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A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Heart Failure

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Objectives This study sought to compare catheter ablation with rate control for persistent atrial fibrillation (AF) in heart failure (HF).

Background The optimal therapy for AF in HF is unclear. Drug-based rhythm control has not proved clinically beneficial. Catheter ablation improves cardiac function in patients with HF, but impact on physiological performance has not been formally evaluated in a randomized trial.

Methods In a randomized, open-label, blinded-endpoint clinical trial, adults with symptomatic HF, radionuclide left ventricular ejection fraction (EF) ≤35%, and persistent AF were assigned to undergo catheter ablation or rate control. Primary outcome was 12-month change in peak oxygen consumption. Secondary endpoints were quality of life, B-type natriuretic peptide, 6-min walk distance, and EF. Results were analyzed by intention-to-treat.

Results Fifty-two patients (age 63 ± 9 years, EF 24 ± 8%) were randomized, 26 each to ablation and rate control. At 12 months, 88% of ablation patients maintained sinus rhythm (single-procedure success 68%). Under rate control, rate criteria were achieved in 96%. The primary endpoint, peak oxygen consumption, significantly increased in the ablation arm compared with rate control (difference +3.07 ml/kg/min, 95% confidence interval: 0.56 to 5.59, p = 0.018). The change was not evident at 3 months (+0.79 ml/kg/min, 95% confidence interval: −1.01 to 2.60, p = 0.38). Ablation improved Minnesota score (p = 0.019) and B-type natriuretic peptide (p = 0.045) and showed nonsignificant trends toward improved 6-min walk distance (p = 0.095) and EF (p = 0.055).

Conclusions This first randomized trial of ablation versus rate control to focus on objective exercise performance in AF and HF shows significant benefit from ablation, a strategy that also improves symptoms and neurohormonal status. The effects develop over 12 months, consistent with progressive amelioration of the HF syndrome. (A Randomised Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; NCT00878384) (J Am Coll Cardiol 2013;61:1894–903) © 2013 by the American College of Cardiology Foundation

Atrial fibrillation (AF), the commonest arrhythmia in humans, causes a substantial burden of morbidity on patients and cost on healthcare systems. In patients with heart failure (HF), AF becomes more common and imposes greater burdens (1–3). Prevalence of AF rises from 10% in mild toward 50% in severe HF (3). Coexistence of AF with HF is associated with increased hospital stay and mortality (4,5) and further increases the stroke risk from AF 3-fold (6).

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Rhythm control with antiarrhythmic drugs has not been shown to confer benefit in randomized trials, whether in patients with (7) or without HF (8,9). The lack of benefit from antiarrhythmic drugs might reflect their poor (<50%) efficacy in maintaining sinus rhythm (7–9). The risk of adverse effects might outweigh the benefits of restoring

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sinus rhythm, and indeed most antiarrhythmics are contraindicated in HF. Nonrandomized studies of catheter ablation, which might avoid such problems, have shown improvements in cardiac function (10–13), exercise capacity (12), and quality of life (14) in patients with HF and AF.

We designed a clinical trial to test the ability of ablation-based rhythm control to improve objective cardiovascular function in patients with HF and persistent AF. Impairment of exercise intolerance is both a hallmark symptom of HF and an important indicator of long-term survival. Given that peak oxygen consumption (VO_2) is a strong prognostic indicator (15–17), we chose a change in peak VO_2 as the primary endpoint. For the control arm we chose the contemporary standard-of-care for persistent AF in HF, a rigorous rate-control strategy that is at least noninferior to pharmacological rhythm control (7).

