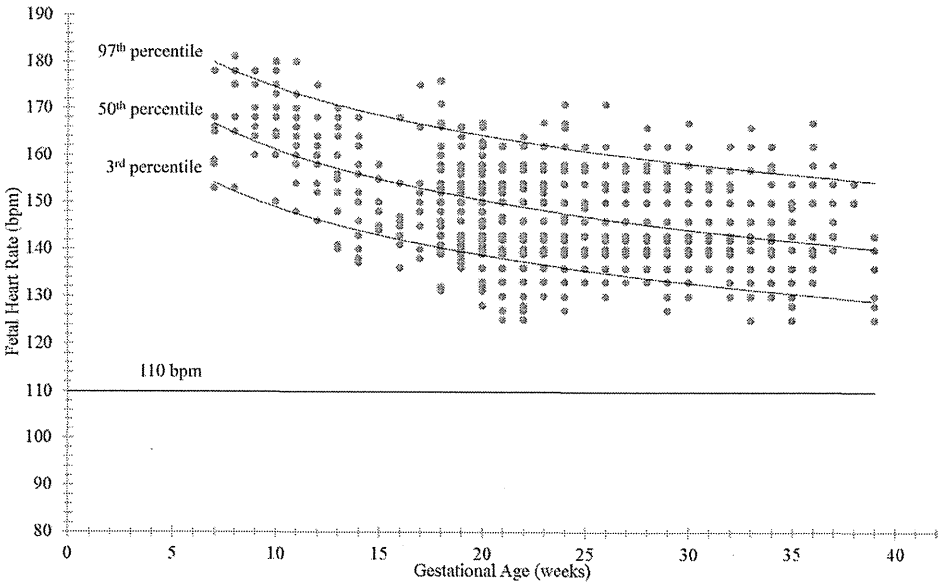

Figure 1. Individual FHR measurements (n=3264 data points) by gestational age of 547 normal fetuses. Curves representing the 3rd, 50th, and 97th percentiles of FHR are shown, as is a horizontal line at 110 bpm, which is the standard obstetric definition of bradycardia. FHR decreases with advancing gestational age. Some normal FHR measurements are <3rd percentile but none are <110 bpm. FHR indicates fetal heart rate; bpm, beats per minute.

subjects #17 and #18, subjects #19 and #20, and subjects #21 and #22. Subjects #41 and #42 in Group 2 were twins. At the time of initial assessment, no Group 2 subject was known to have affected family members; however, subsequent diagnosis in the fetal proband led to a genetic diagnosis of LQTS in undiagnosed members of 6/16 (38%) families. These family members (subjects #5, #6, and #7) were included in Group 1 after diagnosis of LQTS in subjects #32, #33, and #37.

The mean GA at delivery was slightly less for Group 2 (36.4±2.8 weeks) compared with Group 1 (38.0±2.7 weeks) subjects, but this difference was not significant (P=0.08). The mean GA of referral for subjects in Group 2 was 27.6±4.5 weeks. Five subjects in Group 2 were delivered prematurely (≤ 35 weeks of gestation) because of uncontrolled arrhythmia or fetal distress; 1 fetus died in utero from uncontrolled arrhythmia and severe hydrops (Subject # 40).

Among mothers with LQTS, 13 were treated with β-adrenergic blocking agents during pregnancy: 11 throughout pregnancy and 2 during 3rd trimester only. The FHR was not different in fetuses whose mothers were treated (130.1±8.2 bpm) or untreated (127.5±13.6 bpm; P=0.6).

LQTS Mutations in Group 1 Versus Group 2

Mutation in a known LQT gene was found in most subjects (92%) who underwent genetic testing (95%): 23 with LQT1, 4 with LQT2, 6 with LQT3, 2 with LQT5, and 1 with a compound mutation. Three subjects were not tested and 3 subjects had uncharacterized mutations. Among those who had genetic testing, there were differences in genetic results in Group 1 versus Group 2 subjects (Table 1). For example, 83% of Group 1 subjects had a *KCNQ1* or *KCNE1* mutation, 4% had an *SCN5A* mutation, and no subject had an uncharacterized mutation. In contrast, 33% of Group 2 subjects had a *KCNQ1* mutation, 33% had an *SCN5A* mutation, and nearly 20% had uncharacterized mutations (n=3).

Fetal Heart Rates

Normal FHR data from 7 to 40 weeks were obtained from 3264 FHR measurements in 547 normal subjects. The 3rd, 50th, and 97th percentiles for GA are shown in Figure 1. We obtained 318 FHR measures from 42 LQTS fetuses; the mean of FHR measures was ≈8 per fetus and the range was 1 to 12 per fetus. The mean FHR at each of the 3 GA groups (<21 weeks, 21–30 weeks, and 31–40 weeks) was significantly different between normal and LQTS subjects (P<0.001; Table 2). The FHR at the 3rd percentile of normal from the 3 GA groups were all greater than the standard obstetric definition of fetal bradycardia (ie, FHR ≤110 bpm).

We evaluated the individual FHR measures across GA of fetuses based on indication for referral. Figure 2A shows the FHR/GA profile of subjects referred for a family history; Figure 2B shows the FHR/GA profile of subjects referred for evaluation of fetal rhythm. The FHR of the LQTS fetuses decreased with GA as seen in the normal

Table 2. Mean FHR of Normal and LQTS Subjects by GA Group

GA Group	Normal Subjects FHR Mean±SE (bpm)	LQTS Subjects FHR Mean±SE (bpm)	P
<21 wk	152.0±0.4	139.9±1.2	<0.001
21 to 30 wk	146.7±0.2	127.4±1.2	<0.001
31 to 40 wk	143.3±0.4	123.0±1.4	<0.001

LQTS indicates long QT syndrome; GA, gestational age; FHR, fetal heart rate; SE, standard error; and bpm, beats per minute.

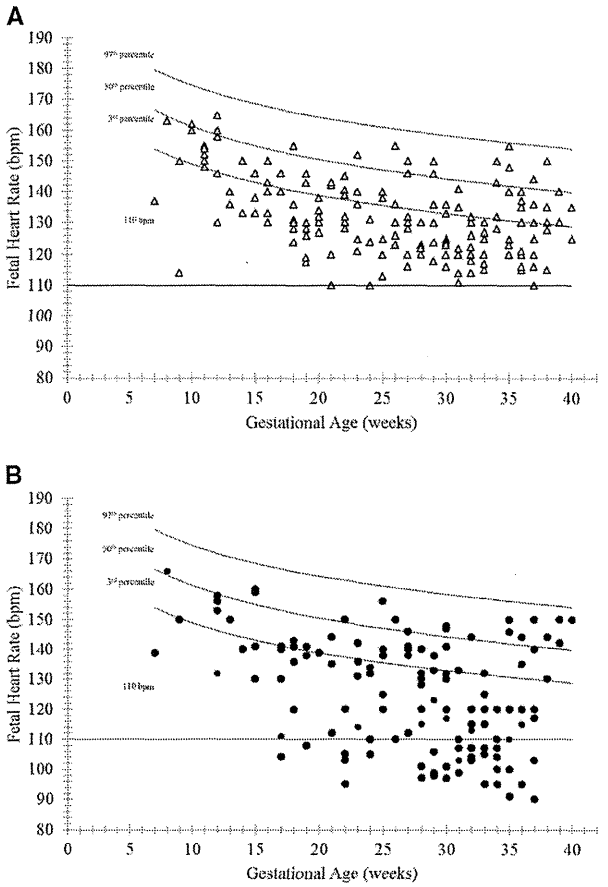

Figure 2. Individual measurements throughout gestation of LQTS fetuses, based on indication for referral. **A**, FHR of individuals referred because of a family history of LQTS (Group 1). **B**, FHR of individuals referred for evaluation of fetal rhythm (Group 2). For reference, the line marking a FHR of 110 bpm across gestation is shown in both panels. FHR indicates fetal heart rate; LQTS, long QT syndrome; and bpm, beats per minute.

fetal cohort, but GA-dependent changes in mean FHR differed between Groups 1 and 2. Early, at <21 weeks of gestation, mean FHRs were not different (141.54±2.02 versus 136.95±2.51; $P=0.15$). However, FHR in Group 2 was lower at both 21 to 30 weeks (130.28±2.66 versus 124.54±2.65; $P=0.04$) and at 31 to 40 weeks (127.72±2.81 versus 117.94±2.83; $P<0.01$). Only subjects in Group 2 had FHR ≤110 bpm.

The Bradycardia Index

Among LQTS subjects, only 15% of FHR readings were ≤110 bpm whereas 66% of the FHR readings were ≤3rd percentile for GA. Thus, 85% of the total FHR readings were higher than the standard obstetric definition of bradycardia (FHR ≤110 bpm), and only 33% of the LQTS FHR readings were >3rd percentile for GA. Using FHR ≤3rd percentile for GA, 38% (16/42) of LQTS fetuses had a bradycardia index of 100% and 67% (28/42) had a bradycardia index between 75% to 100%. Table 3 shows there were significant differences between Groups 1 and 2 in the bradycardia indices for FHR ≤110 bpm and ≤3rd

Table 3. Bradycardia Index of Group 1 and Group 2 Based on GA Group

	FHR≤110 bpm		FHR<3rd Percentile for GA	
GA (Weeks)	Group 1	Group 2	Group 1	Group 2
Overall	1%	31%	50%	68%
<21	0%	6%	48%	45%
21 to 30	2%	26%	61%	68%
31 to 40	2%	49%	42%	81%

LQTS indicates long QT syndrome; GA, gestational age; FHR, fetal heart rate; and bpm, beats per minutes.

percentile for GA. Within Group 2, a bradycardia index of 100% was seen in 2/3 subjects with complex rhythms (Table 4). The findings of more pronounced bradycardia in Group 2 subjects with complex rhythms may be another manifestation of a more severe phenotype in such fetal LQTS subjects.

Although the sample sizes of certain LQTS mutations were small, among genotypes, the bradycardia index for FHR ≤3rd percentile for GA was highest (100%) for uncharacterized mutations and lowest (0%) for LQT5 mutations. Overall, the severity of the bradycardia index was not predicted by the presence of mutations in known LQTS genes.

Fetal Heart Rhythms and FHR

In most of the 42 fetuses, sinus rhythm was observed throughout pregnancy, but in 10 fetuses, 8 of whom were in Group 2, complex arrhythmias characterized by 2° AV block or TdP were observed (Table 4). The mean FHRs of these 10 subjects were lower across GA than those subjects who manifested only fetal bradycardia (120.74±3.56 versus 130.79±2.37; $P<0.01$), and the bradycardia indices for FHR ≤3rd percentile were higher (80% versus 60%).

