Long-Term Outcomes of Pediatric Sinus Bradycardia

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Objectives To delineate the long-term outcomes and mechanisms of pediatric sinus bradycardia.

Study design Participants with sinus bradycardia who were identified from a survey of 432 166 elementary and high school students, were enrolled 10 years after the survey. The clinical course, heart rate variability, and hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (HCN4) gene were assessed.

Results A total of 104 (male:female was 60:44; prevalence, 0.025%) participants were observed to have sinus bradycardia at age 15.5 ± 0.2 years with a mean heart rate of 48.4 ± 0.4 beats per minute; 86 study participants (83%) responded to clinical assessment and 37 (36%) underwent laboratory assessment. Athletes composed 37.8% of the study participants. During the extended 10-year follow-up, 15 (17%) of the participants had self-limited syncopal episodes, but none had experienced life-threatening events. According to Holter recordings, none of the participants had heart rate <30 beats per minute or a pause longer than 3 seconds. Compared with 67 age- and sex-matched controls, the variables of heart rate based on the spectral and time domain analysis of the participants with sinus bradycardia were all significantly higher, indicating higher parasympathetic activity. The results of mutation analysis were negative in the HCN4 gene in all of our participants.

Conclusions The long-term outcomes of the children and adolescents with sinus bradycardia identified using school electrocardiographic survey are favorable. Parasympathetic hyperactivity, instead of HCN4 gene mutation, is responsible for the occurrence of sinus bradycardia. *(J Pediatr 2013;163:885-9)*.

In the pediatric population, sinus bradycardia is a rare finding, and its clinical significance has yet to be described adequately.[1,2] Recently, through a large-scale school electrocardiographic (ECG) survey, we found the prevalence of sinus bradycardia was 0.025% in the school-age pediatric population.[1] Although previously believed to be a benign lesion, the long-term outcomes and underlying mechanisms of bradycardia in school-age children remain unknown.

The cellular electrophysiology of the sinus node is characterized by the diastolic depolarization, the so-called "funny current," which accounts for the pacemaker activity of the heart. In humans, the hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (HCN4) is responsible for the funny current.[3,4] Recently, several family pedigree studies have revealed that the mutation of the HCN4 gene is a prominent cause of sinus bradycardia, especially in young populations.[3,5-7] Some studies even suggested that screening for HCN4 gene mutation may be necessary in children or in patients with familial sinus bradycardia.[8] However, no large-scale analytical data have been obtained on the HCN4 gene in young populations with bradycardia. In addition to the genetic factor, vagotonia is another possible cause of sinus bradycardia.[9] Several previous studies have detected higher heart rate variability (HRV) in elderly patients with sinus bradycardia, indicating the potential role of parasympathetic hyperactivity.[10] In school-age patients with sinus bradycardia, the role and the extent of parasympathetic activity remain unknown. Therefore, this study investigated the long-term outcomes, parasympathetic activities, and the potential genetic mutations in the HCN4 gene in participants with sinus bradycardia who were identified by conducting a citywide school survey.

Methods

From 1999-2001, with the support of the government and the Cardiac Children's Foundation, a citywide school survey program was conducted in Taipei, Taiwan. All students entering first or fourth grade of elementary school or the first year of junior or senior

bpm	Beats per minute
ECG	Electrocardiographic
HCN4	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
N-N	Normal-to-normal
pro-BNP	Pro-brain natriuretic peptide
SDNN	SD of heart rate

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Funded by Cardiac Children's Foundation Republic of China (CCF 100-01) and supported in part by the Department of Medical Research in the National Taiwan University Hospital. The authors declare no conflicts of interest.

 http://dx.doi.org/10.1016/j.jpeds.2013.03.054

high school were evaluated by conducting simplified 4-lead ECGs (Fukuda Denshi ECP-50C and ECP-50CT; Tokyo, Japan). A total of 432 166 students (223 866 male and 208 300 female students) were screened. The age distribution ranged from 6-20 years; 197 012 were elementary school students, and 235 154 were junior or senior high school students.[1] From this database, students with sinus bradycardia (defined as below 60 beats per minute (bpm) in those aged less than 9 years, and below 50 bpm in those older than 9 years) were identified.[11] The data collection was in accordance with the regulation of the institutional review board policy in National Taiwan University Hospital, and all patients signed the informed consent form before further study. The basic clinical characteristics addressed in the questionnaire were recorded. Participants with concomitant congenital heart disease were excluded. The long-term outcome data were obtained by conducting interviews 10 years after the screening (ie, between 2010 and 2011). Through clinical evaluation, we recorded any cardiac symptoms as syncope or life-threatening events. We also invited the participants for further sinus node and heart function evaluation including resting ECG examination, echocardiography, pro-brain natriuretic peptide (pro-BNP) test, 24-hour Holter examination, and treadmill ECG test.

