Contemporary Clinical Trials 39 (2014) 320–326

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Is there a right place to pace the right ventricle? Evaluation of apical and septal positions in a pacemaker population: Study protocol for a prospective intervention-control trial

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ARTICLE INFO

Article history:
Received 9 August 2014
Received in revised form 8 October 2014
Accepted 10 October 2014
Available online 22 October 2014

Keywords:
Pacemaker
Study design
Review
Septal
Dyssynchrony

ABSTRACT

Introduction: The main objective of research in pacemaker therapy has been to provide the best physiologic way to pace the heart. Despite the good results provided by right ventricular pacing minimization and by biventricular pacing in specific subsets of heart failure patients, these options present many limitations for standard pacemaker recipients. In these patients, pacing the right ventricle at alternative sites could result in a lower degree of left intraventricular dyssynchrony. Despite the lack of strong evidence and the difficulty in placing and accurately classifying the final lead position, pacing at alternative right ventricular sites seems to have become a standard procedure at many implanting centers.

Material and methods: The RIGHT PACE study is a multi-center, prospective, single-blind, double-arm, intervention-control trial comparing right ventricular pacing from the apex and from the septal site in terms of left intraventricular dyssynchrony. A total of 408 patients with indications for cardiac pacing but without indications for ICD and/or CRT will be enrolled. Investigators will be divided on the basis of their prior experience of selective site pacing lead implantation and patients will be treated according to the clinical practice of the centers. After device implantation, they will be followed up for 24 months through evaluation of clinical, echocardiographic and safety/system-performance variables.

Discussion: This study might provide important information about the impact of the right ventricular pacing on the left ventricular dyssynchrony, and about acute and chronic responses to selective site pacing, as adopted in current clinical practice. This trial is registered at ClinicalTrials.gov (ID:NCT01647490).

Trial registration: Right Ventricular Lead Placement in a Pacemaker Population: Evaluation of apical and alternative position. ClinicalTrials.gov: NCT01647490.

Abbreviations: TDI, Tissue Doppler echocardiography; SLD, septal-to-lateral delay; SSV, systolic velocity of the septal wall; LWSV, systolic velocity of the lateral wall of the left ventricle; AV delay, atrio-ventricular delay; NYHA class, New York Heart Association class; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDVol, left ventricular end-diastolic volume; LVESVol, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy.

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http://dx.doi.org/10.1016/j.cct.2014.10.006
1551-7144/

1. Introduction

Chronic right ventricular apical pacing is associated with an increased risk of atrial fibrillation, morbidity, and even mortality [1–3]. These observations have raised questions regarding the appropriate pacing mode and site for patients with indications for permanent ventricular stimulation.

A recently published meta-analysis by Shimony et al. [4] seems to have renewed the belief that a more physiologic right ventricular pacing site can be found which would provide a long-term improvement in left ventricular performance, at least in selected patients.

Several studies have shown that acute apical pacing in subjects with normal left ventricular systolic function may result in mechanical dyssynchrony and decreased systolic function [5–8]. Chronic right ventricular pacing results in mechanical dyssynchrony in up to half of patients [9,10]. Pacing at alternative right ventricular sites may be able to reduce dyssynchrony.

Despite the lack of strong evidence in favor of non-apical pacing, and the difficulty in placing [11,12] and accurately classifying [4] the final lead position, pacing at non-apical right ventricular sites has been adopted as a standard procedure at many implanting centers [13].

These considerations were the basis for the Right Ventricular Lead Placement in a Pacemaker Population: Evaluation of Apical and Septal Positions (RIGHT PACE) study.

2. Material and methods

2.1. Hypothesis

In patients with indications for dual-chamber pacemaker according to current guidelines and requiring a high percentage of ventricular stimulation, pacing of the right ventricle in the septal portion of the outflow tract will result in a lower percentage of patients with significant intraventricular dyssynchrony of left ventricular contraction than pacing at the right ventricular apex. It is also hypothesized that the clinical practice of positioning the right ventricular lead at non-apical sites might translate into an improvement of clinical outcome at 12 and 24 months (assessed as secondary end-points).

2.2. Objectives

2.2.1. Acute echocardiographic outcome

The primary objective is to evaluate left ventricular dyssynchrony induced by the right ventricular pacing. It is presumed that pacing at a septal site will induce less variation in the depolarization front and in the temporal pattern of mechanical activation of the left ventricle (secondary to electro-mechanical coupling) than pacing at a standard apical site, since septal sites are closer to the area of first spontaneous electrical activation of the ventricles in the normal subject. Dyssynchrony will be calculated as the delay between the contraction of the septum and that of the lateral wall, as recorded by means of tissue Doppler echocardiography (TDI) in the 4-chamber apical view. This delay, called septal-to-lateral delay (SLD), corresponds the difference in the time required to reach the peak of systolic deformation of the two walls (beginning at ventricular depolarization recorded by continuous single-lead ECG) according to the following formula:

$$SLD = |\text{Time to peak SSV} - \text{Time to peak LWSV}|$$

SSV: systolic velocity of the septal wall; LWSV: systolic velocity of the lateral wall of the left ventricle.

To evaluate dyssynchrony, the researchers are requested to program a dual-chamber pacing mode (DDD) and set the lower pacing rate of the implanted pacemaker to 70 bpm or, in any case, to a frequency of 10 bpm higher than the spontaneous rhythm. To ensure a constant capture of the right ventricle, the value of the AV delay is to be programmed at 40 ms shorter than the measured intrinsic PQ interval and in any case, no more than 120 ms. This value should be maintained for chronic pacing, unless otherwise prescribed. Assessment of the primary end-point will be based on the percentage of patients with an SLD >41 ms [14] on pre-discharge echocardiogram performed during right ventricular pacing. The use of a baseline measurement will avoid the interference of the possible substrate modification that may occur in the period after implantation. Moreover, the difference of SLD measured during pacing and spontaneous rhythm will be compared between study arms before discharge. This end-point is intended to measure the difference in an acutely induced left ventricular dyssynchrony.

2.2.2. Clinical outcome

The clinical outcome of the patients in the study arms will be assessed and compared. The following endpoints will be considered at 12 and 24 months:

- Hospitalizations and deaths for cardiac causes;
- Hospitalizations and deaths for any cause;
- Change in New York Heart Association (NYHA) class in the two study arms over time;
- Change in quality of life, as assessed by means of the SF-12 questionnaire at the baseline (pre-implantation) and 12 and 24 months after the procedure.

In addition, the association between the clinical outcome at 24 months follow-up and baseline variables will be investigated: lead position, percentage of right ventricular pacing, and baseline SLD during spontaneous rhythm (when available) and during paced rhythm.

The following safety endpoints will be considered and compared between the study arms: implantation failures and complications (e.g. cardiac perforations), lead dislodgements, high pacing thresholds, small signal amplitudes, and device-related hospitalizations.

2.2.3. Long-term echocardiographic outcome

In order to assess the impact of the site of right ventricular pacing on ventricular performance and chronic remodeling of the left ventricle, the following variables will be measured at the baseline (pre-discharge) and after 12 and 24 months:

- LVEDD/LVESD: left ventricular end-diastolic/end-systolic diameter;
- LVEDVol/LVESVol: left ventricular end-diastolic/end-systolic volume;
- LVEF: left ventricular ejection fraction;
- Derived systolic pulmonary pressure;