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Association of the H_2FPEF Risk Score with Recurrence of Atrial Fibrillation Following Pulmonary Vein Isolation

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Abstract

Background: While atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) commonly coexist, the efficacy of pulmonary vein isolation in the setting of HFpEF is unclear.

Methods: In a cohort of patients who underwent cryoballoon ablation (CBA) from 2011 to 2016, we calculated the H_2FPEF risk score, a novel 6-item score (scale: 0-9 points) that accurately predicts the probability of HFpEF. We compared characteristics of patients by H_2FPEF score and evaluated the association of H_2FPEF score with 12-month recurrence of AF post-procedure.

Results: Of patients with available data to calculate the H_2FPEF score (n=105), the median H2FPEF score was 5 (interquartile range: 4-6), corresponding to >80% probability of HFpEF. Compared to patients with H_2FPEF scores ≤4 (n=34), patients with H_2FPEF scores of 5 and 6 (n=46) and ≥7 (n=25) carried higher rates of hypertension (≤4: 21% vs. 5 and 6: 63% vs. ≥7: 88%, P<0.001) and diabetes (≤4: 0% vs. 5 and 6: 9% vs. ≥7: 32%, P=0.001). The overall 12-month recurrence rate of AF was 21%. There was no association between H_2FPEF score and recurrence of AF at 12 months (OR per SD increase in log-H_2FPEF score: 0.87, 95% CI: 0.54-1.40, P=0.57).

Conclusion: Among patients undergoing CBA for AF, median H_2FPEF scores are elevated, and screening for occult HFpEF may be warranted in this population. There was no association of the H_2FPEF score and AF recurrence at 12 months, suggesting efficacy of CBA even among patients with high H_2FPEF scores.

Introduction

Atrial fibrillation (AF) and heart failure (HF) with preserved ejection fraction (HFpEF) frequently coexist. Over 60% of patients with HFpEF may experience AF at some point during their lifetime, and AF is more closely associated with incident HFpEF than HF with reduced ejection fraction (HFrEF).[1] Indeed, both in-hospital and long-term outcomes among those burdened with both AF and HFpEF are worse compared to the presence of either syndrome in isolation.[2-4] Recently, AF was identified as the single strongest predictor of the diagnosis of HFpEF among dyspneic patients.[5] Notably, the vast majority of patients with persistent AF and unexplained dyspnea may have occult HFpEF after invasive hemodynamic investigation.[6] Given its predictive ability, AF has been incorporated into a novel risk score for HFpEF, termed the H_2FPEF risk score.[5] This risk score has demonstrated adequate prediction of HFpEF as confirmed by invasive hemodynamic testing.[5] Of the 6 clinical and echocardiographic variables that comprise the H_2FPEF risk score, AF represents the most heavily-weighted variable, accounting for 3 points of the 9-point composite.[5] Despite the close relationship between these 2 syndromes, management of AF in HFpEF remains unclear. While recent randomized clinical trial data have emerged that support the clinical utility of catheter ablation in the setting of HFrEF, parallel investigations in HFpEF are currently lacking.[7, 8] Although pulmonary vein isolation (PVI) is an effective treatment for AF,[9] its efficacy in the setting of HFpEF is unclear. Additionally, the association of the H_2FPEF score with natriuretic peptides, a biomarker frequently used to diagnose HFpEF, is not well-established in AF and could offer insight into the diagnostic utility of natriuretic peptides for HFpEF in the setting of AF. We thus evaluated 1) the distribution of H_2FPEF scores and natriuretic peptide levels among patients undergoing PVI using cryoballoon and 2) the association of the H_2FPEF risk score and recurrence of AF following cryoballoon catheter ablation. We hypothesized that

Key Words

Atrial Fibrillation; Heart Failure With Preserved Ejection Fraction; Ablation; Recurrence; Risk Score

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in patients undergoing PVI, H_2FPEF scores are: 1) relatively high; 2) associated with higher natriuretic peptide levels; and 3) associated with increased risk of AF recurrence.

