Association of Sinus Node Dysfunction, Atrioventricular Node Conduction Abnormality and Ventricular Arrhythmia in Patients With Kawasaki Disease and Coronary Involvement

Naokata Sumitomo, MD; Kensuke Karasawa, MD; Kazuo Taniguchi, MD; Rie Ichikawa, MD; Junji Fukuhara, MD; Osamu Abe, MD; Michio Miyashita, MD; Hiroshi Kanamaru, MD; Mamoru Ayusawa, MD; Kensuke Harada, MD

Background This study was performed to investigate the incidence of arrhythmias in patients with Kawasaki disease (KD).

Methods and Results Electrophysiologic studies (EPS) were performed in 40 patients (mean age: 10.3±5.1 years; 30 males, 10 females) with KD who had severe to moderate coronary artery disease. Clinical arrhythmias were documented in 4 patients (premature ventricular contractions, ventricular tachycardia, atrioventricular block, and ventricular fibrillation). Dual atrioventricular nodal pathways were demonstrated in 3 patients. Nonsustained atrial fibrillation was induced in 1 patient. The AH interval was prolonged in 2 patients. The Wenckebach rate was 164±37 beats/min, and 4 of the patients had a decreased Wenckebach rate. The maximum and corrected sinus node recovery times were 997±257 ms and 281±130 ms, respectively, and 7 patients were thought to be abnormal. The sino-atrial conduction time was 108±64 ms, and 2 patients had prolonged conduction times.

Conclusions Although there was no relationship between coronary stenosis or obstruction and the EPS parameters, the incidence of abnormal sinus node and atrioventricular node function is apparently higher in KD patients than in the normal population. These functional abnormalities may possibly be caused by myocarditis or an abnormal microcirculation in the sinus node and atrioventricular node artery. In some patients, myocardial ischemia may provoke malignant ventricular arrhythmia. (Circ J 2008; 72: 274–280)

Key Words: Atrioventricular block; Kawasaki disease; Sinus node dysfunction; Ventricular tachycardia

Kawasaki disease (KD), first described by Kawasaki in 1967, is an acute febrile illness with mucosal inflammation, skin rash, and cervical lymphadenopathy, predominantly occurring in infants and younger children. Nevertheless, the etiology of KD is still unknown and vasculitis is the major pathologic finding. Diagnostic criteria, treatment, and long-term management of KD have already been proposed. Coronary artery aneurysms or dilatation are the most common associated complications in KD that may lead to myocardial infarction (MI), sudden death, or ischemic heart disease. Based on reports of the acute and long-term clinical course, 24.4% of patients have coronary artery lesions and 0.8% of patients die 4.4±1.6 years after the onset of KD. Although ischemic heart disease is the major cause of death in KD, there are a certain number of patients who develop arrhythmias and a considerable number of sudden deaths may be caused by arrhythmias.

According to the hypothesis, these young patients with KD who have severe coronary artery involvement may develop a fatal arrhythmic event and in order to prevent sudden cardiac death after KD, this study was proposed to evaluate the incidence of arrhythmias and the supraventricular electrophysiologic findings in children with KD.

Methods

Between January 1980 and December 2002, 791 patients with acute KD were admitted and of them 662 patients (84%) had an intact coronary artery and the other 129 (16%) had coronary dilatation or coronary aneurysm. Four (0.5%) died suddenly in the acute stage of illness. One was a 3-month-old boy with left and right large coronary aneurysms. He had severe mitral regurgitation and died suddenly of acute heart failure. The second patient was a 2-month-old boy with a left coronary aneurysm, who also had disseminated intravascular coagulation. He died suddenly, possibly from a MI. The third patient was a 7-month-old girl who developed paralytic ileus during aspirin and steroid treatment for KD and died of intestinal ulcer perforation. The fourth patient was a 3-month-old girl, who was recovering from KD without any coronary dilatation, but was found dead in her bed. The autopsy finding showed no myocardial and coronary abnormalities, so the possible cause of death was arrhythmia.

