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Arrhythmia Phenotype during Fetal Life Suggests LQTS Genotype: Risk Stratification of Perinatal Long QT Syndrome

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Abstract

Background—Fetal arrhythmias characteristic of long QT syndrome (LQTS) include torsades de pointes (TdP) and/or 2° atrioventricular block (AVB), but sinus bradycardia, defined as fetal heart rate <3% for gestational age, is most common. We hypothesized that prenatal rhythm phenotype might predict LQTS genotype and facilitate improved risk stratification and management.

Method and Results—Records of subjects exhibiting LQTS fetal arrhythmias were reviewed. Fetal echocardiograms, neonatal ECG, and genetic testing were evaluated. We studied 43 subjects exhibiting fetal LQTS arrhythmias: TdP ± 2° AVB (Group 1, n=7), isolated 2° AVB (Group 2, n=4) and sinus bradycardia (Group 3, n=32). Mutations in known LQTS genes were found in 95% of subjects tested. SCN5A mutations occurred in 71% of Group 1 while 91% of subjects with KCNQ1 mutations were in Group 3. Small numbers of subjects with KCNH2 mutations (n=4) were scattered in all 3 groups. Age at presentation did not differ among groups, and most subjects (n=42) were live born with gestational ages of 37.5±2.8 wks (mean±SD). However, those with TdP were typically delivered earlier. Prenatal treatment in Group 1 terminated (n=2) or improved

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(n=4) TdP. The neonatal QTc (mean±SE) of Group 1 (664.7±24.9) was longer than neonatal QTc in both Group 2 (491.2±27.6, p=0.004) and Group 3 (483.1±13.7, p<0.001). Despite medical and pacemaker therapy, postnatal cardiac arrest (n=4) or sudden death (n=1) was common among subjects with fetal/neonatal TdP.

Conclusions—Rhythm phenotypes of fetal LQTS have genotype-suggestive features which, along with QTc duration, may risk stratify perinatal management.

Keywords

long QT syndrome; fetal; arrhythmia; torsade de pointes; atrioventricular block; sinus bradycardia

Introduction

Although congenital long QT syndrome (LQTS) may be as common as 1 in 2,500 individuals, findings during fetal life have been reported in fewer than 100 cases. Sinus bradycardia is the most common rhythm manifestation of fetal LQTS but may go unrecognized [1]. Torsades de pointes (TdP) and/or unexplained 2° atrioventricular block (AVB) are the complex, signature fetal LQTS rhythms, but have been reported in only about 25% of fetal LQTS cases. In some cases, the fetal LQTS cardiac arrhythmias may be of short duration and clinically insignificant in utero, while in other cases, they may be prolonged and result in severe heart failure leading to premature delivery or fetal demise [2-8].

In most cases, genetic studies in fetal LQTS subjects have identified mutations in known LQTS-susceptibility genes. Yet, little is known of the genotype-phenotype characteristics of fetal LQTS, that is, do specific genotypes predict clinical severity of arrhythmia phenotype? Nor is the extent to which genotype-phenotype characteristics are age dependent, known, i.e. does the same genotype have a different clinical phenotype in prenatal life compared to postnatal life? We hypothesized that the pre- and postnatal clinical profile of subjects with fetal LQTS arrhythmias might be genotype specific, which in turn could be used to risk stratify patients and improve their perinatal care.

Methods

Study Cohort

The study cohort was derived from a fetal cardiac database as previously described [1]. Fetuses with LQTS were identified because of a family history of LQTS and/or because of a fetal arrhythmia characteristic of LQTS, i.e. sinus bradycardia (fetal heart rate ≤ 3rd percentile for gestational age) [1], 2° AVB (in the absence of maternal Sjögren's antibodies), or ventricular tachycardia with an irregular R-R interval confirmed to be TdP either by fetal magnetocardiography or postnatal ECG. Pre- and postnatal therapy, indications for delivery, and gestational age at delivery were reviewed from the medical record. Long QT syndrome was confirmed by postnatal electrocardiogram (ECG) and genetic testing. The protocol was approved by Institutional Review Boards.

Prenatal Evaluation

Prenatal assessment included indication for evaluation (family history of LQTS or fetal arrhythmia), gestational age at which the LQTS rhythm abnormality was noted, and characteristics of fetal heart rhythm. No fetus underwent prenatal genetic testing. The fetal echocardiogram, used for rhythm surveillance, generally lasted between 15 and 30 minutes. Fetal heart rate was determined by averaging 5 consecutive cardiac cycles measured by Doppler or M-Mode during fetal quiescence. Sinus bradycardia was defined as 1:1 AV conduction, normal mechanical PR interval and rate < 3rd % for gestational age [1]. Detection of non-sustained, irregular tachycardia with AV dissociation, i.e. atrial rate slower than ventricular rate, led to a diagnosis of ventricular tachycardia, presumptively TdP. Second degree AVB was recognized when some atrial contractions did not result in a ventricular contraction, and a regular atrial rate exceeded the ventricular rate.

