IV.　研究成果の刊行物・別刷

Clinical Characteristics and Genetic Background of Congenital Long-QT Syndrome Diagnosed in Fetal, Neonatal, and Infantile Life

A Nationwide Questionnaire Survey in Japan

Hitoshi Horigome, MD; Masami Nagashima, MD; Naokata Sumitomo, MD; Masao Yoshinaga, MD; Hiroya Ushinohama, MD; Mari Iwamoto, MD; Junko Shiono, MD; Koh Ichihashi, MD; Satoshi Hasegawa, MD; Tadahiro Yoshikawa, MD; Tamotsu Matsunaga, MD; Hiroko Goto, MD; Kenji Waki, MD; Masaki Arima, MD; Hisashi Takasugi, MD; Yasuhiko Tanaka, MD; Nobuo Tauchi, MD; Masanobu Ikoma, MD; Noboru Inamura, MD; Hideto Takahashi, PhD; Wataru Shimizu, MD; Minoru Horie, MD

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

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

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

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

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

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From the Department of Child Health (H.H.), Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan; the Department of Cardiology (M.N.), Aichi Children's Health and Medical Center, Ohbu, Japan; the Department of Pediatrics and Child Health (N.S.), Nihon University School of Medicine, Tokyo, Japan; the Department of Pediatrics (M.Y.), National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan; the Department of Cardiology (H.U.), Fukuoka Children's Hospital and Medical Center for Infectious Diseases, Fukuoka, Japan; the Department of Pediatric Cardiology (M. Iwamoto), Yokohama City University School of Medicine, Yokohama, Japan; the Department of Pediatrics (J.S.), Ibaraki Children's Hospital, Mito, Japan; the Department of Pediatrics (K.I.), Jichi Medical University, Shimotsuke, Japan; the Department of Pediatrics (S.H.), Niigata University Graduate School of Medical and Dental Science, Niigata, Japan; the Department of Pediatrics (T.Y.), Sakakibara Heart Institute, Fuchu, Japan; the Department of Pediatric Cardiology (T.M.), International Medical Center, Saitama Medical University, Hidaka, Japan; the Department of Pediatrics (H.G.), Gifu Prefectural General Medical Center, Gifu, Japan; the Department of Pediatrics (K.W.), Kurashiki Central Hospital, Kurashiki, Japan; the Department of Pediatrics (M.A.), Sent Marianna University School of Medicine, Kawasaki, Japan; the Department of Pediatrics (H. Takasugi), Kochi Medical School, Kochi, Japan; the Department of Cardiology (Y.T.), Shizuoka Children's Hospital, Shizuoka, Japan; the Department of Pediatric Cardiology (N.T.), Ogaki Municipal Hospital, Ogaki, Japan; the Department of Pediatrics (M. Ikoma), Japanese Red Cross Nagoya Daiichi Hospital, Nagoya, Japan; the Department of Pediatric Cardiology (N.I.), Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan; the Department of Epidemiology and Biostatistics (H. Takahashi), School of Medicine, University of Tsukuba, Tsukuba, Japan; the Division of Cardiology (W.S.), Department of Internal Medicine, National Cardiovascular Center, Suita, Japan; and the Department of Cardiology and Respiratory Medicine (M.H.), Shiga University of Medical Science, Otsu, Japan.

Correspondence to Hitoshi Horigome, MD, PhD, Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Japan. E-mail hhorigom@md.tsukuba.ac.jp

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Table 1. Questionnaire Items

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

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

Clinical Perspective on p 17

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

Methods

Population

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

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

Genetic Analysis and Genotype-Phenotype Correlation

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

Statistical Analysis

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

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

Results

Population

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

Clinical Features

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

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

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

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

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

Genotype-Phenotype Correlation

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

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

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

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

Treatment

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

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

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

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

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

Outcome

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

Discussion

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

Table 2. Clinicogenetic Details

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

(Continued)

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

Table 2. Continued

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

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

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

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

*LQT8 was retrospectively possible because phenotype included syndactyly.

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

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

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

Table 4. Comparison of Parameters Among the Groups

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

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

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

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

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

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

Therapy

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

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

Study Limitations

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

Conclusion

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

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Disclosures

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CLINICAL PERSPECTIVE

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

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CASE REPORT

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Isolation of pulmonary vein and superior vena cava for paroxysmal atrial fibrillation in a young adult with left ventricular non-compaction

Yoshiaki Kato[1]*, Hitoshi Horigome[1], Miho Takahashi-Igari[1], Kentaro Yoshida[2], and Kazutaka Aonuma[2]

[1]Department of Child Health, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1, Tennnodai, Tsukuba 305-8575, Japan and [2]Cardiovascular Division, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, 305-8575, Japan

* Corresponding author. Tel: +81 29 853 5635; fax: +81 29 853 8819, Email: yoshiakiaisho@hotmail.com

We report a 19-year-old male patient with left ventricular non-compaction who presented with atrial fibrillation (AF) and ventricular tachycardia. Ventricular tachycardia was induced by AF with rapid ventricular response, but was prevented by electrical isolation of the pulmonary veins and superior vena cava.

