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Case Report

# Implantable Cardioverter Defibrillator in a Patient with Eisenmenger Syndrome after Senning Repair for Transposition of the Great Arteries

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# Implantable Cardioverter Defibrillator in a Patient with Eisenmenger Syndrome after Senning Repair for Transposition of the Great Arteries

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An implantation of a cardioverter-defibrillator was attempted in a 32-year-old man with atrial tachycardia, ventricular tachycardia and sinus node dysfunction. He had undergone a Senning operation and half closure of ventricular septal defect in order to correct a transposition of the great arteries. Cardiac catheterization revealed severe pulmonary hypertension and Eisenmenger syndrome. Prior knowledge of the complex cardiac anatomy obtained by magnetic resonance imaging helped in determining the suitable site for implanting the leads and planning the procedural strategy. With repletion of a large amount of saline and oral anticoagulation with warfarin, no complications related to thromboembolism occurred during a 10-month follow-up period.
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**Key words:** Implantable cardioverter defibrillator, Eisenmenger syndrome, Transposition of the great arteries, Senning repair

## Introduction

Arrhythmias are common and generally poorly tolerated in patients with Eisenmenger syndrome and congenital heart disease.[1–3] However, implantation of an implantable cardioverter-defibrillator (ICD) is technically challenging because of the complex anatomy, atrial scar, and presence of artificial tissue. We describe here a case of atrial tachycardia (AT), ventricular tachycardia (VT) and Eisenmenger syndrome after a Senning's operation for a transposition of the great arteries (TGA) (type II) in which an ICD was successfully implanted under the guidance of magnetic resonance imaging (MRI).

## Case Report

A 32-year-old Japanese man was transferred to our hospital for treatment of AT and VT. At the age of 3, he was diagnosed with TGA and underwent

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pulmonary artery banding because his pulmonary artery pressure was elevated due to an increased pulmonary blood flow through a large ventricular septal defect (VSD). Six years later, he underwent an atrial switch operation with a Senning operation and half closure of the VSD because the pulmonary vascular resistance had significantly increased to 2024 dyne·s·cm$^{-5}$ on the cardiac catheterization.

On February 1, 2008, he had a sudden palpitation attack, and was admitted to a hospital. The diagnosis of AT with 2:1 A-V conduction was made, and a 12-lead ECG revealed a sustained wide QRS tachycardia with a right bundle branch block configuration, north-west axis, and heart rate of 134 bpm (**Figure 1A**). Intravenous treatment with verapamil and adenosine triphosphate could not terminate the AT (**Figure 1B**), and the AT was finally terminated by direct current cardioversion (**Figure 1C**). Two days after the first AT episode, the patient developed a sustained monomorphic VT with a right bundle branch block configuration, left axis deviation, and cycle length of 280 msec (**Figure 2**), and was also terminated by direct current cardioversion. Treatment with 200 mg/day of oral amiodarone failed to control both tachycardias, but it resulted in sinus bradycardia.

He was referred to our hospital for further evaluation and treatment of the tachycardias. Despite a reduction in the amount of amiodarone to 100 mg/day, successive 12-lead ECGs after admission demonstrated a sinus bradycardia or junctional escape rhythm with a heart rate of 40 to 45 bpm. Echocardiography disclosed that the left ventricular wall motion was mildly impaired with an ejection fraction of 50%. Right heart catheterization revealed severe pulmonary arterial hypertension with a pulmonary arterial pressure of 105/50 mmHg (mean, 77 mmHg). The anatomical left ventricular and anatomical left atria pressures were 110/13 mmHg and 6/8 (6) mmHg, respectively. A left heart catheterization demonstrated an aortic pressure of 111/70 (87) mmHg. The cardiac index was 2.47

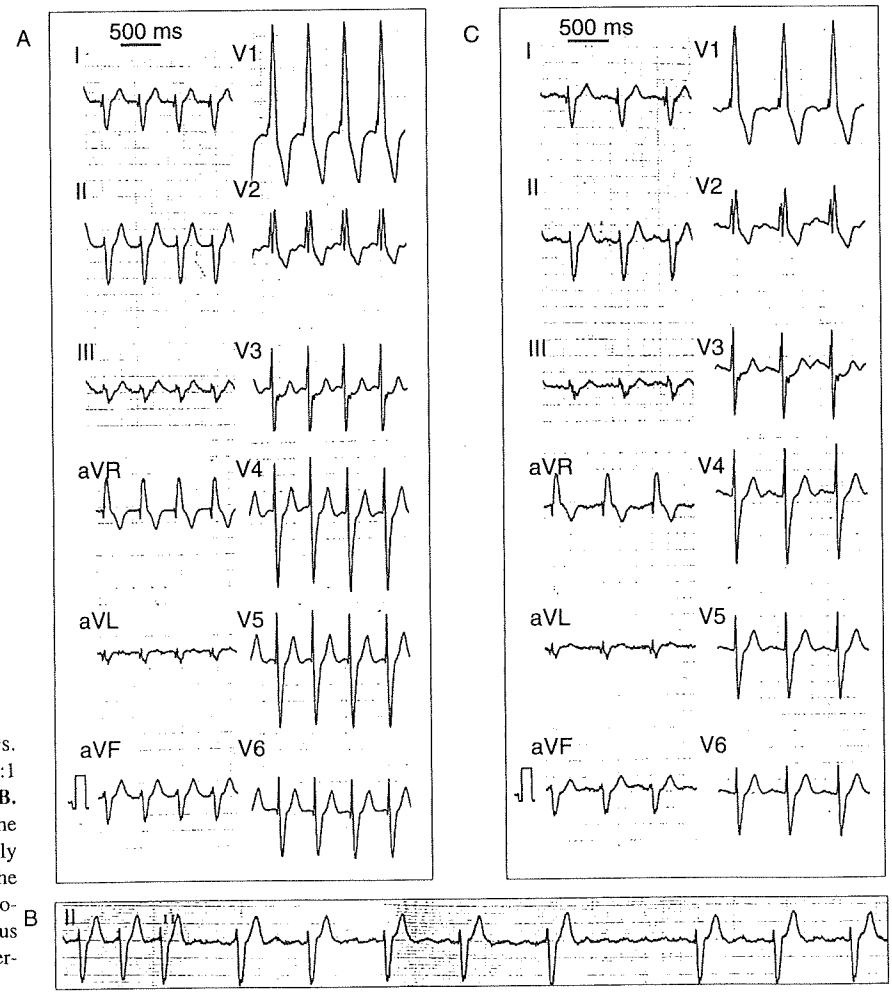


**Figure 1** Twelve-lead ECGs. **A.** Atrial tachycardia with 2:1 atrioventricular conduction. **B.** Small but distinct P waves (the P-P interval was approximately 220 ms) were observed after the application of 20 mg of adenosine triphosphate. **C.** Sinus rhythm after external cardioversion.

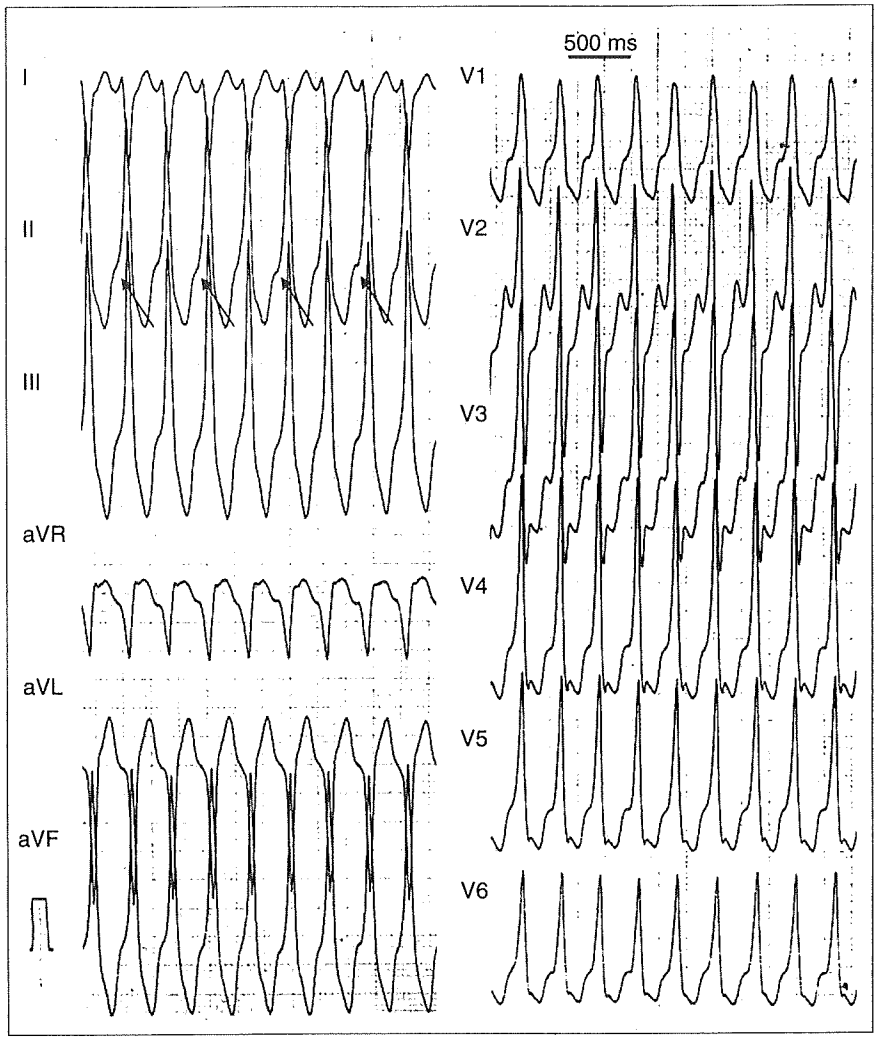


**Figure 2** Twelve-lead ECG of a monomorphic sustained ventricular tachycardia.
P waves, independent of the QRS complex, were observed in lead II (arrows).