Methods

Study Population

Consecutive AF patients who underwent cryoballoon ablation at a single academic center (Northwestern Memorial Hospital, Chicago, IL) between January 1, 2011 and December 31, 2016 were evaluated for study inclusion. Patients included in the analysis were required to have transthoracic echocardiograms of sufficient quality for calculation of the H_2FPEF score obtained within 1 year prior to ablation. Patients with a history of reduced left ventricular ejection fraction (LVEF), defined as <45%, were excluded. This study was approved by the institutional review board of Northwestern University.

Calculation of H_2FPEF Score

The H_2FPEF score was calculated for all patients with available echocardiographic and clinical data based on the components of the score: AF (3 points), age > 60 years (1 point), body mass index (BMI) >30 kg/m2 (2 points), ≥2 anti-hypertensive medications (1 point), pulmonary artery systolic pressure (PASP) >35 mmHg (1 point), and E/e' >9 (1 point). Age and BMI were obtained from the date of cryoballoon ablation. Anti-hypertensive medications were recorded from the most recent pre-procedure clinic visit. Comprehensive 2-dimensional echocardiograms with Doppler were performed at Northwestern Memorial Hospital according to American Society of Echocardiography standards.[10-12] PASP was calculated using the modified Bernoulli equation of peak tricuspid valve regurgitation velocity plus right atrial pressure. The average of septal and lateral E/e' measurements was obtained. Additional echocardiographic indices included left atrial (LA) volume (LAV) and LVEF. LAV was calculated by through the biplane method using apical 2- and 4- chamber views. B-type natriuretic peptide (BNP) levels were additionally recorded if they had been obtained prior to cryoablation.

Cryoballoon Ablation and Rhythm Surveillance Protocols

Cryoballoon ablation was performed as previously described.[13] Cryoballoon ablation was performed by one of six cardiac

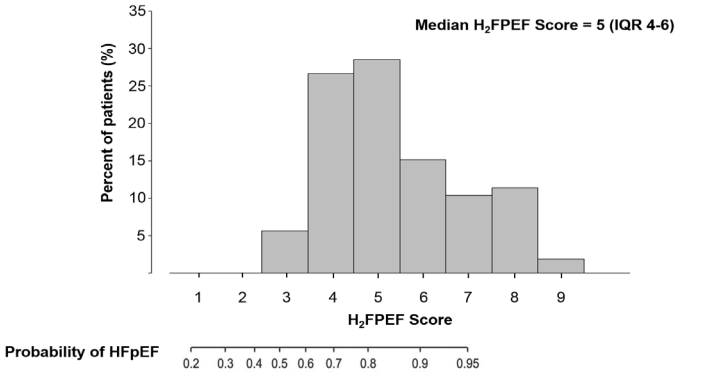

Figure 1: Distribution of H_2FPEF Scores. HFpEF = heart failure with preserved ejection fraction.

Table 1: Baseline Characteristics Stratified by H_2FPEF Score.

