Heart rate, pacing, and outcome in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trials

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BACKGROUND Slower heart rates are believed to confer a better prognosis in heart disease. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial found that patients with ventricular dysfunction and isolated sinus bradycardia (rate <60 with normal PR interval) had an unusually low incidence of heart failure (HF) hospitalization and mortality when paced infrequently.

OBJECTIVES The purpose of this study was to prospectively test our hypotheses that a similar benefit from bradycardia would be conferred in DAVID II as in DAVID but that this would be nullified by the faster heart rate achieved during atrial pacing in DAVID II.

METHODS Effects of atrial versus minimal ventricular pacing on outcome in defibrillator recipients with isolated bradycardia in DAVID II were prospectively evaluated.

RESULTS Ninety-eight DAVID II patients with isolated bradycardia were similar to 502 patients without it but had less baseline HF. HF medications were used comparably in both groups at baseline and throughout the study. Overall, patients with isolated bradycardia were less likely to die or be hospitalized for HF than others (12.2% vs. 26%; $P = .01$). There was no evidence that atrial pacing diminished this association. Adjusted for covariates, particularly baseline HF and its treatment, isolated bradycardia patients had substantially reduced risk for HF/death ($P = .018$) with or without atrial pacing (relative risk 0.47 and 0.71, respectively).

CONCLUSIONS Isolated bradycardia identifies patients at lower risk for HF and mortality, an association that is not necessarily negated by accelerating heart rate with atrial pacing. This apparent conundrum challenges the use of heart rate as a therapeutic target in patients with ventricular dysfunction. Trial Registration: http://www.clinicaltrials.gov NCT00187187.

KEYWORDS Heart failure; Pacing; Implanted defibrillator; Atrial pacing; DAVID; DAVID II

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Introduction

Heart rate is aptly described as a bellwether of the heart. When rapid, it is a recognized independent predictor of adverse cardiovascular outcomes in the general population,[1,2] following acute myocardial infarction,[3] and in chronic heart failure (HF).[4,5] When slow, it can provoke disabling or life-threatening symptoms and worsening HF[6] and may also constrain the use of medications in HF patients. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial evaluated whether dual-chamber rate-responsive pacing at 70 bpm (DDDR-70) or atrial-only pacing at 70 bpm (AAI-70) in DAVID II, as compared with a ventricular standby mode at 40 bpm (VVI-40) that paced infrequently, would permit more intense pharmacological management of ventricular dysfunction and thereby reduce mortality and HF hospitalization. This did not prove to be the case in either trial.[7,8] Notably, in an exploratory analysis of DAVID, an unusually low incidence of HF hospitalization and mortality was observed among patients whose baseline heart rate was <60 and who were randomized to the infrequently paced treatment arm. Although potentially attributable to chance, the consistency of this observation with the favorable effects of bradycardia reported in other populations prompted a comparable prospectively planned analysis in DAVID II to determine whether there is an association between underlying heart rate and outcome in defibrillator recipients.

Methods

DAVID II was a multicenter, randomized, single-blinded, parallel-arm trial of patients with implanted defibrillators and impaired ventricular function that compared an active pacing mode (AAI-70) against infrequent ventricular pacing (VVI-40). All patients had standard indications for a defibrillator but none for bradycardia pacing. Transvenous dual-chamber defibrillators were implanted in all trial partici-

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pants. Patients were randomly assigned after successful implantation to a programmed mode that paced infrequently or that promoted atrial pacing. Follow-up visits were conducted quarterly. Patients were followed to a common termination date (mean follow-up 2.7 years).[8]

All patients were required to be taking appropriate HF medications at study entry, and continued treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, digitalis, diuretics, and spironolactone, titration of which was reviewed at every follow-up visit in accordance with recommendations in the Heart Failure Society of America Practice Guidelines,[9] with the goal of achieving ≥50% of these target daily doses and those reported in clinical HF trials.[10] Because of the wide variety of beta-blockers, ACEIs, and ARBs and their doses used to treat HF, the ratio of the total daily dose to the targeted dose for drugs within these general categories was averaged to compare dosing regimens between treatment groups during follow-up.

