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Influence of left ventricular remodeling on atrial fibrillation recurrence and cardiovascular hospitalizations in patients undergoing rhythm-control therapy ☆

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ABSTRACT

Background: Atrial fibrillation (AF) patients with left ventricular hypertrophy (LVH) and diastolic dysfunction may derive benefit from being in sinus rhythm but no data are available to support this strategy in them. We sought to investigate effect of left ventricular remodeling on cardiovascular outcomes in AF patients undergoing rhythm control strategy.
Methods: We identified 1088 patients with echocardiographic data on left ventricular mass (LVM) enrolled in the AFFIRM trial. Using the American Society of Echocardiography (ASE) criteria, patients were divided into 4 categories: 1) normal geometry, 2) concentric remodeling, 3) eccentric hypertrophy, and 4) concentric hypertrophy. The primary endpoint was AF recurrence and the secondary endpoint was cardiovascular hospitalization (CVH).
Results: In rhythm control arm, median time to recurrence in patients with concentric LVH was 13.3 months (95% CI 8.2–24.5) vs. 28.3 months (95% CI 20.2–48.6) in patients without LVH. Concentric left ventricular hypertrophy (LVH) was independently predictive of AF recurrence (HR 1.49, 95% CI 1.10–2.01, p = 0.01) in rhythm control arm, but not in overall population or rate control arm. Both concentric and eccentric LVH were independently predictive of cardiovascular hospitalization (CVH) in the overall population, with respective HRs of 1.36 (1.04–1.78, p = 0.03) and 1.38 (1.02–1.85, p = 0.04).
Conclusion: Concentric LVH is predictive of AF recurrences when a predominantly pharmacologic rhythm-control strategy is employed. Different patterns of LVH seem to be important determinants of outcomes (AF recurrence and CVH). These findings may have important clinical implications for the management of patients with AF and LVH. Further studies are warranted to confirm our findings.

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1. Introduction

In atrial fibrillation (AF), the loss of a regular and organized atrial systole as well as the increased ventricular rate lead to both immediate and long-term adverse consequences such as deterioration in hemodynamics and progressive dysfunction of left atrium and left ventricle. However, randomized trials that have compared rate and rhythm control approaches in the general population of patients with atrial fibrillation (AF), have demonstrated equivalent outcomes with comparable rates of mortality and stroke in both arms [1,2].

Patients with significant left ventricular hypertrophy (LVH) and diastolic dysfunction do not to tolerate the loss of atrial systole or short diastolic times that occur during episodes of AF. This suggests that they might benefit from being in sinus rhythm. However the lack of evidence of benefit of rhythm control in the current literature may be explained by the limitations of antiarrhythmic drug therapy such as limited efficacy (many patients have AF recurrences), occurrence of proarrhythmogenic side effects and substantial drug–drug interactions.

Left atrial (LA) size has previously been shown to be predictive of atrial fibrillation (AF) recurrence [3–5]. Left ventricular hypertrophy (LVH) leads to diastolic dysfunction, which in turn causes elevation of cardiac filling pressures and consequent atrial enlargement [6]. Different patterns of LVH (concentric vs. eccentric) have dissimilar hemodynamic effects: those with concentric LVH tend to have more restrictive filling, hence potentially deriving a greater benefit from atrial contraction. Consequently, we sought to study the clinical impact of different patterns of LVH (concentric vs. eccentric) on the risk of AF recurrence and cardiovascular hospitalization in patients enrolled in the AFFIRM trial.

2. Methods

We performed a post hoc analysis of patients enrolled in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, which involves older patients (>65 years) with at least one risk factor for stroke. A public-use limited-access dataset that was devoid of all patient identifiers was obtained from the National Heart, Lung and Blood Institute (NHLBI). None of the authors are affiliated with the NHLBI or were part of the AFFIRM trial. The details of AFFIRM have been described previously [7]. AFFIRM was a prospective trial (n = 4060) comparing survival in patients with AF randomized to a strategy of rate (n = 2027) versus rhythm control (n = 2033) [8].

Inclusion criteria were all patients enrolled in AFFIRM trial, who were in sinus rhythm at the time of randomization with available echocardiographic data for estimation of LV mass (LVM) & relative wall thickness (RWT) [both calculated as per ASE guidelines] and with at least one documented follow-up visit thereafter. Exclusion criteria were patients with unavailable or incomplete echocardiographic data.

Echocardiographic categories were as follows: RWT greater than or equal to 0.42 was considered abnormally increased. We used standardized sex-specific cut-offs for LV mass and relative wall thickness proposed by the American Society of Echocardiography [9]. The LV mass categories classified as normal or mildly elevated per ASE were considered 'normal' in our study and the LV mass categories classified as moderately to severely abnormal were considered 'elevated' in our study. Based on these parameters, patients were divided into 4 categories: 1) Normal geometry (normal LVM and normal RWT); 2) concentric remodeling (normal LVM with increased RWT); 3) eccentric hypertrophy (elevated LVM and RWT ≤ 0.42); or 4) concentric hypertrophy (elevated LVM and RWT ≥ 0.42) [9].

The primary end point of our analysis was the first episode of AF recurrence. AF recurrence was defined as either documented atrial fibrillation or flutter in the EKG since the last follow-up or the patient being currently in atrial fibrillation or flutter. This information was provided in the follow-up data files of the AFFIRM trial. All patients with initial sinus rhythm who had a documented EKG with AF at the time of or before any of the follow-up visits were considered to have AF recurrence. We also evaluated hospitalization for cardiovascular causes as a secondary end point. Cardiovascular hospitalization is a broad term and the diagnoses included in cardiovascular hospitalization include: hypertensive crisis, congestive heart failure, acute coronary syndrome, pulmonary embolism, atrial fibrillation, ventricular tachycardia and bradycardia or heart block.