L/min/m$^2$, and the left-to-right and right-to-left (venous blood from the anatomical left ventricle to the right ventricle) shunt ratios were 0.67 and 0.18, respectively. Measurement of the arterial blood gases revealed a pH of 7.528, $CO_2$ tension of 28.8 mmHg, $O_2$ tension of 54.9 mmHg and $O_2$ saturation of 91.7%. Based on those results, the patient was diagnosed with Eisenmenger syndrome. Treatment with oral angiotensin converting enzyme inhibitors and bosentan was started and total doses were gradually increased.

We decided to implant an ICD device with a dual-chamber (DDD) pacing function, transvenously under local anesthesia to resolve the symptoms from his tachycardias and sinus nodal dysfunction. Considering the complex anatomy and the risk of thromboembolic complications, an electrophysiological study and catheter ablation were avoided in this case. Fortunately the AT and VT were completely suppressed with oral medications at that time. Before the operation, cardiac MRI was performed to determine the exact complex anatomy and the appropriate site for implanting the atrial pacing lead. The MRI images disclosed that the superior vena cava (SVC) was connected to the morphological left atrium (LA; **Figure 3A**), and that the roof area of the LA seemed to be the most appropriate site for the implantation of the atrial pacing lead because of the presence of an almost completely intact myocardium and the absence of any complicated structures around that area (**Figure 3A**). The morphology and appearance of the morphological left ventricle was also clearly seen in those images.

The patient underwent an implantation of a dual-chamber ICD (Virtuoso DR D164AWG, Medtronic, Minneapolis, MN, USA). Using a left-sided approach, a subclavian venous access was utilized. Angiography of the SVC was performed in multiple directions with special attention being paid to the SVC–LA junction. Under guidance with MR and

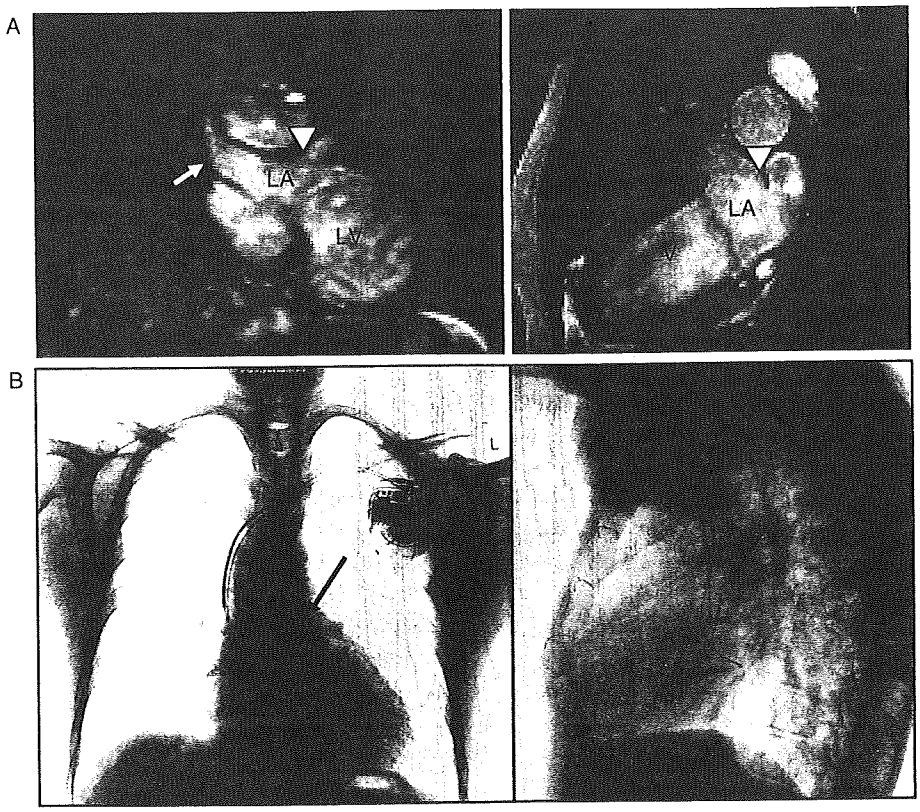


**Figure 3 A.** Images of balanced turbo-field echo cardiac magnetic resonance imaging (MRI) before the operation.
Coronal (left) and sagittal (right) cardiac MRI images demonstrate a superior vena cava to left atrium (LA) conduit (arrow). The arrowheads indicate the site where we planned to implant an atrial pacing lead in the LA roof.
**B.** Posterioranterior (left) and lateral (right) views of the chest X-ray film after the operation.
Note that the atrial lead (arrow) was implanted at the site which we determined it should be implanted using cardiac MRI guidance prior to the operation.

angiographic images and fluoroscopy, an active-fixation atrial lead was inserted into the LA, and the atrial lead (Tendril 1488T 52 cm, St. Jude Medical, St. Paul, MN, USA) was implanted at the exact site of the LA roof that we found to be an appropriate site for the implantation via the MRI (**Figure 3A**). The ICD lead (Riata ST OPTIM 7020, St. Jude Medical) was also placed in the morphological left ventricle with no difficulty (**Figure 3B**). The stability of both leads was excellent. The atrial pacing threshold was 0.9 V at a pulse width of 0.4 ms and the ventricular pacing threshold was also good at 0.5 V at a pulse width of 0.4 ms. The P wave and R wave sensing was good at 3 mV and 14 mV, respectively. There was no diaphragmatic stimulation either with atrial or ventricular pacing at high output. No far-field sensing was observed after connection to the device. Rapid ventricular fibrillation was induced by a T-wave shock and the events were successfully defibrillated with an energy of <20 J. The device was programmed as follows: (i) VT detection = 133–140 bpm for monitoring purposes only; (ii) VT detection = 141–187 bpm, therapies = anti-tachycardia pacing × 2, 20J × 1, 35J × 3 and (iii) VF detection = 188 bpm, therapies = 35J × 6. The total procedure time was 180 minutes, and there were no procedural complications. To avoid dehydration and any thromboembolic complications from the ventricular endocardial lead placement, a large amount (200 mL/h) of intravenous saline was administered during the operation. Warfarin was administered from the next day after the operation in order to keep the PT-INR (prothrombin time-internationalized ratio) at or above 2.5. A dose of 100 mg/day of aspirin was also given to the patient. The patient has done well with no recurrence of any tachycardia or potential complications including a thromboembolism during a 10-month follow-up period.

## Discussion

To the best of our knowledge, this case report demonstrated for the first time that an ICD implantation was possible with no potential complications in a patient with Eisenmenger syndrome after a Senning's operation for a TGA, and that prior knowledge of the complex cardiac anatomy obtained with the MRI helped in determining the suitable site for the insertion of the pacemaker lead and in planning the procedural strategy.

Before the 1980s, most patients with TGA were treated by an atrial inflow correction using a Mustard or Senning operation. While their survival rate has

been improving, arrhythmias and late deaths are well-recognized complications.[4,5] Sudden death has been the common cause of late deaths and AT and VT have been identified as predictors of sudden death.[4,5] Sinus node dysfunction is also common in adult patients with a TGA, and sinus rhythm has been reported to be preserved in only 40% of the patients at 20 years of age.[6] An Eisenmenger physiology is a serious complication of an atrial switch repair for a TGA and occurs in approximately 7% of those who survive to adulthood.[6] Symptoms of tachycardia or a previously documented supraventricular tachycardia are the best predictors of sudden cardiac death,[1] and aggressive therapy with antiarrhythmic medications, pacing, or even an ICD implantation may be recommended. However, a recent study reported that neither drug therapy nor pacemakers reduce the risk of sudden death in patients with a TGA who have undergone an atrial inflow correction operation.[5] In our case, AT, VT and sinus node dysfunction were documented, and an Eisenmenger physiology was also present. Surgery and general anesthesia are well-known critical factors associated with the deterioration and death related to Eisenmenger syndrome.[2] Therefore, we think that the transvenous implantation of an ICD device with DDD pacing was indispensable for preventing any sudden death in this case.

The risk of thromboembolic complications from the ventricular endocardial lead placement was a major concern in our patient. A paradoxical embolism due to the ventricular endocardial lead placement might be a potential source for a thromboembolism, which might result in neurological complications. With repletion using a large amount of saline and oral anticoagulation with warfarin, no complications related to thromboembolisms occurred during the operation and the follow-up period in this case.

The device implantation in this case was technically challenging because of the unusual orientation of the cardiac chambers. The MRI can be used to determine the exact intracardiac anatomy and confirm the location and size of the intracardiac or extracardiac communications, especially in patients with a complex cardiac anatomy and inadequate echocardiographic windows.[7] Compared to ECG-gated computed tomography, this imaging exposes the patient to no ionizing radiation.[8] Furthermore, it can also provide information on the cardiac function and characteristics of the myocardium. In our case, prior knowledge of the cardiac anatomy from the MRI was very helpful in determining the site for the implantation of the atrial lead and in planning the procedural strategy. Therefore, we think that cardiac MRI is a very useful non-invasive method for use prior to the device implantation in patients with a complex cardiac anatomy as in this case, and a detailed assessment of the MRI images before the operation could result in a smooth, safe and successful device implantation without any complications in these patients.