Postnatal Evaluation

Postnatal ECGs were performed on all infants; the heart rate corrected QT interval (QTc) was calculated based on Bazett's formula. Mutation analysis of the 3 canonical LQTS-susceptibility genes and the 9 or 10 minor genes (depending on year of testing) was performed using commercially available testing (Familion, Transgenomic Inc., New Haven, CT; and GeneDx, Gaithersburg, MD). One subject with negative commercial tests participated in a genetic research study [9].

Statistical Analysis

Means are reported with standard deviations (SD) when describing the variability of individual subjects, but means are reported with standard errors (SE) when describing the precision of the mean estimates if the variable is being reported as the outcome variable in a regression model. Given that the 43 subjects were clustered within 32 families, all effect estimation and statistical significance testing was performed using mixed effects, random intercept linear regression models, with specification of an unstructured correlation structure. All p values are for two-sided comparisons. All analyses were performed using SAS 9.2 statistical software (SAS, Inc, NC).

Results

Study Cohort

Over a 13-year period, 43 subjects from 32 families were enrolled including 8 families with 2 or more affected subjects in the cohort. Prenatally, 7 subjects had TdP ± 2° AV block (Group 1), 4 had isolated 2° AVB (Group 2), and 32 had sinus bradycardia alone (Group 3, Table 1). Thus, 11 (26%) of the cohort had complex, signature fetal LQTS arrhythmias. Twenty-seven subjects were monitored consistently between 19-40 weeks of gestation because of a family history of LQTS; only 3 of these 27 developed 2° AVB (at 22 and 32 weeks gestation) or TdP (at 34 weeks gestation). Sixteen subjects were evaluated only after detection of fetal arrhythmias suggestive of LQTS (19-30 weeks gestation); arrhythmias included either sinus bradycardia (n=9) or complex, signature LQTS arrhythmias (n=11). Follow-up time ranged from 1 to 13 years.

The mean (±SD) gestational age of presentation for all subjects was 28.5 ± 4.9 weeks, and age at presentation did not differ by Group. Pregnancy was terminated electively in one case because of incessant TdP associated with hydrops fetalis; other subjects were live born. Subjects in Group 1 were delivered significantly earlier (mean±SE, 34.0 ± 1.0, range 31-39 weeks) than those in Group 2 (38.3 ± 1.5, range 38-39 weeks, p=0.04) or Group 3 (38.1 ± 0.5, range 30-41 weeks, p = 0.008). Indications for delivery included term pregnancy (37 subjects), fetal distress (3 subjects), fetal well-being concerns (1 subject), and rupture of membranes with spontaneous onset of premature labor (1 subject).

Characteristics of Fetal Arrhythmias (Table 2)

Among the 7 Group 1 fetuses, tachycardia rate was 200 to 300 bpm (Figures 1A and 1B). In all subjects TdP was intermittent with periods of sinus bradycardia or 2° AVB between TdP bursts (Figure 1C). The TdP duration was variable and lasted seconds to several minutes.

In Group 2 fetuses, ventricular rate varied from 45-75 bpm (Figure 1D and E). Subjects #8 and #11 had persistent 2° AVB, while in subjects #9 and #10, 2° AVB was seen transiently only at 19 and 28 weeks, respectively. Ventricular rates during 2° AVB were similar between Group 1 and Group 2 subjects (data not shown). Sinus bradycardia rates (Group 3) varied but were <3% for gestational age [1].

Genetic Analysis

Mutations in LQTS-susceptibility genes were found in 38 of 40 subjects undergoing genetic testing, including 23 with *KCNQ1*, 6 with *KCNH2*, 6 with *SCN5A*, and 3 with other mutations. Two subjects had uncharacterized mutations (Table 1). *De novo* mutations were found in 7 subjects: 6 in Group 1 (4 with SCN5A-R1623Q, 1 each with SCN5A-L409P [3] and KCNH2-G628S [10]) and 1 in Group 2 with CALM2 [9]. The portion of subjects with a familial/inherited mutation varied: Group 1 (14%), Group 2 (75%), Group 3 (92%).

Among subjects with complex, signature fetal LQTS arrhythmias (Group 1 and Group 2), 5/11 had familial/inherited mutations. Two mutations were novel: (KCNH2-T612L and CALM2), 2 mutations had been reported previously (KCNQ1-G168R and KCNQ1-G314D), and one subject did not undergo genetic testing. Group 3 subjects had previously reported mutations (Supplemental Table).