We prospectively studied 40 consecutive patients (30 males, 10 females) with KD (mean age 10.4±5.0 years
[1.8–20 years] who were referred for coronary angiography from February 1997 to July 2002. The mean onset of KD in these patients was at 2.3±2.2 years of age and the study was performed 8.1±4.8 years from the onset of KD. All of the patients had moderate to severe coronary artery disease (Table 1), except 2 (patients 18 and 36). Patient 18 complained of chest pain and exercise testing showed mild ST depression. Patient 36 was suspected of having a single coronary artery aneurysm; patients 1 to 3, 6–9) and Patient 26 was unable to perform the exercise test. After catheterization, 6–12h of electrocardiogram (ECG) monitoring was performed in every patient to observe whether any ischemic or arrhythmic events occurred.

After written informed consent was given by the patients’ parents, an electrophysiologic study (EPS) and coronary angiography were performed in the fasting state and under light sedation with 1 mg/kg of promethazine hydrochloride and pethilorfan hydrochloride. Two 5–6Fr hexapolar 2- to 5-mm distance electrode catheters were introduced percutaneously via the femoral vein into the high right atrium and His bundle region. High right atrial and His bundle ECG and surface ECG (leads II and V5) were recorded simultaneously on a thermal recorder (RMC-3000, Nihon Koden, Tokyo, Japan) at a paper speed of 100 mm/s. Stimulation was performed at twice the diastolic threshold with a width of 2 ms using programmed stimulator (SEC-3102, Nihon Koden).

Burst pacing was applied from the high right atrium at a rate of up to 200 beats/min to evaluate sinus node function.
and atrioventricular node (AVN) conduction. Sino-atrial conduction time was measured by the Narula method. Premature atrial pacing from the high right atrium was performed to evaluate high right atrial and AVN effective and functional refractory periods and inducibility of atrial arrhythmias. Dual AVN pathways were defined by more than 50 ms increase in the A2H2 interval with a 10 ms decrement in the A1A2 interval. Sinus node recovery time (SNRT) and corrected sinus node recovery time (CSNRT), and sino-atrial conduction time (SACT) was thought to be abnormal when SNRT > 1,400 ms, CSNRT > 525 ms, and SACT > 250 ms.

One patient underwent programmed ventricular stimulation with up to double extrastimuli from the right ventricular apex and outflow tract under the control state and during isoproterenol infusion because of recurrent sustained ventricular tachycardia (VT).

All numeric data are presented as the mean ± SD. Statistic analysis was performed using Wilcoxon nonparametric analysis or chi-square analysis using JMP v 5.1 (SAS Institute Inc, Cary, NC, USA) when necessary. A p value less than 0.05 was considered significant.
Results

Exercise Stress Test
Ischemic ST depression was noted in 12 patients (37.5%) by exercise stress test; however arrhythmia was induced in 2 patients only: premature ventricular contraction was noted in 1 patient (Patient 15) and 1 patient (Patient 31) developed VT.

Patient 31 had sustained monomorphic VT during exercise (Fig 1). She was referred to us for recurrent palpitations at 13 years of age and had suffered from KD from 6 months of age. Selective coronary angiography showed a giant aneurysm in segment 1 and 90% stenosis in segment 6. Signal-averaged ECG proved there were no late potentials. Verapamil, propranolol, and nicorandil could not prevent induction of VT during exercise, only isosorbide dinitrate. VT was completely prevented after rotational atherectomy of the left coronary artery stenosis.

Coronary Angiography
Left coronary angiography showed aneurysm in 10 patients, aneurysm and stenosis in 3 patients, stenosis in 3 patients, dilatation in 3 patients, calcification in 3 patients, obstruction in 1 patient, and normal or regression of coronary aneurysm or dilatation in 17 patients. The circumflex branch showed aneurysm in 6 patients, dilatation in 3 patients, stenosis in 2 patients, regression in 3 patients and normal anatomy in 26 patients. The right coronary angiography showed aneurysm in 10 patients, stenosis in 1 patient, obstruction in 2 patients, obstruction and recanalization in 2 patients, calcification in 2 patients, dilatation in 4 patients, regression in 7 patients, and was normal in 11 patients.