For the 24-hour Holter ECG examination, we used Philips Zymed Holter monitoring (Philips Medical Systems, Foster City, California), which was designed for outpatient examination. A precise diary of the participants' activities and symptoms was requested to correlate with the Holter monitor findings. Any symptomatic bradycardia less than 40 bpm, asymptomatic bradycardia less than 30 bpm, and a pause longer than 3 seconds was regarded as significant. In addition, we enrolled 78 age- and sex-matched participants who received a Holter examination for suspected arrhythmia in the same study period as the control group. These participants were later shown to have no structural heart disease, coronary artery disease, or pathologic arrhythmia both by the examination and clinical follow-up. For HRV analysis, the ECG wave complex (QRS) over 24 hours was automatically classified and manually verified as normal sinus rhythm, atrial or ventricular premature beats, or noise by comparing the adjacent ECG wave complex morphological features. The normal-to-normal (N-N) intervals were deduced from the adjacent normal sinus beats. The N-N interval time series were then transferred to a personal computer and post-processed by using a program written in Matlab language (v. 6; MathWorks Inc, Natick, Massachusetts). The missing intervals of the raw N-N data were linearly interpolated and resampled at 4 Hz by using the Ron-Berger method.[12] The time-domain measurements of HRV were the SD of heart rate (SDNN) and square root of the mean of the squared successive R-R interval differences. The frequency-domain measurements of HRV included power levels of very low frequency (0.033-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency (HF, 0.15-0.4 Hz), which were calculated using Welch's averaged periodogram of N-N intervals.[13] All of the variables were calculated every hour and were averaged for day and night. For the treadmill ECG test, the Bruce protocol was used. The test was stopped when the target heart rate was achieved, when the patients were too tired to continue, or active symptoms, such as chest pain, occurred.

Five to 10 mL of blood was withdrawn from the participants while they were resting for more than 5 minutes. We performed an *N*-terminal pro-BNP assay (Roche Diagnostics, Mannheim, Germany). We also isolated DNA from the venous blood of the participants for mutation analysis of the HCN4 gene. The primer pairs used in this study were as previously described.[8] We used polymerase chain reaction methods to amplify all 8 of the exons of HCN4 from genomic DNA. Amplification reactions were executed using 40 ng of template DNA, 8 pmol of primers, 1 μL of Master Mix (Promega Co, Fitchburg, Wisconsin) containing deoxynucleotide triphosphates and Taq polymerase, 0.8 μL of 25 mM Mg2+, and $\times$1 of BigDye v 3.1 (Applied Biosystems, Foster City, California). We then directly sequenced all of these exons by performing dye terminator sequencing using an ABI 3730 automatic sequencer (Applied Biosystems, Foster City, California). Any possible polymorphisms or mutations were reconfirmed using reverse primers.

The statistics used in our study included a χ^2 study to compare the categorical variables between the groups. An independent Student *t* test was used to compare numerical data, which were expressed as the mean $\pm$ SEM. Statistical significance was defined as a *P* value of less than .01.

Results

Among the 432 166 students who were screened, 104 (male:female 60:44) were identified with sinus bradycardia (0.025% of all school children surveyed). Four of the 104 participants had initially been diagnosed at ages below 12 years of age (prevalence 0.0025%), and the other 100 participants had initially been diagnosed at ages equal to or over 12 years of age (prevalence 0.045%). The mean initially diagnosed age was 15.5 $\pm$ 0.2 years. The mean heart rate at the initial screening was 48.4 $\pm$ 0.4 bpm, and 2 of the students had a right bundle branch block in addition to sinus bradycardia. None of the students had other ECG abnormalities such as an atrioventricular block or QT prolongation.

Among the 104 participants, 86 (83%) responded to our interview, and 37 (36% of the entire cohort) returned for further examination. None of the patients had exercise intolerance complaints, and all were in the New York Heart Association function class I status. None of the patients had associated congenital disease or hypothyroidism, nor did they have family history of cardiomyopathy. Fifteen of the 86 participants (17%) had experienced syncopal episodes, but all were self-limited. Most of the episodes of syncope were situation related, such as orthostatic or during blood withdrawal. None had any life-threatening events when examined during the 10-year follow-up. Of the 37 patients who underwent the examination, 14 (37.8%) had been athletes during the school years, and 12 (32.4%) engaged in regular exercise at the present time. All but 4 in these 12 participants were athletes in school. All of the 37 participants had pro-BNP values less than 100 ng/L.