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# Role of Echocardiography in Assessing Pregnant Women With and Without Heart Disease

**Chizuko Kamiya, MD, Satoshi Nakatani, MD, Shuji Hashimoto, RMS, Yoshikazu Masuda, RMS, Reiko Neki, MD and Tomoaki Ikeda, MD**

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Review Article

# Role of Echocardiography in Assessing Pregnant Women With and Without Heart Disease

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**Abstract**

The cardiocirculatory changes during pregnancy and delivery are marked. In some diseases and conditions, the maternal and fetal risks are high. Echocardiography plays a very important role to diagnose and to follow up in pregnant women with heart diseases, because it is noninvasive and does not expose the patients to radiation. We reviewed the value of echocardiography to determine the conditions under which women with heart disease can tolerate pregnancy, and the fetomaternal prognosis for major heart diseases.

(J Echocardiogr 2008; 6: 29-38)

***Key words:*** pregnancy, heart disease, echocardiography, fetomaternal prognosis

## Introduction

With recent advances in cardiovascular and neonatal medicine, the number of patients with heart disease who reach childbearing age has increased, and the range and severity of heart diseases with which pregnancy and delivery are possible is expanding. Subsequently, guidelines have been prepared in various countries[1, 2]. In Japan, the Japanese Circulation Society (JCS) joint working group issued guidelines for the management of pregnancy and delivery in women with heart diseases in 2005 (JCS 2005 guidelines)[3]. The cardiocirculatory changes associated with pregnancy and delivery are marked, and in some diseases and conditions, the maternal and fetal risks are high. In this review article, we emphasized the value of echocardiography to (1) examine healthy pregnant women, (2) determine the conditions under which women with heart disease can tolerate pregnancy, and (3) determine the fetomaternal prognosis for major heart diseases.

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## 1. Echocardiographic findings and hemodynamic changes during pregnancy in healthy pregnant women

Echocardiography can assess the hemodynamic changes noninvasively, thus it is widely used to measure cardiocirculatory indexes during pregnancy and after delivery.

From the sixth week of gestation to the second trimester during pregnancy, through the mechanisms such as water and sodium retention mediated by the renin-aldosterone system stimulated by the estrogen increase, the volume of circulating plasma is increased by an average of 1.5 fold. Cardiac output measured by Doppler echocardiography also increases by approximately 50 percent. From weeks 20 to 24, stroke volume increases reaching its peak, and then heart rate increases by 10 to 20 beats/min (Figure 1)[4]. On the other hand, arterial pressure and systemic vascular resistance decrease[5].

During labor and delivery, oxygen consumption increases about three fold, and uterine contraction

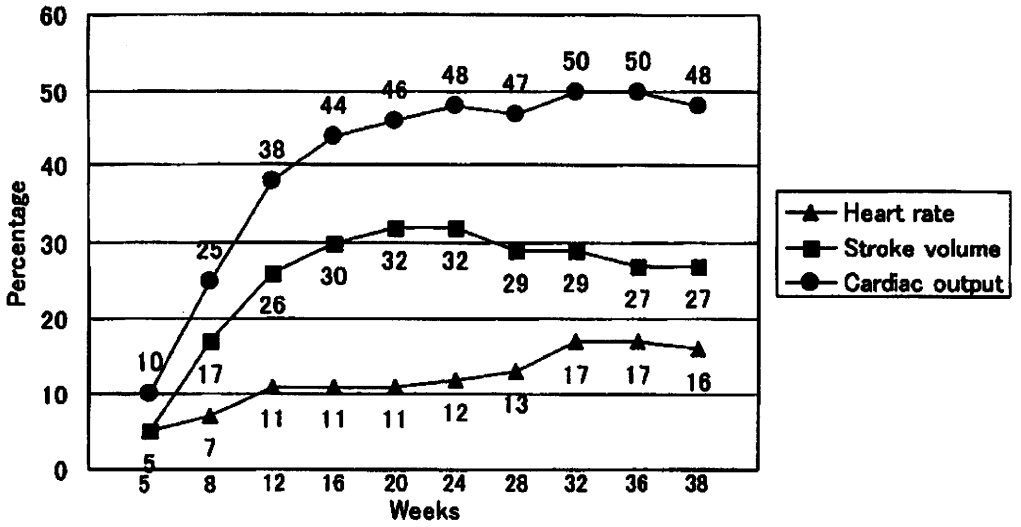


Fig. 1. Percent changes in heart rate, stroke volume, and cardiac output measured by echocardiography in the lateral position throughout pregnancy[4] (modified by and taken from the textbook "Braunwald's heart disease 7th edition, p1966")

accompanying labor increases the amount of circulating blood by 300-500 ml. At the same time, cardiac output increases by 15-25%, exceeding 8-10 L/min. Immediately after delivery, uterus-induced compression of the inferior vena cava is relieved, thereby rapidly elevating venous return. Cardiac output decreases by 10-20% within one hour of delivery. As the amount of circulating blood increases during pregnancy, transient overload persists for 4 to 6 weeks after delivery[6].

With regard to the changes in echocardiographic parameters, left ventricular (LV) end-diastolic and end-systolic dimensions and wall thickness increase, and contractile function enhances. Functional pulmonary, tricuspid and mitral regurgitation, and mild pericardial effusion are occasionally seen in normal pregnancy. About diastolic performance, findings such as significant increases in transmitral peak E velocity in the first trimester and peak A velocity in the third trimester of pregnancy have been reported[7]. Tissue Doppler echocardiography determined mitral annular early diastolic velocity (E') decreases, and late diastolic velocity (A') remains unaltered [8].

## 2. Required conditions for pregnancy based on echocardiographic findings

We have experienced about 70 deliveries of heart disease women over one year. Figure 2 shows the annual number of deliveries by women with heart disease in our hospital. While the number of patients with arrhythmia is almost constant, those with congenital heart disease or other heart diseases tend to increase.

In the past, medical decisions as to whether heart disease patients could become pregnant and deliver were based on the heart function classification system developed by the New York Heart Association (NYHA), and it has been generally accepted that class I or II women can become pregnant. Studies have shown that the maternal mortality for NYHA class I/II was <1% and for NYHA class III/IV was 5-15%[9], and the rate of maternal cardiovascular events such as heart failure, arrhythmia and cerebral infarction for NYHA class I was about 10% and for II/III/IV was about 30%. The rate of live-born infants for NYHA class I was about 80% and for II/III/IV was about 70%[10].

Recently, echocardiographic parameters have been widely used to determine the risk of pregnancy. A study of 562 pregnant women with heart diseases identified the following factors for poor maternal prognosis: prior cardiac event (heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia, NYHA functional class > II or cyanosis, left heart obstruction (mitral valve area < 2 $cm^2$, aortic valve area < 1.5 $cm^2$, or peak left ventricular outflow tract gradient > 30mmHg by echocardiography) and systemic ventricular dysfunction (ejection fraction < 40%). When assigning one point for each condition, the incidence of maternal cardiovascular events during pregnancy was

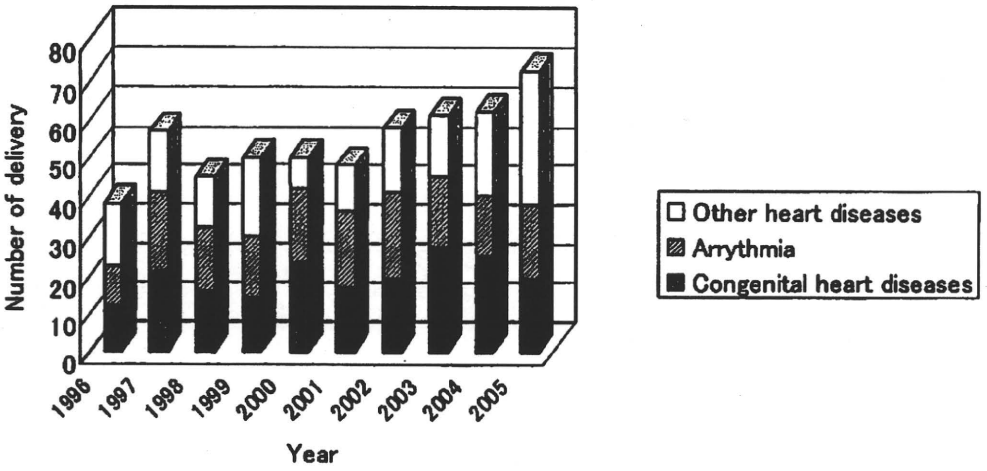


Fig. 2. The annual number of deliveries by women with heart disease at National Cardiovascular Center

Table 1. Multivariate analyses of maternal and neonatal risk predictors

| Complications | Predictor | Odds Ratio (95% CI) | P |
|---|---|---|---|
| Cardiac | Prior cardiac event or arrhythmia | 6 (3-14) | < 0.001 |
| | NYHA functional class > II or cyanosis | 6 (2-22) | 0.009 |
| | Left heart obstruction | 6 (3-14) | < 0.001 |
| | Systemic ventricular dysfunction | 11 (4-34) | < 0.001 |
| Neonatal | NYHA functional class > II or cyanosis | 3 (1.1-6.1) | 0.035 |
| | Heparin/warfarin during pregnancy | 3 (1.4-8.2) | 0.0093 |
| | Smoking | 2 (1.3-3.9) | 0.0045 |
| | Multiple gestation | 22 (6-85) | < 0.001 |
| | Left heart obstruction | 2 (1.01-2.9) | 0.044 |
| Postpartum hemorrhage | Peripartum heparin or warfarin | 7 (2-22) | 0.001 |
| | Cyanosis | 27 (4-177) | < 0.001 |

CI : Confidence Interval, NYHA : New York Heart Association
(Modified by and taken from Siu : Circulation, 104 (5) [11])

5% for a score of 0 point, 27% for a score of 1 point and 75% for a score of 2 or higher. In addition, the incidence of fetal complications such as premature delivery and low birth weight reached 20%, and severe complications such as respiratory distress syndrome, intracranial bleeding and death were confirmed in 5%. The factors that exacerbated fetal prognosis were NYHA class > II or cyanotic heart disease, anticoagulant therapy, smoking, multiple pregnancy and left ventricular obstruction (Table 1) [11]. In addition to the above factors, a recent study documented other risk factors; severe pulmonary regurgitation and right ventricular dysfunction with an odds ratio of 9.0 and 27.2, respectively [12].