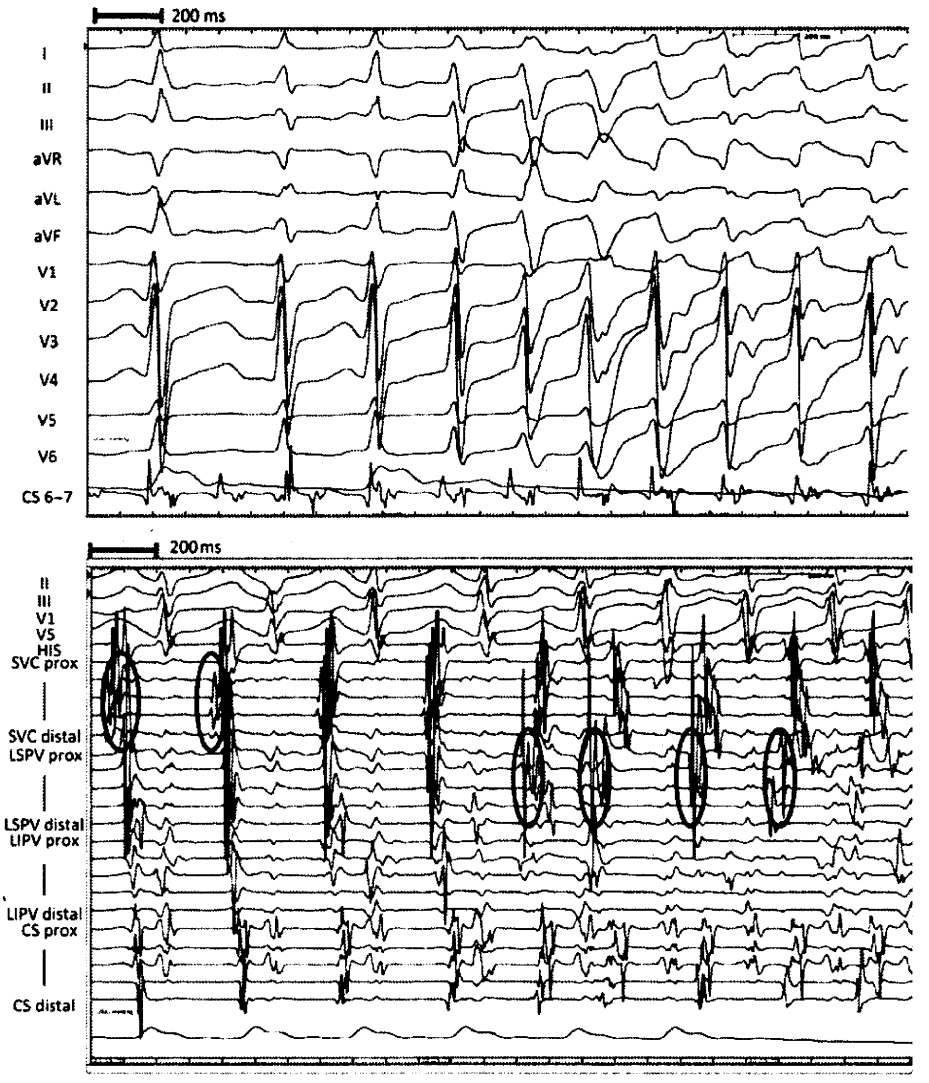

Figure 1 *Top*: wide QRS tachycardia (200 bpm) induced by paroxysmal atrial fibrillation with rapid ventricular response. *Bottom*: discharges from the left superior pulmonary vein (LSPV) and superior vena cava (SVC) that initiated paroxysmal atrial fibrillation were observed with straight multipolar catheters placed in the SVC, LSPV, and left inferior pulmonary vein (LIPV). Discharges from the other three PVs were also recorded but are not included in the polygraph record.

Introduction

Left ventricular non-compaction (LVNC) is a rare congenital cardiomyopathy characterized by prominent trabeculations and deep intra-trabecular recesses in the left ventricular (LV) wall.[1,2] The clinical presentation of LVNC includes heart failure, arrhythmias, and thromboembolic events.[1,2] The diagnosis and management of life-threatening ventricular arrhythmia are particularly important because they correlate with prognosis. We report a case of ventricular tachycardia (VT) induced by atrial fibrillation (AF). Electrical isolation of the pulmonary veins (PVs) and superior vena cava (SVC) aborted these arrhythmias.

Case report

A 19-year-old man was admitted to our hospital for the management of a series of pre-syncopal attacks associated with AF and VT. The first episode of atrial tachycardia (AT) occurred at age 7, which was treated with oral propranolol, and the same treatment was continued for the next 12 years without recurrence of AT. On admission, a Holter recording identified frequent episodes of AF (maximum heart rate, 272 bpm) immediately followed by VT. Transthoracic echocardiography showed prominent trabeculations and deep intra-trabecular recesses in the LV wall. The LV end-diastolic diameter and fractional shortening were 60 mm and 23%, respectively. The left atrium was not dilated. Serum level of brain natriuretic peptide was 18.9 pg/mL.

Electrophysiological study showed no evidence of dual atrioventricular nodal pathway or atrioventricular accessory pathway. Maximal 1:1 atrioventricular conduction was observed at a rate of 272 bpm. Intravenous infusion of isoproterenol (2 μg/min) elicited AF and AT followed immediately by VT due to rapid ventricular response (*Figure 1*), necessitating multiple direct-current shocks. The focal repetitive firing that initiated AF and AT originated from all four PVs and SVC (*Figure 1*). Electrical isolation was achieved by segmental antral radiofrequency ablation (single Lasso technique) applied to all four PVs and SVC. After the procedure, neither AF nor VT was induced by the maximal stimulation protocol even with isoproterenol. Repeated Holter monitoring revealed no tachyarrhythmia during the next 3 years of follow-up.

Discussion

Supraventricular tachycardia due to atrioventricular accessory pathway is one of the major complications in childhood LVNC.[1] In contrast, the incidences of VT and AF increase with age in adult LVNC patients.[2] One interesting finding in our patient was that AF-induced VT developed at a young age. Given the fact that AF in our patient was initiated by ectopic beats from the PVs and SVC, the mechanism of AF might be relatively common. However, considering the rarity of AF among young adults, the pathology of LVNC might be implicated even in atrial arrhythmogenicity. Considering that LV contraction was reduced, probably reflecting ventricular myocardial damage, progressive ischaemia and subsequent scar tissue in the non-compacted lesion could be potential arrhythmogenic substrates for VT.[2] Enhanced atrioventricular conduction and rapid ventricular response might also play important roles in the development of VT, as described in a previous report in another structural heart disease.[3] Unfortunately, the precise mechanism of VT could not be determined due to the unstable condition. Thus, the correlation between LVNC and the development of double tachycardia remains to be investigated. Our report highlights the importance of AF ablation by PVs (and SVC) isolation in preventing AF and hence VT episodes.