Occurrences of symptomatic bradycardia during follow-up were treated by adjustment/discontinuation of medications having rate or conduction effects. If required for clinical indications, a change in pacing mode was permitted.

Definitions

Isolated sinus bradycardia was defined as a basal heart rate of sinus origin <60 bpm with a normal PR interval. These a priori criteria were selected to permit a primary focus on heart rate apart from any confounding effects of abnormal atrioventricular conduction[11] and based on our previously reported findings that QRS duration does not affect the incidence of HF hospitalization or mortality in the absence of right ventricular pacing.[12] QRS duration was defined as normal (QRS <110 ms) or indicative of abnormal ventricular conduction (QRS ≥110 ms); an abnormal PR interval was defined as >0.20 seconds, based on generally accepted normal values.[13] PR and QRS intervals represented an average of three or more measured intervals on the preimplant electrocardiogram (ECG); heart rate was calculated as the number of beats over the time interval of the resting ECG.

Analyses

On the basis of the observations made in DAVID, we hypothesized that isolated sinus bradycardia would be associated with a lower incidence of HF hospitalization and mortality, compared with the corresponding group of patients with a normal basal heart rate or with PR prolongation, and that this benefit would no longer be evident when the basal heart rate was accelerated by atrial pacing. A prospective testing of these hypotheses was planned and subsequently performed in the DAVID II population.

Endpoint

The primary combined endpoint for this study was time to death or hospitalization for new or worsening HF. HF hospitalization was defined as a >24-hour hospital admission due to clinical symptoms or signs consistent with HF and receipt of intravenous diuretic, inotropic therapy, or supplemental dialysis (in renally impaired patients) within the first 24 hours of stay or being formally listed as high priority for heart transplantation. HF events were determined from review of the hospital record and adjudicated by an events committee blinded to treatment assignment.

Statistics

Continuous and dichotomous variables were compared using Student's t-test, χ^2, or Mann-Whitney tests. Event rates were estimated by the product-limit method (SPSS version 15.0; SPSS Inc., Chicago). Cox stepwise regression was used to analyze the interaction of baseline heart rate and pacing mode while accounting for the main effects of baseline covariates. For these analyses, patients lost to follow-up were considered censored at the time last seen. Pacing mode was based on intention to treat. Statistical significance was indicated by $P < .05$.

Results

In DAVID II, 600 defibrillator recipients were randomized equally to AAI-70 versus VVI-40 pacing. Patients averaged 64 years in age, with a mean ejection fraction of 26%; 90% had New York Heart Association (NYHA) functional class I–II HF, and most were men with coronary disease, prior infarction, hypertension, and/or hyperlipidemia. As expected, patients assigned to atrial pacing had a modestly faster average heart rate (±standard deviation [SD]) in follow-up than those in whom pacing was infrequent (72 ± 8 versus 66 ± 13 and 73 ± 6 versus 65 ± 12, at 3 and 24 months, respectively; $P < .001$).

Bradycardia

Ninety-eight patients (16%) in DAVID II had isolated sinus bradycardia (51 of 300 in the VVI-40 arm and 47 of 300 in the AAI-70 arm). The characteristics of these patients compared with the complementary group without isolated bradycardia are shown in Table 1, and within their respective pacing treatment arms (which were well balanced between VVI-40 and AAI-70 pacing modes) in Table 2. Overall, patients with isolated bradycardia had a higher ejection fraction and less advanced NYHA HF symptoms or prior HF history at study entry. As expected, heart rate and PR interval differed significantly between patients with and without isolated bradycardia.

Heart rates and pacing

At 3-month follow-up in the VVI-40 treatment arm, on average 1% of complexes in patients with isolated sinus bradycardia were ventricular paced, as compared with 2% of complexes in those without isolated bradycardia. Conversely, in the AAI-70 treatment arm, patients with isolated sinus bradycardia were more frequently atrially paced (64% of complexes) than in the complementary subgroup (43% of complexes; $P < .001$). These differences in pacing frequency between patients with and without isolated bradycardia in the two pacing arms persisted throughout follow-