Based on these results, the JCS 2005 guidelines list heart diseases that require close monitoring during pregnancy or should avoid pregnancy (Table 2) [3]. Echocardiography plays a pivotal role in assessing these conditions.

Table 2. Heart diseases that require careful monitoring during pregnancy and diseases with which pregnancy should be avoided [3]

| |
|---|
| 1. Pulmonary hypertension (Eisenmenger syndrome) |
| 2. Outflow tract obstruction (severe aortic valve stenosis : >40-50 mmHg) |
| 3. Heart failure (NYHA class: ≥ III, LVEF : <35-40%) |
| 4. Marfan's syndrome (Diastolic aortic diameter : >40 mm) |
| 5. Prosthetic valve |
| 6. Cyanotic disease (oxygen saturation : <85%) |

NYHA : New York Heart Association

## 3. Echocardiographic findings during pregnancy in cardiovascular diseases

Here, we describe major cardiovascular diseases in pregnancy with some case presentations.

### 3-1. Congenital heart disease

*3-1-1. Non-cyanotic heart disease*

Left-to-right shunts, such as atrial sepal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA) are sometimes diagnosed during pregnancy due to loud heart murmur from increased shunt volume caused by increased circulating blood volume (Figure 3). In patients with large shunt volume, decreases in peripheral vascular resistance balances out the increased blood volume, and in most cases, pregnancy and delivery are completed without any complications. However, caution must be exercised in the event of rapid bleeding, as peripheral vasoconstriction may increase shunt blood flow, decrease cardiac output and cause congestive heart failure, shock and ventricular fibrillation.

Masuda et al. reported changes in pulmonary output (Qp) and systemic output (Qs) measured by Doppler echocardiography in 17 pregnant women (10 with VSD and 7 with ASD) in our hospital. During pregnancy, both Qp and Qs increased in all patients, resulting in an insignificant change in Qp/Qs (Table 3) [13].

**(1) ASD:** When compared to normal pregnancy, the risks for miscarriage and premature birth are higher, and these conditions can accompany supraventricular arrhythmia or paradoxical emboli. One study found that when compared to pregnancy after ASD-closure surgery, pregnancy before surgery has higher risks for miscarriage and maternal cardiovascular events[14]. Hence, if surgery is indicated, it should be performed before pregnancy. Recently, non-invasive procedure to close ASD was developed as an alternative treatment. There is a case report of percutaneous closure of ASD during pregnancy[15].

**(2) VSD:** In patients with untreated VSD without heart failure which is discovered during pregnancy, there are few problems, except when there is marked aortic regurgitation (AR) due to right coronary cusp herniation. As shunt volume of VSD is exaggerated by marked AR during pregnancy, surgery is recommended before pregnancy.

In a study of 309 pregnancies in 126 pregnant women with congenital heart diseases including ASD and VSD, the incidence of miscarriage was 17%, average duration of pregnancy was 34 weeks, maternal mortality was 0%, and fetal heart disease was 2.5%[16].

*3-1-2. Non-cyanotic heart disease after surgical correction*

In general, if patients keep good cardiac function, pregnancy and delivery are tolerable. Echocardiography often shows cardiac constrictive signs (such as septal bounce and increased respiratory changes in transmitral/transtricuspid flow) in pregnant patients who had open heart surgery. We think that increased blood volume can cause such a condition, and some should be carefully observed.

*3-1-3. Cyanotic heart disease after surgical correction*

In patients with good functional class (NYHA class I or II) and sinus rhythm, pregnancy and delivery are possible, but the incidence of miscarriage is high.

Repaired tetralogy of Fallot (TOF): In patients who underwent corrective surgery, pregnancy and delivery are possible. In one study of 112 pregnancies in 43

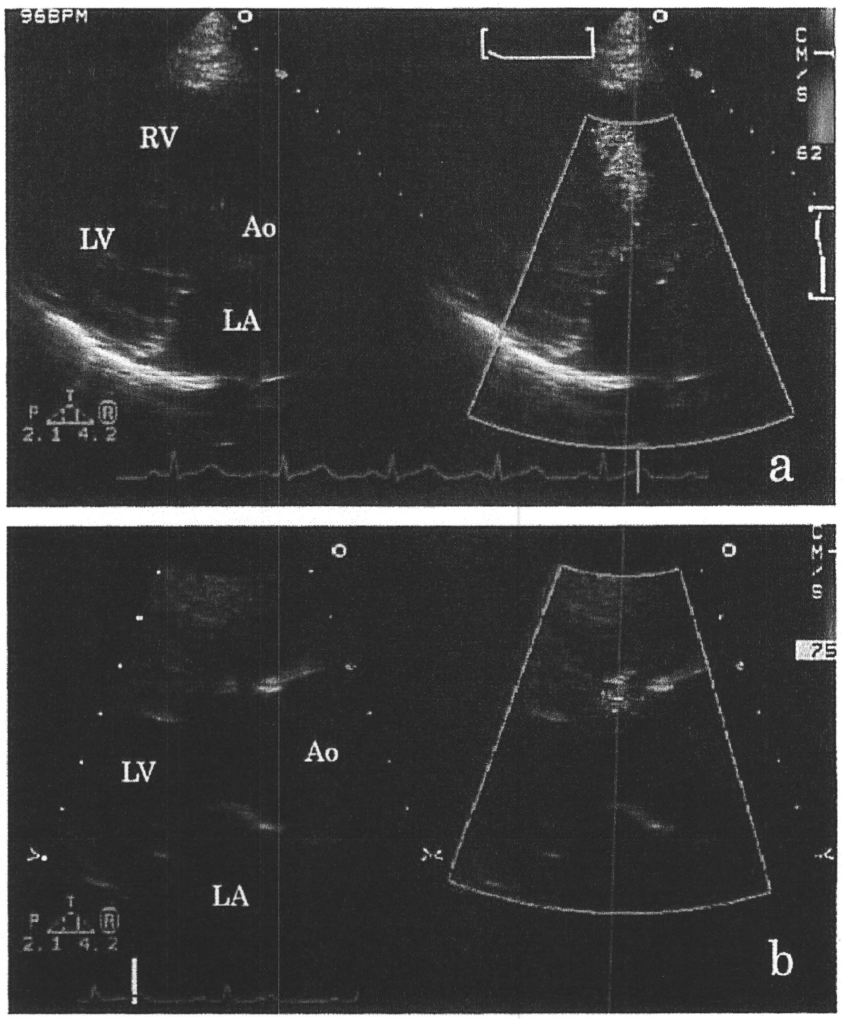


Fig. 3. Echocardiograms from a 29-year-old woman who was diagnosed with a small ventricular septal defect during her first pregnancy
Shunt flow increased in third trimester of her pregnancy (a) compared with 1 year after her delivery (b). Her left atrial dimension was 44mm during pregnancy. In contrast, it was 38mm after delivery.

Table 3. Changes in Qp/Qs measured by Doppler echocardiogram in 17 pregnant women with VSD or ASD

| | Early phase of pregnancy (mean 13.8th week of gestation) | Early phase of pregnancy (mean 32.1th week of gestation) | Postpartum (mean 7.6 weeks after delivery) |
|---|---|---|---|
| Qp/Qs ratio in all patients (n=17) | 1.78 ± 0.99 | 1.80 ± 0.76 | 1.56 ± 0.54 |
| Qp/Qs ratio in VSD patients (n=10) | 1.27 ± 0.17 | 1.52 ± 0.44 | 1.38 ± 0.38 |
| Qp/Qs ratio in ASD patients (n=7) | 2.50 ± 1.23 | 2.20 ± 0.96 | 1.88 ± 0.70 |

Qp; pulmonary output, Qs; systemic output, VSD; ventricular septal defect, ASD; atrial septal defect

patients of repaired TOF, delivery rate was 73%, and six women (14%) had cardiac events[17]. Pregnancy risk factors included: residual VSD, moderate to severe pulmonary valve stenosis and insufficiency, aortic insufficiency, pulmonary hypertension, dilated aorta ( ≥40 mm), ventricular dysfunction, and past history of tachyarrhythmia.

We experienced 14 deliveries in 13 patients of repaired TOF from 1998 to 2006. Three patients (23.1%) needed diuretics or bed rest because of pulmonary hypertension assessed by Doppler echocardiography.