Conflict of interest: none declared.

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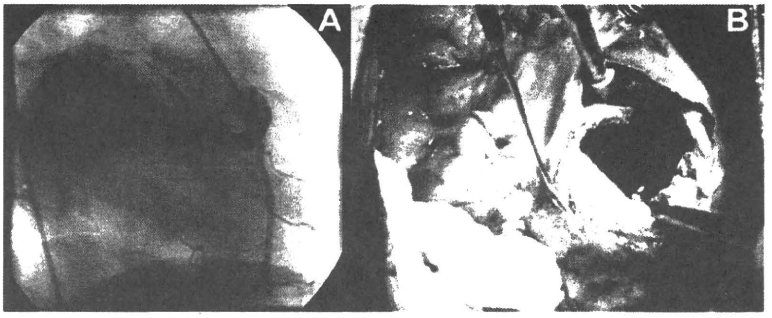

Fig 3. (A) Coronary angiographic image of the right coronary artery. (B) Intraoperative photo showing aneurysm in the right atrium.

monary bypass was discontinued with no ischemic changes on electrocardiogram. The patient recovered uneventfully and was discharged on postoperative day 5, and she continues to do well with subsequent follow-ups. Histologic evaluation of the resected aneurysm revealed changes of atherosclerosis with organized thrombus.

Comment

Causes of giant coronary artery aneurysm have not been well understood. Coronary artery aneurysms, pseudoaneurysms, and its calcification are rare entities in the practice of coronary surgery. The majority of these involve the RCA system. The most common cause is atherosclerosis, which accounts for approximately 50% of the cases. The remaining cases are caused by the inflammatory processes that affect the arterial wall directly, typically mucocutaneous lymph node syndrome (Kawasaki disease), Takayasu's disease, polyarteritis nodosa, systemic lupus, connective tissue disorders (Marfan's, Ehlers-Danlos), septic emboli, syphilis, and *Lyme borreliosis*. Less common causes include cardiac lymphoma, congenital coronary artery aneurysms, and trauma to the coronary arteries during angioplasty [1].

Presentations of coronary artery aneurysms can be misleading as para cardiac or intra cardiac masses [2, 3]. Various imaging modalities are available but lack sensitivity and specificity. Computer tomography scans, magnetic resonance imaging, and cardiac catheterization usually demonstrate the status.

Management is done by excision of the mass, obliteration of the cavity with closure of the fistulous connection by patch or direct suture, repair of chambers and restoration of coronary circulation with or without the graft [4].

The presenting features of superior vena cava obstruction in our patient is explained by compression of the superior vena cava by the mass. Palpitation and progressive increasing dyspnea is explained by the mass in the vicinity of the right atrium leading to changes in the architecture and distortion of the right atrium and a decrease in cardiac output.

The interesting finding in the present case is the occurrence of the aneurysm without any ischemic event and anemia. The cause of arterial pseudoaneurysm is damage to the intima as a result of some trauma in a patient with vascular disease (ie, mainly atherosclerosis). This cause was confirmed on histologic diagnosis of the aneurysmal wall. The patient had this atherosclerotic aneurysm, which probably ruptured in the past leading to pseudoaneurysm and calcification for a period of time. It is interesting to note that only the right coronary system was affected, as the left system was normal. Our case was similar to the second of the two cases reported by Westaby and colleagues [5], although this was diagnosed much earlier [5].

In summary, a case of coronary artery pseudoaneurysm is presented herein that masquerades as a calcified cardiac mass. Its cause is discussed and the management is presented. This report emphasizes the need for coronary artery angiography in patients with a cardiac mass.

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FEATURE ARTICLES

Kawashima Procedure After Staged Unifocalizations in Asplenia With Major Aortopulmonary Collateral Arteries

Yukiko Ban, MD, Mio Noma, MD, PhD, Hitoshi Horigome, MD, PhD, Hideyuki Kato, MD, Chiho Tokunaga, MD, PhD, Yuzuru Sakakibara, MD, PhD, and Yuji Hiramatsu, MD, PhD

Departments of Cardiovascular Surgery and Pediatric Cardiology, University of Tsukuba, Tsukuba, Japan

We report a Kawashima procedure (total cavopulmonary shunt) successfully carried out for asplenia syndrome,

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Address correspondence to Dr Hiramatsu, Department of Cardiovascular Surgery, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, 305-8575, Japan; e-mail: yuji3@md.tsukuba.ac.jp.

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pulmonary atresia, and major aortopulmonary collateral arteries. At the age of 8, the patient underwent staged bilateral unifocalizations using confluent central pulmonary arteries concomitant with bilateral modified Blalock-Taussig shunts. As the result of an interrupted inferior vena cava with azygous continuation, the patient required a Kawashima procedure with augmentation of the central pulmonary arteries for definitive palliation 1 year later. Cyanosis, respiratory distress, and ventricular function improved.

(Ann Thorac Surg 2010;89:971–3)

The presence of major aortopulmonary collateral arteries (MAPCAs) in patients with single ventricle physiology is an extremely rare but serious condition. In this patient group, it is still unclear if pulmonary vascular resistance can be maintained at low enough levels to sustain a stable long-term Fontan-type circulation [1]. We report a successful case of staged unifocalizations (UFs) followed by Kawashima procedure (total cavopulmonary shunt) in asplenia with MAPCAs.