Prenatal Treatment (Table 2)

Because subjects were cared for at multiple institutions and over time, management strategy was not uniform. Only Group 1 fetuses received prenatal treatment; however, 14 mothers with personal history of LQTS were treated with beta adrenergic blocking agents, and 2 fetuses of treated mothers developed TdP (subject #2) or 2° AVB (subject #8). After fetal TdP developed in subject #2, propranolol was given instead of metoprolol because of its relatively favorable transplacental transfer characteristics. Combinations of propranolol, mexiletine, magnesium and lidocaine were used in subjects #1, #2, #4 and #5. Maternal sotalol (120 mg orally every 12 hours) was administered to twin subjects #5 and 6 for 2 days.

Pharmacological treatment restored sinus rhythm in 2 fetuses (subjects #1[10] and #4 [2] with *KCNH2* and *SCN5A* mutations, respectively) and decreased frequency and duration but did not fully abolish TdP in 2 fetuses (subjects #5 and #2 with *SCN5A* and *KCNH2* mutations, respectively). Magnesium was the treatment common to all 4 fetuses who seemed to benefit. Subject #3 did not receive antiarrhythmic treatment because the pregnancy was interrupted.

Postnatal Treatment (Table 2)

All subjects received postnatal treatment. The 6 live-born neonates in Group 1 received oral propranolol (2-3.5 mg/kg/day) or continuous esmolol infusion with transition to propranolol as standard postnatal drug therapy for LQTS. Use of mexiletine was influenced by prenatal treatment experience and response to therapy. In addition to medical therapy, 2 subjects (#1 and #5), received pacemakers in the first 3 days of life because of persistent ventricular bradycardia (rate 48-60 bpm) during 2° AVB. Subject #2, who had transient TdP in the first 48 hours after birth, was discharged with an external cardiac defibrillator.

Despite continued treatment, cardiac arrest or sudden death occurred in subjects #4-7 at ages 2 weeks to 8 months. The 3 cardiac arrest survivors (subjects # 5-7) received implantable cardioverter-defibrillator (ICD) plus cardiac sympathetic denervation (n=3) 1 week to 4 months later. However, all 3 ICD recipients have continued to receive appropriate VF-terminating shocks despite denervation surgery and/or ongoing pharmacological therapy.

All 4 subjects in Group 2 were treated with beta adrenergic blocking agents; subject #10 was also given mexiletine and subject #11 received a pacemaker in the neonatal period. Subject # 10 had cardiac arrest at 4 weeks of age and received ICD implantation. As with the ICD recipients in Group 1, Subject #10 continues to receive appropriate VF terminating shocks.

All subjects in Group 3 were treated with beta adrenergic blocking agents, 2 received additional therapies with mexiletine and 2 received pacemakers for marked sinus bradycardia thought to be secondary to treatment with beta blocking medication. During the follow-up of 2 to 14 years, subjects have remained asymptomatic.

Prenatal/Postnatal Rhythm Concordance

For subjects in Groups 1 and 3, pre- and postnatal rhythm was 100% concordant. All Group 1 subjects with prenatal TdP had postnatal TdP at least once during the first 8 postnatal months. On the other hand, neither TdP nor 2° AV block was identified postnatally in any Group 3 subject. However, for the 4 subjects in Group 2, postnatal rhythm concordance was 50%; 3 subjects had postnatal episodes of 2° AV block, and the subject with the CALM2 mutation (#10) had multiple episodes of postnatal TdP and ventricular fibrillation.

Genotype-Phenotype Relationship

In this cohort, the varied rhythm phenotypes suggested certain genotypes. For example, most subjects in Group 1 had *de novo* mutations and *SCN5A* mutations. In contrast, the majority of subjects in Group 3 had a *KCNQ1* mutation (Table 1).

Predictors of Outcome

As genotype suggested arrhythmia phenotype, arrhythmia phenotype and QTc duration predicted clinical outcome. Table 1 shows the average QTc for each Group, after adjusting for phenotype in a linear mixed effects model, with significant differences found between groups. There was no dependency of QTc on observations from the same family with similar genotype.

Five Group 1 subjects and the one Group 2 subject had postnatal TdP with cardiac arrest; despite medical therapy, all 6 device recipients continued to receive VT/VF-terminating shocks. On the other hand, subjects with sinus bradycardia and most subjects who had isolated prenatal 2° AVB did not have postnatal TdP and did not receive device therapy (Table 2). Subjects in Group 3 have all remained asymptomatic.