Discussion

There are several novel and clinically relevant findings in this study of fetal LQTS. First, as in normal fetuses, the FHR of LQTS subjects trend downward but are generally lower than FHR of normal fetuses as gestation progresses. Second, there are GA-dependent FHR predictors of LQTS; for example, when compared with a GA independent FHR predictor (FHR ≤110 bpm), a FHR ≤3rd percentile for GA improves ascertainment of LQTS subjects from 15% to 85%. Third, there are shades of bradycardia within the LQTS population: compared with subjects who remained in sinus rhythm during pregnancy, subjects with the lowest FHRs were more likely to have had a complex arrhythmia including TdP or 2° AV block, and were more likely to have de novo or uncharacterized mutations. Together, findings from this study should improve ascertainment of fetal LQTS at all GA.

From the first ultrasound visualization of the fetal heart signifying a viable pregnancy to the reactive accelerations signifying fetal well-being during labor and delivery, FHR is the most frequently and thoroughly evaluated parameter

from the beginning to the end of pregnancy. Yet, neither the range of normal nor the definitions of abnormal FHR are GA-specific, emphasizing the shortcomings of a single definition of fetal bradycardia (eg, FHR ≤110 bpm). Sinus bradycardia occurs in LQTS, but the molecular basis for this common occurrence is incompletely understood. Furthermore, the GA at which the sinus beat becomes bradycardic, and indeed the sensitivity and specificity of a GA-independent definition of bradycardia, are poorly understood.

Previous publications have described a range of sinus FHRs ranging from <100 to 130 bpm in LQTS fetuses.[7,3,4] As in our series, many of these LQTS fetuses with FHRs in the normal range (> 110 bpm) had a family history of LQTS. The higher FHR in those with a family history may be ascertainment bias as these subjects, screened preemptively, may be less severely affected. After birth, the majority of subjects, even those with FHR ≤110 bpm, had heart rates in the normal range.[7] Similarly, in a large study evaluating LQTS and SIDS, bradycardia in the neonate was not considered a risk factor for LQTS.[35] Thus, use of a stringent fetal bradycardia definition (ie, FHR ≤110 bpm) may result in failure to recognize fetal LQTS, and continuation of mild bradycardia (ie, heart rate >110 bpm) after birth may fail to raise the suspicion of LQTS in the neonate. This may explain why the older siblings of some fetal probands in this study with mild bradycardia were not suspected as fetuses or neonates to have LQTS.

In the absence of a known family history, the ascertainment of fetal LQTS is based on the correct and timely diagnosis of the signature LQTS rhythms. Although TdP and 2° AV block are usually easily recognized and have high specificity, they occur infrequently in the fetus with LQTS. For example, only 24% of our study cohort had these complex arrhythmias, and none of the 25 subjects in this report with LQT1 mutations had TdP or 2° AV block. Thus, it is important to identify other markers of LQTS; findings in our study suggest that FHR may be useful for this purpose. Our results show that a one size fits all FHR indicator of bradycardia will not be adequate. For example, the bradycardia index of LQT 1 subjects for FHR ≤110 bpm was only 2%, but definition of bradycardia as FHR ≤3rd percentile yielded a bradycardia index of 68%. Using a GA-independent definition of bradycardia would not have led to suspicion of LQTS in many such subjects.

Although our study group is relatively small, we found associations between FHR, rhythm phenotype, and genotype, which could be helpful in the diagnosis of LQTS. For example, individuals with *KCNQ1* mutations tended to have a mild phenotype in utero with sinus rhythm and mild bradycardia. On the other hand, genetically elusive subjects, with no known mutations and a negative family history of LQTS, had profound fetal bradycardia and complex rhythms.

Based on the results of this study, we believe that FHR ≤3rd percentile for GA is a superior definition of fetal bradycardia compared with the widely used obstetric definition. Our study suggests that the fetus with repeated FHR measurements ≤3rd percentile for GA without any other rhythm abnormality should be suspected of having LQTS. This suspicion should lead to detailed family history for LQTS. Regardless of family history, a postnatal 12-lead ECG should be examined for findings of LQTS. If the family history is positive, or the fetal proband manifests complex LQTS rhythms, ECG screening of first-degree relatives is recommended. Even if family members are asymptomatic, ECG evidence of LQTS warrants genetic testing. Finally, if postnatal genetic testing of the fetus with suspected LQTS is positive, but clinical or genetic manifestations of LQTS are negative in first-degree relatives, the possibility of parental mosaicism should be considered, especially if future pregnancies are contemplated.[36]

Table 4. Complex Fetal Rhythms in Relation to Bradycardia Index in LQTS Cohort

ID	LQTS Mutation	Fetal Rhythm	% FHR Readings ≤3rd Percentile GA	% FHR≤110 bpm
Group 1: Referral for Family History of LQTS				
2	Untested	2° AVB	100	100%
17	KCNQ1-G168R	2° AVB	100	0%
Group 2: Referral for Fetal Arrhythmia				
27	KCNH2-G628S	TdP and 2° AVB	100	84%
28	SCN5A-R1623Q	TdP and 2° AVB	100	75%
30	Uncharacterized	2° AVB	100	92%
33	KCNQ1-G314D	2° AVB	86	0%
36	SCN5A-R1623Q	TdP and 2° AVB	71	14%
40	SCN5A-L409P	TdP	100	0%
41	SCN5A-R1623Q	TdP and 2° AVB	22	0%
42	SCN5A-R1623Q	TdP and 2° AVB	11	0%

LQTS indicates long QT syndrome; TdP, torsade de pointes; AVB, atrioventricular block; GA, gestational age; and FHR, fetal heart rate.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Long QT syndrome (LQTS) may be as common as 1/2500 individuals, yet fewer than 100 cases have been recognized during fetal life. Fetal torsades de pointes and 2° AV block are easily attributed to LQTS. However, these complex arrhythmias are present in only 25% of fetal LQTS; the majority of LQTS fetuses have asymptomatic bradycardia that may not be recognized as an LQTS marker due to its subtle features. The standard obstetrical definition of bradycardia is fetal heart rate (FHR) $\leq$ 110 bpm. To improve recognition of perinatal LQTS we evaluated the FHR/gestational age (GA) relationship of fetal LQTS mutations versus a normal control group. We found GA dependent FHR predictors of LQTS; for example, when compared to a FHR of 110 bpm at any GA, a FHR $\leq 3^{rd}$ percentile for GA improves ascertainment of LQTS subjects from 15 to 85%. Fetuses with the lowest FHR tended to have de novo and genetically elusive LQTS mutations, and in addition to bradycardia, also manifested complex LQTS rhythms. Identification of LQTS in the fetus with a heart rate of $<3^{rd}$ also led to diagnosis of LQTS in unsuspecting family members. Thus, postnatal evaluation of individuals with a FHR $\leq 3^{rd}$percentile for GA improves ascertainment of LQTS both before and after birth.

Tachycardia Associated with Twin Atrioventricular Nodes in an Infant with Heterotaxy and Interruption of Inferior Vena Cava

YOSHIAKI KATO, M.D.,* HITOSHI HORIGOME, M.D., PH.D.,* MIHO TAKAHASHI-IGARI, M.D.,* NAOKATA SUMITOMO, M.D., PH.D.,† and KAZUTAKA AONUMA, M.D., PH.D.‡

From the *Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan; †Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan; and ‡Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan

We report a 12-month-old boy with heterotaxy and interruption of inferior vena cava who showed sustained tachycardia associated with twin atrioventricular nodes (AVNs). Atrioventricular reciprocating tachycardia with antegrade conduction through the posterior AVN and retrograde conduction through the anterior AVN were successfully ablated using an upper approach from the left internal jugular vein. (PACE 2012; 30:e302–e305)

heterotaxy, left isomerism, interruption of inferior vena cava, twin atrioventricular nodes

Introduction

Heterotaxy, including left atrial isomerism (LAI) and right atrial isomerism (RAI), is frequently complicated by complex extracardiac and intracardiac malformations.[1] The incidence of tachy- and brady-arrhythmias is also high. Interruption of the inferior vena cava (IVC) with azygos continuation is one of the common malformations of the cardiovascular system in LAI,[1] and may restrict catheter access to the atrial chamber from the femoral vein. It is not unusual that total cavopulmonary shunt (TCPS), an anastomosis of the superior vena cava (SVC) to the pulmonary artery, is planned, though it makes it difficult to access the atrial chamber transvenously after the procedure in patients with univentricular physiology. We report successful catheter ablation of reentrant tachycardia associated with twin atrioventricular nodes (AVNs) in an infant with interruption of IVC and azygos continuation in association with LAI.

Case Report

A 12-month-old boy (body weight 8.3 kg) was admitted to our hospital for the electrophysiological study and catheter ablation of tachycardia. He was prenatally diagnosed with LAI including interruption of IVC, bilateral SVC, common atrium, common atrioventricular valve, single ventricle (right ventricle morphology), double-outlet right ventricle, and severe pulmonary stenosis. To maintain pulmonary arterial blood flow, the Blalock-Taussig shunt operation was performed at the age of 1 month. At the age of 5 months, he developed narrow-QRS tachycardia at a rate of 240 beats/min, which ultimately resulted in heart failure and further cyanosis. Intravenous infusion of adenosine triphosphate was effective in terminating tachycardia. The QRS morphology during tachycardia was similar to that of baseline electrocardiogram (ECG). Initiation of oral propranolol therapy resulted in complete disappearance of tachycardia. Repeat ECG showed only one QRS morphology. Due to the gradual deterioration of cyanosis, TCPS was considered as the next stage palliation. However, before the procedure was performed, it was decided to conduct an electrophysiological study and catheter ablation because catheter access routes to the atrial chamber through the systemic veins would not be available after TCPS.