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# Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life: A Nationwide Questionnaire Survey in Japan

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# Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life
## A Nationwide Questionnaire Survey in Japan

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***Background***—Data on the clinical presentation and genotype-phenotype correlation of patients with congenital long-QT syndrome (LQTS) diagnosed at perinatal through infantile period are limited. A nationwide survey was conducted to characterize how LQTS detected during those periods is different from that in childhood or adolescence.

***Methods and Results***—Using questionnaires, 58 cases were registered from 33 institutions. Diagnosis (or suspicion) of LQTS was made during fetal life (n=18), the neonatal period (n=31, 18 of them at 0 to 2 days of life), and beyond the neonatal period (n=9). Clinical presentation of LQTS included sinus bradycardia (n=37), ventricular tachycardia/torsades de pointes (n=27), atrioventricular block (n=23), family history of LQTS (n=21), sudden cardiac death/aborted cardiac arrest (n=14), convulsion (n=5), syncope (n=5), and others. Genetic testing was available in 41 (71%) cases, and the genotype was confirmed in 29 (71%) cases, consisting of LQT1 (n=11), LQT2 (n=11), LQT3 (n=6), and LQT8 (n=1). Ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively observed in patients with LQT2, LQT3, and LQT8, as well as in those with no known mutation. In LQT1 patients, clues to diagnosis were mostly sinus bradycardia or family history of LQTS. Sudden cardiac death/aborted cardiac arrest (n=14) was noted in 4 cases with no known mutations as well as in 4 genotyped cases, although the remaining 6 did not undergo genotyping. Their subsequent clinical course after aborted cardiac arrest was favorable with administration of β-blockers and mexiletine and with pacemaker implantation/implantable cardioverter-defibrillator.

***Conclusions***—Patients with LQTS who showed life-threatening arrhythmias at perinatal periods were mostly those with LQT2, LQT3, or no known mutations. Independent of the genotype, aggressive intervention resulted in effective suppression of arrhythmias, with only 7 deaths recorded. (***Circ Arrhythm Electrophysiol.* 2010;3:10-17.)**

**Key Words:** arrhythmia ■ long-QT syndrome ■ genes ■ death (sudden)

Congenital long-QT syndrome (LQTS) is an inherited disorder characterized by polymorphic ventricular tachycardia (VT), or torsades de pointes (TdP), syncope, and sudden cardiac death.[1] LQTS is often diagnosed in children from school age to young adulthood[2] and sometimes during fetal, neonatal, and infantile life.[3–5] Previous case reports

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**Table 1. Questionnaire Items**

| | |
|---|---|
| 1. | Patient: Serial No. in each institution, initials, birth year, and month, sex |
| 2. | Age at diagnosis or suspicion (including gestational age for a fetus) |
| 3. | Clinical symptoms: Fetal arrhythmias, fetal heart failure, syncope, convulsion, heart failure, aborted cardiac arrest, others |
| 4. | ECG findings and arrhythmias (heart rate, QTc on ECG at presentation, sinus bradycardia, VT/TdP, atrioventricular block, other arrhythmias) |
| 5. | Family history of LQTS or other arrhythmias or sudden cardiac death (which member, and their outcome?) |
| 6. | Genotype |
| 7. | Treatment (acute therapy and maintenance therapy) |
| | pharmacotherapy (which drug, dose, age at initiation, and duration) |
| | device therapy (pacemaker implantation/implantable cardioverter-defibrillator) and age at application |
| 8. | Duration of follow-up |
| 9. | Outcome (alive or death, and neurological sequels of cardiac arrest) |

suggest that the latter cases are at higher risk of development of life-threatening arrhythmias necessitating emergency treatment[3–5] and show higher mortality rates than the former age groups.[3,5–11] For example, recent progress in molecular biology has clarified that LQTS partly contributes to sudden infant death syndrome (SIDS).[12,13] Unfortunately, prenatal diagnosis of LQTS has been extremely difficult to confirm except for a limited number of cases for which prenatal gene screening[14] or fetal magnetocardiography (fMCG)[15–17] was applied.

**Clinical Perspective on p 17**

Thus, the clinical presentation, the genotype-phenotype correlation, and the outcome of patients with fetal, neonatal, or infantile presentation of LQTS remain to be elucidated. The purposes of this study were first, to report the findings of a nationwide survey conducted to define the clinical characteristics and the genotype-phenotype correlation, and second, to report the outcome of patients with LQTS diagnosed before birth and in the first year of life.

## Methods

### Population

The study population included fetuses, neonates, and infants (<1 year of age) diagnosed with LQTS based on ECG findings including prolonged QTc >0.46 seconds (using Bazett formula), with or without VT/TdP, who had no structural heart disease, family history of LQTS, or had undergone genetic testing. Those with normal QTc duration and no gene mutation known to cause LQTS were excluded. Patient data were collected using questionnaires. The form was sent to those councilors of the Japanese Society of Pediatric Cardiology and Cardiac Surgery who responded to a preliminary survey that they had 1 or more cases of LQTS diagnosed during fetal, neonatal, and infantile life. The items obtained from the responders are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba, and informed consent was obtained from each patient (or parents, if the patient was younger than 15 years of age) by a coordinator in charge in each institution before the patient's data were registered.

### Genetic Analysis and Genotype-Phenotype Correlation

Genetic analyses were performed in 4 established laboratories in Japan. DNA was isolated from blood samples in each patient. Screening for mutations of at least 3 major genes causing LQTS (*KCNQ1, KCNH2, SCN5A*) was performed using polymerase chain reaction (PCR)/single-strand conformation polymorphism or denatured high-performance liquid chromatography analysis. For aberrant PCR products, DNA sequencing was conducted with a DNA sequencer (ABI 3700 and ABI 3130xl, Applied Biosystems, Foster City, Calif). For those subjects in whom genotype was confirmed and those who underwent genetic analysis but found to have no mutation, genotype-phenotype correlations (or mutation-negative phenotype correlations) with the aforementioned items (Table 1) were investigated.

### Statistical Analysis

All statistical calculations were conducted using the R software. Quantitative variables (heart rate [HR] and QTc) are presented as mean±SD and categorized variables (presence of FH, sinus bradycardia, VT/TdP, and atrioventricular block [AVB]) as proportions (percentages). One-way ANOVA was applied for comparisons of continuous variables, followed by pairwise comparisons with Bonferroni adjustment of probability values among 4 groups (LQT1, LQT2, LQT3, and mutation-negative groups). The equality of proportions for categorical variables among the 4 groups was examined by the $\chi^2$ test (global test). When there was a significant difference in proportions, we performed pairwise comparisons between pairs of proportions with correction for multiple testing using Bonferroni inequality of probability values. Tests were 2-sided, and a probability value <0.05 was considered significant.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

## Results

### Population

A total of 58 cases (all Japanese; males 30, females 28) were registered from 33 institutions. Forty-one were born during the last 10 years (between 1999 and 2008), 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. LQTS was diagnosed or suspected during fetal life at 18 to 40 weeks of gestation in 18 individuals, during neonatal life at 0 to 28 days in 31, and in infancy (<1 year) at 1 to 9 months in 9.

### Clinical Features

For 18 fetuses with LQTS, clinical presentation (or clues to diagnosis or suspicion of LQTS) included bradycardia (15 cases), AVB (8 cases), VT/TdP (7 cases), and family history of LQTS (6 cases), including 1 family with a previous intrauterine death (items overlapped in some cases). Two fetuses were confirmed to be LQTS by fMCG, with QTc values of 570 and 680 on fMCG, and 590 and 700 on ECG soon after birth, respectively (these 2 cases have been reported previously).[16,17] No fetal death was noted in this group.

For 31 neonates with LQTS, the most frequent feature was sinus bradycardia (17 cases), followed by VT/TdP (15 cases), positive family history of LQTS (15 cases), including 1 with previous intrauterine death and 1 with infantile death, AVB (10 cases), syncope (5 cases), convulsion (5 cases), and others (items overlapped in some cases). Among the 31 neonatal cases, 18 (70%) were diagnosed within 2 days of life, and 8 of them had some significant fetal presentation (4 bradycardia or bradyarrhythmias, 4 tachyarrhythmias, and 1 hydrops), retrospectively.

As described above, the number of patients with LQTS diagnosed during infancy beyond the neonatal period was only 9. The clinical presentation of these patients included sinus bradycardia (5 cases), sudden cardiac death (SCD)/

aborted cardiac arrest (ACA) (5 cases), AVB (5 cases), VT/TdP (5 cases), and other miscellaneous abnormalities.

The ECG on diagnosis, or immediately after birth for fetal cases, showed that the HR and QTc interval (corrected using Bazett formula) ranged from 50 to 160 (102±28) bpm, and from 360 to 774 (563±70) ms, respectively.

### Genotype-Phenotype Correlation

Among 41 patients who underwent genetic testing, mutations were identified in 29 (71%) cases; including *KCNQ1* gene mutations (LQT1) in 11, *KCNH2* mutations (LQT2) in 11, *SCN5A* mutations (LQT3) in 6, and *CACNA1C* (LQT8) in 1. Twelve patients also underwent genotyping, but no mutation was found. Table 2 lists the demographic and clinical features of these subjects (references 16, 17, and 23 reported the same cases 2, 12, and 27 in Table 2) and of those with no known mutations.

The remaining 17 subjects (6 fetuses, 8 neonates, 3 infants) did not undergo genetic analysis due to lack of such analysis at that time, death soon after birth, or refusal by parents. Five had SCD/ACA (Table 3), including a 1-day-old neonate who had AVB and died at 57 days of age in 1984. This case was later assumed to be LQT8, based on characteristic phenotypes such as syndactyly. AVB and VT/TdP were observed in 7 and 5 cases, respectively, in this group.