Discussion

We evaluated arrhythmias in the largest reported fetal LQTS cohort and sought to determine the extent to which the perinatal arrhythmia clinical profile might be genotype specific. We identified several important findings. First, TdP is most likely to occur in fetuses with sporadic mutations, and although the incidence of SCN5A mutations in our cohort is nearly the same (~10%) as the percentage reported historically for LQTS [11], SCN5A mutations were found much more frequently in fetuses with TdP. In contrast, fetuses presenting with persistent sinus bradycardia were most likely to have *KCNQ1* mutations [6]. Second, we found that prenatal therapy for TdP can be effective, but such fetuses are likely to be delivered prematurely and despite aggressive treatment strategies, provide ongoing postnatal management challenges. In our experience, fetuses tolerate sinus bradycardia or 2° AVB without *in utero* therapy. Thus, prenatal arrhythmia phenotype informs prenatal and neonatal management, while awaiting the results of genetic testing.

The severe arrhythmia phenotypes observed in fetal LQTS have been explained partly by mutations with severe biophysical phenotypes. For example, studies of SCN5A-R1623Q, noted in sporadic LQTS cases with severe perinatal arrhythmia [2, 4, 12], identified a novel LQTS mechanism characterized by early channel re-openings and increased probability of long openings [12]. On the other hand, sporadic occurrence of SCN5A-L409P in combination with H558R caused significant depolarized shifts in voltage-dependence of inactivation and activation, faster recovery from inactivation and a greater level of persistent current potentiated by a developmentally regulated alternative splicing event in *SCN5A*[3]. In contrast, KCNH2-G628S, a mutation in the pore of the *KCNH2*-encoded Kv11.1 potassium channel, was reported to have a dominant negative effect on wild type I_{Kr}[13,14]. However, biophysical phenotype alone does not explain phenotype severity. For example, while subjects in our study with KCNQ1-G168R and KCNQ1-G314D mutations had only 2° AVB, both mutations have been associated with cardiac arrest in adolescence and adulthood [15]. Further, among subjects we studied, 2 of the 3 familial LQTS mutations resulted in fetal arrhythmias in the proband but a much milder phenotype in other family member implicating factors other than the ion channel mutation contributing to variable expressivity, a phenomenon previously noted in studies of large families[16, 17].

Although most TdP episodes we observed spontaneously terminated, the risk of postnatal cardiac arrest in fetuses with TdP was much higher than in LQTS fetuses without TdP. For example, approximately 25% of LQTS fetuses previously reported had complex, signature LQTS arrhythmias and nearly 30% of these fetuses had a subsequent cardiac arrest [2, 9, 17, 18]. In a previous study that limited treatment to beta adrenergic blocking drugs plus pacing, mortality within the first year of life exceeded 60% when complex signature LQTS arrhythmias were documented [18], but was < 10% among subjects when only sinus bradycardia was observed [5,6]. Thus, it is not unexpected that none of the 32 fetuses with isolated sinus bradycardia in the current study had postnatal TdP or cardiac arrest during infancy. However, extrapolating from these findings, one may speculate that fetuses with mutations causing protracted TdP may not survive to delivery.

Previous studies comparing genotype-phenotype relationship to time of presentation (fetal or postnatal) have reported conflicting results. For example, infants presenting during the first year of life with complex LQTS-associated arrhythmias usually had either *KCNH2* or *KCNQ1* mutations, and only 16% had *SCN5A* mutations [5, 6, 17]. In contrast, among individuals with LQTS-associated genotypes in SIDs cohorts, SCN5A mutations were more frequent [19,20]. Similarly, a high prevalence of SCN5A mutations in LQTS subjects presenting with TdP during fetal life has been reported [4, 5, 7, 12, 21], and this was true for >70% of subjects we studied.

The current study suggests that to a limited extent the beneficial effects of perinatal therapy can be predicted by the genotype and/or fetal arrhythmia characteristics. This may be explained partially by previous findings that sodium channel blocking agents, including lidocaine and/or mexiletine, are useful in treatment of LQTS due to gain-of-function *SCN5A* mutations [22]. On the other hand, beta adrenergic blocking agents such as propranolol have been shown to decrease transmural dispersion of repolarization and the induction of TdP partially explaining their superior efficacy for LQT1 and LQT2 [23]. While an anti-fibrillatory effect from cardiac sympathetic denervation has been shown in children and adults with LQTS [24], denervation therapy did not appear to help in this small cohort of fetal LQTS subjects. We are not aware of an effective prenatal therapy for 2° AVB or sinus bradycardia, but in our experience, mothers of fetuses with these rhythms had uncomplicated pregnancies and delivered at term.