	H_2FPEF Score			
Characteristic	**≤4 (n=34)**	**5 and 6(n=46)**	**≥7 (n=25)**	**P value**
Age (years), mean±SD	59.0±13.0	64.7±9.3	66.7±4.2	0.007
Female sex, n (%)	8 (24)	21 (46)	11 (44)	0.10
Asian, n (%)	1 (3)	3 (7)	1 (4)	0.05
Black, n (%)	0 (0)	1 (2)	4 (17)	
White, n (%)	33 (97)	41 (89)	17 (74)	
Persistent atrial fibrillation, n (%)	14 (41)	24 (52)	11 (44)	0.59
Hypertension, n (%)	7 (21)	29 (63)	22 (88)	<0.001
Diabetes mellitus, n (%)	0 (0)	4 (9)	8 (32)	0.001
Coronary artery disease, n (%)	5 (15)	7 (15)	3 (12)	0.93
Obstructive sleep apnea, n (%)	1 (3)	8 (17)	6 (24)	0.05
Stroke or transient ischemic attack, n (%)	2 (6)	2 (4)	1 (4)	0.93
Body mass index (kg/m²), median (IQR)	25.9 (23.4-27.0)	27.3 (24.6-30.4)	33.4 (31.5-36.5)	<0.001
Glomerular filtration rate (mL/min/1.73m²) mean±SD	83.1±19.7	74.9±18.6	73.7±17.4	0.09
Medications				
β blocker, n (%)	14 (41)	27 (59)	17 (68)	0.10
Calcium channel blocker, n (%)	5 (15)	9 (20)	6 (24)	0.66
Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker, n (%)	11 (32)	13 (28)	13 (52)	0.12
Mineralocorticoid antagonist, n (%)	2 (6)	0 (0)	2 (8)	0.19
Statin, n (%)	12 (35)	18 (39)	8 (32)	0.83
Anticoagulation, n (%)	23 (68)	38 (83)	22 (88)	0.12
Echocardiography				
Left ventricular ejection fraction (%,) median (IQR)	60 (55-62)	60 (55-65)	60 (55-64)	0.47
Left atrial volume (mL), median (IQR)	64.9 (51.7-89.2)	67.1 (57.9-86.5)	80.8 (67.1-93.5)	0.14
E/e', median (IQR)	7.6 (6.8-9.4)	9.0 (7.5-11.5)	10.4 (9.3-13.5)	<0.001
Pulmonary artery systolic pressure (mmHg), median (IQR)	26.5 (21.0-31.5)	29.0 (26.0-33.2)	33.0 (28.8-38.0)	<0.001

IQR = interquartile range

electrophysiologists. A Baylis RF needle (Baylis, Burlington, MA) and an SL1 (Abbott, Chicago, IL) or Preface (Biosense Webster, New Brunswick, NJ) sheath were used for trans-septal puncture across the interatrial septum. Intravenous heparin was given with an activated clotting time goal of > 300 s. The Arctic Front Advance cryoballoon (Medtronic Inc., Minneapolis, MN) and lasso catheters were introduced into the LA using the Cryosheath (Medtronic Inc., Minneapolis, MN). Pulmonary vein venograms were performed to confirm balloon occlusion of each pulmonary vein ostium. Target temperatures were -30 to -55°C. Lesion duration evolved over time from two 4-min freezes per vein to two 3-min freezes per vein, with some operators limiting veins to a single 3-min application if time to effect was < 30 s. Entry and exit block were confirmed following

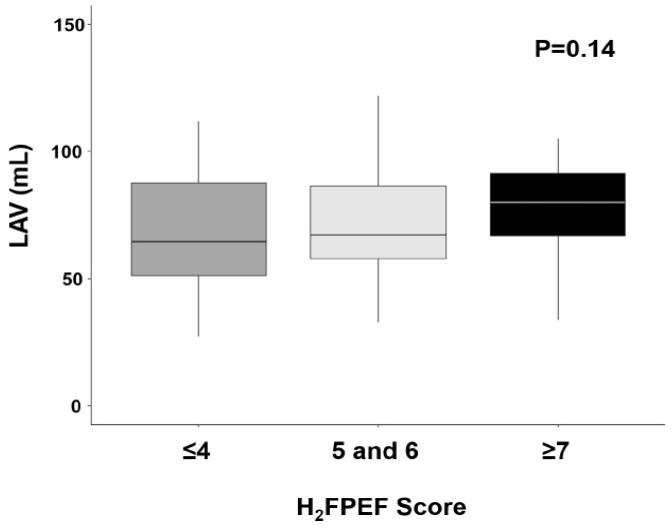

Figure 2: Left Atrial Volumes By H_2FPEF Score. LAV = left atrial volume.

cryoballoon ablation. Cardioversion to sinus rhythm was performed if patients remained in AF after ablation.