*3-1-4. Cyanotic heart disease without pulmonary hypertension*

During pregnancy, systemic vascular resistance decreases to elevate right-to-left shunt, thus exacerbating cyanosis. While the incidence of complications is high in pregnant women with cyanotic heart diseases, cyanosis is treatable and mortality risk is low. However, fetal prognosis is poor, and in severe cyanosis, fetal development is hindered (the rate of live births is 12% at ≤85% oxygen saturation). In one study of 96 pregnancies in 44 patients with cyanotic heart diseases, maternal cardiac complications were seen in 32%, and the rate of live births was 43%. Hemoglobin≦ 16g/dL and oxygen saturation≦ 85% were found to be prognosticators[18].

**3-2. Pulmonary hypertension**

In patients with primary pulmonary hypertension, maternal mortality exceeds 50%, and pregnancy is contraindicated. In patients with Eisenmenger syndrome, maternal mortality ranges from 30 to 70%, and fetal mortality is as high as 50%[19, 20]. Hence, if patients with these diseases wish to continue their pregnancies, they must be admitted to a specialized hospital after week 20 of gestation to be treated with resting, oxygen administration and anticoagulation[21]. In our hospital, we experienced 2 (15.4%) maternal deaths among 13 patients with pulmonary hypertension[22].

Table 4. Maternal and fetal risk for patients with valvular disorders

| | Low risk for mother and child | High risk for mother and child |
|---|---|---|
| Aortic stenosis | · Asymptomatic<br>· Normal LV function<br>· Mild to moderate stenosis : Systolic pressure gradient<40 ~50 mmHg | · Severe stenosis: systolic pressure gradient>40~50 mmHg<br>· LV dysfunction |
| Aortic insufficiency | · NYHA class I/II<br>· Normal LV function | · NYHA class III/IV<br>· LV dysfunction |
| Mitral insufficiency | · NYHA class I/II<br>· Normal LV function | · NYHA class III/IV<br>· LV dysfunction |
| Mitral stenosis | · NYHA class I/II<br>· Mild to moderate stenosis Valvular area:>1.5 $cm^2$ Pressure gradient:<5 mmHg<br>· Without pulmonary hypertension | · NYHA class III/IV<br>· Severe stenosis Valvular area:<1.5 $cm^2$ Pressure gradient:>5 mmHg<br>· With pulmonary hypertension (≥75% systemic blood pressure) |
| High risks for mothers<br>Left ventricular dysfunction (LVEF:<40%)<br>Past history of heart failure<br>Anticoagulation therapy during pregnancy (prosthetic valve patients)<br>Past history of cerebral embolism or transient cerebral ischemia<br>Aortic regurgitation accompanying Marfan's syndrome | | |
| High risks for children<br>Mother's age: <20 years or >35 years<br>Anticoagulation therapy during pregnancy (prosthetic valve patients)<br>Exposure to smoking, drinking or other environmental factors during pregnancy | | |

LV: left ventricular, NYHA: New York Heart Association, EF: ejection fraction
(Modified US ACC/AHA guidelines[25])

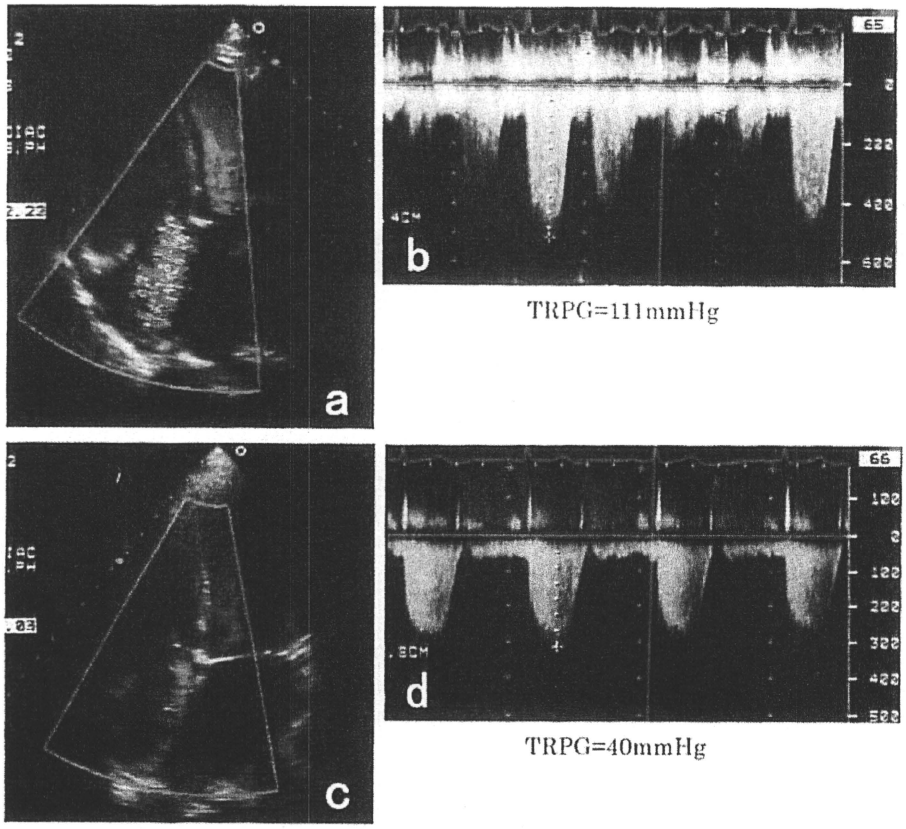


Fig. 4. Doppler echocardiograms from a woman with severe mitral stenosis
A thirty-one year-old woman with severe mitral stenosis (estimated mitral valve area= 0.6 $cm^2$) showed increased tricuspid regurgitation in her 26-week gestation (a) and decreased after cesarean section (c). The RA-RV pressure gradients derived by tricuspid regurgitant velocity (TRPG) also changed from 111 mmHg in her 26-week gestation (b) to 40 mmHg after cesarean section (d).

### 3-3. Patients with valvular disorders or prosthetic valves

During pregnancy, increased circulating blood volume often reduces cardiac function in patients with valvular heart diseases. The incidence of congestive heart failure and arrhythmia is about 40 and 15%, respectively, although maternal mortality is low[23]. Table 4 shows the JCS 2005 pregnancy guidelines for patients with valvular disorders established based on ACC/AHA guidelines[3, 24, 25].

Generally, patients with stenosis are less tolerable for volume overload than patients with regurgitation. We recommend patients with severe mitral or aortic stenosis to be treated by percutaneous transvenous mitral commissurotomy or operation before pregnancy. Figure 4 shows a 31 year-old woman with severe mitral stenosis who showed worsening pulmonary hypertension during her pregnancy and needed medical treatment and a cesarean section.

In patients with mechanical valves, because warfarin is teratogenic, heparin is used from weeks 6 to 12 of gestation, and then they are followed by subcutaneous low-molecular-weight heparin or oral warfarin with another switch to heparin at weeks 34 to 36. The risk for bleeding and embolization is high for both mothers and children. We reported pregnancy outcome in women with prosthetic mechanical valve replacement[26]. Among 16 pregnancies in 12 women with mechanical heart valve, 8 women (50%) had cesarean live births. Two babies died during the neonatal period. Four cases ended in early miscarriage, and one case ended in intrauterine fetal death. Therapeutic abortion was performed in 3 cases. Three mothers developed valve thrombosis, and one died from heart failure.

### 3-4. Marfan's syndrome

During pregnancy, estrogen and other hormones make vessels more fragile, and as a result, in pregnant

women with Marfan's syndrome, the risk for aortic dissection is higher than in non-pregnant women. In patients with annuloaortic ectasia ( ≥44 mm), pregnancy without replacement surgery is contraindicated. At 40-44 mm, while the risks are high, pregnancy and delivery are possible with conservative therapy although weekly echocardiographic observation is desirable. At <40 mm, normal delivery is possible. Under general anesthesia, cesarean section is performed, and blood pressure and pain management are very important.

We reviewed 8 pregnant patients with Marfan's syndrome experienced in our hospital[27]. Aortic dissection occurred in 3 patients (37.5%), one of whom developed rapid dilatation of the ascending aorta during her pregnancy and needed Bentall operation. Luckily, however, all patients tolerated the pregnancy well, with favorable maternal and fetal outcomes. Follow-up echocardiography showed no apparent worsening of cardiovascular status attributable to pregnancy except for one patient. In conclusion, dilatation of the ascending aorta during pregnancy is an important predictor for aortic dissection, and echocardiography must be performed weekly or biweekly.

### 3-5. Cardiomyopathy

Among pregnant women with hypertrophic cardiomyopathy, maternal mortality is around 1%, and most patients can go through pregnancy. However, in about half of the patients who had symptoms before pregnancy, the NYHA functional class was exacerbated (NYHA class III/IV) during pregnancy[28]. We often recognize elevated intraventricular pressure gradient and pulmonary hypertension in obstructive patients. Figure 5 shows a clinical course of a pregnant woman with hypertrophic obstructive cardiomyopathy. In patients at high risk for sudden death, such as those with ≥30 mm maximum wall thickness, past history of cardiac arrest or ventricular tachycardia and family history of sudden death, it is essential to carefully monitor pregnancy and delivery.

