 4 months of age.

Heart rate variability in group 2 fetuses

Atrial and ventricular ectopy were present in 29% and 74% of fetuses with 3° AV block, respectively. Non-sustained VT was seen in 2 fetuses, one of which also had JET during the recording. Five fetuses at 19 to 29 weeks of gestation had JET and sporadic ventricular ectopy, which improved as gestation progressed. Thus, JET or VT was seen in 30% of fetuses with 3° AV block. Ventricular tachycardia was seen only in fetuses with isoimmune 3° AV block.

Based on ventricular accelerations, 2 distinct types of FHR patterns could be discerned in fetuses with AV block. A reactive pattern (Fig. 1A) was seen in fetuses with isoimmune 3° AV block and ventricular rates more than 56 beats per minute. Of 14 fetuses with a reactive

FHR pattern on their last fMCG, only 2 required neonatal pacing. Alternatively, a nonreactive pattern (Fig. 1B) was seen with isoimmune 3° AV block and FHR less than 56 beats per minute, as well as in all but one fetus with structural cardiac defects. Fetuses with a nonreactive HR pattern all required neonatal pacing.

One of the fetuses with isoimmune 2° AV block was found to have AV conduction only across an accessory connection when first studied (Fig. 2A).¹⁸ After 2 weeks of treatment with transplacental dexamethasone, conduction across the AV node, not seen on the first fMCG, was demonstrated (Fig. 2B). Conduction across the accessory connection was not seen again before or after birth.

QTc prolongation, TWA, and strain patterns in group 1, 2, and 3 fetuses

Repolarization abnormalities are summarized in Table 1.

The QTc of fetuses in group 2 was distinctly longer than the QTc of normal fetuses, especially at the extremes of heart rate.⁸

Before in utero valvuloplasty, both fetuses in group 1 with critical aortic stenosis demonstrated atrial and ventricular strain patterns that had resolved on postprocedure fMCG. In addition, QRS and P-wave amplitudes changed after the procedure. T-wave alternans were noted both before and after the procedure despite successfully relieving the aortic valve stenosis.

The fetus in group 3 with dilated cardiomyopathy demonstrated TWA and ischemia immediately before a deep and prolonged HR deceleration (Fig. 3). Surprisingly, HR variability was normal. The other fetus in group 3, with critical aortic stenosis and tricuspid valve dysplasia, showed no repolarization abnormalities but had intermittent 2° AV block and reduced HR variability.

Discussion

The data from this study suggest that some fetuses with SVT, VT, or structural cardiac defects have repolarization abnormalities, unsuspected arrhythmias, and abnormal HR variability. These fetuses frequently have a suboptimal outcome such as neonatal pacing, in the cases of AV block; infant death from torsade des pointes, in congenital LQTS; and in utero demise, in structural or functional cardiac defects accompanied by heart failure.

The hormonal state of pregnancy is known to affect the electrophysiologic substrate. High estrogen levels stabilize cardiac ion channels, and as a result, mothers with LQTS who have less frequent life-threatening events during pregnancy than at any other time.¹⁹ In contrast, fetuses with LQTS can present with life-threatening torsade des pointes.^{20,21} This suggests that estrogen may not be stabilizing the ion channels in the immature heart to the same extent as in the adult heart.

Certain proteins may act to damage the electrophysiologic substrate. For example, Sjogren's antibodies cause inflammation of the conduction system but can also damage the myocardium, resulting in endocardiofibroelastosis, which is indistinguishable echocardiographically from the myocardial damage resulting from critical aortic stenosis. That 2 diverse pathologic processes result in similar electrophysiologic abnormalities seen on fMCG supports a common end process. This process appears echocardiographically to improve as the myocardium matures.

It may also be that hemodynamic changes during sustained arrhythmias or heart failure result in abnormal oxygen delivery to the immature myocardium. Anoxia in the chick

embryo results in a progressive series of arrhythmias—tachycardia, followed by bradycardia, atrial ectopy, followed by progressive AV block. During reoxygenation, ventricular escape beats and Wenckebach periodicity are observed, after which normal conduction is established.²² Mitochondrial and nuclear swelling, which was noted during anoxia, recovered completely after reoxygenation, as did cardiac function, in all but the oldest chick embryos (HH stage 27).²³ In the human fetus, both the timing and the extent of hypoxia may affect the electrophysiologic substrate differently, especially in the fetus with underlying cardiac abnormalities.

Magnetocardiography was instrumental in the clinical management of the patients presented in this report. Prenatally, an accurate diagnosis of VT or SVT guided the choice of antiarrhythmic therapy and prevented treatment with a proarrhythmic agent. In the case of congenital LQTS, medications that further prolong the QT interval, such as amiodarone and erythromycin, were avoided. Postnatal pacing was anticipated in those fetuses with AV block and reduced HR variability and reactivity. Finally, fMCG, although not predictive of outcome, aided greatly in parental counseling for these high-risk pregnancies.