A two-month-old baby girl was diagnosed with asplenia syndrome, single ventricle morphology, common atrioventricular canal, pulmonary atresia, right aortic arch, single left superior vena cava, interrupted inferior vena cava with azygous continuation, and MAPCAs. Because of the size of her central pulmonary arteries, surgery was not an option until age 6 when angiography revealed diminutive but confluent central pulmonary arteries and at least four MAPCAs arising from the descending thoracic aorta (Fig 1). At that time, due to pulmonary over-circulation, the patient's arterial oxygen saturation (SaO_2) was approximately 90% with marked cardiomegaly and it was decided that her best option was surgery.

The patient underwent staged bilateral UFs. The first procedure was a left-sided unifocalization with a modified Blalock-Taussig shunt (5 mm) performed through a left lateral thoracotomy. This procedure was followed 4 months later by a right-sided UF and a modified Blalock-Taussig shunt (4 mm) through a right lateral thoracotomy.

Catheterization 10 months after the second UF showed low pulmonary vascular resistance (1.4 Wood units), relatively low pulmonary arterial pressure (mean right and left pulmonary arterial pressures of 12.5 and 14 mm Hg, respectively), and reasonable pulmonary vascular beds (pulmonary arterial index, 140 mm^3/m^2).

At 9 years of age, she underwent the Kawashima procedure, augmentation of the central pulmonary arteries with an autologous pericardial patch, and takedown of bilateral modified Blalock-Taussig shunts. Catheterization after the Kawashima procedure showed a well-reconstructed pulmonary blood pathway with no remarkable obstruction and acceptable pulmonary arterial pressure (mean, 15 mm Hg) (Fig 2). Two years after this final procedure, the patient is in good condition with SaO_2 of 85%.

Comment

The surgical strategy for pulmonary atresia with ventricular septal defect and MAPCAs has evolved substantially, and general principles have been well established. The standard protocol includes early midline single-stage UF of all sources of pulmonary flow and intracardiac repair. This strategy has provided a high rate of early complete repair with favorable right ventricular pressure [2]. It has been reported that more than 90% of patients with MAPCAs have pulmonary atresia with ventricular septal defect, as their intracardiac anatomy with very few having single ventricle physiology [1]. In a recent study of patients with MAPCAs who underwent UFs, only 4.1% (14 patients) had single ventricles, including 6 with asplenia [1]. Among the 6 with asplenia, only 1 patient successfully underwent the Fontan procedure.

The prevalence and clinical implications of MAPCAs in patients with asplenia remain unclear. The natural long-term fate of unifocalized MAPCAs often follows progressive stenosis, occlusion, or growth failure, which results in the loss of bronchopulmonary segments [3]. As a result, the presence of MAPCAs may lead to less favorable pulmonary vascular resistance before or even after completion of cavopulmonary connections and preclude the maintenance of long-term Fontan circulation in these patients.

A survey of the literature revealed only 4 reported patients with asplenia and MAPCAs who had undergone successful staged repair. One patient underwent biventricular repair [4], and 3 other patients achieved Fontan-

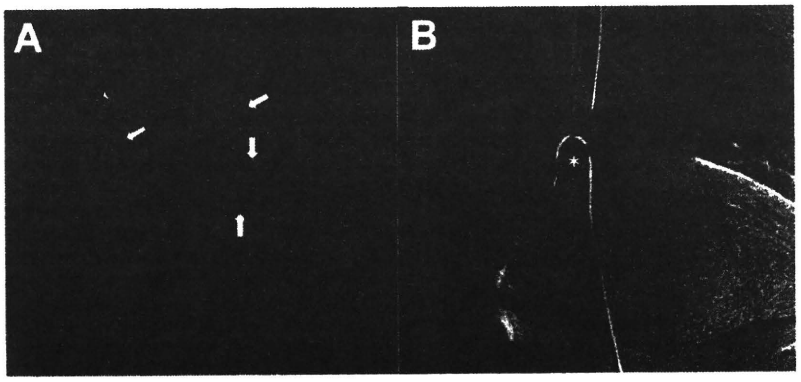

Fig 1. (A) Angiogram before unifocalizations showing multiple major aortopulmonary collateral arteries (white arrows) arising from the descending aorta. (B) Diminutive but confluent central pulmonary arteries (*) are connecting to a right upper lobe collateral.

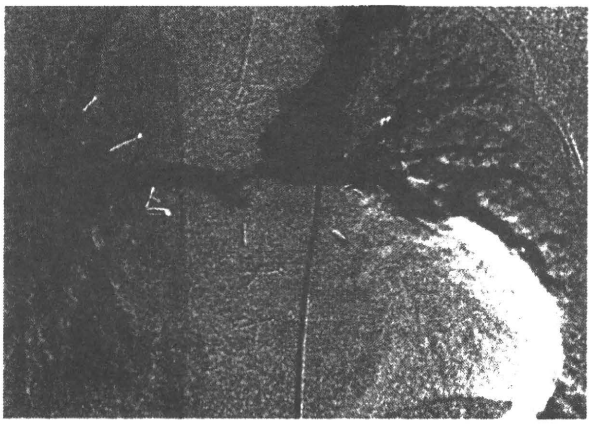

Fig 2. Angiogram after Kawashima operation showing well reconstructed pulmonary vasculature. The catheter is passed antegrade into the left superior vena cava through the azygos vein.

type completion [1, 5, 6]. Our report should be an important addition to the literature as we believe it is the first case of Kawashima procedure carried out successfully in a patient with asplenia and MAPCAs.

The Kawashima procedure incorporates most (approximately 85%) of the systemic venous return into the pulmonary circulation, excluding coronary sinus and hepatic venous flow [7]. Although this particular near-total Fontan circulation usually brings SaO_2 into the range of 85% to 90%; the inability to use a two-stage approach to achieve Fontan-type permanent palliation is associated with higher surgical risk. Recent reports recommend various fenestration techniques in high-risk Kawashima procedures [8]. However, because fenestrated Kawashima may result in unsatisfactory oxygen saturation levels, it should not be considered a definitive procedure [7]. Therefore, in staged UFs in patients with MAPCAs and IVC interruption, recruitment of as many pulmonary segments as possible to the central pulmonary artery is a prerequisite for creating a greater chance of Kawashima completion without fenestration. In this case we carefully looked for the chances to recruit MAPCAs to the diminutive but confluent central pulmonary arteries, and we successfully reconstructed a reasonable pulmonary vasculature by staged UFs.