There remain unanswered questions regarding genotype-phenotype of LQTS in general and fetal LQTS specifically. The LQTS genotypes in the fetus with complex arrhythmias differ from the more common familial mutations because of their sporadic occurrence and severe, life-threatening phenotype. In spite of these unanswered questions, we are encouraged by observations that suggest that fetal LQTS arrhythmia phenotype and QTc measured after birth can risk stratify the care of these subjects in early life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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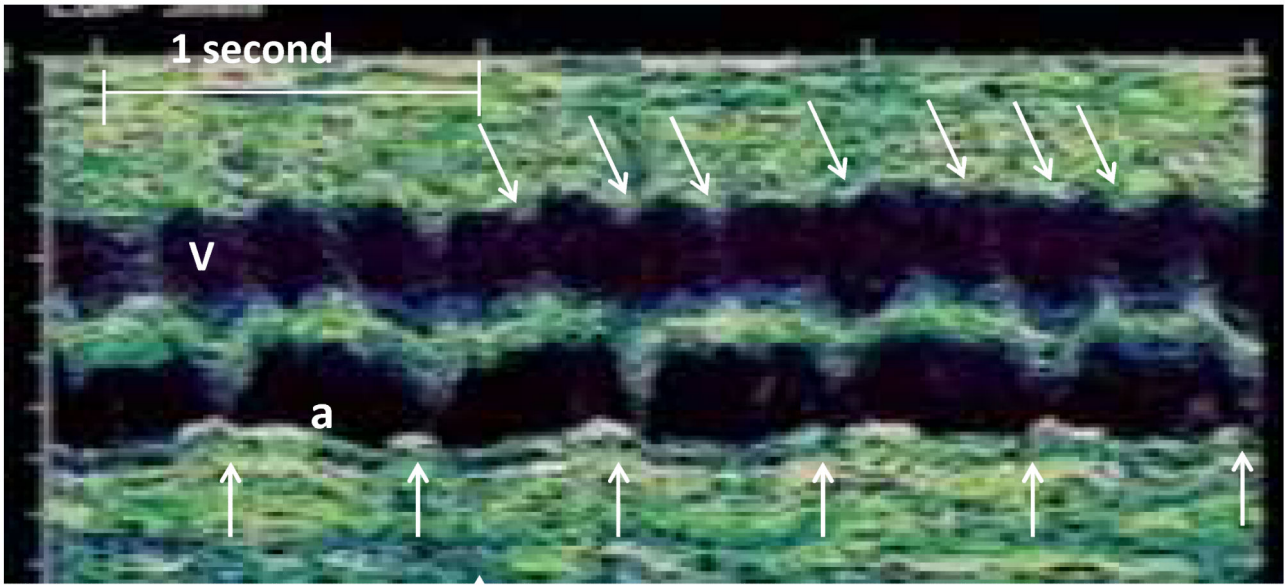

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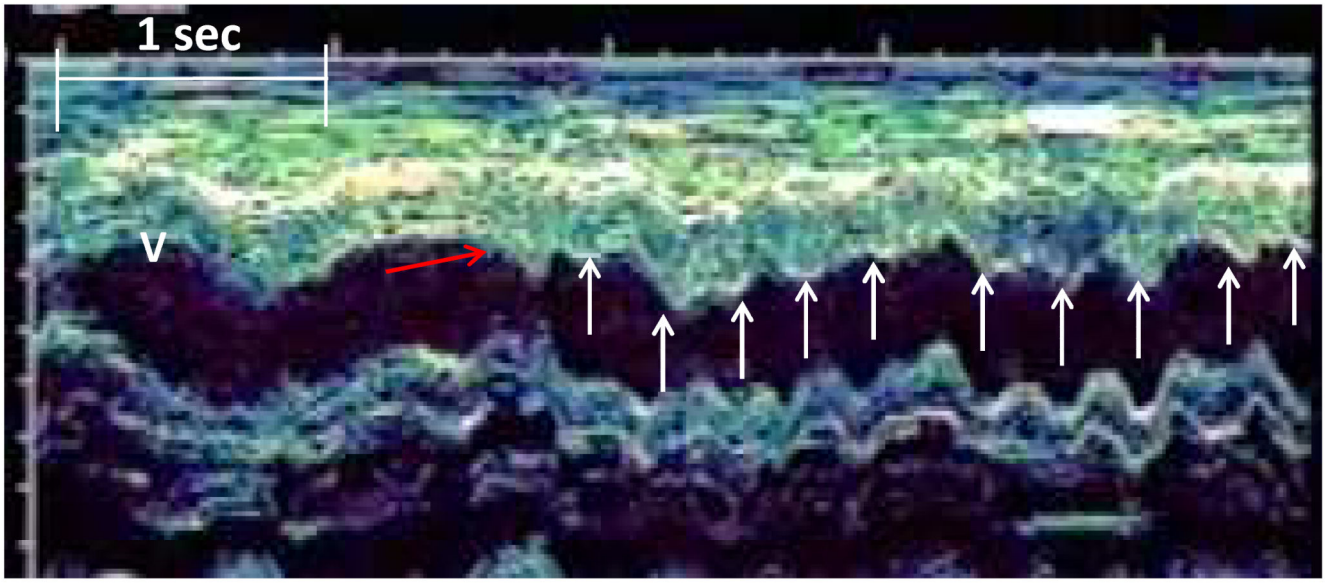