Although HR and QTc values were not different among LQT1, LQT2, LQT3, and mutation-negative groups, the incidence of VT/TdP was higher in LQT2 and LQT3 compared with LQT1 (Table 4). The incidence of AVB tended to be higher in LQT3 compared with LQT1 but statistically insignificant. On the other hand, the presence of family history of LQTS was more frequent in LQT1 than the mutation-negative group. The incidence of sinus bradycardia was comparable among the 4 groups (Table 4).

Table 3 lists cases with SCD/ACA; only 4 genetically confirmed cases were included, and 4 were mutation-negative, although the remaining 6 cases did not undergo genotyping. These individuals showed bradycardia (97±31 bpm; 10/14 showed HR <110 bpm) and markedly prolonged QTc (617±81 ms).

### Treatment

With regard to the treatment of fetal VT/TdP, antiarrhythmic agents were administered transplacentally in 4 of 18 fetal cases (propranolol in 3 cases, lidocaine in 1, mexiletine in 1, flecainide in 1, and magnesium in 1), using the method described in detail in our previous report.[17] None of the 4 cases was genetically confirmed prenatally. When 2 or 3 of the following findings of sinus bradycardia, VT, and AVB were observed in a structurally normal heart, LQTS was strongly suggested, and β-blockers, sodium channel blockers (lidocaine, mexiletine), and magnesium (Mg) were selected as typical antiarrhythmic agents, instead of amiodarone or sotalol, which may prolong the QT interval. These drugs were used in combination until VT/TdP was controlled and proved effective in all 4 cases. However, preterm delivery was conducted in 2 cases both at 33 weeks of gestation due to recurrent VT/TdP and depression of fetal physical activity in one and to fetal hydrops and distress in the other. In the remaining 14 cases, pharmacotherapy was initiated after confirmation of the type of arrhythmias after birth. However, no fetal death was noted.

For 15 neonatal cases who presented with VT/TdP (including those who did not undergo genotyping), acute pharmacotherapy consisted of 2 or more of the following drugs: β-blockers, mexiletine, lidocaine, Mg, phenytoin, and others, except for 2 cases who were treated with phenytoin alone and 1 with mexiletine alone. Most of these cases were judged to respond the combination therapy. In 5 neonates in whom LQT3 was strongly suggested based on a typical ECG finding called late-appearing T wave, mexiletine was first administered but proved insufficient, and β-blockers were also added in all 5.

For those with LQTS presenting in infancy, 6 cases received acute pharmacotherapy (2 or all of propranolol, mexiletine, and Mg). No additional agent was administered. Thus, in all age groups, the acute therapy for VT/TdP consisted of a single drug to which 1 or more drugs was then added until the arrhythmia was controlled, independent of the genotype. Actually, the genotype was not identified during the acute phase in most cases. Furthermore, genotyping was not conducted in those 17 cases who presented before 1999.

Maintenance therapy consisted mainly of β-blockers (or no therapy) for LQT1 and mostly of mexiletine/β-blockers for LQT2 and LQT3 (Table 2). β-Blockers were added in 8 LQT2 cases after confirmation of the genotype. In all 6 LQT3 cases, mexiletine was maintained (combined with β-blockers) from acute through chronic phase after determination of the genotype.

Nine patients underwent pacemaker implantation (PMI), 5 with ventricular pacing mode (VVI) and 1 with atrial pacing mode (AAI), from age 1 day to 8 years due to severe bradycardia caused by AVB, inducing VT/TdP. In 6 cases, VT was completely suppressed after PMI. Only 2 patients had an implantable cardioverter-defibrillator (ICD) at ages 4 (LQT3) and 25 months (mutation negative), respectively, due to recurrent VT/TdP with satisfactory results.

### Outcome

During the follow-up period of 8 days to 23.5 years (median, 4.25 years), 7 SCD and 7 ACA were registered (age at SCD or ACA range, 8 days to 10 years; median, 10.5 months); 6 did not have genetic testing, whereas 4 showed no mutation. Only 4 were genetically confirmed (Table 3). One case was later suspected to be LQT8, based on the phenotype including syndactyly. Among the 14 SCD/ACA cases, 12 had been under pharmacotherapy, 5 with both β-blockers and sodium channel blockers, and 2 had had PM or ICD. Four cases developed significant neurological deficits after cardiorespiratory resuscitation.

## Discussion

The noteworthy finding of the present study was that 49 of 58 cases (84%) were diagnosed at the fetal or neonatal period, although this survey covered the entire infantile period. Remarkably, two thirds of the neonatal cases were diagnosed within 2 days of life; this period should be recognized as the most vulnerable period. The number of cases diagnosed after the neonatal period was only 9. Considering that the average age at appearance of symptoms in LQT2 and LQT3 is after

**Table 2. Clinicogenetic Details**

| Case | LQT Type | Mutation | Age at Diagnosis/Sex | Clinical Presentation | FH | HR, bpm | QTc, ms |
|---|---|---|---|---|---|---|---|
| 1 | LQT1 | Thr587Met | Fetus/M | FH, brady | + | 109 | 561 |
| 2 | LQT1 | Ala341Val | Fetus/M | Brady | + | 110 | 590 |
| 3 | LQT1 | Ala341Val | Neonate/M | FH | + | 110 | 520 |
| 4 | LQT1 | Ile313Lys | Neonate/M | FH | + | 102 | 589 |
| 5 | LQT1 | Ile313Lys | Neonate/M | FH | + | 115 | 554 |
| 6 | LQT1 | 276delSer | Neonate/M | Prolonged QT | + | 115 | 570 |
| 7 | LQT1 | Asp611Tyr | Neonate/M | Brady | + | 80 | 550 |
| 8 | LQT1 | Asp611Tyr | Neonate/F | FH | + | ND | ND |
| 9 | LQT1 | Thr458Met | Neonate/M | FH | + | 126 | 530 |
| 10 | LQT1 | Gly643Ser | Infant/M | ACA | − | 109 | 554 |
| 11 | LQT1 | Gly269Ser | Infant/F | Cyanosis | − | 113 | 586 |
| | | | | | 82% | 109±12 | 560±24 |
| 12 | LQT2 | Gly628Ser | Fetus/M | VT/TdP, AVB | − | 50 | 631 |
| 13 | LQT2 | del(7)(q32qter) | Fetus/F | TdP | − | 111 | 492 |
| 14 | LQT2 | Ser243+112X | Fetus/F | FH | + | 160 | 360 |
| 15 | LQT2 | Gly628Ala | Fetus/F | Syncope, VT/TdP, AVB | + | 78 | 570 |
| 16 | LQT2 | Thr613Met | Fetus/M | VT/TdP, AVB | − | 60 | 578 |
| 17 | LQT2 | Ala561Val | Neonate/M | Cyanosis, VT/TdP | − | 86 | 520 |
| 18 | LQT2 | Gly628Ser | Neonate/M | TdP, brady | − | 111 | 550 |
| 19 | LQT2 | Thr613Met | Neonate/M | convulsion, VT | − | 140 | 599 |
| 20 | LQT2 | Gly572Ser | Neonate/F | TdP, AVB | − | 91 | 520 |
| 21 | LQT2 | Ala614Val | Neonate/F | Syncope, VT | + | 98 | 500 |
| 22 | LQT2 | Asn633Ser | Infant/F | VT/TdP, AVB | − | 60 | 600 |
| | | | | | 27% | 95±34 | 538±74 |
| 23 | LQT3 | Ala1186Thr | Fetus/M | AVB | + | 78 | 679 |
| 24 | LQT3 | Asn1774Asp | Fetus/M | convulsion, VT/TdP, AVB | − | 115 | 670 |
| 25 | LQT3 | Val176Met | Neonate/F | TdP, AVB | + | 63 | 600 |
| 26 | LQT3 | Asn406Lys | Neonate/M | Syncope, TdP | + | 129 | 598 |
| 27 | LQT3 | Arg1623Gln | Neonate/F | Heart failure | − | 79 | 483 |
| 28 | LQT3 | Leu1772Val | Infant/M | ACA | − | 138 | 520 |
| | | | | | 50% | 100±31 | 592±79 |
| 29 | LQT8 | Gly406Arg | Neonate/M | AVB | − | 141 | 581 |
| 30 | Unidentified | − | Fetus/F | Brady | + | 80 | 554 |
| 31 | Unidentified | − | Fetus/M | Brady | − | 100 | 510 |
| 32 | Unidentified | − | Fetus/M | VT | − | 85 | 590 |
| 33 | Unidentified | − | Fetus/M | AVB | − | 80 | 600 |
| 34 | Unidentified | − | Neonate/F | Syncope | − | 100 | 647 |
| 35 | Unidentified | − | Neonate/F | Arrhythmia | − | 126 | 586 |
| 36 | Unidentified | − | Neonate/F | ACA | − | 111 | 638 |
| 37 | Unidentified | − | Neonate/M | Brady | − | 93 | 550 |
| 38 | Unidentified | − | Neonate/F | FH | + | 120 | 520 |
| 39 | Unidentified | − | Infant/F | ACA | − | 160 | 470 |
| 40 | Unidentified | − | Infant/F | ACA | − | 100 | 774 |
| 41 | Unidentified | − | Infant/F | PAC with block | − | 60 | 460 |
| | | | | | 17% | 104±32 | 575±86 |

(Continued)

Cases 2, 12, and 27 are reported in references 16, 17, and 23, respectively. ACA indicates aborted cardiac arrest; AVB, atrioventricular block; BB, β-blocker; brady, bradycardia; FH, family history; HR, heart rate; ICD, implantable cardioverter-defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; PAC, premature atrial contraction; Pheny, phenytoin; PM, pacemaker; SCD, sudden cardiac death.