After obtaining informed consent from the parents, electrophysiological study and catheter ablation were performed under general anesthesia. An octapolar catheter was inserted in the ventricle, through the right femoral vein and the left azygos vein. Another quadripolar catheter was placed on the right wall of the common atrium, through the left femoral vein. The CARTO XP system (Biosense Webster Inc., Diamond Bar, CA, USA) was used, with a 7-Fr Navistar catheter (Biosense Webster Inc.), which was inserted through the left jugular vein with its tip placed in the atrium. Two separate His bundle electrograms (HBEs) were recorded around the common atrioventricular

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Address for reprints: Yoshiaki Kato, M.D., Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1–1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan. Fax: 81-29-853-8819; e-mail: yoshiakiaisho@hotmail.com

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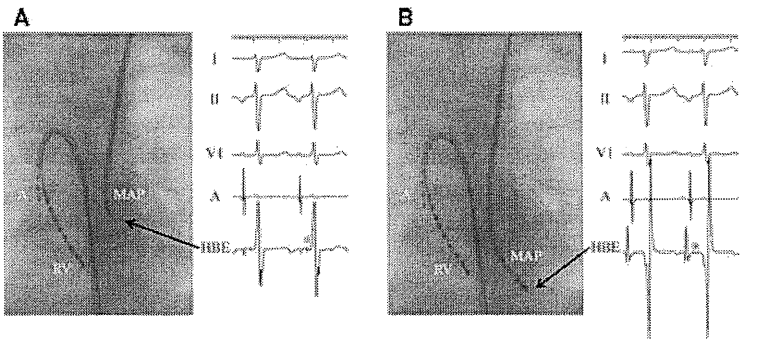

Figure 1. *Fluoroscopic images in the anteroposterior view, showing the quadripolar catheter in the right wall of the common atrium (A), the octapolar catheter in the right ventricle (RV) placed via the azygos vein and superior vena cava, and MAP catheter placed through the left jugular vein. The proximal side of the octapolar catheter was positioned inside the atrium. Surface ECG and intracardiac electrograms during lower atrial rhythm showed two separate His bundle electrograms (HBEs) recorded by MAP catheter: one HBE located at the anterior region of the common atrioventricular valve (A) and the other at the posterior region (B). *His potential.*

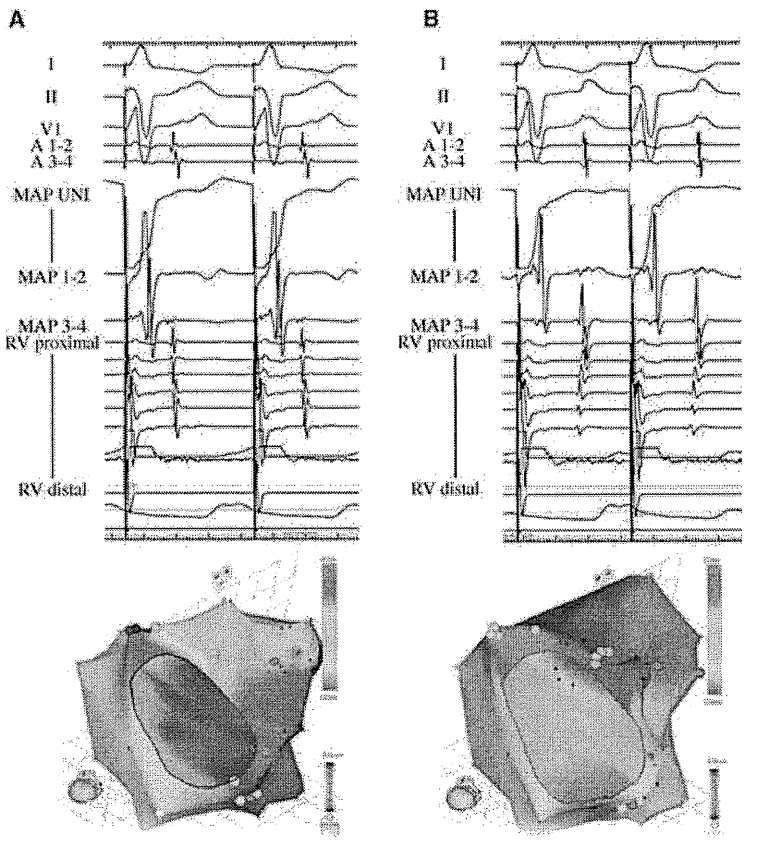

Figure 2. *Intracardiac electrograms and propagation map during ventricular pacing. Before radiofrequency ablation (A), the anterior HBE site was the atrial earliest activation site. After radiofrequency ablation (B), the atrial earliest activation site shifted to the posterior HBE site. A = atrium; MAP = MAP catheter; RV = right ventricle.*

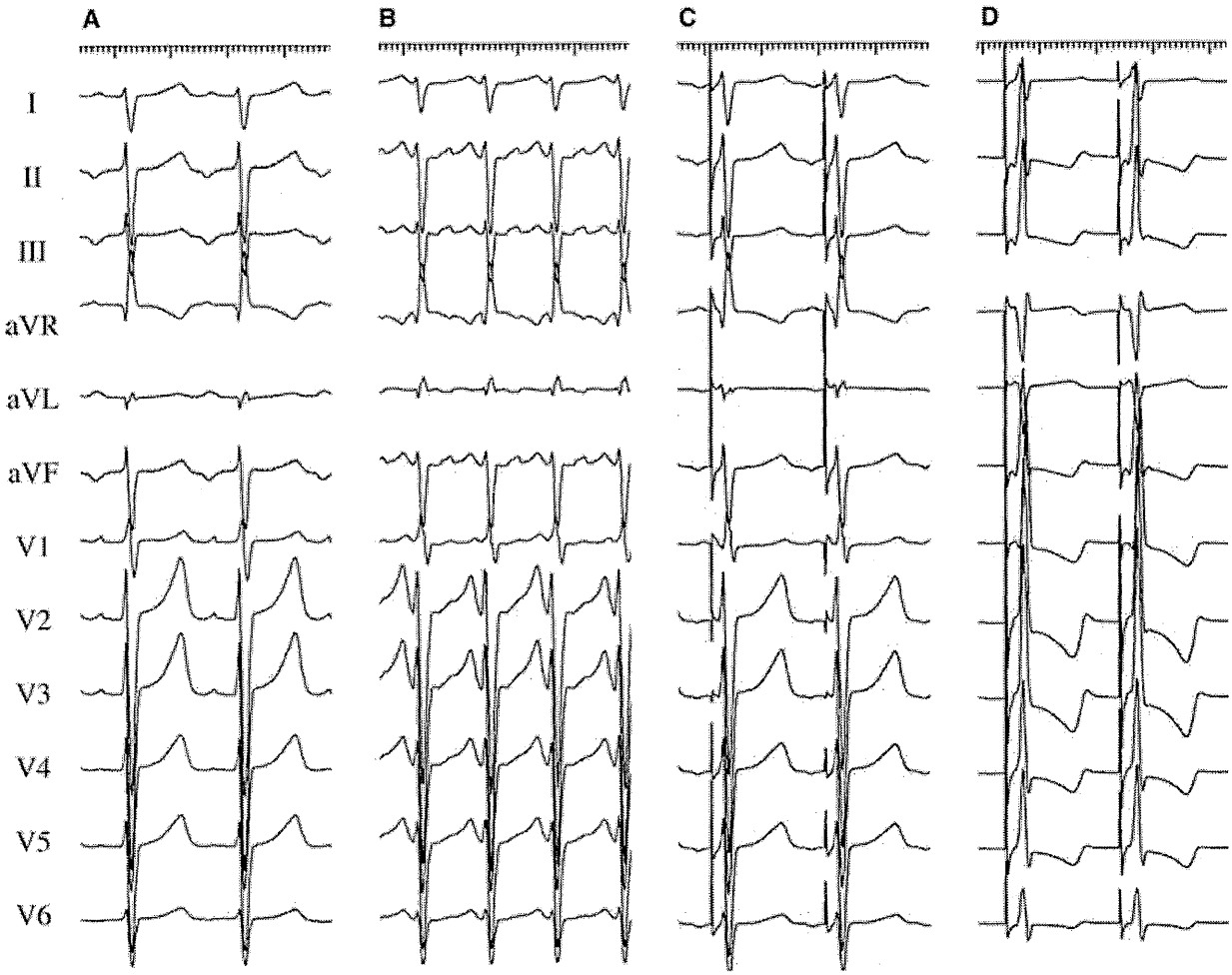

Figure 3. *Twelve-lead surface ECG during lower atrial rhythm (A), tachycardia (B), atrial pacing near posterior HBE (C), and atrial pacing near anterior HBE (D). QRS morphologies in the former three phases (A, B, C) were similar to each other with the same polarity: northwest axis without ventricular preexcitation. In contrast, different QRS morphology with an inferior axis was observed during atrial pacing near anterior HBE (D).*

valve; one HBE was located in the anterior region of the valve and the other in the posterior region (Fig. 1). Two discrete QRS morphologies, without ventricular preexcitation, were recorded with atrial pacing from sites near each HBE (Figs. 3C and D), and decremental conduction properties were demonstrated at both sites of pacing. The earliest atrial activation site during ventricular pacing was the anterior HBE site (Fig. 2A). The decremental conduction property and ventriculoatrial block were confirmed by intravenous infusion of adenosine triphosphate. Narrow-QRS tachycardia, with morphology similar to that in sinus rhythm (Fig. 3A), was reproducibly induced by programmed atrial pacing (Fig. 3B), and the earliest atrial activation site was the anterior HBE site. The above findings suggested the existence of twin AVNs, which caused atrioventricular reciprocating tachycardia: antegrade conduction through the posterior AVN and retrograde conduction through the anterior AVN. Radiofrequency energy was applied (power: 30 W, target temperature: 40°C) at the site of anterior AVN, and accelerated junctional rhythm occurred soon after the initiation. After the ablation, the earliest atrial activation site during ventricular pacing changed to the posterior HBE (Fig. 2B). No tachycardia was induced by the maximal stimulation protocol even with intravenous infusion of isoproterenol. Three weeks after the procedure, the patient underwent TCPS, which resulted in the disappearance of cyanosis.

There was no evidence of atrioventricular block or recurrence of tachycardia during the next 2 years of follow-up.