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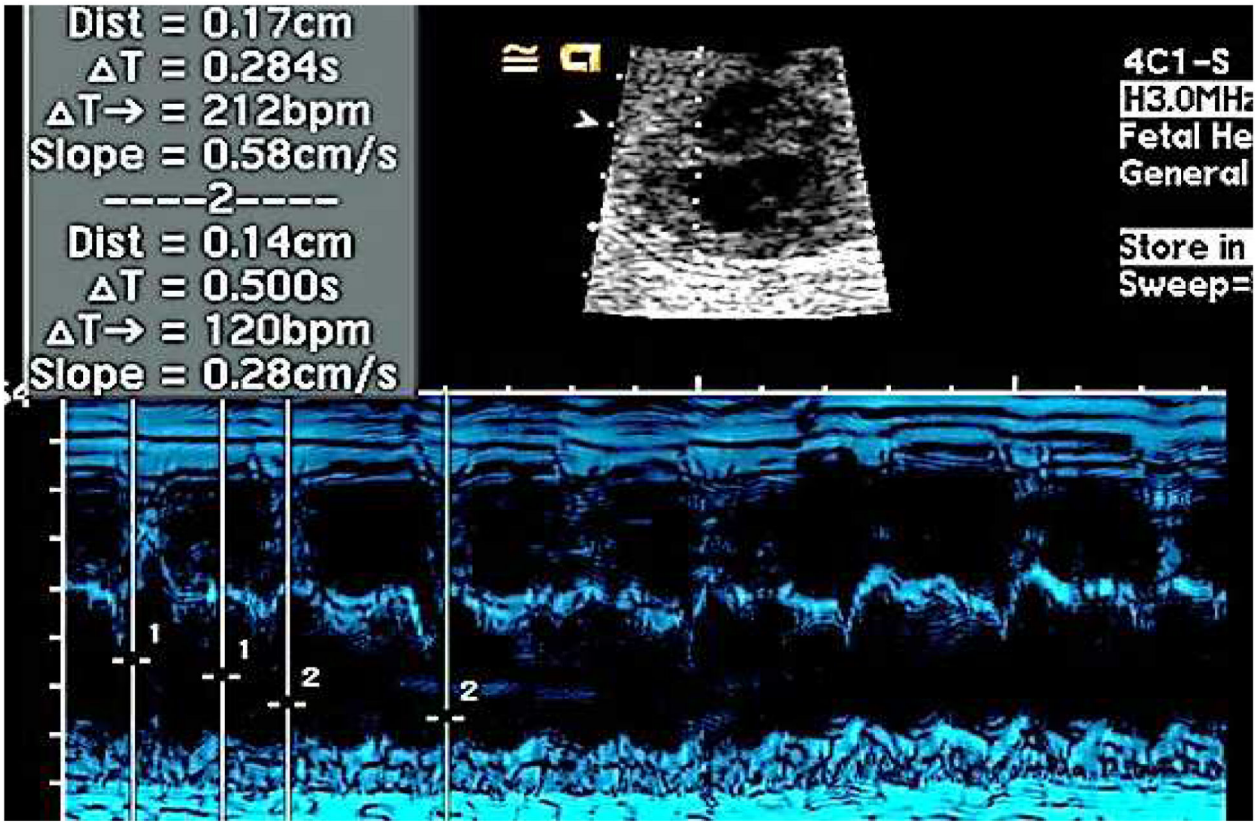