**Table 2. Continued**

| Sinus Brady | VT/TdP | AVB | Acute Therapy | Maintenance Therapy | PMI/ICD | Follow-Up | Outcome |
|---|---|---|---|---|---|---|---|
| + | – | + | – | – | – | 0 mo | Alive |
| + | – | – | – | BB | – | 9 y | Alive |
| + | – | – | – | BB | – | 4 y, 1 mo | Alive |
| + | – | – | – | BB | – | 11 y, 10 mo | Alive |
| + | – | – | – | BB | – | 10 mo | Alive |
| + | – | – | – | – | – | 11 mo | Alive |
| + | – | – | – | – | – | 7 y, 3 mo | Alive |
| + | – | – | – | – | – | 5 y, 8 mo | Alive |
| – | – | – | – | – | – | 4 y, 5 mo | Alive |
| + | – | – | Lido, Mexil | Mexil | – | 9 y, 1 mo | Alive |
| + | – | – | – | – | – | 7 y, 8 mo | Alive |
| 73% | 0% | 9% | | | | Median 68 mo | |
| + | + | + | Lido, Mg, BB, Mexil, Pacing | BB, Mexil | PM | 3 y | Alive |
| + | + | – | – | BB | – | 1 y | Alive |
| – | – | – | – | BB | – | 2 y, 2 mo | Alive |
| + | + | + | Lido, Mg, BB, Mexil, pacing | BB, Mexil | PM | 8 y, 1 mo | Alive |
| + | + | + | Mg, Mexil | BB, Mexil | – | 8 mo | Alive |
| + | + | – | Lido, Mg, Mexil | BB, Mexil | – | 11 y, 4 mo | Alive |
| + | + | + | Mexil | BB, Mexil | – | 7 mo | Alive |
| – | + | – | Mg, BB | BB | – | 8 y | Alive |
| + | + | + | Pheny | BB, Mexil | – | 18 y, 5 mo | Alive |
| + | + | – | Pheny, DC | Pheny, BB | – | 23 y, 6 mo | Alive |
| + | + | + | – | BB, Mexil | PM | 15 y, 4 mo | Alive |
| 82% | 91% | 55% | | | | Median 96 mo | |
| + | + | + | Mexil | Mexil | PM ICD | 3 y, 4 mo | Alive |
| + | + | + | BB, Mexil, Mg | BB, Mexil, Flecainide | PM | 11 y, 4 mo | Alive |
| + | + | + | Lido, Mg, BB, Mexil | BB, Mexil | – | 1 y, 3 mo | Alive |
| + | + | – | Lido, BB | BB, Mexil | – | 11 mo | Alive |
| + | + | + | BB, Mexil, Lido | BB, Mexil | PM | 8 y | Alive |
| – | + | + | Mg, BB, Mexil | BB, Mexil | – | 3 y, 2 mo | Alive |
| 83% | 100% | 83% | | | | Median 39 mo | |
| – | + | + | BB, Mexil, Nifed | BB, Mexil, Nifed | – | 3 y, 2 mo | Alive |
| + | – | + | – | BB, Mexil | – | 2 y, 5 mo | Alive |
| + | – | – | – | BB | – | 6 y, 5 mo | Alive |
| + | + | – | Lido, Mg | Mexil | – | 5 y, 5 mo | Alive |
| + | – | + | BB, Mexil, Mg | BB, Mexil | – | 4 mo | Alive |
| + | – | – | Lido, Mg, Isp | Mexil | – | 4 y, 3 mo | Died |
| + | + | – | BB, Mg | BB | – | 9 y, 5 m | Alive |
| – | + | – | Lido, BB, pheny, Mexil | Mexil | – | 11 y, 9 mo | Alive |
| + | – | – | – | – | – | 9 y, 6 mo | Alive |
| – | – | – | – | – | – | 6 mo | Alive |
| – | + | – | BB, Mexil | BB, Mexil | ICD | 7 y, 2 mo | Alive |
| + | + | + | Mexil | Mexil | – | 4 y3 mo | Alive |
| + | – | – | BB, Mexil | BB, Mexil | – | 7 y, 5 mo | Alive |
| 75% | 42% | 25% | | | | Median 71 mo | |

**Table 3. Clinicogenetic Details of Cases With Sudden Cardiac Death or Aborted Cardiac Arrest**

| Case | Case No. in Table 2 | Genotyping | Age at Diagnosis | Age at SCD or ACA | HR, bpm | QTc, ms | Maintenance Therapy Until SCD/ACA | Acute Therapy for SCD/ACA Event |
|---|---|---|---|---|---|---|---|---|
| 1 | 23 | LQT3 (Ala1186Thr) | Fetus (28 wk) | 1 y, 10 mo (aborted) | 78 | 679 | Mexil | Mexil, DC |
| 2 | ... | No gene test | Fetus (31 wk) | 8 d | 60 | 570 | ... | Lido, Isp, Pacing, DC |
| 3 | ... | No gene test | Fetus (36 wk) | 57 d | 90 | 600 | BB, Mexil | DC |
| 4 | 29 | LQT8 (Gly406Arg) | Neonate (0 d) | 1 y, 5 mo (aborted) | 141 | 581 | BB, Nifed | Mexil, Mg |
| 5 | ... | Negative result | Neonate (0 d) | 4 y | 100 | 647 | Mexil | DC |
| 6 | ... | Negative result | Neonate (0 d) | <1 mo (aborted) | 111 | 638 | Mexil | Lido, Mexil, BB, Pheny |
| 7 | 17 | LQT2 (Ala561Val) | Neonate (1 d) | 10 y (aborted) | 86 | 520 | BB, Mexil | Lido, Mexil, Mg, DC |
| 8 | ... | No gene test (possible LQT8)* | Neonate (1 d) | 57 d | 70 | 640 | BB | ... |
| 9 | ... | No gene test | Neonate (4 d) | 5 y, 4 mo | 60 | 590 | ... (refused) | ... |
| 10 | ... | No gene test | Infant (1 mo) | 2 y | 130 | 640 | BB, Mexil | Lido, Mg |
| 11 | ... | No gene test | Infant (1 mo) | 1 y, 10 mo | 60 | 740 | BB, Mexil, PM | Lido, Mexil, BB, Mg, Pacing |
| 12 | 10 | LQT1 (Gly643Ser) | Infant (1 mo) | 1 mo (aborted) | 109 | 554 | Mexil | Lido |
| 13 | 39 | Negative result | Infant (2 mo) | 4 mo (aborted) | 160 | 470 | BB, Mexil, ICD | (aborted by ICD) |
| 14 | 40 | Negative result | Infant (2 mo) | 2 mo (aborted) | 100 | 774 | Mexil | Mexil |
| | | | | median 10.5 mo | 97±31 | 617±81 | | |

ACA indicates aborted cardiac arrest; BB, β-blocker; ICD, implantable cardioverter-defibrillator; Isp, isoproterenol; Lido, lidocaine; Mexil, mexiletine; Mg, magnesium; Nifed, nifedipine; Pheny, phenytoin; SCD, sudden cardiac death.

*LQT8 was retrospectively possible because phenotype included syndactyly.

school age,[2] we speculate a considerable number of patients are considered to go through infancy uneventfully.

Garson et al[4] reported 287 patients with LQTS age <21 years; their mean±SD age at presentation was 6.8±5.6; and 9% presented with cardiac arrest, 26% with syncope, and 10% with seizures. Although 20% of their subjects were <1 month of age, they did not investigate that age group separately. In the present study, confined to the subjects age <1, clinical features were largely different; that is, the incidence of malignant arrhythmias and bradycardia was high[6,7] whereas that of syncope and seizures was low.

Regarding genotype-phenotype correlations, Zareba et al[18] investigated child and adult LQTS and reported that LQT1 was associated with the highest risk of first cardiac event among the 3 most typical genotypes (LQT1–3). By the age of 15, syncope, ACA, or SCD was noted in 53% of their patients with LQT1 compared with 29% of LQT2 and 6% of LQT3, although cardiac events occurred in LQT3 were more lethal compared with those in LQT1 or LQT2. In contrast, the present study demonstrated that patients complicated by VT/TdP or AVB were almost exclusively those with LQT2 or LQT3 (and LQT8). LQT3 patients in the present study showed the most severe clinical course, similar to those in later-presenting LQT3. Further, patients with LQT1 mostly showed an uneventful clinical course apart from sinus bradycardia,[6] and the reason for diagnosis was bradycardia or prolonged QT interval itself on ECG identified on family screening. Another remarkable feature in our young age group was that a considerable number of patients with malignant arrhythmias were mutation-negative as far as LQT1–3 genes were typically examined. This suggests that this age group includes individuals with rare known mutations that were not examined in the present study as well as those with currently unidentifiable mutations.

**Table 4. Comparison of Parameters Among the Groups**

| Parameter | LQT1 (n=11) | LQT2 (n=11) | LQT3 (n=6) | Negative (n=12) | Global Test | Pairwise Comparison |
|---|---|---|---|---|---|---|
| HR, bpm | 109±12 (n=10*) | 95±34 | 100±31 | 104±32 | NS | |
| QTc, ms | 560±24 (n=10*) | 538±74 | 592±79 | 575±86 | NS | |
| Proportion with family history, % | 82 | 27 | 50 | 17 | $P<0.05$ | LQT1–Negative, $P<0.05$ |
| Proportion with sinus bradycardia, % | 73 | 82 | 83 | 75 | NS | |
| Proportion with VT/TdP, % | 0 | 91 | 100 | 42 | $P<0.05$ | LQT1–LQT2, $P<0.001$<br>LQT1–LQT3, $P<0.005$ |
| Proportion with AVB, % | 9 | 55 | 83 | 25 | $P<0.05$ | (LQT1–LQT3, $P=0.068$) |

Data are mean±SD or %. One-way ANOVA was used to compare mean values of HR and QTc. $\chi^2$ test was used to test differences in proportions of subjects with family history, sinus bradycardia, VT/TdP, and AVB among the 4 groups. Pairwise comparisons were conducted using Bonferroni adjustment and Bonferroni inequality of $P$ value. NS indicates not significant; Negative, gene mutation-negative group.