In dilated cardiomyopathy, because prognosis is poor, especially for young patients, and most patients take medication such as an ACE inhibitor, very few patients become pregnant. In general, maternal prognosis is also poor, and as a result, caution must be exercised, even in patients with mild cardiac dysfunction. In our hospital, in fact, we experienced 4 maternal deaths (death within 2 years after delivery) out of 8 patients with cardiomyopathy[22]. Figure 6 shows

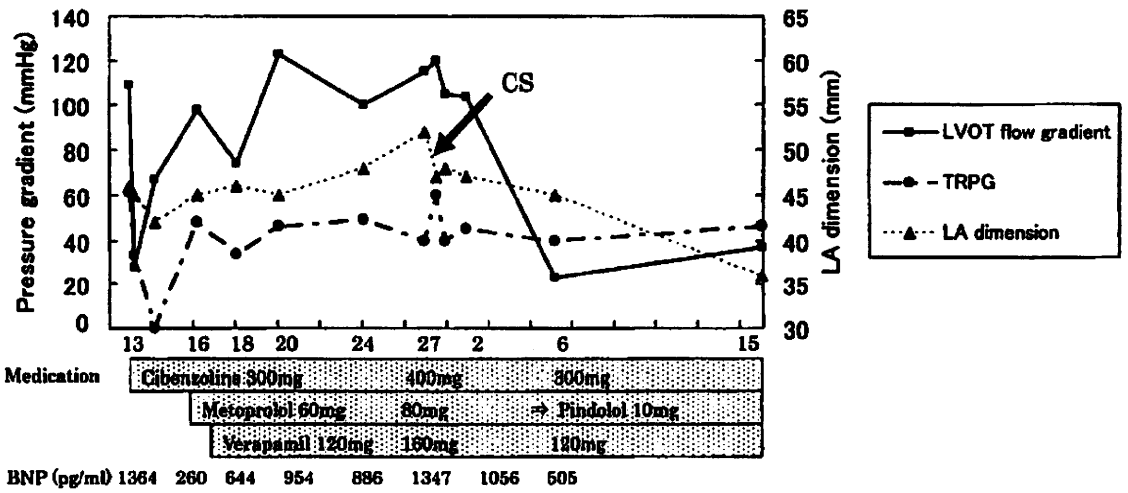


Fig. 5. The clinical course of a 30 year-old pregnant woman with hypertrophic obstructive cardiomyopathy
The patient was admitted during her 13th week of gestation. After she started to take cibenzoline, left ventricular outflow (LVOT) pressure gradient decreased from 109 mmHg to 28 mmHg and RA-RV pressure gradient derived by tricuspid regurgitant velocity (TRPG) also decreased. Then, the velocity gradually increased again, and additional medications were not effective to decrease it. At her 27th week of gestation, she started to complain of dyspnea on mild effort, and echocardiography showed increased left atrial (LA) dimension from 48 mm to 52 mm and increased mitral regurgitation from 2/4 to 3/4. She was taken for a cesarean section (CS) 3 days later. After delivery, LVOT pressure gradient decreased to around 30 mmHg.

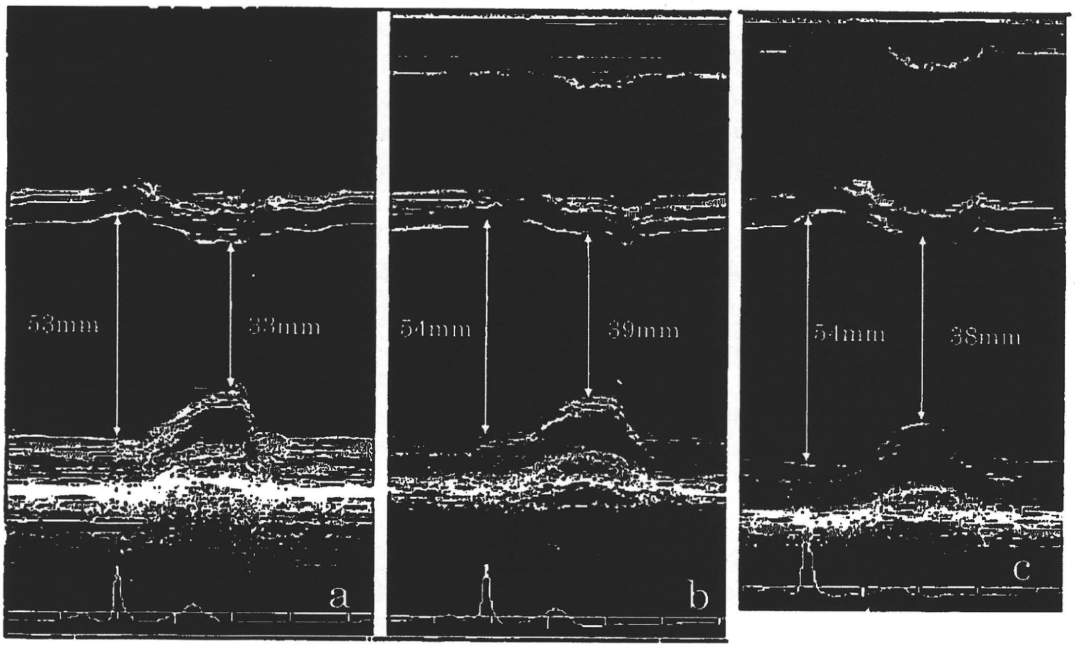


Fig. 6. M-mode echocardiographic changes in a woman with dilated cardiomyopathy (DCM) during her pregnancy and after delivery
The patient was a 26 year-old woman with slightly dilated left ventricle and history of ventricular tachyarrhythmia. At 16th week of gestation, left ventricular end-diastolic /end-systolic dimensions (LVDd/Ds) were 53/33 mm with fractional shortening (FS) of 37.7% (a) and at 36th week of gestation, LVDd/Ds were 54/39 mm (FS, 27.8%) (b). At 8 weeks after delivery, LVDd/Ds were 54/38 mm (FS, 29.6%) (c). Even in a mild DCM patient, peripartum left ventricular function is decreased.

changes in cardiac function during pregnancy and after delivery in a patient with dilated cardiomyopathy.

In peripartum cardiomyopathy, cardiac function recovers in about half of patients, but in this relatively rare disease, 20% of patients die or require a heart transplant. In patients with a past history of peripartum cardiomyopathy, multiple deliveries would worsen cardiac function, and as a result, caution must be exercised if a patient becomes pregnant again. The risk for cardiac events during first or subsequent pregnancy is dependent on the severity of left ventricular dysfunction[29], and assessment of left ventricular function by echocardiography is important.

## 4. Conclusions

In pregnant women with heart diseases, echocardiography plays a very important role because it is noninvasive and does not expose the patients to radiation. Long-term maternal prognosis has not been fully clarified, and there have been few studies investigating the relationship between echocardiographic findings and prognosis. Moreover, there are no reports about changes of cardiac function during pregnancy measured by new echocardiographic techniques such as tissue Doppler imaging and three-dimensional echocardiography[30, 31]. Further investigations are thus warranted.

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**Malignant Perinatal Variant of Long-QT Syndrome Caused by a Profoundly Dysfunctional Cardiac Sodium Channel**

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# Malignant Perinatal Variant of Long-QT Syndrome Caused by a Profoundly Dysfunctional Cardiac Sodium Channel

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***Background***—Inherited cardiac arrhythmia susceptibility contributes to sudden death during infancy and may contribute to perinatal and neonatal mortality, but the molecular basis of this risk and the relationship to genetic disorders presenting later in life is unclear. We studied the functional and pharmacological properties of a novel de novo cardiac sodium channel gene (*SCN5A*) mutation associated with an extremely severe perinatal presentation of long-QT syndrome in unrelated probands of different ethnicity.

***Methods and Results***—Two subjects exhibiting severe fetal and perinatal ventricular arrhythmias were screened for *SCN5A* mutations, and the functional properties of a novel missense mutation (G1631D) were determined by whole-cell patch clamp recording. In vitro electrophysiological studies revealed a profound defect in sodium channel function characterized by ≈10-fold slowing of inactivation, increased persistent current, slowing of recovery from inactivation, and depolarized voltage dependence of activation and inactivation. Single-channel recordings demonstrated increased frequency of late openings, prolonged mean open time, and increased latency to first opening for the mutant. Subjects carrying this mutation responded clinically to the combination of mexiletine with propranolol and survived. Pharmacologically, the mutant exhibited 2-fold greater tonic and use-dependent mexiletine block than wild-type channels. The mutant also exhibited enhanced tonic (2.4-fold) and use-dependent block (≈5-fold) by propranolol, and we observed additive effects of the 2 drugs on the mutant.

***Conclusions***—Our study demonstrates the molecular basis for a malignant perinatal presentation of long-QT syndrome, illustrates novel functional and pharmacological properties of *SCN5A*-G1631D, which caused the disorder, and reveals therapeutic benefits of propranolol block of mutant sodium channels in this setting. (***Circ Arrhythmia Electrophysiol.*** **2008;1:370-378.)**

**Key Words:** antiarrhythmia agents ■ arrhythmia ■ death, sudden ■ heart arrest ■ ion channels

Sudden unexplained death attributable to cardiac arrhythmia may occur at any age. When death occurs during infancy for no apparent reason, a diagnosis of the sudden infant death syndrome (SIDS) may be appropriate.[1,2] Recent evidence suggests that 9% to 10% of SIDS victims carry germ line mutations in arrhythmia susceptibility genes such as those associated with the congenital long-QT syndrome (LQTS).[3] Anecdotally, ventricular arrhythmias occurring during the perinatal or neonatal periods are associated with a poor prognosis and a low survival rate.[4–7] Whether cardiac arrhythmia susceptibility presenting in early life represents a biologically distinct disease is an unanswered question.

