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Interatrial septal pacing to suppress atrial fibrillation in patients with dual chamber pacemakers: A meta-analysis of randomized, controlled trials

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ABSTRACT

Background: Atrial fibrillation (AF) is of frequent occurrence in a population with bradycardia indicated for permanent dual chamber pacing. Whether selective site pacing at interatrial septum (IAS) could better prevent AF as compared with standard atrial pacing (AP) from right atrial appendage or high right atrium in these conditions remains in question. Its safety profile has yet to be elucidated.

Methods: Major web databases were searched up to February 2015 for controlled, randomized clinical trials on IAS versus conventional pacing. The primary end point was freedom from persistent/permanent AF. Secondary outcomes included device-recorded AF burden and frequency of AF episodes, lead-related complications, and major adverse events (MAEs).

Results: We identified 10 eligible studies incorporating a total of 1245 patients. Compared to conventional AP, IAS pacing conferred no additional benefit on the persistent/permanent AF free survival (hazard ratio 0.76, 95% confidence interval [CI] 0.48 to 1.22); it was associated with notably reduced device-detected AF burden (standard mean difference [SMD] −0.32, 95% CI −0.55 to −0.09) and AF frequency (SMD −0.54, 95% CI −0.83 to −0.24). The odds of lead-related complications (odds ratio [OR] 1.64, 95% CI 0.87 to 3.08) and combined rate of MAEs (OR 1.05, 95% CI 0.60 to 1.82) were similar between two groups.

Conclusions: IAS pacing has no influence on the persistent/permanent AF progression and MAEs, although it appears to lower device-detected AF burden and AF frequency, and may carry similar risks of lead-related complications as compared to standard AP.

1. Introduction

Atrial fibrillation (AF) is common in patients with sick sinus syndrome (SSS) or advanced atrioventricular block (AVB) who had standard indications for permanent pacing [1]. It carries increased risks of stroke, heart failure and death [2]. Atrial-based pacing and maximized intrinsic ventricular stimulation have been demonstrated to be favorable to prevent AF in dual chamber pacemaker populations with SSS [3]. However, it remains unclear whether the selection of atrial pacing (AP) sites yields additional benefits. Conventional pacing from right atrium appendage (RAA) or high right atrium (HRA) is associated with prolonged interatrial conduction delay (IACD), especially in the posterior triangle of Koch that may predispose to AF [4]. Selective site pacing at interatrial septum (IAS), on the other hand, has been shown to reduce the atrial dispersion of refractoriness by shortening the total IACD, which subsequently inhibits a re-entry that initiates AF in some acute laboratory studies [5,6]. The preventive effect of long-term pacing at either low (e.g., coronary sinus ostium), middle (e.g., fossa ovalis) or high (e.g., Bachmann's bundle region) septum on AF has been previously evaluated in several prospective, randomized clinical trials (RCT) [7–16], which have yielded equivocal results.

In this study, we aimed to assess whether the meta-analysis of RCTs on IAS pacing versus conventional AP in dual chamber Pacemaker recipients identifies a significant benefit in AF suppression that supports alternative AP at a septal location, and whether their safety profiles are comparable.

Abbreviations: AF, atrial fibrillation; SSS, sick sinus syndrome; AVB, atrioventricular block; AP, atrial pacing; VP, ventricular pacing; RAA, right atrium appendage; HRA, high right atrium; IACD, interatrial conduction delay; PWD, P wave duration; AVI, atrioventricular interval; HR, hazard ratio; OR, odds ratio; SMD, standard mean difference; CIs, confidence intervals; RCT, randomized clinical trial; MAE, major adverse event.

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2. Methods

2.1. Literature search and eligibility criteria

Medline, PubMed, the Cochrane Central Register of Controlled Trials, and the ISI Web of science were searched up to February 2015 for eligible studies. The search items were "atrial septal pacing" or "interatrial septal pacing" and "atrial fibrillation" (see Supplementary Appendix 1 for complete search strategy). Neither language nor year restriction was imposed. A manual search was also performed for additional sources including relevant citations and conference proceedings from the American College of Cardiology, American Heart Association, and European Society of Cardiology. After title and abstract screening, trials that randomly assigned patients to IAS pacing versus conventional AP were selected for full text review. Studies were considered eligible by meeting all of the following criteria: (i) including patients with bradycardia that fulfill standard indications for permanent dual chamber pacing, with or without paroxysmal AF history; (ii) minimal follow-up period of 6 months; (iii) unchanged antiarrhythmic drug status; and (iv) reporting on any of the following outcomes of interest: (a) time to persistent/permanent AF event data, (b) device-classified AF burden, (c) frequency of device-classified AF episodes, (c) atrial lead-related complications, (d) stroke, (e) heart failure, and (f) cardiac death. Studies reporting less than 15 patients in each arm or including subjects with persistent/permanent AF were excluded.