Clinical Arrhythmias
Patient 40 was hospitalized with severe chest pain, paleness, and arrhythmia at 11 years of age. She had been diagnosed with KD just 1 year prior to this admission. She had been treated with aspirin and dipyridamole for bilateral coronary aneurysms (left coronary artery (LCA): 6 mm, right coronary artery (RCA): 7 mm). ECG on admission showed second-degree atrioventricular block (Fig 2) and the next day showed a typical MI pattern (Fig 3). Coronary angiography 5 months after the MI showed total obstruction of the RCA and LCA aneurysms.

Patient 20 suffered from KD from 2 years of age. He had a right coronary aneurysm and the LCA was dilated (RCA: 6 mm, LCA: 3.7 mm). At 3 years of age he became pale and complained of chest pain while running and a heart attack was suspected; however, coronary aneurysms had regressed on follow-up echocardiogram. He was referred to us at 13 years of age for coronary angiography. During selective left coronary angiography, ventricular fibrillation was induced (Fig 4). There was no QT interval prolongation or ST-T abnormalities on the ECG and no late potentials on the signal-averaged ECG. We also performed gene analysis for SCN5A mutation, but it was negative.
Induced Arrhythmias

Dual AVN pathways were demonstrated in 3 patients (Patients 6, 16, and 18), but AVN reentrant tachycardia was not induced in any of these patients. Patient 39 had induced nonsustained atrial flutter during atrial extrastimulus pacing. No other supraventricular tachycardias were induced by programmed atrial pacing.

Basic Electrophysiologic Measurements

The sinus cycle length was 725±175 ms (mean±SD), AH interval was 86±21 ms, HV interval was 43±9 ms, high right atrial effective refractory period was 238±43 ms, high right atrial functional refractory period was 257±38 ms, AVN effective refractory period was 302±65 ms, and AVN functional refractory period was 414±80 ms. All these values were normal (Table 1).

Sinus Node Function

Recovery Time  The SNRT and CSNRT were 1,001±256 ms and 282±130 ms, respectively, and 1 value was thought to be prolonged (Table 1). Fig 5 shows a prolonged SNRT in Patient 17 whose coronary angiogram seemed normal; however, perfusion imaging showed decreased perfusion in the anterior wall of the left ventricle (Fig 6).

AVN Function  The Wenckebach rate was 166±37 beats/min, and 4 patients (Patients 14, 17, 26, and 37) had rates that were <120 beats/min (Table 1). All the patients had some type of coronary lesion.

Relationship Between Coronary and Electrophysiologic Abnormalities  Prolonged SNRT, prolonged SACT and decreased Wenckebach rate had no relationship with coronary abnormalities, either with respect to coronary angiography or SPECT findings.

Programmed Ventricular Stimulation  In Patient 31, programmed ventricular stimulation was performed up to double ventricular extra stimuli and burst pacing from the right ventricular apex and right ventricular outflow tract, then same protocol was repeated under 0.02μg/kg/min isoproterenol infusion. VT was not induced.

Fig 5.  Sinus node recovery time in Patient 17 is prolonged to 1,680 ms. Burst atrial pacing was performed at 100 beats/min. HRA, high right atrial electrocardiogram; HBE, His bundle electrocardiogram; S, stimulus; A, atrial wave.

Fig 6.  99mTc tetrofosmin myocardial perfusion imaging in Patient 17 shows decreased perfusion in the anterior wall of the left ventricle. His coronary angiography showed no abnormalities.
by programmed ventricular stimulation.

**Follow-up**

Twenty nine patients were followed up for 8.3±2.2 years. Neither arrhythmias or life-threatening events were documented during the follow-up period of these patients. Also, there was no need for pacemaker or ICD implantation in this study group. Eleven patients were dropped out of follow-up, because their coronary aneurysms had regressed and they no longer required any medication.

**Discussion**

Sinus node dysfunction and atrioventricular block are sometimes associated with inferior wall infarction caused by right coronary obstruction. This dysfunction and block are thought to be caused by ischemia of the sinus node and AVN, stimulation of the Bezold-Jarish reflexes through activation of inhibitory cardiac receptors in the inferior wall of the left ventricle, and intracellular electrolyte or metabolic abnormalities.