Rhythm surveillance included, at a minimum, a 3-week extended rhythm monitor at 3 months post-ablation, followed by 24- and 48-hour Holter monitors at 6 month intervals, transmissions from implanted devices, and tracings from Kardia smartphone monitors (AliveCore, Mountain View, CA). 12-lead electrocardiograms were also obtained at each clinic visit. Additional monitoring was performed among patients with symptoms suggestive of AF recurrence. Recurrence of AF was defined as AF lasting >30 seconds occurring, as outlined by the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society.[14] We determined AF recurrence at 12 months based on this definition and after a 3-month blanking period from the date of ablation, at which time anti-arrhythmic drugs were stopped.

Statistical Analysis

Clinical variables were compared by H_2FPEF score using Chi-square tests for categorical variables and one-way analysis of variance tests for continuous variables. Probabilities of HFpEF were determined based on the derivation report of the H_2FPEF score.[5] Given their skewed distributions, H_2FPEF scores and BNP were log-transformed and standardized (expressed as per 1-standard deviation) for all analyses. We evaluated the association of H_2FPEF scores and BNP levels (dependent variable) using linear regression. Multivariable logistic regression was used to assess the association of H_2FPEF scores and recurrence of AF at 12 months. Two-sided $\propto$ levels <0.05 were considered statistically significant. Statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing).

Results

Of 611 patients who underwent cryoballoon ablation between 2011 and 2016, 126 patients had echocardiograms within 1 year prior to the procedure that contained sufficient data to calculate the H_2FPEF score. Among this group, 21 patients were excluded due to a history of reduced LVEF. Of the final analytic cohort (n=105), the median H_2FPEF score was 5 (interquartile range [IQR]: 4-6), corresponding to >80% probability of HFpEF (Figure 1). Compared to patients with H_2FPEF scores ≤4 (n=34), patients with H_2FPEF scores of 5 and 6 (n=46) and ≥7 (n=25) had a higher prevalence of diabetes (≤4: 0% vs. 5 and 6: 9% vs. ≥7: 32%, P=0.001) and obstructive sleep apnea (≤4: 3% vs. 5 and 6: 17% vs. ≥7: 24%, P=0.05) (Table 1). As expected, based upon the components of the H_2FPEF risk score, patients with higher scores were more likely to have hypertension (≤4: 21% vs. 5 and 6: 63% vs. ≥7: 88%, P<0.001). There were no differences in rates of persistent AF (≤4: 41% vs. 5 and 6: 52% vs. ≥7: 44%, P=0.59) or duration of AF (≤4: 65±91 months vs. 5 and 6: 46±61 months vs. ≥7: 49±49 months, P=0.50) by H_2FPEF score. Of note, there was no difference in LAV by H_2FPEF score (Table 1; Figure 2). Patients with higher aggregate H_2FPEF scores had significantly higher levels of all component variables, including age, BMI, PASP, and LV filling pressures as measured by E/e'. There were trends of lower GFR and higher rates of female sex with increasing H_2FPEF scores (Table 1).

Associations of H_2FPEF Score with Natriuretic Peptides and AF Recurrence

Among 44 patients with BNP levels available prior to cryoballoon ablation, median BNP levels were similar across H_2FPEF scores: (≤4: 128 [IQR: 95-227] pg/mL vs. 5 and 6: 193 [IQR: 106-279] pg/mL vs. ≥7: 192 [IQR: 111-314] pg/mL, P=0.75). There was no association between H_2FPEF score and BNP levels on linear regression analysis (β coefficient per SD-increase in H_2FPEF score: 0.06, 95% CI: -0.32, 0.44, P=0.76).