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Staged Repair of Truncus Arteriosus With Interrupted Aortic Arch: Adjustable Pulmonary Artery Banding

Tohru Kobayashi, MD, PhD, Takashi Miyamoto, MD, PhD, Tomio Kobayashi, MD, PhD, Kentaro Ikeda, MD, Kyoko Koizuka, MD, Hirotsugu Okamoto, MD, PhD, and Kagami Miyaji, MD, PhD

Department of Pediatrics, Gunma University Graduate School of Medicine, Gunma, Departments of Cardiology, Cardiovascular Surgery, and Anesthesia, Gunma Children's Medical Center, Gunma, Departments of Anesthesia, and Cardiovascular Surgery, Kitazato Medical School, Kanagawa, Japan

We report a successful two-stage treatment for an infant with truncus arteriosus with aortic arch interruption. The treatment consisted of flow-adjustable bilateral pulmonary artery banding using clipping and postoperative balloon dilation, followed by staged repair. The merits of this strategy are as follows: (1) bilateral pulmonary artery banding is less invasive than neonatal one-stage repair; (2) use of cardiopulmonary bypass can be avoided in the newborn period; and (3) control of pulmonary blood flow adjusted for body size is possible. Although further studies are needed, our therapeutic strategy might provide a clinically important option for managing severe congenital heart disease.

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Although the outcomes after repair of truncus arteriosus (TA) are improving, the overall mortality rates continue to be higher than those for neonatal correction of many other congenital heart diseases. Herein, we report a successful two-stage treatment that consisted of flow-adjustable bilateral pulmonary artery banding using clipping and postoperative balloon dilation, followed by staged repair for an infant with TA, with an interrupted aortic arch (IAA).

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Address correspondence to Dr Kobayashi, Department of Pediatrics, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi, Gunma, 371-8511, Japan; e-mail: torukoba@nifty.com.

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Determinants of Blood Rheology in Healthy Adults and Children Using the Microchannel Array Flow Analyzer

Yasutomi Katayama, PhD, Hitoshi Horigome, MD, PhD, Hideto Takahashi, PhD, Kiyoji Tanaka, PhD, and Masao Yoshinaga, MD, PhD

Purpose: The reference values of blood rheology in healthy participants, especially children, are not available. The purpose of this study was to determine the blood passage time (BPT) as an index of blood rheology, in healthy children and adults, using the microchannel array flow analyzer, and to investigate the hematological factors that define BPT. *Methods:* Participants were 61 healthy children (35 boys, 26 girls; age 5-6 years) and 71 healthy adults (24 men, age 35.2 ± 14.1 years; 47 women, age 44.7 ± 14.1 years, mean ± standard deviation [SD]). Blood passage time and various hematological variables (blood cell count, serum lipids, and fibrinogen) were measured and compared among the 4 study groups. *Results:* Blood passage time values were significantly higher in adult men (48.8 ± 5.8 seconds) than in boys (41.9 ± 4.0 seconds), girls (43.7 ± 7.8 seconds), and adult women (42.4 ± 4.8 seconds). Stepwise regression analysis identified erythrocyte count and hemoglobin (Hb) as the significant and independent determinants of BPT ($P < .05$). *Conclusion:* Our study demonstrates that BPT is significantly longer in healthy adult men than in adult women and children, and that erythrocyte count and Hb are significant determinants of blood rheology.

Keywords: blood rheology; child; erythrocyte; viscosity

Introduction

Reduced blood rheology, or increased blood viscosity, correlates with thrombus formation through perturbation of blood coagulation and fibrinolysis system and is a risk factor for cardiovascular disease. Recently, Kikuchi et al[1,2] developed the microchannel array flow analyzer (MC-FAN) to measure blood rheology. The principal of the device is filtration, and the method has been applied for screening lifestyle-related disease, because it can easily detect abnormal blood rheology in patients with fatty liver disease,[3] hypercholesterolemia,[4] and metabolic syndrome.[5] In addition, Kamada et al[6] indicated that MC-FAN can be used for evaluation of thrombus formation.

Lifestyle-related diseases are believed to develop early in childhood,[7-10] and intervention from that period is required to prevent adulthood cardiovascular complications. We demonstrated that multiple cerebrovascular infarctions can develop even in children if blood rheology is markedly reduced in the presence of secondary erythrocytosis associated with cyanotic congenital heart defects.[11,12] In another study, we demonstrated that blood rheology is reduced even in young patients with cyanotic congenital heart disease, expressed as prolonged blood

From the Faculty of Education, Kogakkan University, Ise, Mie, Japan (YK); Department of Child Health, Graduate School of Comprehensive Human Sciences (HH), Epidemiology and Biostatistics, School of Medicine (HT), and Department of Sport Medicine, Graduate School of Comprehensive Human Sciences (KT), University of Tsukuba, Ibaraki, Japan; and Department of Pediatrics, National Hospital Organization Kagoshima Medical Center, Kagoshima, Japan (MY).

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Address correspondence to: Yasutomi Katayama, Faculty of Education, Kogakkan University, 1704 Kodakujimoto-cho, Ise, Mie, 516-8555 Japan; e-mail: katayama@kogakkan-u.ac.jp.

passage time (BPT), using MC-FAN.[13] Among the hematological parameters, the most significant factor that defines rheology was erythrocytosis. However, the reference values of blood rheology in children are not available. In this study, we measured BPT using MC-FAN in healthy children and compared the values with those of healthy adults. In the current study, we also investigated the hematological factors that define BPT.