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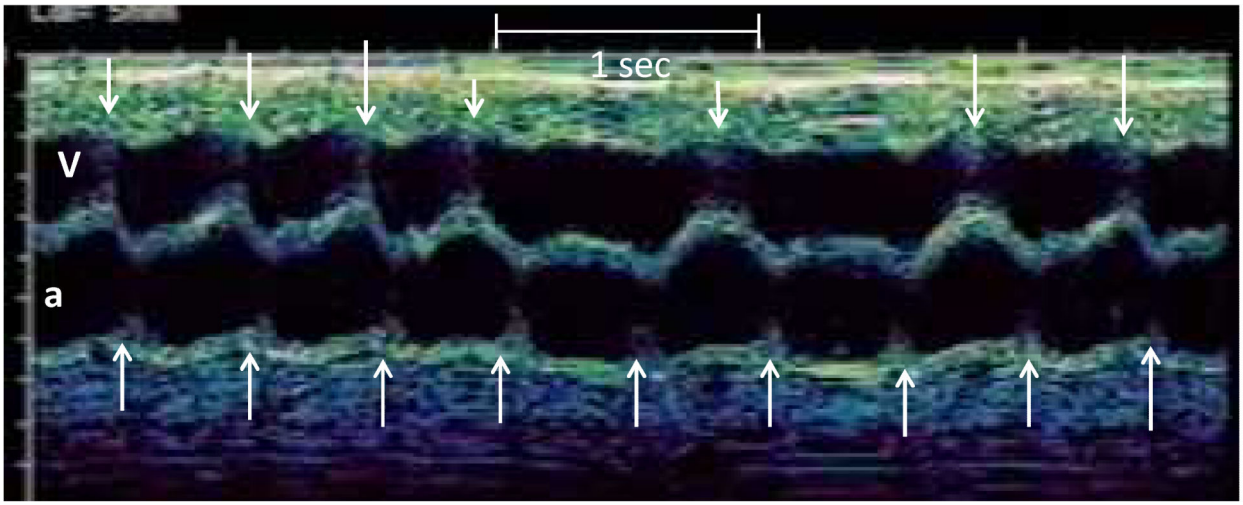

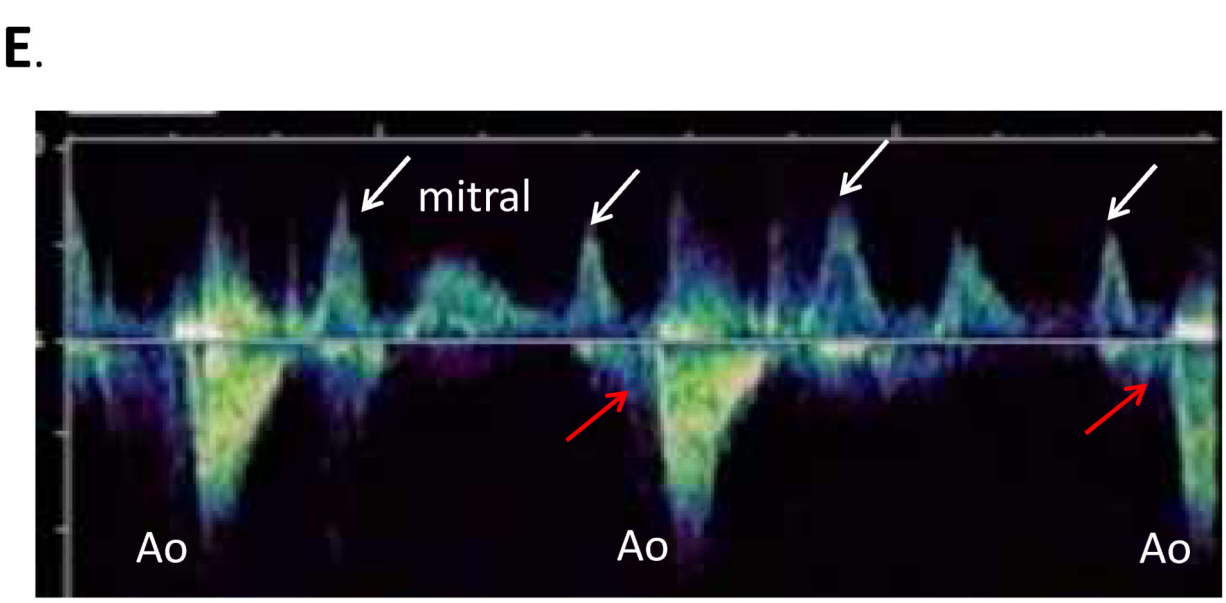

Figure 1.