**Clinical Perspective see p 378**

Mutations in *SCN5A* encoding the cardiac voltage-gated sodium channel $Na_v1.5$ have been associated with a spectrum of increased sudden death risk extending from fetal life to adulthood. Recurrent third trimester fetal loss has been observed in the setting of occult *SCN5A* mutations.[8] In older children and adults with LQTS of known genotype, only ≈10% carry mutations in *SCN5A*,[9–11] but the proportion of *SCN5A* mutations among SIDS victims with an LQTS gene defect approaches 50%.[3] Further, among older children and adults with LQTS those individuals harboring *SCN5A* mutations exhibit a greater likelihood of severe symptoms including sudden death when compared with the majority of

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individuals who carry mutations in 2 potassium channel genes (*KCNQ1*, *KCNH2*).[9,11] The higher proportion of *SCN5A* mutations among SIDS victims with known genotype when compared with older LQTS subjects might be explained by negative selection for more deleterious alleles. Support for this hypothesis requires evidence that mutations with greater functional consequences are responsible for severe and earlier onset arrhythmia syndromes.

Here, we present an extensive characterization of a novel *SCN5A* mutation that occurred de novo in unrelated and ethnically distinct newborns. In mutation carriers, life-threatening ventricular arrhythmias occurred within hours of birth. The mutation caused a profound degree of sodium channel dysfunction that was more severe than that observed for any previous *SCN5A* variant. Despite the extreme nature of the mutation and the associated dire clinical scenario, the subjects survived owing to prompt therapeutic interventions including treatment with the combination of mexiletine and propranolol, 2 drugs that exhibited enhanced and additive activity against the mutant allele. These observations illustrate the role of severe sodium channel mutations in a malignant perinatal variant of LQTS and successful use of combination pharmacotherapy to prevent perinatal mortality in this setting.

## Methods

### Molecular Genetics

Informed consent for performing genetic studies was obtained using methods approved by the Ethics Review Board of IRCCS Fondazione Policlinico San Matteo (Pavia, Italy) or by the Institutional Research Board and Ethics Committee and the Committee on Genetic Analysis and Gene Therapy of the National Cardiovascular Center (Suita, Japan). Genomic DNA was isolated from whole blood and coding exons of *SCN5A*, *KCNQ1*, *KCNH2*, *KCNE1*, and *KCNE2* were screened for genetic variants using previously described methods.[12,13]

### Mutagenesis and Heterologous Expression of Na Channels

Mutations were engineered in a human heart sodium channel ($Na_V1.5$) cDNA (hH1) using recombinant polymerase chain reaction. Final constructs were assembled in the mammalian expression plasmid pRc/CMV-hH1 and then sequenced to verify creation of the mutation and to exclude polymerase errors. Cells (tsA201) were transiently transfected with pRc/CMV-hH1 or mutants using FuGene6 (Roche Diagnostics) combined with a bicistronic plasmid (pEGFP-IRES-hβ1) encoding enhanced green fluorescent protein and the human β1 subunit (hβ1) under the control of the cytomegalovirus immediate early promoter. Additional methods are provided in an online supplement.

### Statement of Responsibility

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

## Results

### Malignant Perinatal Arrhythmia Associated With a Novel *SCN5A* Mutation

We identified a novel *SCN5A* mutation in 2 unrelated newborns that experienced life-threatening perinatal ventricular arrhythmias. The first subject was an Italian male

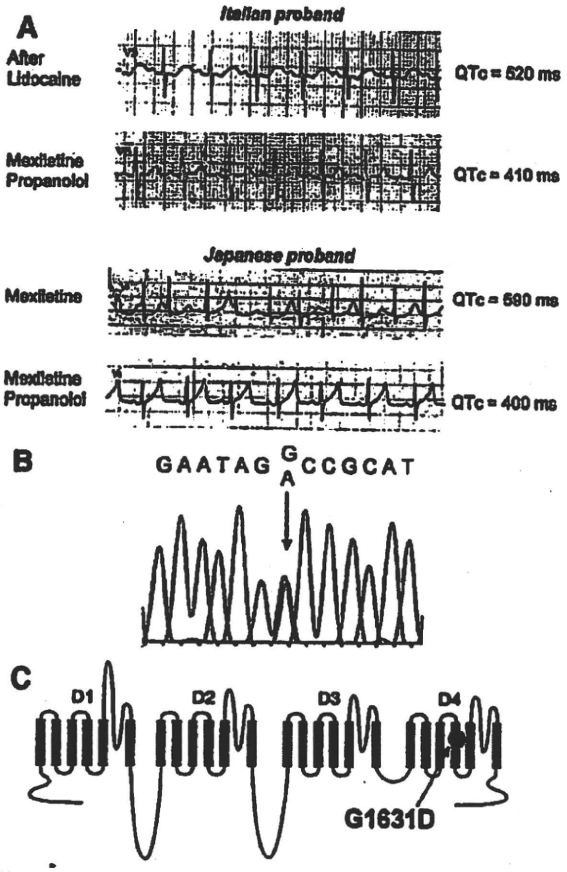


Figure 1. Electrocardiographic responses to pharmacotherapy and genotype of probands. A, Representative ECG traces (lead V5) showing responses to mexiletine and propranolol for the Italian and Japanese probands. Rate-corrected QT interval (QTc) measurements are indicated to the right of each tracing. B, Sequencing electropherogram (Italian proband) illustrating heterozygosity for a G to A mutation corresponding to G1631D. C, Location of G1631D in the predicted transmembrane topology of $Na_V1.5$.

delivered by emergency C-section at 32-weeks gestation for abnormal fetal heart rhythm. Initially, he appeared healthy (APGAR score 8) but then, within hours of his birth, developed polymorphic ventricular tachycardia with periods of bradycardia and frequent premature ventricular beats. Initial treatments with intravenous magnesium and isoproterenol were not effective, but administration of intravenous lidocaine suppressed ventricular arrhythmias and restored sinus rhythm revealing a prolonged QTc interval (520 ms). Empirical treatment with propranolol (1.3 mg/kg/d) and mexiletine (11 mg/kg/d) controlled arrhythmias and normalized the QTc (410 ms) (Figure 1A). One month after discharge, the infant survived an episode of ventricular fibrillation. Ventricular arrhythmia was further controlled by rapid pacing (120 bpm) with increased dosages of propranolol (3 mg/kg/d) and mexiletine (16 mg/kg/d). During the following 12 months, the child exhibited no further ventricular arrhythmias but required recurrent hospitalizations for paroxysmal atrial flutter that was eventually controlled by

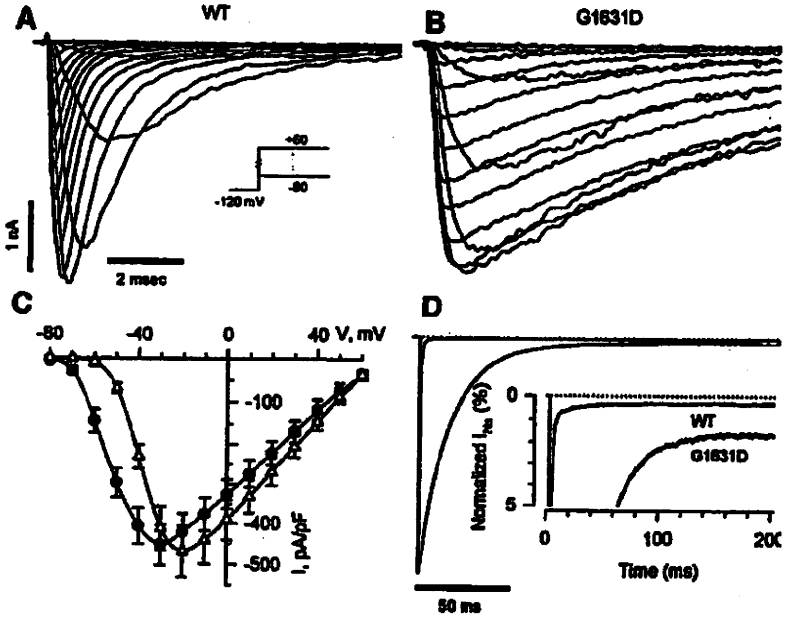


Figure 2. Whole-cell current recordings of WT and G1631D sodium channels. Representative sodium currents recorded from cells expressing WT (A) or G1631D (B) elicited by depolarizing steps from −80 mV to +60 mV in 10-mV increments from holding potential −120 mV. C, Comparison of current-voltage relationships for WT (n=15) and G1631D (n=16). Current is normalized to cell capacitance to give sodium current density. D, Increased tetrodotoxin (TTX)-sensitive persistent sodium currents for G1631D. Peak sodium currents were normalized. The zero-current level is indicated by a dotted line. The inset shows an expanded *y* axis scaled to emphasize the relative proportion of persistent current for WT (n=8) and G1631D (n=9).

ablation. The child has survived beyond the age of 26 months without further ventricular or atrial arrhythmias.