*No. of cases is 10 because data were not available in 1 case.

Notably, many patients in the present study showed sinus bradycardia, although HR was not significantly different among LQT1, LQT2, and LQT3. Sinus bradycardia has been considered a significant presentation of LQTS, especially in the fetal-neonatal period,[3,19,20] and is often a clue to the diagnosis of LQTS. The present study verified that sinus bradycardia is common among all types of LQTS in this age group, especially in fetal-neonatal periods.

Another remarkable feature of the present study was the high incidence of AVB (55% in LQT2, 83% in LQT3), compared with 5% or less in child or adult LQTS.[4,20] It is intriguing that mutations in our LQT2 patients were almost exclusively located at the pore region of HERG gene (amino acid residues 550 through 650),[21] as mutations in that region are related to high risk for cardiac events.[21,22] Lupoglazoff et al[6] reported similar phenotype tendency for neonates with LQTS, that AVB is associated with LQT2 and sinus bradycardia with LQT1. Most of their LQT2 cases also had a mutation in the pore region of the HERG gene, although this was not mentioned in their report. AVB in neonates with an SCN5A mutation have also been reported in single case reports.[8,11,23,24] Considering the implication of sodium channel dysfunction in many other hereditary arrhythmias,[25] the association between LQT3 and AVB is an important finding.

SCD/ACA was seen in 14 cases (24% of all subjects) (7 SCD, 7 ACA), even though 12 of them were under treatment with β-blockers, mexiletine, or both when the events occurred (Table 3). The direct trigger of SCD/ACA remains to be determined, but the mean QTc interval of those patients was apparently prolonged (617±81 ms), and patients with no gene test (6 cases) were included as well, possibly making the selection of drugs inappropriate, such that only β-blockers were given to a possible LQT3 patient. Furthermore, 4 other cases had no known mutation on genotyping. It is possible that the cryptogenic mutations unidentifiable in the current era could be resistant to many drugs.

### Therapy

Because individuals with LQT3 showed serious clinical disorders, they were treated aggressively with multiple antiarrhythmic drugs including mexiletine, β-blockers, lidocaine, Mg, and PM/ICD, and only 1 definite LQT3 patient showed ACA. For LQT2, malignant arrhythmias were a little more controllable with the same kind of pharmacotherapy than for LQT3. Again, only 1 definite LQT2 patient showed ACA. Thus, no death was ultimately observed in LQT2 and LQT3. This favorable clinical course might be derived from implicit strategy prevalent among pediatric cardiologists in our country that early-onset LQTS should be treated with the combination of β-blockers and mexiletine at the start of therapy because the genotype is not easy to confirm immediately. In other words, treatment strategies in Japan have been driven more by the clinical symptoms than by the genotype. Nevertheless, the response to the multiple antiarrhythmic pharmacotherapy and the long-term outcome presented in this study are encouraging.

It should be noted that the number of patients who underwent PMI/ICD was small in the present cohort compared with other reports.[5,6] It is known that TdP tends to follow a prolonged R-R interval in LQT2 and LQT3, in which conduction disturbances or sinus node dysfunction are common features.[25,26] Thus, PMI/ICD should be considered without delay even when the patient who shows drug-resistant, bradycardia-induced VT/TdP is a small baby.[27]

### Study Limitations

Because of the retrospective nature of the present survey using questionnaires, the extent of clinical data that could be obtained varied among cases. Although approximate tendency in genotype-phenotype correlations for infants with LQT1, LQT2, and LQT3 was determined, most cases registered in the present study did not undergo genetic analysis for genes other than the 3 typical types. One case with LQT8 was registered in addition to LQT1–3, but no cases with the other types (LQT4–7) were found. Also, decision of treatment strategy depended on the in-charge physician in each case without the use of a uniform protocol for VT/TdP and/or AVB, making it difficult to evaluate the effects of pharmacotherapy and to determine the event rate beyond infancy for each genotype other than the last outcome, alive or death. Therefore, we should wait for accumulation of more cases for establishment of the genotype-specific strategy.

## Conclusion

Our nationwide survey indicates that early-onset malignant LQTS are mostly those with LQT2 and LQT3 among the 3 major genes, and the most vulnerable age to life-threatening arrhythmias is from 0 to 2 days of age. A combination pharmacotherapy with a β-blocker and mexiletine sometimes combined with Mg and PMI/ICD is recommended as the initial therapy. Prospective study of a large number of patients with LQTS diagnosed from fetal to infantile periods and further application of gene testing are needed to establish the most appropriate treatment strategies for those patients.

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## CLINICAL PERSPECTIVE

The congenital long-QT syndrome (LQTS) diagnosed at perinatal life and through infancy is associated with high morbidity and mortality rates. However, data on the clinical presentation and genotype-phenotype correlation of this youngest age group of LQTS are limited. A nationwide survey was conducted in Japan, and 58 cases (18 fetuses, 31 neonates and 9 infants) were registered. Among them, the peak age at diagnosis was 0 to 2 days, and the 3 most frequent clinical presentations included sinus bradycardia, ventricular tachycardia/torsades de pointes, and atrioventricular block. The genotype was confirmed in 29 (71%) of 41 patients who underwent genotyping; the incidence resembled that of child LQTS. Patients who presented with early-onset ventricular tachycardia/torsades de pointes and atrioventricular block were almost exclusively those with LQT2 and LQT3 among the 3 major genes, but a considerable number of genetically unidentified ones were included. Sudden cardiac death/aborted cardiac arrest were prevalent in the latter. LQT1 patients tended to show only sinus bradycardia or positive family history of LQTS. These results mean that many life-threatening episodes observed in early-onset LQTS should be treated immediately and aggressively even without knowledge of the genotype. On the other hand, the present study was encouraging in that the outcome of patients was favorable with multiple pharmaceutical agents, typically with β-blockers, mexiletine, and magnesium and with pacemaker implantation/ implantable cardioverter-defibrillator, independent of the genotype. Further application of gene testing is needed to establish the most appropriate genotype-specific strategy for these patients.

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# Fetal arrhythmia: Prenatal diagnosis and perinatal management

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## Abstract

The importance of managing fetal arrhythmia has increased over the past three decades. Although most fetal arrhythmias are benign, some types cause fetal hydrops and can lead to fetal death. With the aim of improving the outcome in such cases, various studies for prenatal diagnosis and perinatal management have been published. Detailed analysis of the type of arrhythmia *in utero* is possible using M-mode and Doppler echocardiography. In particular, a simultaneous record of Doppler waveform at the superior venous cava and the ascending aorta has become an important and useful method of assessing the interval between atrial and ventricular contractions. Common causes of fetal tachycardia (ventricular heart rate faster than 180 bpm), are paroxysmal supraventricular tachycardia (SVT) with 1:1 atrioventricular (AV) relation and atrial flutter with 2:1 AV relation. Of fetal SVT, short ventriculo-atrial (VA) interval tachycardia due to atrioventricular reentrant tachycardia is more common than long VA interval. Most fetuses with tachycardia are successfully treated *in utero* by transplacental administration of antiarrhythmic drugs. Digoxin is widely accepted as a first-line antiarrhythmic drug. Sotalol, flecainide and amiodarone are used as second-line drugs when digoxin fails to achieve conversion to sinus rhythm. Fetal bradycardia is diagnosed when the fetal ventricular heart rate is slower than 100 bpm, mainly due to AV block. Approximately half of all cases are caused by associated congenital heart disease, and the remaining cases that have normal cardiac structure are often caused by maternal SS-A antibody. The efficacy of prenatal treatment for fetal AV block is limited compared with treatment for fetal tachycardia. Beta stimulants and steroids have been reported as effective transplacental treatments for fetal AV block. Perinatal management based on prospective clinical study protocol rather than individual experience is crucial for further improvement of outcome in fetuses with tachycardia and bradycardia.

**Key words:** fetal arrhythmia, fetal echocardiography, prenatal diagnosis, prenatal treatment.

The importance of managing fetal arrhythmia has increased over the past three decades. Fetal arrhythmia is often found during fetal heart monitoring or routine prenatal ultrasound examination. Although most fetal arrhythmias are benign, some cause fetal hydrops and can lead to fetal death.[1,2] To improve the outcome in such cases, various studies of prenatal diagnosis and perinatal management have been published. Up-to-date knowledge of effective methods of diagnosing fetal arrhythmia and the selection of appropriate perinatal treatment is crucial for managing affected fetuses. In the present paper, we summarize the current method of prenatal diagnosis and perinatal management of fetal arrhythmia based on recent publications.

