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Right bundle branch block without overt heart disease predicts higher risk of pacemaker implantation: The study of atomic-bomb survivors☆,☆☆

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ABSTRACT

Background: We investigated the clinical course of complete right bundle branch block (RBBB) or RBBB with axis deviation (AD) in terms of subsequent pacemaker implantation for high-degree atrioventricular (AV) block or sick sinus syndrome (SSS).

Methods and results: Among the 16,170 atomic-bomb survivors in our biennial health examination between July 1967 and December 2010, we detected 520 newly-acquired RBBB subjects with no organic heart disease, and selected 1038 age- (at RBBB diagnosis) and sex-matched subjects without RBBB to serve as comparison subjects. Multivariate Cox regression analysis was used to estimate the hazard ratios (HRs) for the risk of pacemaker implantation due to all causes, AV block or SSS between RBBB and comparison subjects and between RBBB subjects with and without AD. The risk of pacemaker implantation for RBBB was 4.79 (95% confidence interval [CI] 1.89–12.58; $P = 0.001$), 3.77 (95% CI, 1.09–13.07; $P = 0.036$), and 6.28 (95% CI, 1.24–31.73, $P = 0.026$) when implantation was for all causes, AV block and SSS, respectively. RBBB subjects with AD had a higher risk for all-cause pacemaker implantation than subjects without AD (HR, 3.03; 95% CI, 1.00–9.13, $P = 0.049$). RBBB subjects with AD were younger than subjects without AD at the time of RBBB diagnosis (59.4 ± 7.6 vs 74.4 ± 3.1 years old, $P = 0.019$), and their progression from diagnosis to pacemaker implantation took longer (15.1 ± 6.6 vs 6.4 ± 3.0 years, $P = 0.032$).

Conclusions: RBBB, especially with AD, progresses to AV block and SSS that requires pacemaker implantation; the mechanisms by which the conduction defect progresses differ among patients with and without AD.

1. Introduction

The long-term outcome of complete right bundle branch block (RBBB) is generally benign, and there is a low incidence (0–0.3%) of progression to complete atrioventricular (AV) block in young subjects [1–3]. However, in previous studies, the number of subjects was limited, and RBBB was not precisely distinguished from RBBB with axis deviation (AD).

Moreover, previous studies showed that sinus node dysfunction was common in patients with bundle branch block based on electrophysiological examination [4]. However, to the best of our knowledge, a long term follow up study to elucidate the relationship between sick sinus syndrome (SSS) and RBBB or RBBB with AD has not been performed. To ascertain the association between RBBB or RBBB with AD and life-threatening high-degree AV block or SSS, we prospectively examined

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the clinical course of newly-acquired RBBB (incident RBBB) with and without left or right AD in terms of subsequent pacemaker implantation for high-degree AV block or SSS.

2. Methods

2.1. General procedure

Since 1958, 23,418 atomic-bomb survivors (9553 men, 13,865 women) have undergone biennial health examinations in Hiroshima and Nagasaki (the Adult Health Study) as part of a follow-up program conducted by the Radiation Effects Research Foundation to determine the long-term effects of radiation. A detailed description of the study rationale, design, and examination procedures has been published elsewhere [5,6]. The electrocardiograms used for the diagnoses were stored in a database starting on July 1, 1967. The Adult Health Study comprised 16,170 subjects who had at least one electrocardiogram (ECG) between July 1, 1967 and December 31, 2010; these subjects were reviewed in this study. During follow-up, these 16,170 subjects had an average of 10.1 ± 6.8 ECGs. We identified subjects with RBBB during this period and subsequently conducted a cohort follow-up study with stratified sampling based on the presence of RBBB. With this design, all eligible subjects with RBBB were included, but only a matched random sample of those without RBBB was used as a comparison group.

2.2. Selection of patients and comparison subjects

RBBB was defined as follows: (1) QRS duration > 120 ms; (2) PQ interval > 120 ms; (3) an rSR' in lead V1 or V2; and (4) an S wave in lead I and in either V5 or V6. Left-axis deviation was defined as the mean QRS axis in the frontal plane of −30° to −90° and right-axis deviation as the mean QRS axis in the frontal plane of +120° to −150°. Physicians in charge of the ECG diagnosis checked the ECG records on the basis of this definition at the time of examination. To reconfirm all diagnoses, one of the authors (S.K.), who was blinded to all other patient information, reviewed the ECG records of subjects who had RBBB with or without AD at least once during follow-up. We defined the date of RBBB diagnosis as the date of the first appearance of RBBB following a previous normal ECG pattern. We defined the date of AD diagnosis as the date of the first appearance of AD after a normal ECG axis. S.K. also reviewed all ECG records in subjects who had atrial fibrillation and complete left bundle branch block (LBBB) (QRS duration > 120 ms, PQ interval > 120 ms, predominantly upper right complexes with slurred R waves in the left precordial leads or lead I, absence of septal Q waves in the left precordial leads, and small or absent R waves in leads V_1 and V_2).