At 12 months post-procedure, the overall rate of recurrence of AF was 21%. The rates of recurrence of AF by H_2FPEF score

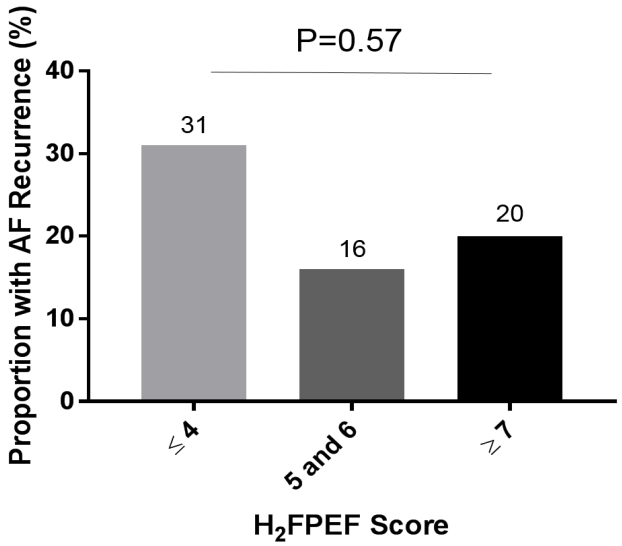

Figure 3: Recurrence Rates of Atrial Fibrillation at 12 Months By H_2FPEF Score. AF = atrial fibrillation.

groups were: ≤4 (31.2%, n=10), 5 and 6 (16.3%, n=7), and ≥7 (20.0%, n=5) (Figure 3). There was no association between H_2FPEF score and recurrence of AF at 12 months (OR per SD increase in log-transformed H_2FPEF score: 0.87, 95% CI: 0.54-1.40, P=0.57).

Discussion

In this analysis of a contemporary cohort of AF patients undergoing cryoballoon ablation, we describe the distribution of the H_2FPEF risk scores and BNP levels, and also evaluate the association of the H_2FPEF score with recurrence of AF post-procedure. The median H_2FPEF score in our study was 5, corresponding to a >80% probability of HFpEF. Patients with higher H_2FPEF scores represented an elderly cohort with higher prevalence of hypertension, diabetes, and obstructive sleep apnea and more adverse cardiac functional remodeling as indicated by higher PASP and E/e', but similar LA anatomic remodeling as evidenced by comparable LA volumes. There was no association of the H_2FPEF score with AF recurrence at 12 months in our study.

HFpEF remains a challenging syndrome to diagnose due to its heterogeneous clinical presentation and the inability of biomarkers or imaging studies to reliably identify patients burdened by this syndrome. Furthermore, AF and HFpEF often share overlapping symptoms, such as non-specific dyspnea and fatigue, which creates additional barriers to identify patients who truly possess both comorbidities.[15] Elevated BNP, a neurohormone of myocardial stretch, and increased LAV, an anatomic surrogate of presumed chronic pressure overload of the LA, are considered signs of HFpEF and serve as common inclusion criteria in clinical trials of HFpEF.[16, 17] However, the predictive abilities of BNP and LAV for diagnosing HFpEF were not strong enough for either variable to be incorporated into the H_2FPEF risk score.[5] In our study of AF patients undergoing cryoballoon ablation, the H_2FPEF risk score was not associated with BNP levels, and there was no significant difference in LA volumes across the spectrum of H_2FPEF scores. These findings suggest that the H_2FPEF risk score may be particularly useful for diagnosing HFpEF in the setting of pre-existing AF, as AF independently results in elevation in BNP and LA remodeling, which limits the clinical utility of these measurements. We demonstrate that AF patients undergoing ablation have high H_2FPEF scores, thus offering additive diagnostic information compared to natriuretic peptides or indices of LA anatomic remodeling. Given the high overall H_2FPEF scores among this population, our study suggests that AF patients who have symptoms requiring ablation represent a cohort that should be systematically screened for concomitant, occult HFpEF.