The electrophysiologic standard value for children is reportedly shorter than the adult standard. However, we used stricter adult criteria in the present study, because we wanted to know if sinus node dysfunction truly exists in the patient with KD.

In the pediatric age group, ischemic heart disease is an extremely rare condition and KD is one of the most common underlying causes. Despite the relatively common coronary involvement in KD, only a few patients develop acute MI, because of the development of collateral circulation.

Coronary artery obstruction following KD may cause MI or sudden cardiac death, and some of the sudden cardiac deaths following KD may be related to arrhythmias. Ventricular arrhythmias have also been reported in the late stage of KD. However, the precise mechanism of sudden death remains unknown. Frequent ventricular premature beats, second degree atrioventricular block, Wenckebach-type atrioventricular block, and ST-segment depression accompanied by chest pain have been recognized by 24-h Holter monitoring in patients with KD.

Although there have been many follow-up reports of coronary angiography and SPECT, there have been none regarding the electrophysiologic findings in patients with KD. We evaluated the incidence of bradycardia in patients with KD, but right and left coronary perfusion had no relationship with sinus node or AVN abnormalities. Although there was no relationship between coronary flow and electrophysiologic parameters in this study, the incidence of abnormal sinus node and AVN function in KD patients is apparently higher than in the normal population.

Based on autopsy studies of KD patients, the lesions of the atrioventricular conduction system are classified according to the time since onset of KD. Within 9 days, inflammatory cell infiltration and edema are the major findings, then between 3 and 4 weeks, compression of conduction cells because of perivascular edema and cell infiltration is the major finding. From 7 weeks to 7 months, perivascular fibrosis and fatty infiltration are noted. PQ prolongation may be a sensitive indicator of acute inflammation of the atrioventricular conduction system. Although there is no report of the precise pathologic finding around the sinus node in patients with KD, similar inflammatory changes may occur in this area. We speculate that in Patient 17, who had normal right and left coronary arteries, inflammation may have caused sinus node dysfunction. Also, this patient had a decreased perfusion in the left ventricular anterior wall. We cannot confirm a sinus node microcirculation abnormality by perfusion imaging, but decreased microcirculation of the coronary artery may contribute to dysfunction of the conduction system in patients with KD.

Recently, abnormal findings on signal-averaged ECG have been reported patients in the late stage of KD, even without stenotic lesions. They also had abnormal histologic features, such as hypertrophy of the myocytes, interstitial and replacement fibrosis, and abnormal branching and bizarre nuclei of myocytes. Four cases of myocarditis with severe left ventricular dysfunction in the acute phase of KD have been reported.

In the present study, only 1 patient (Patient 31) developed VT. It is usually possible to initiate VT in patients with VT after old MI; however, initiation of VT is usually impossible in patients with VT after acute MI. Late potentials were reported to detect 79–92% of patients with VT after MI. The mechanism of VT is thought to be reentry in patients with old MI, and automaticity or triggered activity in those with acute MI. In Patient 31, VT was induced by exercise testing, but not by programmed ventricular stimulation nor by isoproterenol infusion. Her late potential was negative, isosorbide dinitrate prevented her VT, and her VT was completely abolished after rotational atherectomy of the coronary artery. These facts indicate that the mechanism of this VT was automaticity induced by myocardial ischemia.

In the VF patient, the late potential was negative. We did not perform programmed ventricular stimulation, but from the ECG findings, exercise stress test, negative late potential, and gene analysis, we excluded Brugada syndrome, long QT syndrome, short QT syndrome, and catecholaminergic polymorphic VT.

According to our results, sinus node dysfunction and atrioventricular block may possibly be caused by myocarditis or abnormal microcirculation in the sinus node and AVN artery. The bradycardia in KD may potentially cause cardiac arrest and sudden death. In some patients with KD, myocardial ischemia may provoke malignant ventricular arrhythmia and cause sudden death.

**References**