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## History of Managing Fetal Arrhythmias

Prenatal recognition and treatment of fetal tachycardia began in the 1970s. After the first report of prenatal diagnosis using M-mode echocardiography was published in 1980 by Kleinman *et al.*,[3] many reports of prenatal treatment of fetal tachycardia using various types of antiarrhythmic drugs were published in the 1980s. In the 1990s, researchers were more focused on refractory cases.[4–6] To enable a more detailed prenatal diagnosis, measurement of the ventriculo-atrial (VA) interval was reported in 1998,[7] and the magnetocardiogram was introduced as a useful modality.[8] In the 21st century, researches began to focus on better strategies to manage fetal arrhythmia by conducting multicenter trials with larger numbers of patients.[9]

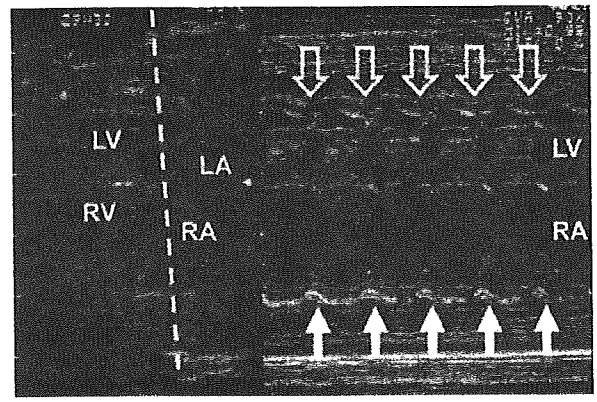


**Figure 1** Simultaneous M-mode recording of both ventricles and atria. M-mode recording in a fetus with supraventricular tachycardia reveals 1:1 relation of atrial (closed arrow) and ventricular contraction (open arrow) with a ventricular rate of 210 bpm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

## Definition and Method of Prenatal Diagnosis

There are three types of fetal arrhythmias.[1,2] The most common form is irregular heartbeat, mainly caused by ectopic beats. When the ventricular rate is faster than 180 bpm or slower than 100 bpm, such fetal arrhythmia is classified as fetal tachycardia or fetal bradycardia, respectively. Detailed analysis of the type of arrhythmia *in utero* is possible using M-mode and Doppler echocardiography.

### M-mode echocardiography

An M-mode trace of ventricular and atrial motion demonstrates cardiac rhythm and rate. A simultaneous record of both ventricular and atrial contractions with a four-chamber view is especially useful for assessing the relation of atrioventricular (AV) mechanical connection in fetuses with arrhythmias, and can determine the mechanism causing the fetal arrhythmia (Figs 1,2).[1,2]

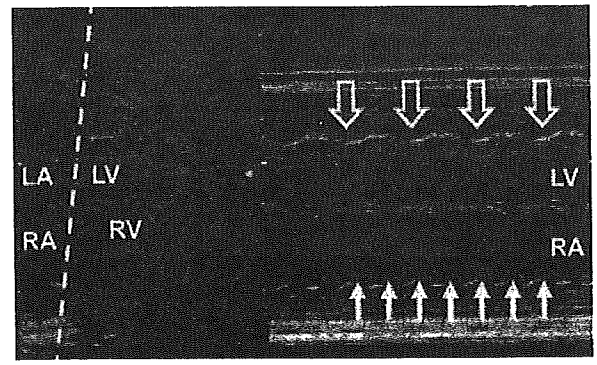


**Figure 2** M-mode recording in a fetus with atrial flutter and 2:1 atrioventricular conduction, with an atrial (closed arrow) rate of 510 bpm and a ventricular (open arrow) rate of 255 bpm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

### Doppler echocardiography

Recently, a simultaneous record of Doppler waveforms at the superior venous cava (SVC) and the ascending aorta (aAo) was introduced as a useful method of assessing cardiac arrhythmias (Fig. 3).[10,11] The beginning of reverse flow at the SVC created by atrial contraction and the beginning of forward flow at the aAo created by ventricular contraction are interpreted as the beginning of P and QRS wave by electrocardiogram (ECG), respectively. Using Doppler waveform, the relation and time intervals of the atrial and ventricular contractions can be measured.[12,13] The pulmonary vein and the pulmonary artery,[14] or the innominate vein and the aortic arch can also be used as alternative methods of assessing simultaneous venous and arterial waveforms.[12]

Another method of measuring AV conduction time interval is the simultaneous record of left ventricular inflow and outflow waveforms.[2] Although this method is relatively easy, AV contraction relation cannot be assessed once the tachycardia begins because E wave, first peak, and A wave, second peak of the inflow pattern cannot be distinguished in this condition.

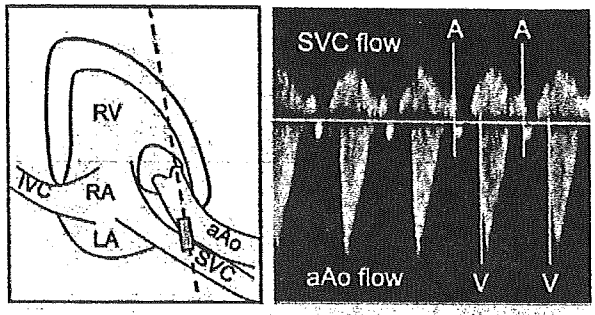


**Figure 3** Simultaneous Doppler trace of the ascending aorta (aAo) and the superior vena cava (SVC). Beginning of reverse flow at SVC (A) and forward flow at aAo (V) represent the timing of atrial and ventricular contraction, respectively. IVC, inferior vena cava; LA, left atrium; RA, right atrium; RV, right ventricle.

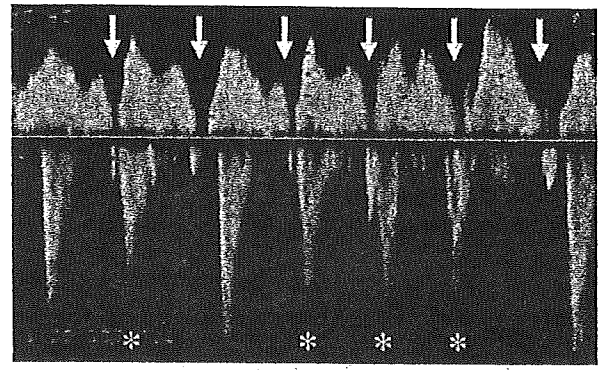

**Figure 4** Simultaneous Doppler trace of the ascending aorta and the superior vena cava in a fetus with ventricular or junctional tachycardia reveals regular atrial contraction with reversal flow at the superior vena cava (arrows) and faster ventricular contraction (asterisk).

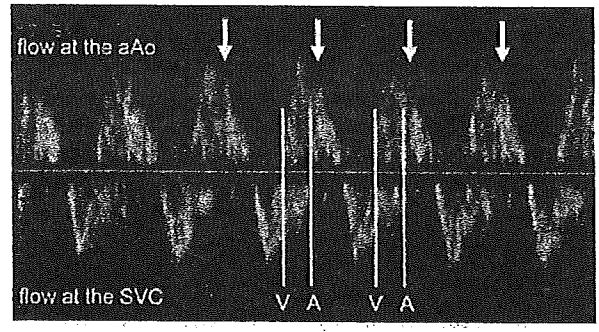


**Figure 5** Simultaneous Doppler trace of the ascending aorta (aAo) and the superior vena cava (SVC) in a fetus with supraventricular tachycardia with short ventriculo-atrial interval. Although high-velocity reversal flows of SVC is almost over-wrapped to the flow of aAo, the starting point of the reversal flow can be detected from the interrupted forward flow of SVC.

Simple measurement of the time length of A wave may be another method to screen the prolongation of AV interval.

Tissue Doppler echocardiography, which can demonstrate detail timing of myocardial contraction, is a useful tool for evaluating fetal arrhythmia.[13,15] Because the tissue Doppler method has become available in the equipment used currently, this technique may become part of routine examination in the near future to diagnose fetal arrhythmias.

## Tachycardia

### Prenatal diagnosis

Fetal tachycardia is diagnosed when the fetal ventricular heart rate is faster than 180 bpm.[1,2,11] Common causes of fetal tachycardia are paroxysmal supraventricular tachycardia (PSVT) and atrial flutter (AFL). There are other rare types of fetal arrhythmias, such as ventricular tachycardia (VT), junctional tachycardia, and multiforcal atrial tachycardia (MAT). Fetal tachycardia is classified based on the relation of the AV contraction observed by fetal echocardiography. Fetal PSVT has a 1:1 AV relation (Fig. 1). Fetal AFL has a very fast atrial heart rate, such as 400 or 500 bpm, and 2:1 (occasionally 3:1 or 4:1) AV relation (Fig. 2). Fetal VT has ventricular tachycardia with dissociated atrial contraction (Fig. 4). Fetal MAT shows irregular atrial tachycardia and ventricular contraction. Although tachycardia is sometimes intermittent during prenatal examination, the chance of hemodynamic complications and development of fetal hydrops remain high.

PSVT in most fetuses is caused by atrioventricular reentrant tachycardia (AVRT) due to Wolff–Parkinson–White syndrome.[8,11] Both the atrial and ventricular heart rates range from 200–300 bpm (Fig. 1). Measurement of the time interval from the ventricular contraction to the following atrial contraction (VA interval) by Doppler echocardiography reveals a short VA interval (Fig. 5).[10,11] The measurement of this VA interval is very useful to distinguish AVRT (short VA interval) from other types of fetal tachycardias, such as atrioventricular nodal reentrant tachycardia (AVNRT) and permanent junctional reciprocating tachycardia (PJRT), which demonstrates a long VA interval (Fig. 6).