Discussion

Even without surgical myocardial damage or hemodynamic stress, the unique malformations of the conduction system in heterotaxy (e.g., absent/single/twin sinus node, absent/single/twin AVN, and sling of conduction tissue between two AVNs) can cause various arrhythmias. Previous studies indicated that patients with RAI are at risk (26%) of supraventricular tachycardia.[2] Meanwhile, patients with LAI are at risk of bradyarrhythmias (e.g., junctional rhythm, sinus bradycardia, and atrioventricular block).[3] Most of the reported cases with tachycardia involving reentry between twin AVNs had RAI or discordant atrioventricular connection.[2,4,5] However, detailed morphological analysis of heterotaxy showed relatively high incidence of twin AVNs in LAI (28%),[1] suggesting that LAI also has the potential of tachycardia through reentry mechanism between twin AVNs. In this case, we applied radiofrequency energy to the anterior AVN because it was the retrograde limb of the circuit and contributed less to antegrade conduction during sinus rhythm. Our treatment strategy for twin AVNs-related tachycardia was ablation of one AVN, similar to that applied for RAI. However, the catheter approach to the target is sometimes limited because of the extracardiac venous malformations in LAI. The prevalence of interruption of IVC is 0.1% in the general population,[6] and that in LAI is 44–82%.[1,3] For catheter stability, the catheter approach should be selected based on the site of ablation. Some groups prefer the lower approach via the azygos vein or SVC,[7,8] whereas others prefer the upper approach via the jugular vein or subclavian vein.[9] In this case, considering the vessels size, we chose the upper approach, and were able to secure catheter stability during ablation.

Heterotaxy complicated by tachyarrhythmias should be assessed by electrophysiology and catheter ablation should be performed at an appropriate period in staged-palliation surgery to avoid losing catheter access routes to the atrial chamber. This case illustrated the feasibility of catheter ablation of an AVN in a young infant with interruption of IVC.

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Outcomes of Childhood Pulmonary Arterial Hypertension in *BMPR2* and *ALK1* Mutation Carriers

Ayako Chida, MD[a,c], Masaki Shintani, PhD[c], Hisato Yagi, PhD[d], Maya Fujiwara, MD, PhD[c,f], Yasuko Kojima, MD[c,f], Hiroki Sato, MS[b], Shinichiro Imamura, PhD[c,g], Masato Yokozawa, MD[h], Norio Onodera, MD, PhD[i], Hitoshi Horigome, MD, PhD[j], Tomio Kobayashi, MD, PhD[k], Yoshiho Hatai, MD, PhD[a], Tomotaka Nakayama, MD, PhD[f], Hiroyuki Fukushima, MD[l], Mitsunori Nishiyama, MD, PhD[m,n], Shouzaburo Doi, MD, PhD[n], Yasuo Ono, MD[o], Satoshi Yasukouchi, MD[p], Fukiko Ichida, MD, PhD[q], Kazuto Fujimoto, MD[r], Shinichi Ohtsuki, MD, PhD[s], Hidetaka Teshima, MD[t], Tatsuya Kawano, MD[u], Yuichi Nomura, MD, PhD[v], Hong Gu, MD[w], Takahiro Ishiwata, MD, PhD[a], Yoshiyuki Furutani, PhD[c], Kei Inai, MD, PhD[c], Tsutomu Saji, MD, PhD[f], Rumiko Matsuoka, MD, PhD[d,e,x], Shigeaki Nonoyama, MD, PhD[a], and Toshio Nakanishi, MD, PhD[c,*]

Mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) gene and the activin receptor–like kinase 1 (*ALK1*) gene have been reported in heritable pulmonary arterial hypertension (HPAH) and idiopathic pulmonary arterial hypertension (IPAH). However, the relation between clinical characteristics and each gene mutation in IPAH and HPAH is still unclear, especially in childhood. The aim of this study was to determine, in a retrospective study, the influence and clinical outcomes of gene mutations in childhood IPAH and HPAH. Fifty-four patients with IPAH or HPAH whose onset of disease was at <16 years of age were included. Functional characteristics, hemodynamic parameters, and clinical outcomes were compared in *BMPR2* and *ALK1* mutation carriers and noncarriers. Overall 5-year survival for all patients was 76%. Eighteen *BMPR2* mutation carriers and 7 *ALK1* mutation carriers were detected in the 54 patients with childhood IPAH or HPAH. Five-year survival was lower in *BMPR2* mutation carriers than mutation noncarriers (55% vs 90%, hazard ratio 12.54, p = 0.0003). *ALK1* mutation carriers also had a tendency to have worse outcome than mutation noncarriers (5-year survival rate 64%, hazard ratio 5.14, p = 0.1205). In conclusion, patients with childhood IPAH or HPAH with *BMPR2* mutation have the poorest clinical outcomes. *ALK1* mutation carriers tended to have worse outcomes than mutation noncarriers. It is important to consider aggressive treatment for *BMPR2* or *ALK1* mutation carriers. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;110:586–593)

Pulmonary arterial hypertension (PAH) is a progressive, devastating disease. In the absence of treatment, PAH leads to death, with median survival of 2.8 years for adults.[1] However, the median survival of children with PAH without treatment is <10 months.[2,3] Furthermore, although <25% of adults with idiopathic PAH (IPAH) are acutely responsive to vasodilator testing, >40% of children with

[a]Department of Pediatrics and [b]Department of Preventive Medicine and Public Health, National Defense Medical College, Tokorozawa; [c]Department of Pediatric Cardiology, [d]International Research and Educational Institute for Integrated Medical Sciences, and [e]International Center for Molecular, Cellular and Immunological Research, Tokyo Women's Medical University; [f]Department of Pediatrics, Toho University Omori Medical Center, Omori Hospital, Tokyo; [g]Department of Medical Engineering, Faculty of Health Care Sciences, Himeji Dokkyo University, Himeji; [h]Department of Pediatrics, Hokkaido Medical Center for Child Health and Rehabilitation, Sapporo; [i]Department of Pediatrics, Iwate Prefectural Kitakami Hospital, Kitakami; [j]Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba; [k]Department of Cardiology, Gunma Children's Medical Center, Shibukawa; [l]Department of Pediatrics, Keio University School of Medicine, Tokyo; [m]Department of Pediatrics and Cardiovascular Surgery, Sakakibara Memorial Hospital, Tokyo, Japan; [n]Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo; [o]Department of Pediatric Cardiology, Shizuoka Children's Hospital, Shizuoka; [p]Department of Cardiovascular Surgery and Pediatric Cardiology, Nagano Children's Hospital, Nagano; [q]Department of Pediatrics, Graduate School of Medicine, University of Toyama, Toyama; [r]Department of Pediatrics, Kyoto Second Red Cross Hospital, Kyoto; [s]Division of Pediatric Cardiology, Department of Pediatrics, Okayama University, Okayama; [t]Division of Pediatrics, Organization Nagasaki Medical Center, Nagasaki; [u]Department of Pediatrics and Child Neurology, Oita University Faculty of Medicine, Oita; [v]Division of Pediatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan; [w]Department of Pediatric Cardiology, Anzhen Hospital, Capital Medical University, Beijing, China; and [x]School of Medicine, Faculty of Medicine, Toho University, Tokyo, Japan. Manuscript received January 27, 2012; revised manuscript received and accepted April 3, 2012.

*Corresponding author: Tel: 81-3-3353-8112 ext. 24067; fax: 81-3-3352-3088.

E-mail address: pnakanis@hij.twmu.ac.jp (T. Nakanishi).

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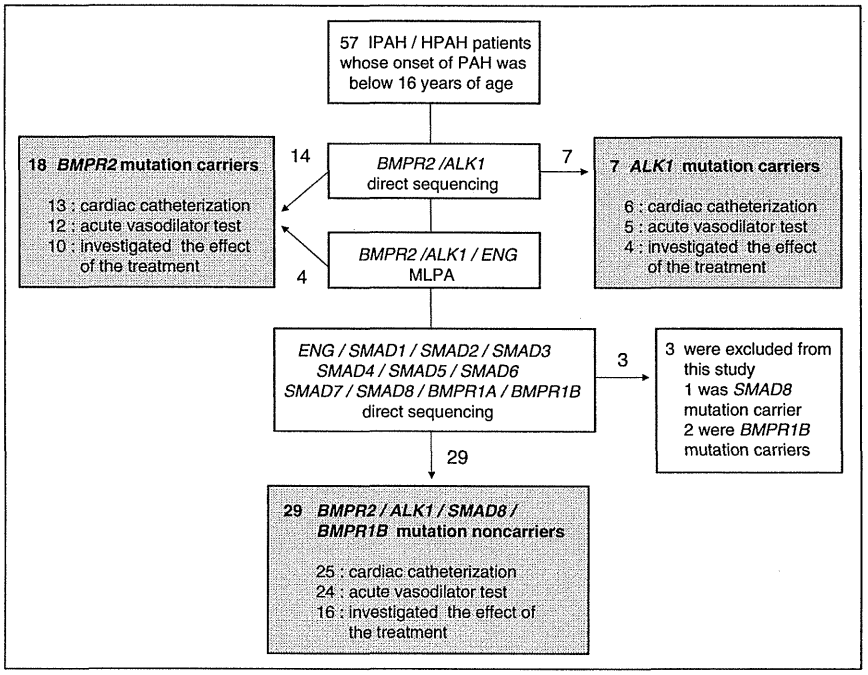

Figure 1. Patient disposition. *BMPR1A* = bone morphogenetic protein receptor type 1A; *BMPR1B* = bone morphogenetic protein receptor type 1B. *ENG* = endoglin.

IPAH are responders.[4] Thus, the prognosis and clinical features of IPAH in children may be different from those in adults. The clinical features of IPAH and heritable PAH (HPAH) in children, however, remain unclear. Bone morphogenetic protein receptor type 2 (*BMPR2*) has been identified as a primary gene for HPAH.[5,6] Heterozygous mutation of the activin receptor–like kinase 1 gene (*ALK1*) has also been demonstrated in patients with hereditary hemorrhagic telangiectasia (HHT) in association with PAH.[7] In addition, our group reported 5 *ALK1* mutations in PAH children.[8] Even rarer mutations in endoglin have been identified in patients with PAH, predominantly with coexistent HHT.[9] In contrast, we reported the first nonsense mutation of *SMAD8* and 2 missense mutations of *BMPR1B* in patients with IPAH.[10,11] The differences in clinical outcomes in each gene mutation carrier in IPAH and HPAH are still unclear. There are several studies referring to this relation,[12–14] but no report has investigated it in childhood IPAH and HPAH. In this study, we attempted to screen for other genes associated with these genes in pediatric patients and conducted a follow-up survey to clarify the clinical features and interrelations between gene mutations and outcomes in pediatric IPAH and HPAH.

Methods

Fifty-seven unrelated patients aged ≤15 years at diagnosis with PAH were selected from 19 hospitals throughout Japan and China (Figure 1). There was no duplication in this selection process. Some of these patients have been described in previous reports.[8,10,11] Written informed consent was obtained from guardians of all study subjects in accordance with the Declaration of Helsinki. We assessed each patient by clinical history, physical examination, current therapy, 6-minute walking distance, and a review of medical records through March 2011.

