ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2017) **18**, 725–729
doi:10.1093/ehjci/jex038

Echocardiographic predictors of atrial fibrillation in patients with heart failure with preserved ejection fraction

Wesley T. O'Neal[1]*, Pratik Sandesara[1], Nikhil Patel[2], Sanjay Venkatesh[2], Ayman Samman-Tahhan[1], Muhammad Hammadah[1], Heval M. Kelli[1], and Elsayed Z. Soliman[3,4]

[1]Department of Medicine, Emory University School of Medicine, 101 Woodruff Circle, Woodruff Memorial Building, Atlanta, GA 30322, USA; [2]Department of Internal Medicine, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA; [3]Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA; and [4]Epidemiological Cardiology Research Center, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Received 5 January 2017; editorial decision 9 February 2017; accepted 17 February 2017; online publish-ahead-of-print 30 March 2017

Aims To determine if markers of diastolic dysfunction are associated with atrial fibrillation (AF) development among patients with heart failure with preserved ejection fraction (HFpEF).

Methods and results We examined the association of several echocardiographic measures of diastolic dysfunction with incident AF in 573 patients (mean age = 68 ± 9.5 years; 48% men; 79% white) with HFpEF from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) who were free of baseline AF. Echocardiograms were analysed at a core laboratory. Incident AF cases were identified by follow-up study electrocardiograms and review of relevant medical records through May of 2013. Over a median follow-up of 3 years, 40 patients developed AF (incidence rate = 2.2 per 100 person years). Increasing values of the E/A ratio [per 0.1 increase: hazard ratio (HR) = 1.11, 95% confidence interval (CI) = 1.06–1.17], left atrial volume (per 5 mL increase: HR = 1.13, 95% CI = 1.03–1.23), and left atrial area (per 5 cm^2 increase: HR = 1.51, 95% CI = 1.03–2.22) were associated with greater risk of AF. The risk of AF decreased with increasing peak A wave velocities (per 10 cm/s increase: HR = 0.83, 95% CI = 0.72–0.96). The risk of AF was not materially altered when peak A wave velocity was further adjusted for left atrial volume (HR = 0.83, 95% CI = 0.71–0.96) and area (HR = 0.83, 95% CI = 0.71–0.96). However, the associations of left atrial volume (HR = 1.10, 95% CI = 0.99–1.22) and area (HR = 1.48, 95% CI = 0.96–2.28) were no longer significant when accounting for peak A wave velocity.

Conclusion Diastolic parameters of left atrial function possibly are more important markers of AF risk than left atrial dilation in HFpEF.

Keywords echocardiogram • heart failure • preserved ejection fraction • atrial fibrillation

Introduction

Diastolic dysfunction and abnormal left ventricular relaxation, the hallmarks of heart failure with preserved ejection fraction (HFpEF), result in higher left atrial pressure and a subsequent need for effective atrial contraction to maintain normal left ventricular filling.[1] This compensatory measure of the left atrium to augment normal ventricular filling leads to left atrial dilation and dysfunction, providing the necessary substrate for atrial fibrillation (AF) propagation. This is supported by reports that have linked diastolic dysfunction,[2] and enlargement of the left atrium,[2–4] with incident AF in community-based cohorts.

Although the link between diastolic dysfunction and AF has been shown, it is yet to be established if AF risk varies by the severity of diastolic dysfunction in those with HFpEF. Such a finding could provide important prognostic information regarding AF risk in HFpEF,

* Corresponding author. Tel: 404-727-4724; Fax: 404-712-8335. E-mail: wesley.oneal@emory.edu

and identify a subgroup who possibly will benefit from aggressive measures, such as volume control to reduce left atrial pressure. Therefore, we examined the association of several echocardiographic measures of diastolic dysfunction with incident AF in patients with HFpEF from the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT).[5]

Methods

Study design and patients

TOPCAT was a multi-centre, international randomized, double blind, placebo-control study to examine the efficacy of spironolactone in patients with HFpEF. The design, inclusion criteria, and baseline characteristics of the trial have been published previously.[6,7] Briefly, 3445 patients with symptomatic HFpEF from 270 sites in 6 countries were enrolled between August 2006 and January 2012. The primary goal of the trial was to determine if spironolactone was associated with a reduction in the composite outcome of cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization in patients with HFpEF (e.g. documented ejection fraction ≥ 45%).