Methods

Participants

We studied 61 healthy children (35 boys and 26 girls) and 71 healthy adults (24 men and 47 women). We excluded from the study those who were taking medications and those with hematological or lifestyle-related diseases. Before the commencement of the study, informed consent was obtained from the adult participants and from parents of the children. The study was approved in advance by the ethics committee for human research of University of Tsukuba.

Blood Sampling

Blood samples were collected from an antecubital vein between 9 AM and 10:30 AM after an overnight fast (except for water) and after at least a 15-minute rest immediately before sampling. The first sample was drawn into 2 polypropylene tubes (Venoject II; Terumo Co, Tokyo, Japan), 1 for serum collection and 1 containing 2.4 mg of ethylenediaminetetraacetic acid-2 kalium (EDTA-2K) for whole blood cell count. The latter sample was used for the measurement of erythrocyte count, hemoglobin (Hb) concentration, hematocrit (Hct), mean corpuscular volume (MCV), leukocyte count, and platelet (PLT) count using the Cell-Dyn (model 4000; Dianabot Inc, Tokyo, Japan). The second sample was gently introduced into a polypropylene tube containing 1/10 volume of 3.13% sodium citrate for measurement of plasma level of fibrinogen (Fbg). The serum sample was used for the measurement of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels using standard laboratory method. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald equation.[14]

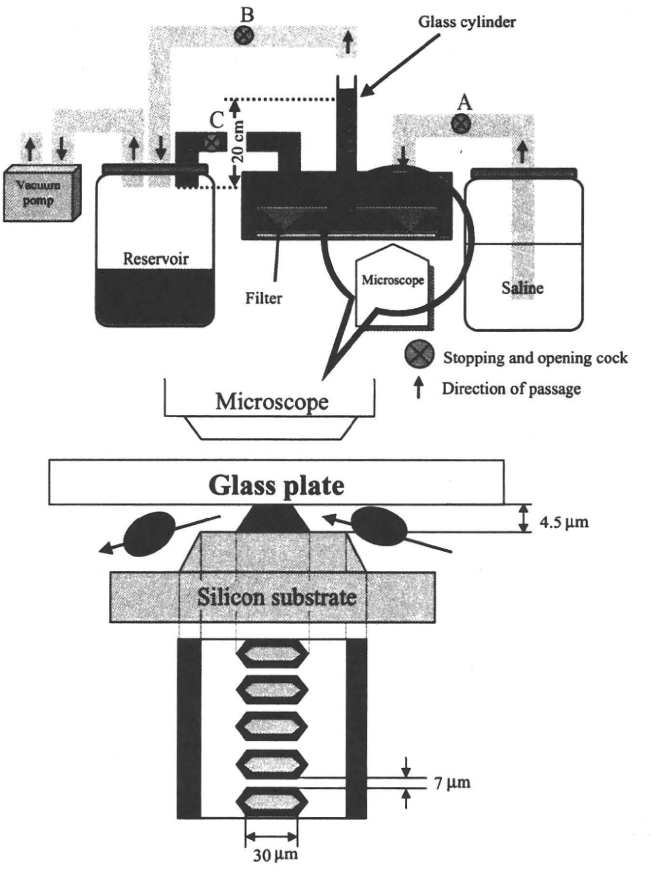

Figure 1. Schematic representation of the microchannel array flow analyzer (MC-FAN) and microchannel array (filters). The whole sample is introduced into a glass cylinder and is passed through a siliconized chip with 8736 slits (7 μm wide × 30 μm long) under negative pressure of 20 cm H_2O.

Measurement of BPT Using MC-FAN

Blood passage time was measured using MC-FAN system (Hitachi Haramachi Electronic Industrial Company, Ibaraki, Japan; Figure 1). The blood sample (1.9 mL) was stored in a polypropylene tube containing 2.4 mg of EDTA-2K and 0.1 mL of heparin sodium (Novo-Heparin 1000 units/mL; Mochida Pharmaceutical, Tokyo, Japan), and then 0.1 mL of the whole sample was introduced into a glass cylinder and passed through the siliconized chip with 8736 slits measuring 7 μm wide and 30 μm long under a negative pressure of 20 cm H_2O. The time for the blood sample of 0.1 mL to pass through the filters was measured as BPT. Calibration with saline (0.1 mL) was performed immediately before each new measurement. Reproducibility of BPT using MC-FAN was not verified in the current study as it

was repeatedly investigated in our previous studies with satisfactory results.[15,16] Furthermore, BPT has been confirmed to be proportional to blood viscosity.[17] Blood passage time was measured within 1 hour of sampling.

Statistical Analysis

All continuous variables were expressed as mean ± SD. Two-way analysis of variance (ANOVA), in which 2 factors were sex (men or boys, women or girls) and age categories (child, adult), was conducted with the interaction term of sex and age category. Multiple comparison of Tukey type was also conducted among the interaction levels to determine the significance of differences among variables.

The relationship between BPT and hematological variables was tested by simple linear regression model. Furthermore, stepwise linear regression model was carried out to assess independent predictors among the significant variables of simple linear regression analysis. A P value $< .05$ was considered statistically significant.

Results

Physical Characteristics of Participating Participants

Table 1 shows the anthropometric data of participating participants. There were significant differences in height, weight, body mass index (BMI), waist, systolic blood pressure (SBP), and diastolic blood pressure (DBP) based on age. Furthermore, there were significant differences in age, height, weight, and waist based on sex. Age, height, and weight showed significant interaction effects. Age, height, and weight showed significant difference based on interactions of sex and age category. For all 6 comparisons of every 2 variables among boys, girls, men, and women, 4 comparisons except boys-girls and men-women were significant for BMI, waist, SBP, and DBP.