The second proband was a Japanese male delivered by emergency C-section at 34-weeks gestation because of ventricular arrhythmia (torsade de pointes, TdP) documented in utero by magnetocardiography. Initial APGAR scores were 8 and 9, but his QTc interval was 567 ms and he had multiple episodes of TdP. Intravenous injection (3 mg/kg) followed by continuous infusion of mexiletine abolished TdP. He was discharged on oral mexiletine (20 mg/kg/d) but was readmitted for treatment of recurrent TdP approximately 2 months later (QTc=590 ms). Continuous infusion of mexiletine combined with oral mexiletine (serum drug concentration: 1.3 to 1.4 μg/mL) considerably abbreviated the QTc (462 to 499 ms) but did not completely suppress episodes of TdP. The addition of continuous infusion propranolol (0.5 mg/kg/d, serum drug concentration: 18.4 to 25.1 ng/mL) further shortened QTc (395 to 424 ms) and fully suppressed ventricular arrhythmias. Finally, combination therapy with oral mexiletine and oral propranolol was effective in suppressing ventricular arrhythmias through age 8 months (Figure 1A).

A novel *SCN5A* missense mutation (G1631D) was discovered in both probands (Figure 1B). Family histories were negative for arrhythmia syndromes. The results of ECG testing were normal for both sets of parents, and they were mutation negative. Paternity testing demonstrated that the mutation was de novo in both cases. No other mutations were identified in *SCN5A*, *KCNQ1*, *KCNH2*, *KCNE1*, or *KCNE2* in either proband.

## Profound Dysfunction of G1631D Channels

The mutation results in substitution of a highly conserved glycine residue with a negatively charged glutamic acid in the S4 segment of domain 4 (D4/S4; Figure 1C). This residue is 100% conserved in all known voltage-gated sodium channel sequences from several diverse phyla. This structural domain in sodium channels participates as a component of the voltage-sensor important for activation and inactivation.[14,15] Introduction of a negatively charged side group into this domain was predicted to have a significant functional effect. To test this hypothesis, we engineered G1631D in recombinant human $Na_V1.5$ for heterologous expression and then performed electrophysiological studies.

Figure 2 illustrates the general functional properties of wild-type (WT) and mutant $Na_V1.5$ channels expressed heterologously in human tsA201 cells. Representative whole-cell current tracings demonstrate that the mutant exhibits a profound level of dysfunction characterized by substantial delays in activation and inactivation. Overall current density was similar between cells expressing WT or mutant channels but there was a positive shift in the peak current-voltage (I-V) relationship for the mutant (Figure 2C). Mutant channels exhibited increased steady-state persistent current measured 200 ms after the peak transient current (Figure 2D; persistent current as % of peak current: WT, 0.31±0.04%, n=8; G1631D, 1.63±0.31%, n=9; $P<0.001$). Although increased persistent current is characteristic of *SCN5A* mutations associated with LQTS,[16,17] no previously characterized mutation had such a profound inactivation defect.

Figure 3 illustrates quantitative assessments of activation and inactivation. Mutant channels exhibited a global slowing of activation across the range of tested potentials as assessed by time to peak current (Figure 3A). Similarly, G1631D exhibited a profound slowing of inactivation as illustrated by the voltage dependence of inactivation time constants (Figure 3B). The degree of slowing of inactivation was approximately 10-fold compared with WT. The mutant also exhibited significant depolarizing shifts in the voltage dependence of activation (+12 mV) and steady-state inactivation (+14 mV; Figure 3C and 3D; supplemental Table I, available online). These asymmetrical depolarizing shifts in activation and steady-state inactivation predict an increased window current

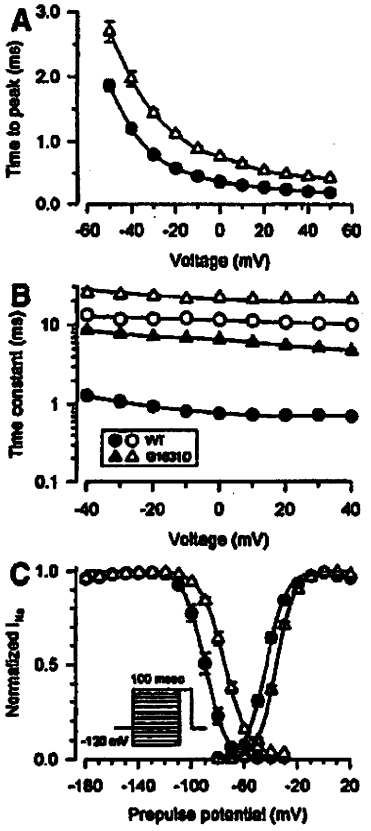


Figure 3. Activation and inactivation of WT and mutant channels. A, Time to peak activation in the voltage range of −50 to +50 mV. Differences between WT (n=15) and G1631D (n=16) were significant at the $P<0.001$ level for all tested voltages. B, Voltage dependence of inactivation time constants (same number of replicates as in A). Filled and open symbols indicate fast and slow component values, respectively. C, Voltage dependence of activation and steady-state inactivation elicited by a 100-ms conditioning pulse to various voltages (same number of replicates as in A).

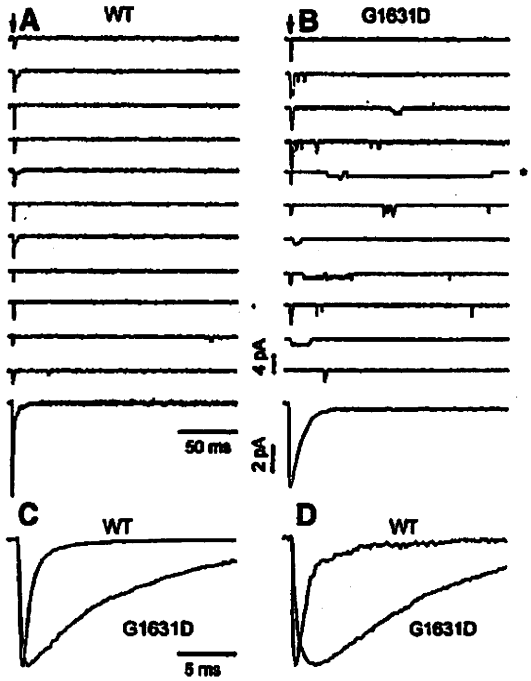


Figure 5. Single-channel properties of WT and G1631D channels. Sodium channel activities recorded at −20 mV from a multichannel outside-out patch excised from a cell expressing WT (A) or G1631D (B). Vertical arrows indicate the onset of patch depolarization from −120 mV to −20 mV. Lower traces show the ensemble averaged current obtained from 100 consecutive traces for WT and G1631D, respectively. C and D are comparisons of normalized and superimposed current traces of WT and G1631D at test potential of −20 mV from whole-cell recordings (C) and single-channel recordings (D).

defined as the overlap of these 2 curves (see Supplemental Figure I).

In Figure 4A, the time course of recovery from inactivation after a 100-ms conditioning pulse illustrates that the mutant has profound slowing of recovery. This difference was explained by a larger slow component of recovery from inactivation as determined by double exponential fitting (see Supplemental Table I). For WT channels, the majority of recovery occurs with a time constant of approximately 10 ms. By contrast for G1631D channels, the predominant fraction of channels recover from inactivation with a time constant of approximately 100 ms. The marked slowing of recovery from inactivation exhibited by G1631D correlated with a greater loss of channel availability during repetitive membrane depolarizations at frequencies exceeding 1 Hz (Figure 4B).

These profound gating abnormalities were correlated with aberrant single-channel events. Figure 5 illustrates representative single-channel recordings from cells expressing WT or mutant channels. Wild-type channels exhibited brief and transient openings clustered at the onset of the test depolarization. By contrast, the mutant exhibited a marked increase

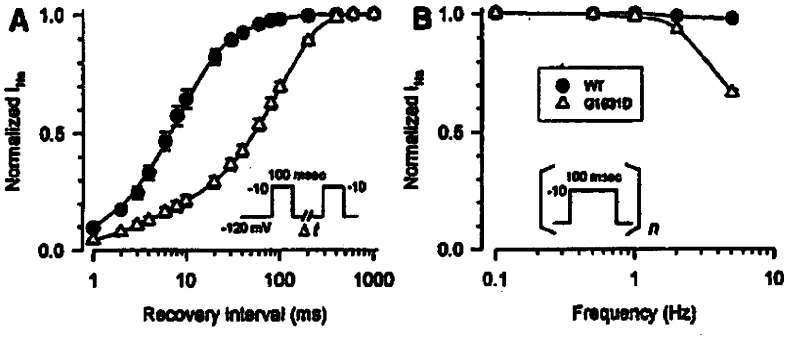


Figure 4. Recovery from inactivation. A, Time course of recovery from inactivation for WT (n=12) and G1631D (n=16) was elicited using the 2-pulse protocol shown in the inset. Time constants and fractional amplitudes are given in supplemental Table I. B, Activity dependent loss of channel availability following trains of 100 ms pulses to −10 mV from a holding potential of −120 mV applied at the frequency indicated (n=10 to 18 cells). Residual current following the 100th pulse was normalized to the first pulse current amplitude.

in probability of late reopenings and occasional prolonged openings (asterisk). Single-channel conductance levels were similar for WT (24pS) and G1631D (25pS), but mutant channels exhibited significantly longer latency to first opening (WT: 0.59±0.03 ms; G1631D: 1.15±0.03 ms; n=3; $P<0.001$), increased mean open time (WT: 0.34±0.09 ms; G1631D: 0.98±0.03 ms; n=3; $P=0.029$), and increased $NP_o$ (WT:. 0.14±0.02; G1631D: 0.22±0.03; n=3; $P=0.042$) when assessed at a test pulse of −20 mV. Ensemble averaged currents derived from single-channel records closely resemble those obtained from whole-cell recordings. These findings collectively indicate that G1631D causes a fundamental defect in channel activation and inactivation associated with dramatic clinical consequences.