Fig. 1 shows the subject selection process. We identified 828 potential subjects (447 men, 381 women) presenting with RBBB and excluded 189 who either were >85 years old at the time of RBBB diagnosis or had a secondary (organic) cause of RBBB and conduction disease (myocardial infarction, valvular heart disease, endocarditis, cardiomyopathy, myocarditis, pulmonary artery hypertension, pulmonary embolism, LBBB and/or atrial fibrillation). Of the remaining 639 RBBB subjects (343 men, 296 women), 520 had incident RBBB (262 men, 258 women). This group had a mean age at diagnosis of 67.8 ± 10.6 years.

Due to the difficulty in following all of the remaining 15,342 non-RBBB subjects, we randomly selected two age- and sex-matched comparison subjects without RBBB, LBBB, atrial fibrillation or organic heart disease for each of the 520 incident RBBB subjects. For example, if RBBB was diagnosed for the first time in 1995 in a 53-year-old male, we randomly selected two male comparison subjects who were aged 50–54 years and examined by ECG in 1993–1997. The comparison group consisted of a total of 1038 subjects (523 men, 515 women) with a mean age of 67.3 ± 10.6 years. We followed all incident RBBB and comparison subjects prospectively until either pacemaker implantation or the end of the follow-up period.

2.3. Defining underlying clinical diagnoses and identifying subjects with implanted pacemakers

We defined myocardial infarction, valvular heart disease, endocarditis, cardiomyopathy, myocarditis, pulmonary artery hypertension, pulmonary embolism, hypertension, diabetes mellitus, dyslipidemia, stroke and chronic obstructive pulmonary disease as underlying diseases and confirmed them at any time during follow-up using the *International Classification of Disease* (ICD) codes. We identified subjects with implanted pacemakers by examining the ICD code and using ECG diagnosis and chest x-ray codes for post-operative thoracic sites. We reviewed all the selected subjects to reconfirm pacemaker implantation. The procedures of pacemaker implantation were undertaken in each hospital based on each physician's decision taking the guideline at each time into consideration. The reason and indication for pacemaker implantation was ascertained from medical histories and records from hospitals where the devices were implanted. Pacemaker implantation due to all causes, high-degree AV block or SSS was the primary endpoint.

2.4. Atomic-bomb radiation dose

We used the Dosimetry System 2002 (DS02) to estimate total kerma with a weighting factor of 10 for neutrons relative to γ rays [7]. We adjusted gamma and neutron doses assuming 35% random error and truncated them at 4 Gy (the adjustment reduces effect estimation bias due to dose estimation error) [8].

2.5. Statistical analysis

We compared the baseline characteristics between subjects with incident RBBB and the age- and sex-matched comparison subjects using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. We used a Cox proportional hazards model that was adjusted for age at RBBB diagnosis, sex, body mass index (BMI) and hypertension to compare the risk of pacemaker implantation resulting from all causes, AV block or SSS between incident RBBB subjects and their comparison subjects. We then compared the risk between incident RBBB subjects with and without AD and between comparison subjects with and without AD after adjusting for age at RBBB diagnosis and sex. To validate the proportional hazards assumptions in the Cox regression model, we used visual inspection of the diagnostic log-log plots to check each dichotomous variable in the model for proportionality. These diagnostic tests revealed that proportional hazards assumption was satisfied. The follow-up period was defined as elapsed time from the date of RBBB diagnosis to the date of pacemaker implantation or last visit date prior to December 31, 2010. We censored subjects who migrated, died or survived without accepting a recommended pacemaker implant until December 31, 2010; 506 subjects were censored in RBBB and 1032 subjects were censored in the

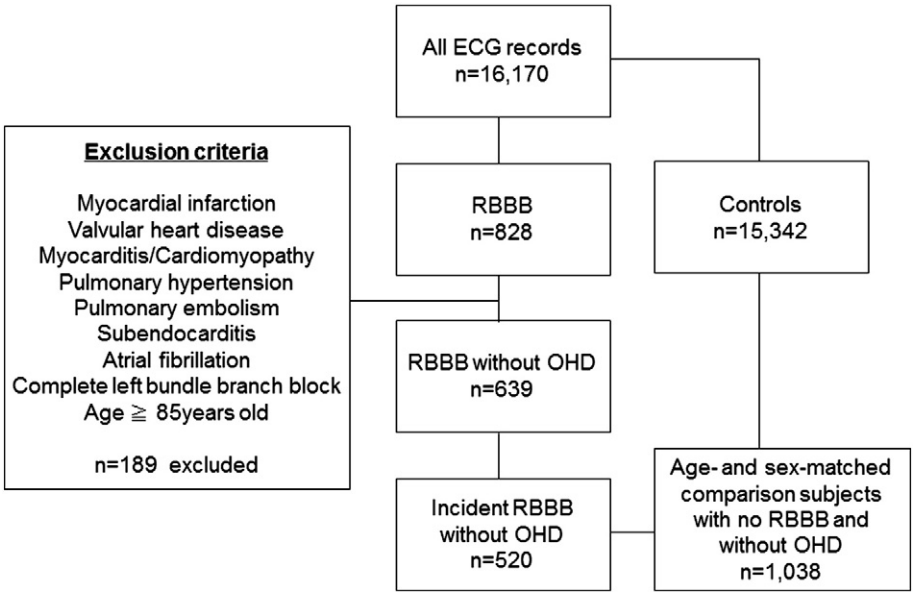

Fig. 1. Selection of subjects. OHD, organic heart disease; ECG, electrocardiography; RBBB, right bundle branch block.