Hematological Variables

Table 2 shows the comparison of hematological variables. There were significant differences based on age in Hct, Hb, MCV, leukocyte count, platelet count, total cholesterol (TC), HDL-C, and TG. There were also significant differences in erythrocyte count, Hct, Hb, and LDL-C based on sex. Significant interaction was noted in erythrocyte count, Hct, Hb, TC, and HDL-C. For all 6 comparisons of every 2 variables among boys, girls, men, and women, there were mainly 3 types of difference patterns. The first pattern was significant differences in boys-women (A-D), girls-women (B-D), and men-women (C-D) for erythrocyte count, TC, and HDL-C. The second pattern was significant differences in boys-men (A-C), girls-women (B-D), and men-women (C-D) in Hct, Hb, and BPT. The third pattern was significant differences in boys-men (A-C), boys-women (A-D), girls-men (B-C), and girls-women (B-D) in MCV, leukocyte count, platelet count, and TG.

Blood Passage Time

Based on multiple comparison on the interaction term, BPT was significantly longer in adult men (48.8 ± 5.8 seconds) than in boys (41.9 ± 4.0 seconds), girls (43.7 ± 7.8 seconds), and adult women (42.4 ± 4.8 seconds). There was no difference in BPT values between boys and girls (Figure 2).

Relationship Between BPT and Hematological Variables

Table 3 shows the results of univariate analysis. Erythrocyte count, Hb, and Hct correlated significantly with BPT. Stepwise linear regression analysis of baseline characteristics identified erythrocyte count and Hb as significant independent determinants of BPT (Table 4).

Discussion

The current study demonstrated that BPT was significantly longer in healthy adult men than in the other groups, and there were no differences in BPT values by gender for children (Table 2, Figure 2). Among the anthropometric characteristics of the participants, BMI, SBP, and DBP also showed significant relationship between age categories but not sex categories. Waist showed similar significance pattern, except the presence of significance of sexes (Table 1).

Using the BPT values obtained in the current study, blood viscosity can be estimated with the following formula based on the fact that BPT correlates with blood viscosity ($R^2 = 0.973$, BPTs = 12.1 × viscosity [mPa·s at 1000 s^{-1}]), where BPT is the value

Table 1. Baseline Anthropometric Characteristics[a]

	Children		Adults		Between Age Categories (Child, Adult)	Between Sexes	Interaction (Age Category × Sex)	Multiple Comparison on Interaction Terms ($P < .05$)
	Boys	Girls	Adult Men	Adult Women				
	A	B	C	D	*P* Value	*P* Value	*P* Value	
n	35	26	24	47	$P < .0001$ (for χ^2 test of independence between sex and age category)			
Age, years	5.77 (0.49), 35	5.46 (0.58), 26	35.2 (14.1), 24	44.7 (14.1), 47	<.0001	<.05	<.01	A-C,A-D, B-C,B-D,C-D
Height, cm	115.9 (5.4), 35	111.6 (6.6), 26	172.5 (5.3), 24	157.2 (5.0), 47	<.0001	<.0001	<.0001	A-B, A-C,A-D, B-C,B-D,C-D
Weight, kg	21.0 (3.9), 35	19.0 (2.6), 26	66.5 (6.4), 24	53.9 (5.5), 47	<.0001	<.0001	<.0001	A-C,A-D, B-C,B-D,C-D
Body mass index, kg/m^2	15.6 (1.9), 35	15.2 (1.1), 26	22.0 (1.4), 24	21.8 (1.8), 47	<.0001	.348	.863	A-C,A-D, B-C,B-D
Waist, cm	52.9 (4.9), 35	51.0 (3.2), 26	81.3 (7.5), 10	76.4 (6.3), 22	<.0001	<.01	.216	A-C,A-D, B-C,B-D
Systolic blood pressure, mm Hg	94.4 (7.1), 35	93.1 (8.2), 26	120.3 (6.8), 17	116.7 (11.4), 40	<.0001	.162	.501	A-C,A-D, B-C,B-D
Diastolic blood pressure, mm Hg	53.9 (8.2), 35	53.3 (11.2), 26	78.2 (8.5), 17	74.0 (8.1), 40	<.0001	.165	.29	A-C,A-D, B-C,B-D

[a] Values are mean (SD), n.

Table 2. Hematological Variables of Participating Participants

	Children		Adults		Between Age Categories (Child, Adult)	Between Sexes	Interaction (Age Category × Sex)	Multiple Comparison on Interaction Terms ($P < .05$)
	Boys	Girls	Adult Men	Adult Women				
	A	B	C	D	*P* Value	*P* Value	*P* Value	
Erythrocyte count, $10^4/\mu L$	476.5 (31.1), 11	471.3 (21.1), 9	488.9 (45.8), 24	430.9 (27.5), 47	.109	<.01	<.01	A-D, B-D,C-D
Hematocrit,%	39.4 (1.99), 11	38.4 (2.56), 9	45.3 (3.53), 24	39.6 (3.10), 47	<.0001	<.0001	<.01	A-C, B-C,C-D
Hemoglobin, g/dL	12.8 (0.84), 11	12.60 (0.77), 9	15.2 (1.30), 24	12.9 (1.15), 47	<.0001	<.0001	<.01	A-C, B-C,C-D
MCV, fL	82.8 (2.96), 11	81.4 (3.64), 9	92.7 (5.75), 24	92.1 (5.90), 47	<.0001	.423	.858	A-C,A-D, B-C,B-D
Leukocyte count, per μL	6709 (2255), 11	6689 (1621), 9	5096 (1314), 24	4630 (1137), 47	<.0001	.502	.538	A-C,A-D, B-C,B-D
Platelets, $10^4/\mu L$	31.0 (4.89), 11	31.0 (9.95), 9	21.5 (5.53), 24	24.1 (5.74), 47	<.0001	.425	.396	A-C,A-D, B-C,B-D
TC, mg/dL	170.1 (19.3), 35	177.7 (22.9), 26	179.1 (25.2), 24	202.6 (27.6), 47	<.01	<.01	.073	A-D, B-D,C-D
HDL-C, mg/dL	68.3 (11.9), 35	60.7 (10.63), 26	63.0 (16.3), 24	78.1 (16.8), 47	<.05	.149	<.0001	A-D, B-D,C-D
LDL-C, mg/dL	94.2 (14.1), 35	107.7 (15.5), 26	100.6 (23.4), 24	111.3 (20.1), 47	.139	<.0001	.672	A-B, A-D
Triglycerides, mg/dL	37.9 (25.3), 35	46.2 (16.0), 26	77.4 (30.7), 24	65.6 (26.0), 47	<.0001	.699	<.05	A-C, A-D, B-C, B-D
Fibrinogen, mg/dL	243.1 (52.4), 35	258.1 (58.2), 26	265.7 (97.6), 15	265.9 (458.8), 28	.227	.543	.557	—
BPT, seconds	41.9 (4.04), 35	43.7 (7.75), 26	48.8 (5.79), 24	42.4 (4.78), 47	<.01	<.05	<.0001	A-C, B-C,C-D