## Enhanced Mexiletine Sensitivity of G1631D Channels

Despite the profound nature of the sodium channel dysfunction caused by G1631D, both probands survived likely because of prompt intervention including pharmacological treatments. We compared the effect of mexiletine on WT and mutant channels. Figure 6A illustrates the responses of WT and G1631D to repetitive membrane depolarizations delivered at a frequency of 1 Hz in the presence of mexiletine (100 μmol/L). Both channels exhibited an initial drop in channel availability followed by further use-dependent loss of activity, but the effect is substantially greater for G1631D suggesting that the mutant has enhanced mexiletine sensitivity. Concentration-response relationships for tonic (Figure 6B) and use-dependent (Figure 6C) mexiletine block of WT and G1631D supported this hypothesis. Mexiletine block of WT channels exhibited $EC_{50}$ values of 120.9 μmol/L and 50.9 μmol/L for tonic and use-dependent block, respectively. By contrast, G1631D was 1.8-fold and 2.8-fold more sensitive to tonic ($EC_{50}$ 66.7 μmol/L) and use-dependent ($EC_{50}$ 18.3 μmol/L) mexiletine block, respectively. Further, mexiletine induced a hyperpolarizing shift in steady-state inactivation of mutant channels such that this property became more similar to WT channels (G1631D $V_{½}$: no drug, −74.8±1.1 mV, n=16; 3 μmol/L mexiletine, −85.5±1.3 mV, n=9; $P<0.001$). By contrast, the same drug concentration has no significant effect on steady-state inactivation of WT channels (WT $V_{½}$: no drug, −89.3±1.1 mV, n=16; 3 μmol/L mexiletine, −86.6±3.2 mV, n=6; NS). Mexiletine also had moderate effects on the kinetics of G1631D inactivation (Figure 6B and 6C), illustrated by significant reductions in the time constants for inactivation, and significantly reduced the level of persistent current (no drug: 1.63±0.31%, n=9; 10 μmol/L mexiletine, 0.54±0.06%, n=8; $P=0.0098$).

## Propranolol Block of WT and G1631D Channels

We also considered the role of propranolol in modulating mutant sodium channel behavior. Propranolol is a widely used β-adrenergic receptor antagonist, but early studies indicated that this drug also exhibits antiarrhythmic (membrane stabilizing) properties at high serum concentrations possibly from effects on voltage-gated sodium channels.[18,19] Figure 7A illustrates that both WT and G1631D channels are blocked by 3 μmol/L propranolol during repetitive stimula-

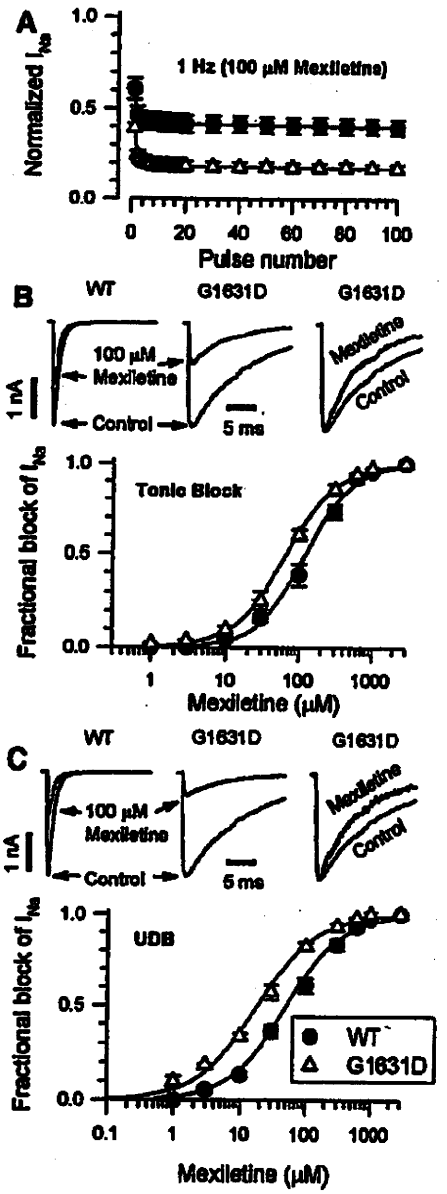


Figure 6. Effects of mexiletine on WT and G1631D. A, Mexiletine (100 μmol/L) block of WT (n=8) and G1631D (n=8) during a 1-Hz train of depolarizing pulses to −10 mV from a holding potential of −120 mV. B, Tonic mexiletine block of WT and G1631D. Upper traces (left, middle) illustrate the effects of 100 μmol/L mexiletine during a single depolarizing voltage step to −10 mV. Normalized traces (right) recorded in the absence (control) or presence of drug illustrate the effect of mexiletine on the inactivation time course. The plot illustrates the concentration-response relationships for tonic block by mexiletine (each data point represents the mean of 4 to 12 cells). C, Use-dependent mexiletine block of WT and G1631D. Upper traces (left, middle) illustrate the steady-state effects of 100 μmol/L mexiletine during a 1-Hz pulse train. Normalized traces (right) recorded in the absence (control) or presence of drug (100th pulse) illustrate the effect of mexiletine on the inactivation time course. Time constants in the absence of drug were: $\tau_1$=7.7±0.7 ms, $\tau_2$=19.7±0.6 ms, n=8; and in the presence of 100 μmol/L mexiletine: $\tau_1$=4.5±0.7 ms, $\tau_2$=10.9±1.0 ms, n=8 ($P=0.0085$ for $\tau_1$; $P<0.0001$ for $\tau_2$). The plot illustrates the concentration-response relationships for use-dependent block by mexiletine (each data point represents the mean of 4 to 12 cells). The lines in B and C were fit to the data according to the Hill equation.

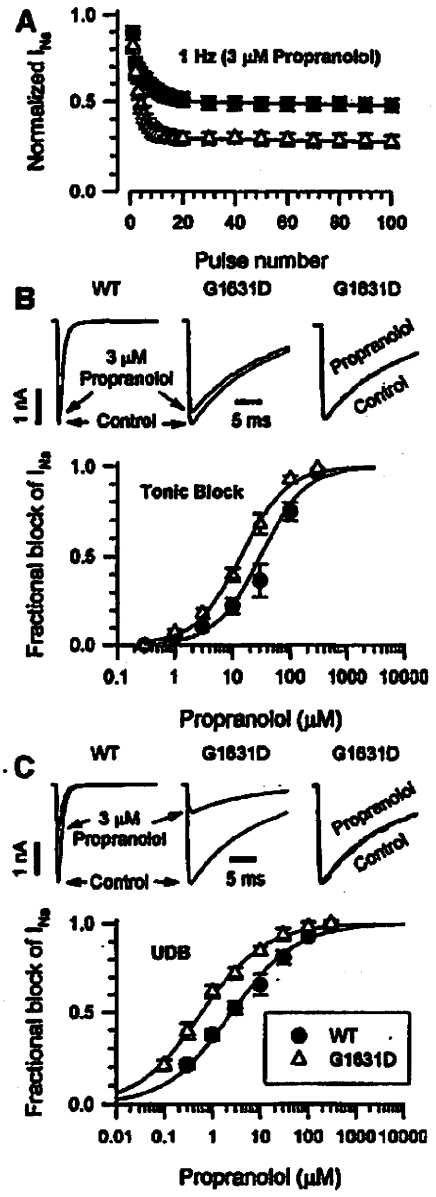


Figure 7. Effects of propranolol on WT and G1631D. A, Propranolol (3 μmol/L) block of WT (n=5) and G1631D (n=4) during a 1-Hz train of depolarizing pulses to −10 mV from a holding potential of −120 mV. B, Tonic propranolol block of WT and G1631D. Upper traces (left, middle) illustrate the effects of 3 μmol/L propranolol during a single depolarizing voltage step to −10 mV. Normalized traces (right) recorded in the absence (control) or presence of drug illustrate the effect of propranolol on the inactivation time course. The plot illustrates the concentration-response relationships for tonic block by propranolol (each data point represents the mean of 4 to 11 cells). C, Use-dependent propranolol block of WT and G1631D. Upper traces (left, middle) illustrate the steady-state effects of 3 μmol/L propranolol during a 1-Hz pulse train. Normalized traces (right) recorded in the absence (control) or presence of drug (100th pulse) illustrate the effect of propranolol on the inactivation time course. Time constants in the absence of drug were: $\tau_1$=7.8±0.5 ms, $\tau_2$=19.5±0.7 ms, n=4; and in the presence of 3 μmol/L propranolol: $\tau_1$=6.9±1.1 ms, $\tau_2$=18.1±1.0 ms n=4 (no significant differences in $\tau_1$ or $\tau_2$). The plot illustrates the concentration-response relationships for use-dependent block by propranolol (each data point represents the mean of 4 to 11 cells). The lines in B and C were fit to the data according to the Hill equation.