### Perinatal management

Most fetuses with both PSVT and AFL are successfully treated *in utero* by transplacental administration of

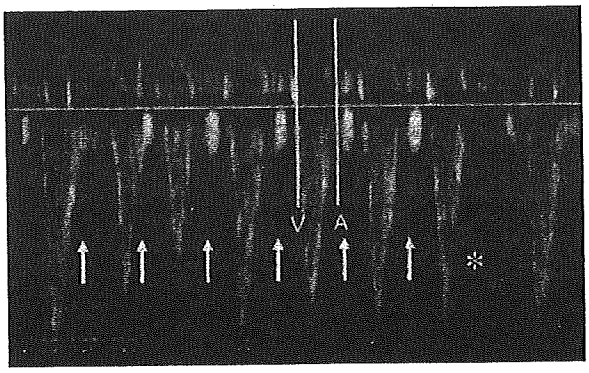


**Figure 6** Simultaneous Doppler trace of the ascending aorta and the superior vena cava in a fetus with 1:1 atrioventricular conducted tachycardia with long ventriculo-atrial interval. Tachycardic atrial contraction (A, arrows) disappears after the seventh ventricular contraction (asterisk), and the tachycardia is stopped.

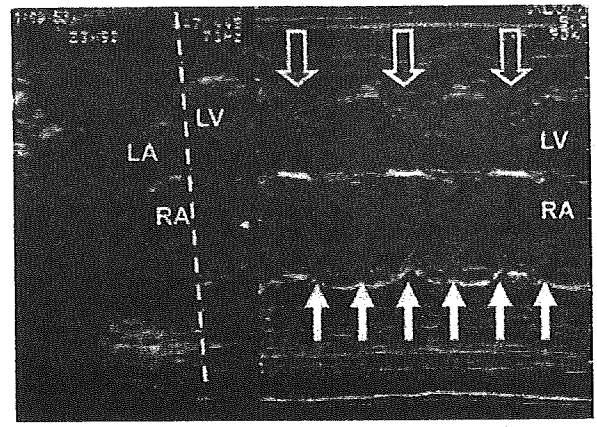


**Figure 7** Simultaneous M-mode recording of both ventricles and atria in a fetus with complete atrioventricular block reveals complete dissociation of atrial and ventricular contraction with a ventricular rate of 65 bpm. Large arrows, ventricular contractions; small arrows, atrial contractions; LA, left atrium; LV, left ventricle; RA, right atrium.

antiarrhythmic drugs.[6,9,10,11] Digoxin is widely accepted as a first-line antiarrhythmic drug. Sotalol, flecainide and amiodarone are used as second-line drugs when digoxin fails to achieve conversion to sinus rhythm.[16–21] For fetuses with hydrops and fetal PSVT with long VA interval, digoxin is rarely effective.[11] For fetuses with hydrops, the placental transfer of the digoxin is limited. Hence, sotalol or flecainide, which have good placental transfer ability, should be used from the beginning of fetal treatment for hydrops. Fetal intramuscular administration of digoxin with maternal administration of amiodarone is another effective method.[21]

Although intrauterine treatment is very effective in fetuses with tachycardia, treatment after delivery is also very effective. Hence, decisions for which cases are treated *in utero* or postnatally is often difficult. Management of a premature neonate under hemodynamically unstable conditions with tachycardia and decreased cardiac function is difficult.[22] Hence, it is important not to select postnatal treatment too quickly in premature gestation, even when the fetus has already developed hydrops. Once the tachycardia is converted to sinus rhythm, the hydrops will recover and the fetus can be delivered at term by vaginal birth. However, when the hydrops continues for more than 2 weeks without conversion of tachycardia, postnatal treatment is recommended.

It is difficult to predict when the fetus will develop hydrops.[23,24] Several Doppler echocardiographic parameters that demonstrate congestive heart failure cannot be used at this extremely high heart rate. Serial measurement of the cardiothoracic ratio may be useful for monitoring the degree of heart failure. The presence of atrioventricular valve regurgitation, especially at the mitral valve, may represent severe congestive heart failure.

The safety of the mother is of great concern when managing fetal tachycardia. Administration of antiarrhythmic drugs for intrauterine treatment may cause pro-arrhythmia and threaten the mother. ECG monitoring, especially of the QT prolongation of the mother is very important when a new drug is started or the dosage is increased.

## Bradycardia

### Prenatal diagnosis

Fetal bradycardia is diagnosed when the fetal ventricular heart rate is slower than 100 bpm, mainly due to AV block (Fig. 7).[1,11,25] Approximately half of all cases are caused by associated congenital heart disease (CHD), and the remaining cases that have normal cardiac structure are often caused by maternal SS-A antibody.[26–28] The two most common CHD associated with AV block are left atrial isomerism (Fig. 8) and discordant AV connection. Maternal SS-A antibody to AV block is usually that for 52kd SS-A, and many mothers are rarely diagnosed with collagen disease when the fetus develops AV block.[29–32] Although rare, the other important cause of fetal bradycardia is long QT syndrome, which can cause 2:1 AV block or sinus

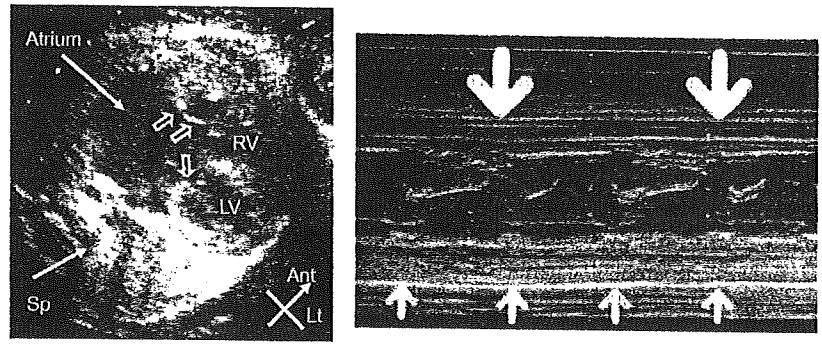


**Figure 8** Left panel reveals four-chamber view of polysplenia with the single atrium, the common atrioventricular valve (open arrows) and cardiomegaly. Right panel reveals simultaneous M-mode recording of ventricles (large arrows) and atria (small arrows) in this case, which demonstrates 2:1 atrioventricular block. Ant, anterior; Lt, left; LV, left ventricle; RV, right ventricle; Sp, spine.

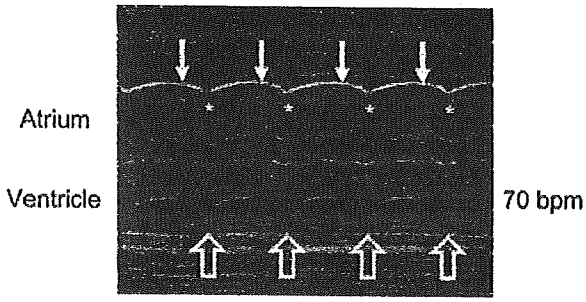


**Figure 9** Simultaneous M-mode recording of ventricles and atria in a fetus with blocked paroxysmal atrial contraction (PAC) with bigeminy. The PAC (asterisk) shortly after regular atrial conduction (small arrows) does not conduct to the ventricle causing bradycardia with a ventricular rate of 70 bpm.

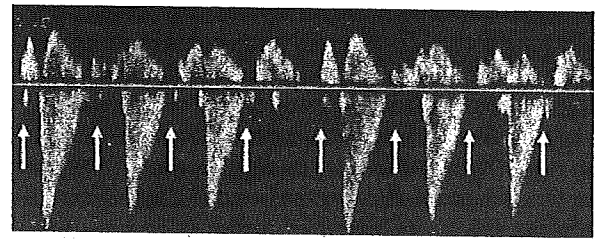

**Figure 10** Wenckebach type atrioventricular block. Simultaneous Doppler trace of the ascending aorta and the superior vena cava reveals atrial contraction with regular rhythm (arrows), atrioventricular conducting time of gradual prolongation, and block with pose of ventricular contraction.

bradycardia.[33] Blocked paroxysmal atrial contraction (PAC) with bigeminy also mimics 2:1 AV block and causes fetal bradycardia (Fig. 9).[11]

Doppler echocardiography is useful for diagnosing fetal bradycardia. The relation and interval of atrial and ventricular contractions revealed by SVC and aAo Doppler flow can demonstrate the severity of AV block, not only complete dissociation of AV contraction, but also first-degree and Wenckebach-type second-degree AV block (Fig. 10).[11,34]

Fetal bradycardia with either CHD or fetal hydrops has a significantly worse prognosis.[26,27] Although a heart rate of less than 55 bpm is thought to be the cut-line for congestive heart failure, some recent reports included cases without heart failure even when the fetal heart rate was less than 50 bpm.[27] Cardiac function or presence of CHD affects the severity of congestive heart failure.[35] It is important that transferred maternal IgG can cause pleural, pericardial and peritoneal effusion, in addition to myocarditis and poor cardiac function in the fetus, even if there is no hydrops.[36]

## Perinatal management

Efficacy of prenatal treatment for fetal AV block is limited compared with treatment for fetal tachycardia. Beta stimulants and steroids have been reported to be effective transplacental treatments for fetal AV block.[11,37,38] Beta stimulants, such as ritodrine, terbutaline, and salbutamol effectively increase fetal ventricular rate by approximately 10–20% and reverse hydrops in some fetuses with AV block. Several reports have demonstrated that transplacental administration of steroids, such as dexamethasone and betamethasone, are effective for fetuses with AV block caused by anti-SSA antibody.[39–41] Jaeggi *et al.* recently reported that prenatal steroid treatment improves the outcome of fetuses with AV block.[32]

There are two targets for prenatal steroid therapy. The most attractive target is the direct effect of treating AV block. The prompt administration of steroids immediately after the onset of AV block has improved the degree of AV block.[39] However, other studies have shown spontaneous improvement of the degree of AV block without any steroid therapy.[42] Hence, the direct effect of steroids for AV block remains uncertain.