Diagnosis of IPAH and HPAH was made through clinical evaluation, chest x-ray, electrocardiography, echocardiography, and cardiac catheterization on the basis of current international consensus criteria (mean pulmonary artery pressure >25 mm Hg at rest or >30 mm Hg during exercise).[15] Patients with PAH associated with other diseases such as portal hypertension, congenital heart disease, or persistent pulmonary hypertension of the newborn were systematically excluded from this study by trained cardiologists using a diagnostic algorithm. A significant acute response to nitric oxide and/or epoprostenol was defined by the following 3 criteria: (1) a >20% decrease in mean pulmonary artery pressure, (2) no change or an increase in cardiac index, and (3) no change or a decrease in the ratio of pulmonary vascular resistance to systemic vascular resistance.[16]

The *BMPR2* and *ALK1* coding regions and exon-intron boundaries were amplified from patients' genomic deoxyribonucleic acid. Amplified products were purified using the QIAquick polymerase chain reaction purification method (Qiagen, Hilden, Germany) and screened using bidirectional direct sequencing with an ABI 3130xl DNA Analyzer (Applied Biosystems, Foster City, California). Fourteen *BMPR2* mutations and 7 *ALK1* mutations were identified by direct sequencing (Figure 1). Regarding *BMPR2* and *ALK1*, mutation-negative samples, multiplex ligation–dependent probe amplification (MLPA) was used to detect exonic deletions or duplications in *BMPR2*, *ALK1*, and endoglin. MLPA was performed according to the manufacturer's instructions using a SALSA MLPA HHT/PPH1 probe set (MRC-Holland, Amsterdam, The Netherlands). MLPA

Table 1
Baseline characteristics of patients with pulmonary arterial hypertension

Variable	*ALK1* Mutation Carriers (n = 7)	*BMPR2* Mutation Carriers (n = 18)	Mutation Noncarriers (n = 29)	All Patients (n = 54)	p Value
Male gender	3 (43%)	10 (56%)	11 (38%)	24 (44%)	0.496
Family history of PAH	4 (57%)	3 (17%)	3 (10%)	10 (19%)	0.012
Age at onset (years)	9.3 ± 4.2	9.1 ± 3.7	8.0 ± 4.0	8.5 ± 3.9	0.589
Brain natriuretic peptide (pg/ml)*	94.8 (7.8–752.0)	159.2 (18.8–1,451.5)	39.6 (12.2–117.1)	57.0 (12.8–335.9)	0.366
6-minute walking distance (m)*	525 ± 176	379 ± 93	448 ± 113	442 ± 126	0.125

Data are expressed as number (percentage), as mean ± SD, or as median (interquartile range).

* Although the period of 6-minute walking distance and brain natriuretic peptide measurement depended on the patient, we selected the newest data through March 2011. Brain natriuretic peptide could be measured in 12 *BMPR2* mutation carriers, 6 *ALK1* mutation carriers, and 22 mutation noncarriers and 6-minute walking distance in 8 *BMPR2* mutation carriers, 5 *ALK1* mutation carriers, and 15 mutation noncarriers.

Table 2
Hemodynamic parameters in patients with pulmonary arterial hypertension

Variable	*ALK1* Mutation Carriers (n = 6)	*BMPR2* Mutation Carriers (n = 13)	Mutation Noncarriers (n = 25)	All Patients (n = 44)	p Value
Mean pulmonary artery pressure (mm Hg)	61.8 ± 18.2	69.8 ± 19.7	62.1 ± 21.8	64.3 ± 20.6	0.529
Right atrial pressure (mm Hg)	6.7 ± 4.5	7.5 ± 4.5	6.6 ± 2.9	6.8 ± 3.6	0.758
Cardiac index (L/min/m^2)	3.7 ± 0.8	2.8 ± 1.1	3.3 ± 0.9	3.2 ± 1.0	0.196
Total pulmonary resistance (Wood units/m^2)	14.8 ± 4.3	26.3 ± 14.2	21.6 ± 11.9	21.9 ± 12.0	0.321
Pulmonary vascular resistance (Wood units/m^2)	17.1 ± 10.4	23.9 ± 14.6	17.6 ± 10.5	19.1 ± 11.6	0.411
Pulmonary artery wedge pressure (mm Hg)	9.0 ± 2.8	9.0 ± 2.9	9.0 ± 2.6	9.0 ± 2.7	0.999
Acute vasodilator responder	1/5 (20%)	4/12 (33%)	10/24 (42%)	15/41 (37%)	0.646

Data are expressed as mean ± SD or as number (percentage).

Table 3
Current therapy in patients with pulmonary arterial hypertension

Variable	*ALK1* Mutation Carriers (n = 4)	*BMPR2* Mutation Carriers (n = 10)	Mutation Noncarriers (n = 23)	All Patients (n = 37)	p Value
Intravenous epoprostenol	2 (50%)	6 (60%)	13 (57%)	21 (57%)	0.781
Cardiotonic drugs	1 (25%)	4 (40%)	9 (39%)	14 (38%)	0.709
Sildenafil/tadalafil	3 (75%)	8 (80%)	17 (74%)	28 (76%)	0.485
Bosentan/ambrisentan	4 (100%)	7 (70%)	15 (65%)	26 (70%)	0.273
Other vasodilators per os	4 (100%)	8 (80%)	14 (61%)	26 (70%)	0.179
Anticoagulant or antiplatelet agents	3 (75%)	6 (60%)	16 (70%)	25 (68%)	0.654
Diuretics	2 (50%)	6 (60%)	16 (70%)	24 (65%)	0.134
Oxygen	3 (75%)	10 (100%)	21 (91%)	34 (92%)	0.310

Patients who underwent lung transplantation and those who died were excluded because it was difficult to assess current therapy.

analysis revealed that 4 of 36 patients had exonic deletions in *BMPR2* (Figure 1). In patients with no mutations in *BMPR2* or *ALK1*, all coding exons and adjacent intronic regions for endoglin, *SMAD1*, *SMAD2*, *SMAD3*, *SMAD4*, *SMAD5*, *SMAD6*, *SMAD7*, *SMAD8*, *BMPR1A*, and *BMPR1B* were amplified using a polymerase chain reaction. Polymerase chain reaction–amplified products were purified and directly sequenced like *BMPR2* and *ALK1*. One *SMAD8* nonsense mutation and 2 *BMPR1B* missense mutations were detected, as described previously.[10,11] They were excluded from this analysis because the number of cases representing each mutation was too small. No mutations were identified in endoglin, *SMAD1*, *SMAD2*, *SMAD3*, *SMAD4*, *SMAD5*, *SMAD6*, *SMAD7*, or *BMPR1A* in 29 patients who had no mutations in *BMPR2*, *ALK1*, *SMAD8*, or *BMPR1B* (Figure 1). When a mutation was detected, we confirmed that it was not present in >200 healthy controls by direct sequencing.

Clinical features are expressed as mean ± SD, median (interquartile range), or number of patients (percentage), as appropriate. Univariate comparisons between *ALK1* mutation carriers, *BMPR2* mutation carriers, and mutation noncarriers were done using 1-way analysis of variance or the median test for continuous measures and the chi-square test for categorical measures. Death rate is presented as the

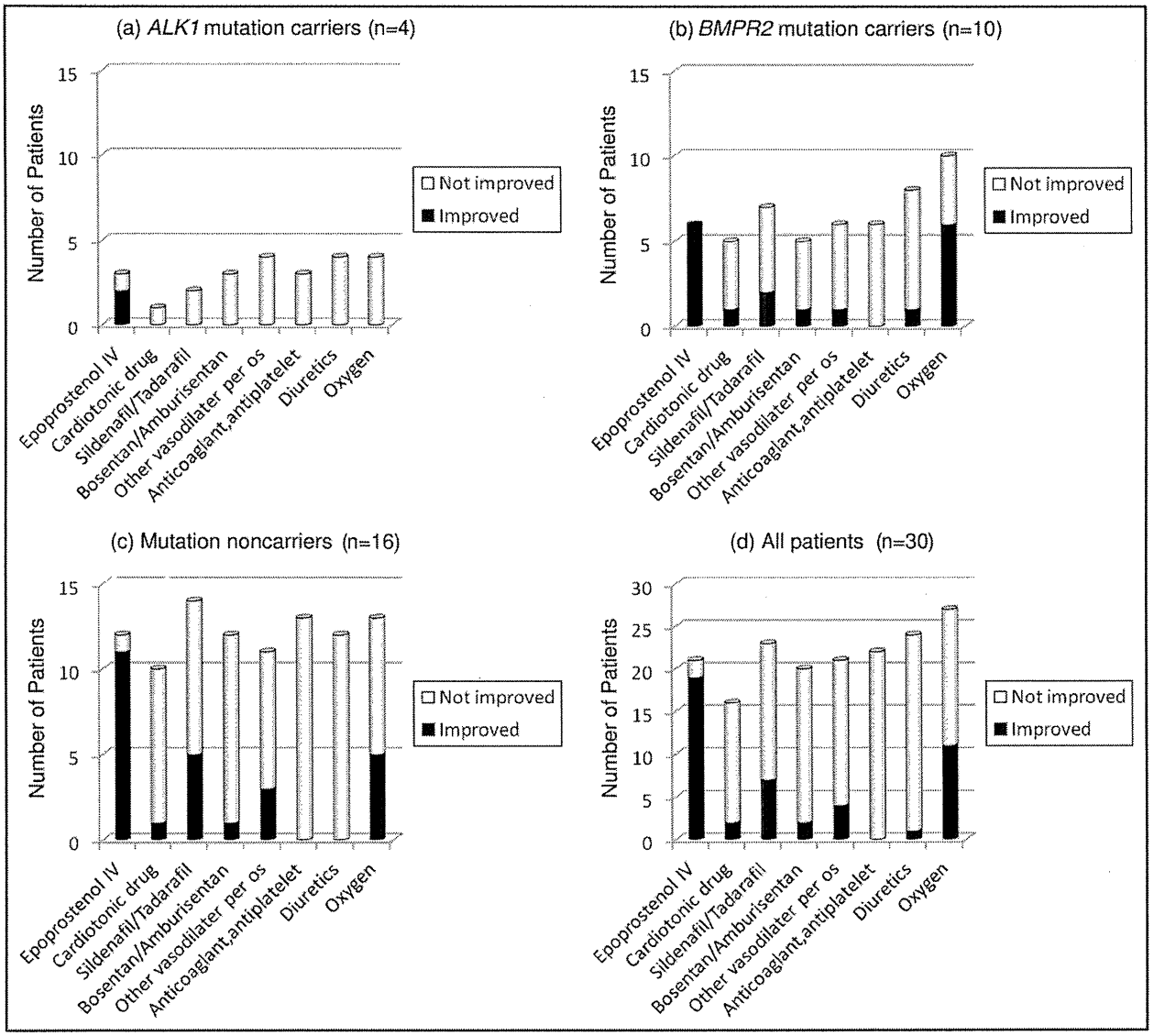

Figure 2. Functional class improvement through treatment in *ALK1* mutation carriers *(a)*, *BMPR2* mutation carriers *(b)*, mutation noncarriers *(c)*, and all patients *(d)*. Four of 7 *ALK1* mutation carriers, 10 of 18 *BMPR2* mutation carriers, and 16 of 29 mutation noncarriers could be investigated for the effects of the treatment. Changes in functional class were assessed by each attending physician retrospectively in March 2011. *BMPR1A* = bone morphogenetic protein receptor type 1A; *BMPR1B* = bone morphogenetic protein receptor type 1B; IV = intravenous.

number per person-year, and the difference between gene mutations was evaluated using a Poisson regression model.