Illustrative cardiac rhythms of Group 1 and Group 2 subjects. (A) Simultaneous atrial and ventricular M-Mode of established ‘TdP’ in a fetus with R1623Q mutation at 32 weeks of gestation. Although M-mode cannot definitively diagnose TdP, AV dissociation and the irregular tachycardia (arrows, top tracing) at a cycle length varying from 200-300 ms is highly suggestive of TdP. The atrial (bottom tracing, ‘a’) rhythm is regular (arrows) and the cycle length is 540 ms. (B) Ventricular (V) m-mode at initiation (red arrow) of ‘TdP’ in the same fetus. Based on the ‘V-V#x2019; interval of about 1000 ms, rhythm preceding the initiation of TdP is probably 2° AV block (C) Simultaneous ventricular and atrial M-Mode of established TdP in a fetus with KCNH2 mutation and at 34 weeks of gestation. The atrial (‘a’) cycle length is regular at a rate of 120 bpm (cycle length 500 ms) and the ventricular rhythm is irregular at a rate of 212 bpm (cycle length 284 ms, arrows, bottom tracing). (D). Simultaneous atrial and ventricular M-Mode of sinus bradycardia and intermittent 2° AV block in a 34 week fetus with KCNH2 mutation. Atrial contractions (“a”, bottom arrows) are regular at a cycle length of 517 ms. The AV relationship is initially 1:1, but there is ventricular silence between the 4^{th} and 5^{th} and 5^{th} and 6^{th} ventricular contractions while atrial contractions continue at the original rate. This identifies 2° AV block. (E) Pulsed Aortic (Ao) and mitral valve Doppler tracing of the same fetus during a period of sustained 2° AV block. The mitral “a” waves (white arrows) occur at a regular rate while only every other aortic outflow waveform is conducted. Together, these findings indentify 2° AV block.

Table 1

43 Fetal LQTS Subjects

Group	QTc (ms) (mean ±SE)*	LQTS Mutation					
		KCNQ1	KCNH2	SCN5A	Un-characterized	Un-tested	Other
Group 1 TdP (n=7)	664.4 ± 24.9	0	2	5	0	0	0
Group 2 2° AVB (n= 4)	491.2 ± 27.6 (p=0.004)**	2	0	0	0	1	1
Group 3 Sinus Brady (n=32)	483.1 ± 13.7 (p<0.001)**	21	4	1	2	2	2

* Adjusted group means, after adjusting for genotype in a mixed effects linear regression model.

** p value comparing Group 2 to Group 1, and comparing Group 3 to Group 1.

Table 2

Characteristics of 11 LQTS Subjects with Complex Fetal Arrhythmias

Group 1: Fetal TdP ± 2° AVB

#	FH	Rate (bpm)	GA Rhythm	GA Delivery	Gene/ Mutation	Prenatal Rhythm	Prenatal Rx	QTc (ms)	Postnatal Rhythm	Postnatal Rx	Outcome
1	No	192-200	28	33	KCNH2 G628S*	TdP+2° AVB	BB, lido, Mg, mex	700	TdP+2° AVB	BB PM	AAW
2	yes	225-240	34	38	KCNH2 T612L†	TdP+2° AVB	BB, Mg	677‡	TdP+2° AVB	BB, mex ECD	AAW
3	No	200-300	19	-	SCN5A L409P*	TdP	none	604‡	none	--	TOP
4	No	300-320	28	34	SCN5A R1623Q*	TdP +2° AVB	lido, Mg mex	690	TdP	BB, mex	SCD
5	No	270-300	30	35	SCN5A R1623Q*	TdP+2°AVB	BB, Mg mex	592	TdP+2° AVB	BB, mex PM,ICD, LSCD	CA
6	No	270-300	30	31	SCN5A R1623Q*	TdP+ 2° AVB	sotalol	647	TdP+2° AVB	BB, mex ICD, LCSD	CA
7	No	270-300	30	31	SCN5A R1623Q*	TdP+2° AVB	sotalol	655	TdP+2° AVB	BB, mex ICD, LCSD	CA

Group 2: Fetal Isolated 2° AVB

#	FH	Rate (bpm)	GA Rhythm	GA Delivery	Gene/ Mutation	Prenatal Rhythm	In utero Rx	QTc (ms)	Postnatal Rhythm	Postnatal Rx	Outcome
8	yes	61	27	39	KCNQ1 G168R	2° AVB	none	516	SR	BB	AAW
9	yes	70	19	39	KCNQ1 G314D	2° AVB	none	463	SR	BB	AAW
10	No	58	28	39	LQT1-13 Negative CALM2	2° AVB	none	680	TdP+2° AVB	BB, mex ICD	CA
11	yes	45	36	38	Untested	2° AVB	none	550	2° AVB	BB PM	AAW

AAW = alive and well; AVB = atrioventricular block; bpm = beats per minute; BB= beta adrenergic blocking agent; CA = cardiac arrest; SCD = sudden cardiac death; ECD= external cardiac defibrillator; FH = family history; GA = gestational age; ICD = internal cardiac defibrillator; LCSD = left cardiac sympathetic denervation; lido= lidocaine; mex= mexiletine; Mg = magnesium; PN= postnatal; Rx= treatment; TdP= torsades de pointes; TOP = termination of pregnancy; wks = weeks;

* = de novo mutation;

† = novel mutation;

‡ = QTc measured by fetal magnetocardiogram.