Multivariate Cox proportional hazards models were constructed, which included concentric hypertrophy and eccentric hypertrophy as the major factors, with adjustments for age, gender, and other pertinent patient characteristics (Table 1). The multivariate models were adjusted for age, gender, first episode of AF, duration of AF, previously failed treatment for AF, history of pulmonary disease, history of valvular disease, history of coronary artery bypass grafting (CABG), history of hypertension, history of congestive heart failure, history of coronary artery disease, history of stroke, history of diabetes, history of pacemaker implantation, smoking status, use of warfarin, angiotensin converting enzyme inhibitors/angiotension receptor blockers, beta blocker, calcium channel blocker, amiodarone, sotalol, class I anti-arrhythmic, mitral regurgitation, left atrial size (LA) and LV ejection fraction (EF). The analysis was performed for the entire cohort, and separately for the rate and rhythm control arms. A p value of <0.05 was considered statistically significant, and analysis was performed using STATA software, version 11.0 (College Station, Texas).

3. Results

Baseline characteristics of study population stratified by the presence or absence of AF recurrence are listed in Table 1. There were 1088 patients with complete echocardiographic data available. There

Table 1
Baseline characteristics.

	Overall population (n = 1088)	No atrial fibrillation recurrence (n = 325)	Atrial fibrillation recurrence (n = 763)	p-Value
Mean age (±SD)	69.10 ± 8.08	69.57 ± 8.44	68.91 ± 7.92	0.080
Male	592	164 (50.4%)	428 (56.0%)	0.090
Pulmonary hypertension	151	50 (15.3%)	109 (14.2%)	0.600
Valve disease	137	47 (14.4%)	90 (11.8%)	0.200
History of CABG	109	29 (8.92%)	80 (10.4%)	0.400
History of pacemaker	33	5 (1.5%)	28 (3.6%)	0.060
History of CAD	385	110 (33.8%)	275 (36.0%)	0.400
History of CHF	220	58 (17.8%)	162 (21.2%)	0.200
History of hypertension	771	230 (70.7%)	541 (70.9%)	0.900
History of stroke	156	44 (13.5%)	112 (14.6%)	0.600
History of diabetes	230	62 (19.0%)	168 (22.0%)	0.200
Current smoker	132	43 (13.2%)	89 (11.6%)	0.400
First episode of AF	467	168 (51.6%)	299 (39.1%)	<0.001
History of heart failure	140	21 (6.4%)	119 (15.6%)	<0.001
Medication use				
Beta blocker	485	145 (44.6%)	340 (44.5%)	0.900
Calcium channel blockers	357	134 (41.2%)	223 (29.2%)	<0.001
Digoxin	568	157 (48.3%)	411 (53.8%)	0.090
Warfarin	890	244 (75.0%)	646 (84.6%)	<0.001
ACEI/ARB	402	104 (32.0%)	298 (39.0%)	0.020
Amiodarone	194	95 (29.2%)	99 (13.0%)	<0.001
Sotalol	182	58 (17.9%)	124 (16.3%)	0.519
Class I antiarrhythmics	156	52 (16%)	104 (13.6%)	0.307
Mitral regurgitation	212	60 (18.4%)	152 (19.9%)	0.500
Left atrial size				0.002
<4 cm (%)	490	173 (53.2%)	317 (41.5%)	
4.1–4.5 cm (%)	300	78 (24.0%)	222 (29.1%)	
≥4.6 cm (%)	298	74 (22.7%)	224 (29.3%)	
LV ejection fraction (>50% = referent)				0.700
>50%	863	257 (79.0%)	606 (79.4%)	
40–49%	119	35 (10.7%)	84 (11.0%)	
30–39%	59	16 (4.9%)	43 (5.6%)	
<30%	47	17 (5.2%)	30 (3.9%)	
Rhythm control arm	542	207 (63.7%)	335 (43.9%)	<0.001

ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

were 763 (70.1%) AF recurrences, with 428 (78.4%) in the rate control arm and 335 (61.8%) in the rhythm control arm, over a 6-year follow-up period. The only statistically significant differences among patients with and without AF recurrence were the presence of heart failure, use of calcium channel blocker or warfarin, and left atrial (LA) size. The relationship between LA size and AF recurrence has been shown previously [3]. Of those who had an AF recurrence, 41.2% were on a calcium channel blocker (CCB) compared to only 29.2% of those who had an AF recurrence, with p < 0.01. In an article by Niwano et al. [10], the authors say that intracellular calcium overload may play an important role in electrical atrial remodeling which converts paroxysmal AF to chronic AF. Hence, the use of L-type calcium channel blockers like verapamil may have a role in reducing AF recurrence through this mechanism. Interestingly, left ventricular systolic function was similar in those with and without AF recurrences.

3.1. Atrial fibrillation recurrence models

Concentric remodeling, concentric hypertrophy or eccentric hypertrophy was not significantly predictive of AF recurrence in the overall population or the rate control arm (n = 546) (Table 2, Fig. 1). Interestingly, concentric LVH was independently predictive of AF recurrence in the rhythm control arm (n = 542), with an adjusted HR of 1.49 (1.10–2.01, p = 0.01). In this arm, the median time to recurrence was 13.3 months in patients with concentric LVH (95% CI: 8.20–24.50), versus 28.3 months in patients without LVH (95% CI: 20.20–48.60) (Fig. 2). Concentric remodeling and eccentric hypertrophy were, however, not significantly predictive of AF recurrence in the rhythm control