Continuous optimization of cardiac resynchronization therapy reduces atrial fibrillation in heart failure patients: Results of the Adaptive Cardiac Resynchronization Therapy Trial

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BACKGROUND Data from randomized trials have suggested a modest or no effect of conventional cardiac resynchronization therapy (convCRT) on the incidence of atrial fibrillation (AF). AdaptivCRT (aCRT, Medtronic, Mounds View, MN) is a recently described algorithm for synchronized left ventricular (LV) pacing and continuous optimization of cardiac resynchronization therapy (CRT).

OBJECTIVE We compared the long-term effects of aCRT with convCRT pacing on the incidence of AF.

METHODS The Adaptive CRT trial randomized CRT-defibrillator (CRT-D)–indicated patients (2:1) to receive either aCRT or convCRT pacing. The aCRT algorithm evaluates intrinsic conduction every minute, providing LV-only pacing during normal atrioventricular (AV) conduction and AV and ventriculoventricular timing adjustments during prolonged AV conduction. The primary outcome of this subanalysis was an episode of AF >48 consecutive hours as detected by device diagnostics.

RESULTS Over a follow-up period with a mean and standard deviation of 20.2 ± 5.9 months, 8.7% of patients with aCRT and 16.2% with convCRT experienced the primary outcome (hazard ratio [HR] = 0.54; 95% confidence interval [CI] = 0.31–0.93; $P = .03$). In patients with prolonged baseline AV, the incidence of the primary outcome was 12.8% in patients randomized to aCRT compared with 27.4% in convCRT patients (HR = 0.45; 95% CI = 0.24–0.85; $P = .01$). Also, patients with AF episodes adjudicated as clinical adverse events were less common with aCRT (4.3%) than with convCRT (12.7%) (HR = 0.39; 95% CI = 0.19–0.79; $P = .01$).

CONCLUSION Patients receiving aCRT had a reduced risk of AF compared with those receiving convCRT. Most of the reduction in AF occurred in subgroups with prolonged AV conduction at baseline and with significant left atrial reverse remodeling.

KEYWORDS Atrial fibrillation; AV conduction; Cardiac resynchronization therapy; Clinical outcome; Heart failure; LV pacing

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Introduction

Atrial fibrillation (AF) is a common comorbidity among heart failure (HF) patients and is associated with an increased risk of hospitalization, stroke, and death.[1–4] The prevalence of AF reported in recent HF studies and registries ranges from 10% to 15% in mild-to-moderate chronic HF and up to approximately 50% in patients with severe HF.[5–7] According to

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the Framingham Heart study, 20% of HF patients develop AF within 4 years.[5]

In numerous trials, cardiac resynchronization therapy (CRT) consistently improved quality of life, reduced HF hospitalizations, and reduced risk of death.[8–10] However, the effect of CRT on AF is less clear. Many observational studies have suggested that CRT reduces the risk of AF.[11–16] Yet data from 3 large clinical trials have shown conflicting results; 1 study found no benefit,[17] another found benefit only in patients with significant left atrial (LA) remodeling,[18] and a third found a trend toward an increased incidence of AF.[19]

The AdaptivCRT algorithm (aCRT, Medtronic, Mounds View, MN) was designed to continually adjust CRT to the patient's intrinsic atrioventricular (AV) conduction. The algorithm adjusts AV and interventricular pacing intervals and withholds right ventricular (RV) pacing when normal AV conduction exists—fusing the left ventricular (LV) stimulation to intrinsic conduction. During periods of prolonged AV conduction, the algorithm continuously optimizes AV and ventriculoventricular (VV) intervals. The algorithm is noninferior to conventional CRT (convCRT) pacing and may increase responder rates and improve clinical outcomes.[20–22]

RV pacing has been shown to increase the risk of AF in patients with sinus node dysfunction.[23–25] As aCRT significantly reduces RV pacing, we hypothesized that the incidence of AF would be reduced with the algorithm. This study examines the long-term effects of aCRT on the incidence of AF using data from the Adaptive CRT trial.

Methods

The aCRT algorithm

The aCRT algorithm aims to provide fusion pacing by evaluating intrinsic conduction every minute. During normal AV conduction (≤200 ms), synchronized LV-only pacing is provided by preempting the atrial to RV sense interval by ≥40 ms. During prolonged AV conduction (>200 ms), aCRT pacing is provided with adjustment to the AV and VV timing based on intervals of atrial to RV sense, atrial to P-wave end, and RV sense to QRS end.[26,27]

The Adaptive CRT trial

The trial design and primary results of the Adaptive CRT trial have been previously published, and the protocol was approved by the ethics committee at each participating institution and associated national and local regulatory agencies.[22,26] The Adaptive CRT was a noninferiority study to test the performance of aCRT vs convCRT. Patients implanted with CRT with defibrillation therapy (CRT-D) for clinical indications of New York Heart Association functional class III or IV HF symptoms, LV ejection fraction ≤35%, and QRS duration ≥120 ms were randomized in a 2:1 ratio to receive aCRT or echo-optimized convCRT pacing. Patients and clinicians were both blinded to the assigned treatment. Primary objectives were met, demonstrating the algorithm's safety and effectiveness of improving the patient clinical composite score by 6 months at a rate similar to that of the control arm. Q2

AF substudy

Atrial arrhythmia information was extracted from the device diagnostics report for all patients at each study visit. Continuous data were available from randomization through to the end of the follow-up period. As a post hoc analysis, the primary outcome was defined as time to ≥2 consecutive days of ≥23 hours of device-detected AF (ie, >48 consecutive hours of AF). This outcome was chosen because of its relationship with thromboembolic risk.[28]

Additional outcomes and analyses

To explore the relationship between the 2 components of the aCRT algorithm, we examined the incidence of the primary end point in subgroups of patients with normal AV conduction and prolonged AV conduction at randomization. In patients with normal baseline AV conduction (defined as intrinsic AV ≤200 ms when in sinus rhythm or AV ≤250 ms when receiving atrial pacing), the expectation is that much of the time they will receive synchronized LV pacing. In patients with prolonged AV conduction, the expectation is that most of the time the patient will receive biventricular pacing with optimized AV and VV intervals.

In addition to the primary end point of 48 hours of AF, the time to the first occurrence of other shorter and longer durations of AF was analyzed. Also, we examined the incidence of the primary end point in a number of additional subgroups. In addition, the incidence of AF episodes that met the protocol definition of new or worsening adverse event, including all deaths and all hospitalizations, were compared. Such adverse events were collected prospectively and defined as any untoward medical occurrence in a participant. All adverse events were reviewed and adjudicated by a blinded independent committee for relatedness and severity. We also examined incidence of persistent AF (defined as continuous episode >7 days). Finally, we assessed baseline and change (after 6 months) in LA area by 2-dimensional echocardiography measured by a blinded core laboratory at the University of Pittsburgh. For this latter analysis patients were classified as LA responders (LA area decreased >20% between baseline and 6 months) or LA nonresponders (LA area decreased <20% or increased between baseline and 6 months).[18]

Statistical analysis

Continuous variables are reported as mean plus or minus standard deviation (SD). Cumulative incidence curves are based on the Kaplan–Meier method, with time 0 being the date of randomization unless otherwise specified. Comparisons are made using the log-rank test. Cox proportional hazard methods are used to compare subgroups, with the *P* value of the interaction between randomization and the subgroup reported. Adverse event rates were