A Kaplan-Meier overall survival curve was constructed to demonstrate the overall survival difference among mutation groups and compared using the log-rank test. Cox proportional-hazards regression modeling was performed to examine the relation between mutations and all-cause death. Similar survival analyses were performed by gender.

A p values <0.05 was considered significant. Statistical analyses were performed using JMP for Windows version 9 (SAS Institute Inc., Cary, North Carolina).

Results

From January 1, 1995, to March 31, 2011, 54 pediatric patients with IPAH or HPAH, corresponding to 24 male and 30 female patients, were included in this analysis. Eighteen (33%) were *BMPR2* mutation carriers, 7 (13%) were *ALK1* mutation carriers, and the rest were without these mutations (Figure 1, Table 1). The average age at diagnosis was 8.5 years, and there was no significant difference in ages among the 3 groups. Familial cases in *ALK1* mutation carriers were largest in these groups. No significant differences were seen in brain natriuretic peptide or 6-minute walking distance. Cardiac catheterization was performed in 44 of 54 patients (Figure 1, Table 2). Forty-one of 54 patients were subjected to acute vasodilator response testing, 15 of whom were responders. There were no significant differences among the 3 groups in terms of hemodynamic characteristics or response to vasoreactivity testing (Table 2).

There were no significant differences in current therapy among the 3 groups (Table 3). As shown in Figure 2,

Table 4
Prognosis of patients with pulmonary arterial hypertension

Variable	*ALK1* Mutation Carriers (n = 7)	*BMPR2* Mutation Carriers (n = 18)	Mutation Noncarriers (n = 29)	All Patients (n = 54)	p Value
NYHA class I or II	4 (57%)	7 (39%)	18 (62%)	29 (54%)	
NYHA class III or IV	0	3 (17%)	5 (17%)	8 (15%)	
Lung transplantation	1 (14%)	0	3 (10%)	4 (7%)	
Death	2 (29%)	8 (44%)	3 (10%)	13 (24%)	
Rate of death (deaths/person-year)	0.051	0.159	0.012	0.038	0.0002

NYHA = New York Heart Association.

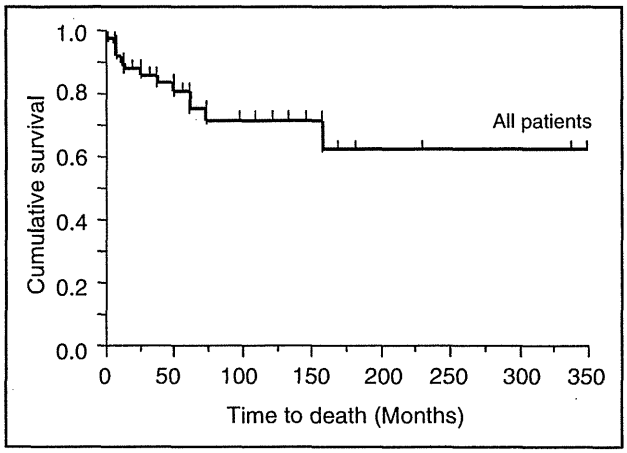

Figure 3. Kaplan-Meier curves for survival of all patients. Five- and 10-year survival probabilities were 76% and 72%, respectively.

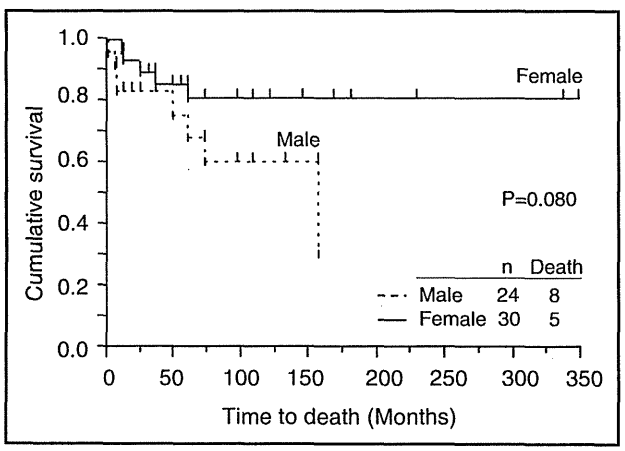

Figure 4. Time to death in all patients according to gender (log-rank test, p = 0.08).

intravenous epoprostenol strongly improved functional class in all groups. Sildenafil, vasodilators except sildenafil or tadalafil and bosentan or ambrisentan, and oxygen also improved functional class moderately. The difference of each drug effect among each group was not significant (data not shown).

Eight of 18 *BMPR2* mutation carriers died, and the causes of death were all directly related to PAH. Two of 7 *ALK1* mutation carriers died of PAH. Three of 29 mutation noncarrriers died, and the causes of death were related to PAH. The rate of death was worst in *BMPR2* mutation

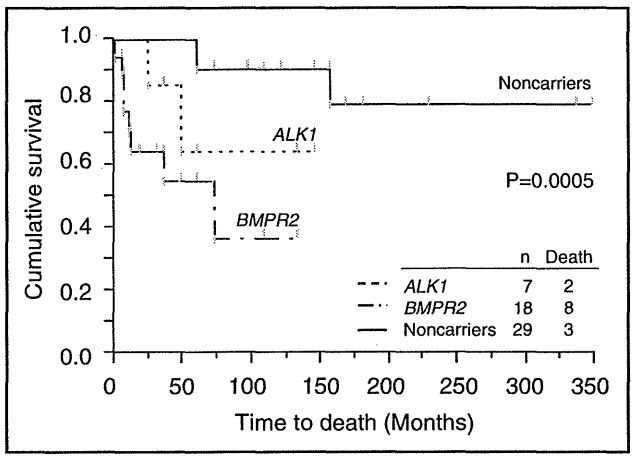

Figure 5. Survival of *BMPR2* and *ALK1* mutation carriers and mutation noncarriers with PAH (log-rank test, p = 0.0005).

Table 5
Univariate Cox proportional-hazards model for time to death in patients with pulmonary arterial hypertension

Characteristic	Hazard Ratio (95% Confidence Interval)	p Value
Gene mutation		
ALK1 mutation vs mutation noncarriers	5.14 (0.61–43.03)	0.1205
BMPR2 mutation vs mutation noncarriers	12.54 (3.06–84.21)	0.0003
Gender (male vs female)	2.62 (0.87–8.73)	0.0869

carriers (Table 4). Overall 5- and 10-year survival of all patients was 76% and 72%, respectively (Figure 3). As shown in Figure 4, male patients' outcomes tended to be worse than female patients' outcomes. In Figure 5, overall mortality was worst in *BMPR2* mutation carriers. Five- and 10-year survival was lower in *BMPR2* mutation carriers than mutation noncarriers (55% and 37% vs 90% and 90%, respectively). *ALK1* mutation carriers also had a tendency to have worse outcomes than mutation noncarriers (5- and 10-year survival rates were 64%). A multivariate Cox proportional-hazards model for time to death indicated that *BMPR2* mutation carriers had significantly worse outcome than mutation noncarriers (Table 5). The difference in outcomes between *ALK1* mutation carriers and mutation noncarriers was marginally significant. No significant differences were observed in time to death among the 3 subgroups of *BMPR2* mutation carriers (Figure 6).

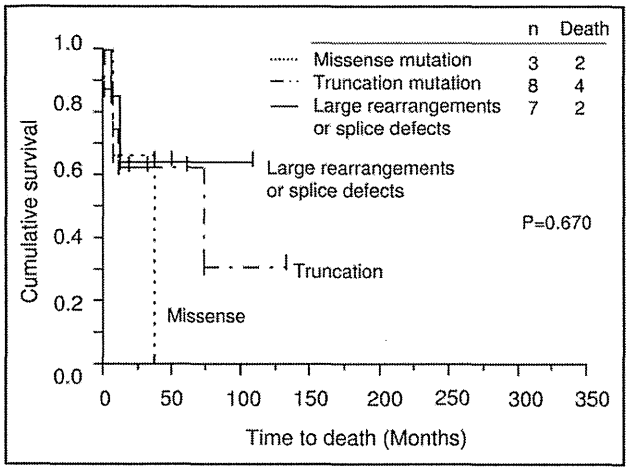

Figure 6. Influence of *BMPR2* mutation types on clinical outcomes of patients with PAH (log-rank test, p = 0.670).

Some *BMPR2* and *ALK1* mutations have been previously reported by other groups, and 7 *BMPR2* mutation cases and 5 *ALK1* mutation cases have been previously published by our colleagues (Tables 6 and 7).[6,8,17–25] Of 18 *BMPR2* mutations, 6 were nonsense mutations, 3 were missense mutations, 2 were small deletions resulting in frame shifts, and 3 were splice-site mutations. MLPA analysis detected 4 exonic deletions (Table 6). We identified 5 *BMPR2* mutations that were not previously reported. All *ALK1* mutations were missense mutations (Table 7). One patient previously diagnosed with HHT subsequently developed features of PAH at the age of 11 years. We identified 2 *ALK1* mutations that were not previously reported.