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Fig. 1. Changes in HR and variability pattern in one fetus with isoimmune AV block. Each line is one RR interval. A, HR over time at 28 weeks of gestation. Normal pattern of HR variability —HRs range from 63 to 90 beats per minute. B, HR over time of same fetus at 34 weeks of gestation. Not only has the HR fallen dramatically, but there is also virtual absence of variability.

A **B** **Fig. 2.**

Fetus with isoimmune 2° AV block at 32 weeks. A, Before transplacental treatment with dexamethasone, the fMCG rhythm shows AV conduction only through an accessory connection and not through the AV node. B, Two weeks later, after dexamethasone therapy, the rhythm is still 2° AV block, but AV conduction is through the AV node, not the accessory connection. Arrows indicate P waves.

Fig. 3. Rhythm strips of the fetus with cardiomyopathy before in utero demise. A, Ischemia (ST-segment elevation in first QRS complex) before a prolonged deceleration in HR. B, TWA during sinus rhythm.

Table 1

Diagnosis and outcome of fetuses with repolarization abnormalities

Diagnosis (n)	Findings	QTc $\pm$ SD (ms)	Outcome
Dilated cardiomyopathy (1)	TWA	447	In utero demise
Critical aortic stenosis (2)	TWA		In utero valvuloplasty, live birth, and neonatal valvuloplasty
Critical aortic stenosis and tricuspid valve dysplasia (1)	Minimal HR variability; 2° AV block		In utero demise
Sinus bradycardia (3)	No TWA; HR, 104 ± 8 beats per minute	530 ± 17	Live births
LQTS (1)	TWA, torsade, 2° AV block, sinus bradycardia	690	Live birth, sudden death (4 mo)
3° AV block (2)	TWA; HR, <60 beats per minute; minimal HR variability	692 ± 42	Live birth, neonatal pacing
3° AV block (15)	No TWA; HR, 64 ± 9 beats per minute	557 ± 50	Live birth
SVT (1)	TWA	390	Live birth
VT (2)	TWA	490 ± 12	Live births
Blocked atrial bigeminy (4)	No TWA	525 ± 21	Live births

Table 2

In utero treatment of sustained arrhythmia

Arrhythmia	Rx, No hydrops	Rx, Hydrops	FHR <56 beats per minute
Atrial flutter ^a	TP digoxin; TP digoxin + amiodarone	TP + direct digoxin; + amiodarone	
Atrial flutter ^b	Sotalol	Sotalol	
SVT	TP digoxin; TP digoxin + amiodarone	TP + direct digoxin; + amiodarone	
VT ^c	IV lidocaine + mexiletine	IV lidocaine + mexiletine	
VT	Amiodarone	Amiodarone	
Isoimmune 1°, 2°, or 3° AV block	Dexamethasone	Dexamethasone + terbutaline	Dexamethasone + terbutaline
AV block + CHD ^d		Terbutaline	Terbutaline

TP indicates transplacental; direct, intramuscular injection into the fetal thigh or buttock.

^aPresenting before 2000.

^bPresenting after 2000.

^cVentricular tachycardia associated with long QT syndrome.

^dCongenital heart disease, consisting either of ventricular inversion with l-transposition of the great vessels or the complex structural defects associated with left atrial isomerism.

Table 3

Treatment and outcome of fetuses in the study population

Diagnosis (n)	Treatment	Outcome (n)
Group 1 (3)		
Critical aortic stenosis	Digoxin	Alive and well
Group 2 (53)		
SVT (14)	Digoxin + amiodarone	Alive and well
VT (3)	Amiodarone; lidocaine *	Death at 6 mo (1) *
Sinus bradycardia (4)	None	Alive and well
Nonconducted PAC (4)	None	Alive and well
Isoimmune AV block (21)	Dexamethasone	
2° AV block (5)	Dexamethasone	Alive and well; 3° AV block (2)
3° AV block (16)	Dex or Dex + terbutaline **	Alive and well; PM (14)
AV block with CHD (9)		
3° with left atrial isomerism (7)	Terbutaline **	Neonatal death (6)
2° with L-transposition (1)	None	Alive and well, 2° AV block
3° with L-transposition (1)	Terbutaline **	Alive and well, PM
Group 3 (2)		
Dilated cardiomyopathy (1)	None	In utero demise
Critical AS and tricuspid dysplasia	Digoxin + terbutaline	In utero demise

PAC indicates premature atrial contractions; Dex, dexamethasone; CHD, coronary heart disease; PM, pacemaker; L-transposition, levo transposition; AS, aortic stenosis.

* Lidocaine was used in one fetus with torsade des pointes and congenital LQTS.

** Terbutaline used if ventricular rate was less than 56 beats per minute.