Optimal management strategies of AF in HFpEF remain unknown. Several concerning factors, including more advanced LA remodeling (i.e., LA fibrosis), high rates of persistent AF, and increased comorbidity burden have led to uncertainty regarding efficacy of AF ablation in HFpEF.[18] Further uncertainty has mounted given the potential for catheter ablation to increase LA pressure or result in stiff LA syndrome among a select AF population with multiple comorbidities,[19, 20] which may be poorly tolerated in the setting of HFpEF. Previous studies evaluating radiofrequency catheter ablation have suggested that the presence of diastolic dysfunction on echocardiography is associated with increased risk of AF recurrence.[21] Conversely, among a cohort patients with HFpEF, radiofrequency catheter ablation was associated with improvement in several indices of LV systolic and diastolic function and success was achieved in 73%, albeit after multiple procedures.[22] Additionally, AF radiofrequency ablation in HFpEF has been associated with reduced HF hospitalization compared with medical therapy.[23] The efficacy of cryoballoon catheter ablation in HFpEF has not been investigated in previous investigations. Additionally, these previous studies have typically defined HFpEF based on review of the electronic medical record, which may lack sensitivity and specificity in identifying true cases of HFpEF.[24] Our study, which defined risk of HFpEF on a continuum using a validated risk score, demonstrated that AF recurrence after cryoballoon ablation is similar regardless H_2FPEF risk score. Given the poor tolerance of loss of sinus rhythm among patients with HFpEF, these findings suggest that catheter ablation may be a reasonable therapeutic strategy, as its efficacy does not appear to be attenuated by increasing risk score. Indeed, dedicated randomized controlled trials evaluating the efficacy of catheter ablation for AF in HFpEF are needed to understand its role in mitigating symptoms and reducing clinical events in this vulnerable cohort.

Limitations

There are limitations to our study. Overall, the proportion of patients with data to calculate the H_2FPEF risk score was small, which introduces selection bias, raises the possibility that population may be underpowered to detect differences, and may account for the overall rates of AF recurrence in this study. Nonetheless, we were able to comprehensively quantify the H_2FPEF risk score in over 100 patients undergoing cryoballoon ablation and assess recurrence of AF. As the H_2FPEF score was initially derived in a population with dyspnea, its performance among an AF cohort undergoing ablation is unclear. However, participants with higher H_2FPEF scores in our study had increased rates of known risk factors for HFpEF, including diabetes and hypertension. BNP was drawn in a subset of the PVI cohort for clinical reasons, which may introduce bias in our findings of the lack of association between H_2FPEF scores and BNP. We did not assess the association of the H_2FPEF risk score and additional outcomes after ablation, including HF hospitalizations and symptom burden. Further investigations are required to evaluate the efficacy of catheter ablation with respect to these outcomes in HFpEF. Despite our comprehensive assessment of AF recurrence through clinic ECGs, Holter monitors, and smartphone and/or implantable device transmissions, the recurrence of AF in our study may have been underestimated due to the lack of continuous rhythm monitoring in all patients post-procedure. Continuous rhythm monitoring has become more frequent given recent technological advances. However, the method of AF detection in this study is reflective of guideline-prescribed clinical practice. Our procedural cohort was specific to cryoballoon-based PVI, as these patients are part of a prospectively maintained database, which may limit the generalizability of our findings. However, PVI using either cryoballoon or radiofrequency ablation has demonstrated similar long-term outcomes.[9] While the cryoballoon ablation protocol in our retrospective study was not specifically standardized, previous studies have demonstrated similar efficacies using a variety of procedural techniques.[25, 26] This study was performed among patients referred to a single tertiary care center

for PVI and thus our findings may not be generalizable to other AF populations. Specifically, the associations of the H_2FPEF risk score and recurrence of AF noted in our study may not be generalizable to older patients undergoing AF ablation or patients being treated through other methods (e.g., direct current cardioversion).

Conclusion

Among a cohort of AF patients undergoing cryoballoon ablation, H_2FPEF risk scores are generally high, and consideration of screening for occult HFpEF among this population may be warranted. While patients with high H_2FPEF risk scores were older and carried higher rates of diabetes, hypertension, and obstructive sleep apnea, there were no significant differences in BNP levels or LA volumes by H_2FPEF score. There was no association of the H_2FPEF risk score and AF recurrence at 12 months, suggesting efficacy of cryoballoon ablation even among patients with high H_2FPEF risk scores.

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