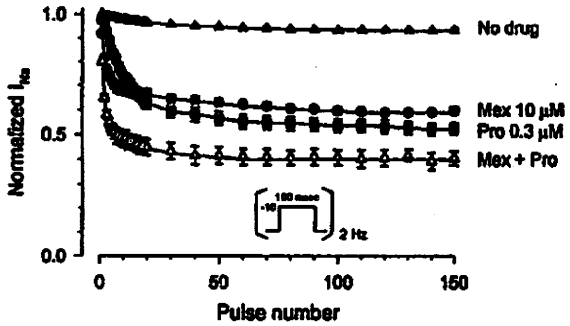


Figure 8. Effects of mexiletine with or without propranolol on G1631D channels. Sodium current was measured sequentially during a 2-Hz train of depolarizing pulses to −10 mV from a holding potential of −120 mV and values normalized to the current level after the initial pulse. Steady-state residual normalized sodium current after the 150th pulse was significantly lower for the combination of 10 μmol/L mexiletine with 0.3 μmol/L propranolol (fractional residual current, 0.4±0.03, n=3), when compared with either drug alone (mexiletine, 0.6±0.02; n=6; $P$=0.0039; propranolol, 0.5±0.03; n=6; $P$=0.041).

tion (1 Hz). Mutant channels exhibited a greater degree of steady-state block than WT channels under these conditions. Concentration-response curves demonstrated that propranolol exerts greater tonic (Figure 7B) and use-dependent (Figure 7C) block of G1631D than that of WT channels. Propranolol use-dependent block was enhanced 5-fold by the mutation ($EC_{50}$: WT, 3.0 μmol/L; G1631D, 0.6 μmol/L). The effect of propranolol, a racemic mixture, was not likely mediated through endogenous β-adrenergic receptors in the heterologous cell system because we observed similar blocking potency for R-(+)-propranolol, which has no receptor antagonist properties (see supplemental Figure II). Propranolol at a concentration similar to that observed in the Japanese proband (0.1 μmol/L) normalized steady-state inactivation of mutant channels (G1631D $V_h$: no drug, −74.8±1.1 mV, n=16; propranolol, −84.5±1.7 mV, n=10; $P$<0.001) but had no effect on steady-state inactivation of WT channels (WT $V_h$: no drug, −89.3±1.1 mV, n=16; propranolol, −88.8±0.9 mV, n=5; NS). Propranolol did not affect the kinetics of inactivation for WT or mutant channels (Figure 7B and 7C) or the level of persistent current observed for G1631D (no drug: 1.63±0.31, n=9; 1 μmol/L propranolol, 1.44±0.29, n=9; NS).

Because both probands responded clinically to the combination of mexiletine and propranolol, we tested the effects of both drugs together on G1631D channels. To closely simulate the clinical conditions, we tested use-dependent block at 2 Hz, which was the approximate resting heart rate of the Japanese proband and the frequency of cardiac pacing in the Italian child. The combination of mexiletine (10 μmol/L) and propranolol (0.3 μmol/L) caused a substantial loss of channel availability during a 2-Hz pulse train (Figure 8) when compared with the drug-free condition. The level of channel inhibition observed for the combination of mexiletine and propranolol was greater than either drug applied alone indicating additive effects.

## Discussion

During late fetal development through shortly after birth, there is a vulnerable period when death occurs at a rate of 6 to 12 per 1000 live births per year,[20] and congenital arrhythmia susceptibility may be a significant contributor to this problem.[21,22] Life-threatening cardiac arrhythmias during infancy and the perinatal period may go unnoticed owing to the lack of routine use of electrocardiographic monitoring of the fetus and newborn. Studies of 2 large series of autopsied SIDS victims demonstrated that up to 10% of SIDS cases may represent genetic disorders of congenital arrhythmia susceptibility such as the LQTS,[3,23] short-QT syndrome,[24,25] and catecholaminergic polymorphic ventricular tachycardia.[26] Understanding the genetic risks for perinatal mortality should promote efforts to identify and treat at-risk newborns.

### Malignant Perinatal Variant of LQTS

The profoundly dysfunctional *SCN5A* mutation, G1631D, produced a clinical entity distinct from typical LQTS (LQT3 subtype). Clinically, subjects with typical LQTS first develop symptoms (syncope, cardiac arrest, and sudden death) during late childhood, adolescence, or early adulthood.[9,27] Many mutation carriers may in fact be asymptomatic. The 2 probands we described seem to be affected by a very severe and life-threatening process.

At the molecular level, most *SCN5A* mutations associated with LQTS cause a subtle gain-of-function defect characterized by increased persistent current.[16,17] The markedly abnormal channel function we observed for G1631D including a 10-fold slowing of inactivation, substantial shifts in voltage dependence of activation and inactivation along with greatly impaired recovery from inactivation represent distinct molecular defects that distinguish this mutation from typical LQT3 alleles. Other *SCN5A* alleles may similarly predispose to early onset and severe perinatal arrhythmia syndromes,[4,5,28,29] but the functional aberrations associated with most of these reported alleles resemble mutations found in older individuals.

### Negative Selection Against *SCN5A* Mutations

Mutations in *SCN5A* are represented disproportionately among SIDS victims who carry occult congenital arrhythmia susceptibility gene mutations when compared with older LQTS subjects. The lower proportion of *SCN5A* mutations among older children and young adults with LQTS when compared with the higher proportion in SIDS victims may be the result of negative selection against mutations in the sodium channel gene. Negative selection would cause an ascertainment bias for genotypes in living individuals in whom survival is favored when carrying mutations having less severe physiological consequences. In the case of SCN5A-G1631D, we assumed that without immediate treatment, this mutation would have been lethal. However, survival after successful treatment confounds the argument for negative selection.

Congenital arrhythmia susceptibility occurring in the perinatal and neonatal periods caused by *SCN5A* mutations appears biologically distinct from LQTS in older subjects. Carriers of certain *SCN5A* mutations may present with earlier onset and severe congenital arrhythmia syndromes. An illustration of this idea is recurrent third-trimester fetal loss attributable to inheritance of an *SCN5A* mutation (R1623Q) from a mother who was mosaic for this deleterious allele.[8] The R1623Q mutation, which affects a conserved residue in the D4/S4 segment nearby the location of G1631D, was originally identified in a Japanese child with a severe clinical presentation of LQTS,[30] and the molecular defect associated with this allele compromised inactivation to a greater extent than typical LQT3 mutations.[31] Our observations regarding the severity of biophysical defects associated with G1631D also support the idea that earlier onset cardiac symptoms may sometimes correlate with a severe molecular phenotype.

### Genotype-Specific Pharmacological Treatment

The clinical consequences of G1631D were perinatal arrhythmias successfully managed in part by pharmacotherapy with the combination of mexiletine and propranolol. Mexiletine as well as other sodium channel blockers have been proposed as gene-specific therapeutic agents in LQT3.[32–34] In vitro studies have demonstrated the capability of these drugs to selectively suppress increased persistent current conducted by mutant channels[29,35] and to normalize ventricular repolarization in animal models.[36,37] One study suggested that certain biophysical properties of mutant $Na_v1.5$ channels may be predictive of mexiletine responsiveness. Specifically, Ruan et al[38] found that among 4 distinct *SCN5A* mutations, clinical benefit from mexiletine treatment was observed only in subjects carrying mutations that caused a hyperpolarizing shift in steady-state inactivation and this correlated with in vitro effects of the drug. However, this observation cannot be extrapolated to all *SCN5A* mutations as evidenced by the favorable response of G1631D to mexiletine both clinically and experimentally despite a depolarizing shift in steady-state inactivation (Figure 3). Similarly, another recently reported *SCN5A* mutation (F1473C) was also associated with a favorable clinical response to high-dose mexiletine despite having depolarized steady-state inactivation.[29] Additional factors besides those emphasized by Ruan et al[38] are likely to determine the clinical efficacy of mexiletine.

By contrast, use of β-blockers in the setting of *SCN5A* mutations has less certain benefits. Three studies have reported that β-blockers are generally less efficacious in LQT3 subjects, but the specific drug used varies considerably.[9,39,40] For example, in the report by Priori et al[40] the specific β-blocker was known in 69% of cases, and this was either propranolol or nadolol. As we have demonstrated in this study, propranolol may offer specific advantages in treating certain *SCN5A* mutations because of apparent local anesthetic-like properties of the drug.[18,19] By contrast, we recently determined that nadolol has no activity against sodium channels (Wang DW, unpublished observations, 2007). The role of propranolol in treating individuals with *SCN5A* mutations warrants further study.

Combination pharmacotherapy in the 2 probands with G1631D may have uniquely contributed to their survival. In the Japanese newborn, mexiletine alone was not adequate to control ventricular arrhythmia despite shortening of the QT interval. The addition of propranolol to the treatment regimen conferred better arrhythmia control and survival. In the Italian