Discussion

We studied 54 patients with HPAH or IPAH whose onset of disease was at ≤15 years of age. Overall 5-year survival for all patients was 76%. This result was similar to that of recent studies.[26,27] In this study, hemodynamic and clinical characteristics of significant gene mutation carriers and noncarriers were compared. We demonstrated that *BMPR2* mutation carriers have more severe overall mortality than mutation noncarriers, despite similar therapeutic approaches, hemodynamic parameters, brain natriuretic peptide, and 6-minute walking distance. Although *ALK1* mutation carriers also tended to have poorer prognoses than mutation noncarriers, we were unable to adequately prove it. This result may have been caused by the small number of cases in *ALK1* mutation group. Many more patients need to be studied to find a solution for this problem. These results, however, indicate the importance of early gene analysis in patients with PAH. When patients with PAH have *BMPR2* or *ALK1* mutations, physicians should consider aggressive treatment involving lung transplantation, even if patient's current clinical conditions are not serious.

It is difficult to explain the differences in prognosis among *BMPR2* and *ALK1* mutation carriers and mutation noncarriers. In this study, there was only 1 *ALK1* mutation carrier with HHT, who is still alive. Because of this complication of HHT, the poor prognosis in *ALK1* mutation carriers could not be explained. It is possible that there are unknown gene mutations even in mutation noncarriers. Other signal pathways that are not related to *BMPR2* and *ALK1* may also directly be connected to the pathogenesis of PAH.

Girerd et al[12] reported that *ALK1* mutation carriers have more severe overall mortality than *BMPR2* mutation carriers or *BMPR2* or *ALK1* mutation noncarriers. They also reported that no significant difference was observed in clinical outcome between *BMPR2* mutation carriers and mutation noncarriers.[13] Sztrymf et al[14] also demonstrated that the *BMPR2* mutation carrier group and noncarrier group showed similar overall survival, but time to death or time to lung transplantation was shorter in the *BMPR2* carrier group. The gap between these reports and our study may be due to the age of onset of the subjects. Because the death rate of *BMPR2* mutation carriers whose onset of disease was at <16 years of age was very high (Table 4), it may be difficult to comparatively include mutation carriers in an all-generation follow-up study. The discrepancy observed in the results of each study may also be caused by the difference of PAH pathogenesis between children and adults. Although little is known about the difference, Wagenvoort and Wagenvoort[28] reported that pulmonary artery medial hypertrophy was severe in patients aged <15 years and was most often the only abnormality seen in infants. With increasing age, intimal fibrosis and plexiform lesions were often seen. These features may be connected with clinical observations that infants with PAH are more likely to die from sudden death than adults and may provide an explanation for the difference of survival rate between adults and children.[29]

In our study, young male patients with PAH tended to have poorer prognoses than female patients. The difference in overall survival between male and female patients was marginally significant (Figure 3). Girerd et al,[13] however, demonstrated no differences in survival or time to death between male and female patients in all generations. In contrast, Moledina et al[27] reported that worse survival was associated with female gender in childhood IPAH. Further studies may be needed to investigate the relation between clinical outcomes and gender.

Austin et al[30] demonstrated that patients with *BMPR2* missense mutations have more severe disease than those with *BMPR2* truncating mutation carriers. Girerd et al,[13] however, reported that no significant differences were observed in survival, time to death, or time to lung transplantation among missense mutation, truncating mutation, and large rearrangements or splice defects in *BMPR2* mutation carriers. In our study, the difference of overall mortality among missense mutations, truncating mutations, and other mutations was not significant (Figure 6). Although it is difficult to explain the difference in results, it may be caused by the number of patients or the age of onset of patients.

This is the first study to attempt to evaluate the efficacy of treatment in every mutation carrier or noncarrier group. Although the difference of each drug effect in each group was not significant, this result suggests that most therapies, except intravenous epoprostenol, were not effective for *ALK1* mutation carriers. Furthermore, in our study, intravenous epoprostenol strongly improved functional class in all

Table 6
Details of *BMPR2* mutations

Proband	Mutation Location	Mutation Category	Domain	Nucleotide Change	Amino Acid Change	Reference
1	Exon 1	Nonsense	ECD	c.38 G>A	W13X	This study
2	Intron 2	Splice-site	ECD	c.248-3 T>G	—	This study
3	Exon 3	Nonsense	ECD	c.339 C>G	Y113X	Fujiwara et al[8]
4	Exon 3	Nonsense	ECD	c.339 C>G	Y113X	Fujiwara et al[8]
5	Exon 3	Missense	ECD	c.367 T>C	C123R	Machado et al[17] Fujiwara et al[8]
6	Exon 3	Deletion	ECD	c.247-? _420+? del	—	Machado et al[18]
7	Exons 2-3	Deletion	ECD	c.76-? _420+? del	—	Machado et al[18]
8	Exons 2-3	Deletion	ECD	c.76-? _420+? del	—	Machado et al[18]
9	Intron 4	Splice-site	ECD	c.529+2 T>C	—	This study
10	Exon 6	Nonsense	KD	c.631 C>T	R211X	Thomson et al[19]
11	Exon 6	Missense	KD	c.727 G>C	E243Q	This study
12	Intron 8	Splice-site	KD	c.1128+1 G>T	—	Pfarr et al[20]
13	Exon 9	Nonsense	KD	c.1207 C>T	Q403X	Uehera et al[21] Fujiwara et al[8]
14	Exons 8-9	Deletion	KD	c.967-? _1275+? del	—	Aldred et al[22]
15	Exon 10	Frameshift	KD	c.1376_1377 del GA	R459fsX10	Sankelo et al[23]
16	Exon 10	Nonsense	KD	c.1397 G>A	W466X	Koehler et al[24]
17	Exon 11	Missense	KD	c.1472 G>A	R491Q	Deng et al[6]
18	Exon 12	Frameshift	CD	c.2289 del C	T762fsX9	This study

CD = cytoplasmic domain; ECD = extracellular domain; KD = kinase domain.

Table 7
Details of *ALK1* mutations

Proband	Mutation Location	Mutation Category	Domain	Nucleotide Change	Amino Acid Change	Reference
1	Exon 7	Missense	KD	c.854 T>C	L285P	This study
2	Exon 7	Missense	KD	c.936 C>G	H312Q	Fujiwara et al[8]
3	Exon 8	Missense	KD	c.1142 T>C	L381P	Fujiwara et al[8]
4	Exon 9	Missense	KD	c.1270 C>A	P424T	Fujiwara et al[8]
5	Exon 10	Missense	KD	c.1433 C>A	A478D	This study
6	Exon 10	Missense	KD	c.1436 G>A	R479Q	Fujiwara et al[8]
7	Exon 10	Missense	KD	c.1451 G>A	R484Q	Harrison et al[25] Fujiwara et al[8]

ALK1 = activin receptor-like kinase 1; KD = kinase domain.

groups. Sildenafil, vasodilators except for sildenafil or tadalafil and bosentan or ambrisentan, and oxygen also moderately improved functional class. In the present study, we could perform a follow-up study of the efficacy of treatment in only 35 patients. In addition to this limitation, it may be hard for physicians to assess changes in the functional class at an early stage of treatment. Some patients may even be treated with several drugs simultaneously. It may be necessary to consider a prospective study to reduce these biases.

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Heart Vessels
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CASE REPORT

A left ventricular noncompaction in a patient with long QT syndrome caused by a *KCNQ1* mutation: a case report

Kentaro Nakashima · Isao Kusakawa · Tsuyoshi Yamamoto · Shinsuke Hirabayashi · Ryohta Hosoya · Wataru Shimizu · Naokata Sumitomo

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Abstract A 5-year-old girl developed cardiopulmonary arrest after crying. From the electrocardiogram and echocardiography, a left ventricular noncompaction (LVNC) with long QT syndrome (LQT) was suspected as the cause of the cardiopulmonary arrest, and treatment with a β-blocker and a calcium antagonist was then begun. A genetic screening of LQT-related genes revealed a previously reported heterozygous *KCNQ1* mutation. The association of LVNC and LQT is an extremely rare condition, and long-term treatment based on the characteristics of both disorders is required. Also, the association of cardiomyopathy and LQT could become a new clinical entity in the future.

Keywords Long QT syndrome · Left ventricular noncompaction · Epilepsy · Cardiopulmonary arrest · *KCNQ1* mutation

K. Nakashima · I. Kusakawa · T. Yamamoto · S. Hirabayashi · R. Hosoya
Department of Pediatrics, St. Luke's International Hospital, 9-1 Akashi-cho, Chuou-ku, Tokyo 104-8560, Japan
e-mail: bluesky199067@yahoo.co.jp; nakashima.k@nk-cc.go.jp

Present Address:
K. Nakashima
Department of Pediatrics, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka City, Fukuoka 811-1395, Japan

W. Shimizu
Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan

N. Sumitomo (✉)
Department of Pediatrics and Child Health, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
e-mail: sumitomo.naokata@nihon-u.ac.jp

Background

Long QT syndrome (LQT) is a group of ion-channel disorders of the myocardium that may prolong the repolarization of the cardiac cycle [1]. According to the genotype investigation, 12 subtypes (LQT1–12) have been reported [2]; each subtype has its own clinical characteristics, and the treatment strategy differs for each subtype. Long QT syndrome is known as the most important cause of sudden cardiac death in the young [3], and may mostly result from the occurrence of ventricular fibrillation (VF) or torsade de pointes (TdP).

Here we report the case of a girl with left ventricular noncompaction (LVNC) and LQT, which were confirmed after resuscitation from cardiopulmonary arrest.

Case report

A 5-year-old girl had syncope after intense crying at her kindergarten. Her mother noticed cyanosis around her lips and then she developed cardiopulmonary arrest. Bystander cardiopulmonary resuscitation (CPR) was started immediately by a kindergarten teacher, who called for an ambulance. An automated external defibrillator (AED) revealed pulseless electrical activity, and there was no indication for defibrillation. She was transported to our hospital under continuous CPR.

She had been followed up for a diagnosis of epilepsy after two episodes of afebrile convulsions when she was 3 years old. She had a syncopal attack during the follow-up period, and multifocal spike waves were noted on the electroencephalogram. She had been administered carbamazepine since then, after which the spike waves disappeared during the follow-up period. Except for an

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episode of afebrile convulsions at age 4 years, she did not experience any further episodes of convulsions or syncope. Magnetic resonance imaging revealed no brain abnormalities.

On arrival at our hospital, sinus rhythm had resumed; however, she required intubation and respiratory support for her respiratory failure and cardiac dysfunction. Her cardiac function then improved gradually, but about 6 h after arrival, TdP and VT emerged in the intensive care unit. While we were preparing to defibrillate her, performing cardiac compressions for about 1 min, sinus rhythm resumed spontaneously (Fig. 1) and her cardiac function improved.