NOTES: BPT = Blood passage time; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Values are mean (SD), n; MCV, mean corpuscular volume; TC, total cholesterol.

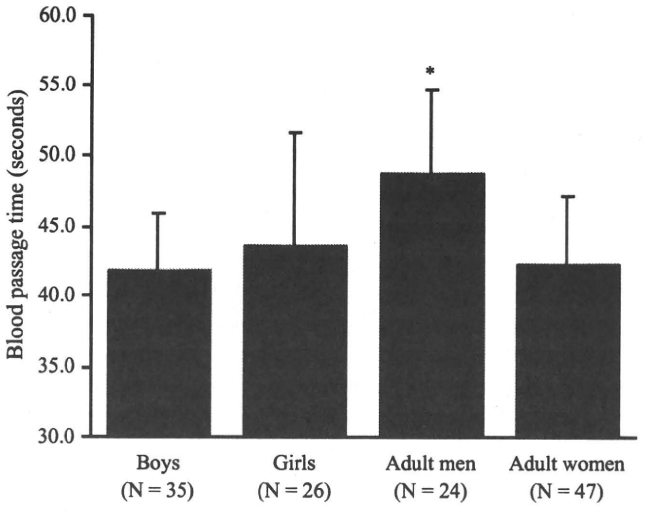

Figure 2. Blood passage time. Data are mean ± SD. *$P < .05$ versus the other 3 groups.

measured using MC-FAN as in the current study, and blood viscosity is the value measured by a viscometer.[17] Thus, the estimated values of blood viscosity are as follow: 3.5 mPa·s for healthy boys, 3.6 mPa·s for girls, 4.0 mPa·s for adult men, and 3.5 mPa·s for adult women. These standard data would be useful for comparison of blood viscosity between those with at risk of cardiovascular disease and those without.

It has been reported that blood viscosity is significantly influenced by erythrocyte count, Hct, and Hb levels and increases exponentially with increases in Hct.[18,19] Our data demonstrated that adult men have the longest values of BPT (Figure 2). Stepwise regression analysis identified erythrocyte count and Hb as the significant predictors of BPT, that is, blood rheology, among blood components studied in the present investigation (Tables 3 and 4). Erythrocyte count was lower in adult women than in children, but Hb and Hct were not different between adult women and children. Blood passage time was also not different between adult women and children. This is probably derived from the difference in MCV values, that is, the volume of individual erythrocyte, which was larger in adult women than in children. The results of multiple comparison of interaction in our study showed that there was difference between age categories for MCV but not sex categories, and that only adult men showed difference for BPT, Hb, and Hct (Table 2). Previous studies reported that MCV is an index of erythrocyte deformability, and reduced MCV correlates with

Table 3. Prognostic Factors of BPT by Simple Linear Regression

Variables	Coefficient	Standard Error (SE)	*t* Value	*P* Value
Age category	1.830	1.037	1.76	.080
Sex	−1.886	1.040	−1.81	.072
Erythrocyte count	0.071	0.014	4.88	<.0001
Hemoglobin	1.913	0.404	4.73	<.0001
Hematocrit	0.702	0.154	4.57	<.0001
MCV	−0.011	0.100	−0.11	.909
Platelet count	−0.130	0.098	−1.33	.186
Leukocyte count	0.0004	0.0004	1.02	.310
Total cholesterol	−0.005	0.019	−0.28	.778
HDL-C	−0.023	0.033	−0.70	.487
LDL-C	−0.016	0.027	−0.60	.553
Fibrinogen	0.007	0.010	0.70	.488

NOTES: BPT = Blood passage time; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MCV, mean corpuscular volume.

Table 4. Multiple Stepwise Linear Regression Analysis of Baseline Characteristics, Erythrocyte Count, Hb, and Hct

Variables	Coefficient	Standard Error (SE)	*F* Value	*P* Value
Erythrocyte count	0.044	0.019	5.20	<.05
Hb	1.079	0.538	4.02	<.05

NOTES: Hb = Hemoglobin; Hct = hematocrit.

reduced erythrocyte deformability, that is, reduced blood rheology.[20,21] Mean corpuscular volume is considered to have qualitative effects on blood rheology rather than quantitative effects like Hct.

This conclusion is compatible with the result that MCV was not identified as a significant independent determinant of BPT by stepwise regression analysis in the current study. However, further studies in a large number of participants are needed to clarify the effects of MCV on blood rheology.

Hyperlipidemia is considered to be associated with increased plasma viscosity. Lee et al[4] demonstrated that TC, LDL-C, and HDL-C influence BPT in patients with hypercholesterolemia, that is, even HDL-C correlates positively with BPT, which is in contrast to the present findings. In addition, it is possible that the increase in serum levels of TG and