Abbreviations and Acronyms

AF = atrial fibrillation
BNP = B-type natriuretic peptide
CI = confidence interval
ECG = electrocardiogram
EF = ejection fraction
HF = heart failure
LA = left atrium/atrial
PVI = pulmonary vein isolation
VO_2 = peak oxygen consumption

Methods

Patients. The enrollment criteria were 18 to 80 years of age, persistent AF (>7 days), symptomatic HF (New York Heart Association functional class II to IV) on optimal HF therapy, and left ventricular ejection fraction (EF) ≤35%. Exclusion criteria included cardiovascular implantable electronic device insertion or cerebrovascular event within 6 months; coronary revascularization or atrioventricular nodal ablation within 3 months; reversible causes of AF or HF including thyroid dysfunction, alcohol, primary valvular disease, or recent major surgery; prior heart transplant or on urgent transplant waiting list; pregnancy; active malignancy; severe renal impairment; single chamber pacemaker and atrioventricular block; and contraindications to general anesthesia or oral anticoagulation. Optimal HF therapy was defined as taking or having tried angiotensin-converting enzyme inhibitor (or angiotensin blocker), beta-blocker, and other therapy as recommended by their HF specialist; having had therapy for >1 month; and symptoms for >3 months. Prior failure of rhythm control by electrical or pharmacological cardioversion was not a prerequisite for enrollment, and no pre-enrollment rate-control criteria were specified.

The study, approved by the local research ethics committee in December 2008, was conducted at Royal Brompton and Harefield hospitals between April 2009 and June 2012. Patients were consecutively screened and enrolled after referral from cardiology services based locally and at linked referring hospitals. All patients provided written informed consent.

Baseline assessment. Baseline assessment comprised history, physical examination, blood tests including B-type natriuretic peptide (BNP), radionuclide ventriculography, cardiopulmonary exercise testing, 2-dimensional echocardiography, Minnesota Living with Heart Failure Questionnaire (MLHFQ), 6-min walk test, and 24-h Holter electrocardiogram (ECG).

Cardiopulmonary treadmill exercise testing was performed with the modified Bruce protocol. Peak VO_2 (ml/kg/min) was defined as the mean of the highest 2 consecutive values of 15-s averages of VO_2. The ventilation/carbon dioxide (ventilatory efficiency) slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise (16,18).

Because ejection fraction varies between beats in AF, we avoided methods that involve selecting beats for EF calculation (19). We chose radionuclide ventriculography, which systematically averages across hundreds of heartbeats.

Randomization and masking. After baseline investigations, eligible patients underwent 1:1 randomization by computer-generated sequence, stratified for age (above and below 50 years) and known atrioventricular block. The study was open-label; however, those conducting cardiopulmonary exercise testing, blood assays, and imaging analysis were blinded to randomization. The VO_2 results were investigator-blinded until completion of follow-up.

Rate control. Patients received pharmacological therapy (beta-blockers and/or digoxin) targeted to achieve a mean heart rate (assessed by apical auscultation over 30 s) ≤80 beats/min at rest before and ≤110 beats/min after a 6-min walk (7,8). If rate-control criteria were not met at baseline or during follow-up, patients re-attended at 4-week intervals for repeat assessment and adjustment of drug therapy until targets were achieved. In patients with pacemakers, if the base rate (≤80 beats/min) was not exceeded, no additional medication was prescribed for rate control. Atrioventricular node ablation and pacing was not adopted as a protocol, because it had just been reported to be inferior to pulmonary vein isolation (20).

Catheter ablation. The procedure was performed under general anesthesia. Transesophageal echocardiography was performed to exclude left atrial thrombus and to guide transseptal puncture. Patients were heparinized to maintain the activated clotting time over 300 s. Atrial anatomy was reconstructed with the NavX mapping system with an AFocusII catheter (St. Jude Medical, St. Paul, Minnesota). Radiofrequency ablation was performed with a 3.5-mm irrigated-tip catheter (ThermoCool, Biosense Webster, Diamond Bar, California) and comprised the following stepwise strategy: 1) pulmonary-vein isolation; 2) linear ablation at the left atrial roof and mitral isthmus; and 3) ablation of left atrial complex fractionated electrograms guided by high-density multipolar mapping as previously described (21). If atrial tachycardia occurred, the protocol was terminated, and the tachycardia was mapped and ablated. If AF persisted, sinus rhythm was restored by external cardiover-