The electrocardiogram obtained after the CPR exhibited a prolonged QTc interval (Fig. 2, QTc = 0.6 s), and the patient was suspected as having LQT. There were no electrolyte imbalances at the time of hospitalization. Her cardiac function improved gradually after CPR. An echocardiogram revealed a spongy dysplastic left ventricular myocardium with prominent trabeculations and deep recesses, indicating LVNC (Fig. 3). We therefore started the patient on propranolol and verapamil to control her VT. Her respiratory support was discontinued 3 days after hospitalization. After administration of propranolol and verapamil, TdT and VT no longer emerged.

Electrocardiographic examinations and a genetic screening of LQT-related genes were performed on the patient, her sister and brother, her parents, her paternal and maternal grandfathers and grandmothers, and a maternal uncle (Fig. 4). She, her brother, her father, and her paternal grandmother were found to have a previously reported heterozygous *KCNQ1* mutation c.1831 G > T in exon 15 (p. D611T). No prolongation of QT intervals or echocardiographic abnormalities were found in family members (her brother, her father, and her paternal grandmother) who had a *KCNQ1* mutation. Although her development had been normal until this event, the patient manifested mild mental retardation because of ischemic brain damage. She underwent rehabilitation and attended a school for handicapped children with a restriction on swimming.

Discussion

Left ventricular noncompaction is a congenital cardiomyopathy with a spongy morphological appearance and deep intertrabecular sinusoids in communication with the ventricular cavity [4]. The diagnosis is mainly made by two-dimensional echocardiography, cardiac magnetic resonance imaging, or left ventricular angiography.

The echocardiogram reveals that prominent trabeculations and deep recesses are noted in the ventricular myocardium [5]. However, so far there has been no distinct definition of LVNC [6]. Koh et al. [7] reported that a left ventricular myocardial deformation is reduced in the longitudinal and circumferential dimensions and manifests with tight systolic–diastolic coupling in children with LVNC.

Genetic mutations were first reported in the *G4.5* gene in patients with an isolated LVNC [8]. Z-line and mitochondrial mutations and X-linked inheritance resulting from mutations in the *G4.5* gene encoding tafazzin could be a pathogenesis for the disease. In this report, the gene defect differed among the families, and thus there did not appear

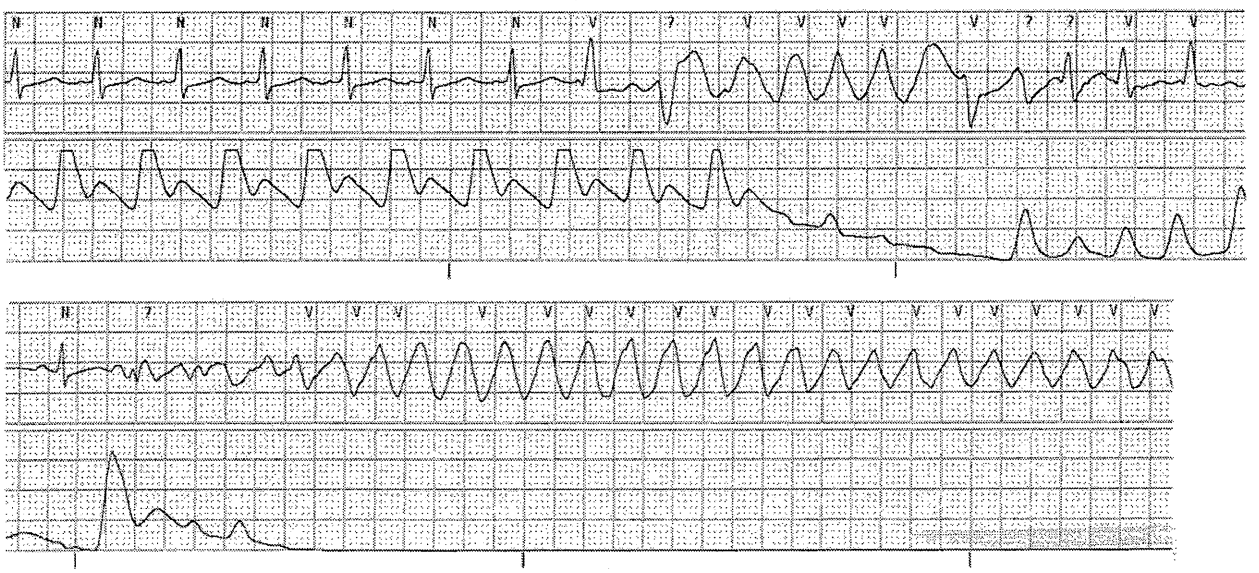

Fig. 1 Monitor recording obtained while the patient was in the intensive care unit. *Upper panel* occurrence of torsade de pointes (TdP), which terminated within several beats. *Lower panel* occurrence of long-lasting TdP or ventricular fibrillation

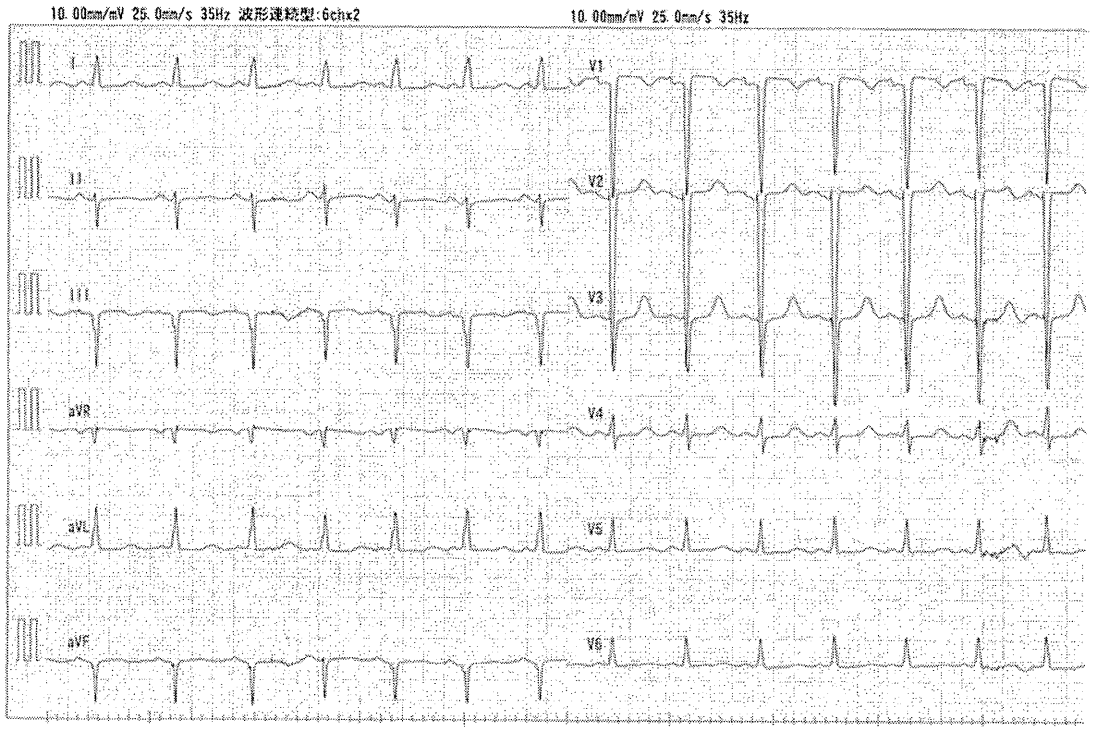

Fig. 2 Electrocardiogram recorded after the resuscitation. The electrocardiogram after the resuscitation showed normal sinus rhythm with left QRS axis deviation (−15°). The QTc interval was prolonged to 0.6 s. There were also flattened T waves in the left precordial leads (V5 and V6)

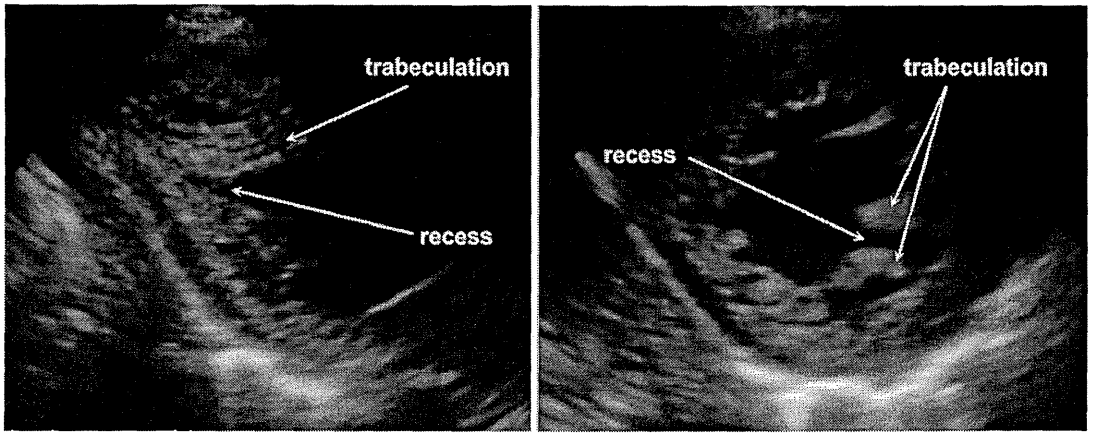

Fig. 3 Echocardiogram. Prominent trabeculations and a deep recess were detected

to be any obvious genotype–phenotype correlation that would allow for the differentiation of the clinical course to be predicted. In addition, the cardiac phenotypes that occur as a result of *G4.5* mutations may vary significantly. On the other hand, in patients with LVNC associated with congenital heart disease, a so-called nonisolated LVNC, mutations in the α-dystrobrevin gene have been reported [9]. In this report, the α-dystrobrevin mutation resulted in a phenotype of a dilated hypertrophic cardiomyopathy with deep trabeculations associated with congenital heart disease, consistent with the criteria for LVNC. However, the phenotype in this family had considerable variability. Consequently, the details of the relation between an ion-channel dysfunction and the maldevelopment of the ventricular myocardium are not well described. Further genetic studies are needed to discover whether a combined mutation with *G4.5* or α-dystrobrevin and *KCNQ1* could have contributed to this clinical manifestation in this patient.

The association of LVNC with LQT is extremely rare. *SCN5A* mutations are frequently associated with LVNC.