2.2. Data extraction and quality assessment

Data extraction was performed independently by two reviewers (S.S. and S.Y.G.). Any divergence was resolved by consensus. Studies were screened to extract general study characteristics and device programming information. Data regarding baseline patient characteristics and pacing parameters were abstracted as well. The primary outcome of this study was persistent/permanent AF free survival. The secondary outcomes included device-recorded AF burden and AF frequency, lead-related complications as well as combined endpoint of major adverse events (MAEs), including stroke, heart failure and cardiac death. We accepted the definition of AF and complications as adopted by each individual study. All included trials were assessed on the basis of the following criteria: blinding of participants, random sequence generation, allocation concealment, incomplete data addressing, and free from selective reporting.

2.3. Data synthesis and analysis

The pooled effect of IAS pacing on primary endpoint was reported as hazard ratio (HR) with 95% confidence intervals (CIs). Individual Hazard ratio, including 95% CI, was collected directly from the study if it was provided. Otherwise, they were estimated through the survival curve using a previously reported approach [17]. For the secondary endpoints, data were summarized by calculating standard mean difference (SMD) with 95% CI in case of continuous variables, while binary outcomes were presented as odds ratio (OR) with 95% CI. Presence of between-study heterogeneity was assessed using the Cochrane Q test and I^2 index, with statistical significance set at a P value <0.10, and with I^2 >50% denoting substantial heterogeneity. The random effect was preferentially adopted in the presence of statistical or potentially clinical heterogeneity, and sensitivity analysis was carried out by omitting one study at a time to find the potential outliers. Subgroup analyses were performed to appraise the influence of AF suppression algorithms on the summarized effect. Publication bias was explored both visually (Funnel plot) and by formal tests (Begg's and Egger's test). A P value <0.05 was considered statistically significant (2-tailed). Data analysis and artwork creation were performed using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 10.1 (STATA Corporation, College Station, Texas, U.S.).

3. Results

3.1. Search results and study selection

Fig. 1 outlines the results of the study selection process. Among 404 potentially eligible articles, we finally identified 10 randomized trials,

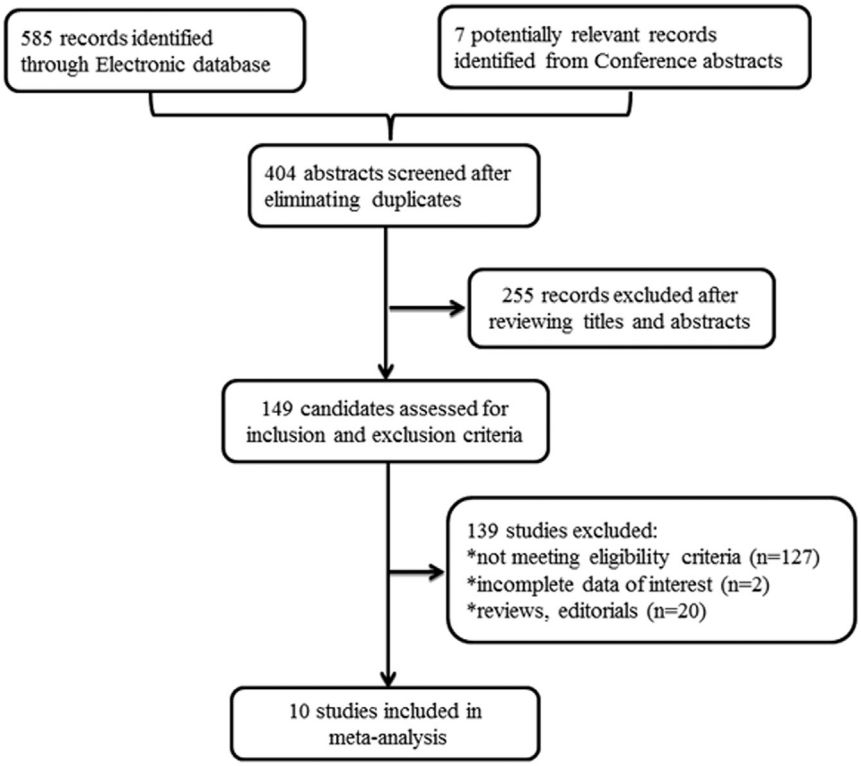

Fig. 1. Study selection process.