Echocardiographic measurements

A subset of patients enrolled in TOPCAT were consented to participate in the echocardiographic substudy. For the 27 sites that participated in this substudy, 1017 patients underwent detailed echocardiographic assessment and 935 imaging studies were suitable for quantitative analysis. Details of the design and baseline assessment of the echocardiographic substudy, including intraobserver reproducibility for the quantitative measures obtained, have been previously reported.[8] Quantitative measures on all were performed according to the American Society of Echocardiography (ASE) recommendations by dedicated analysts at the core laboratory, blinded to clinical information and randomized treatment assignment.[9] Doppler data were available in 607 (65%) of the 935 available studies. Of the remaining 328 (35%) patients, all Doppler measures were missing in 181 (19%) and tissue Doppler were missing in an additional 147 (16%) patients. We included TOPCAT patients with good-quality echocardiograms who did not have evidence of baseline AF.

The following echocardiographic parameters were included in this analysis: left ventricular mass, ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, E/A ratio, peak E wave velocity, peak A wave velocity, diastolic dysfunction grade, left atrial volume, left atrial width, and left atrial area.[9] Manual tracings of left ventricular endocardial borders were obtained at end-diastole and end-systole in the apical views, and respective volumes were derived using the modified biplane Simpson rule or Teicholz method, depending on image quality.[10] Left ventricular mass was computed by the ASE recommended formula for linear dimensions and indexed to body surface area.[9] Left atrial volume, width, and area were obtained using the biplane area-length method from apical views. Mitral inflow patterns (e.g. E/A ratio, peak E wave velocity, and peak A wave velocity) were obtained by pulsed wave Doppler from the apical 4-chamber view. Diastolic dysfunction grade was defined as mild, moderate, and severe, as previously described.[7]

Incident atrial fibrillation

Incident AF cases were identified by follow-up study electrocardiograms and review of relevant medical records. An events adjudication committee ascertained all incident cases. Paroxysmal, persistent, and permanent cases were grouped together. Follow-up was complete through May of 2013.

Baseline characteristics

Patients who participated in TOPCAT underwent a detailed baseline visit to obtain medical histories, and a physical examination was performed.[7] Age, gender, race, and smoking were obtained by self-reported history. Smoking was defined as the current use of cigarettes. Medical history for the following diagnoses was obtained by self-report and medical record review: diabetes, coronary heart disease, stroke, New York Heart Association Class, and prior heart failure hospitalization. Systolic blood pressure and body mass index were obtained by trained staff and laboratory data included serum creatinine. Medication data also were obtained during the initial study visit and the following were included in this analysis: aspirin, beta blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and statins.

Statistics

Baseline characteristics were compared by incident AF. Categorical variables were reported as frequency and percentage, while continuous variables were recorded as mean ± standard deviation. Statistical significance for categorical variables was tested using the Fisher's exact test and for continuous variables the Wilcoxon rank sum procedure was used. Cox regression was used to examine the risk of AF associated with each echocardiographic parameter. Multivariable models were constructed as follows: Model 1 was unadjusted; Model 2 adjusted for age, sex, race, smoking, systolic blood pressure, diabetes, body mass index, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, randomization group, New York Heart Association Class, coronary heart disease, and region of enrolment (Americas vs. Russia/Georgia). Region of enrolment (Americas vs. Russia/Georgia) was included in our multivariable model due to differences in the baseline characteristics and event rates observed between patients recruited from both regions.[11] A separate analysis was performed with region of enrolment excluded to determine if our effect estimates were materially altered by excluding this variable. To determine if the relationship between left atrial function (peak A wave velocity) was dependent on left atrial size (left atrial volume/area), a sensitivity analysis was performed with both measurements in the same model. Statistical significance was defined as $P < 0.05$. SAS Version 9.4 (Cary, NC, USA) was used for all analyses.

Results

A total of 573 patients (mean age = 68 ± 9.5 years; 48% men; 79% white) were included in this analysis. The baseline characteristics stratified by AF development are shown in Table 1. Patients who developed AF were older and less likely to be located in Russia/Georgia.

Over a median follow-up of 3.0 years (25th–75th percentiles = 1.9, 4.5 years), 40 patients (6.9%) developed AF [incidence rate = 2.2 per 100 person years, 95% confidence interval (CI) = 1.6–3.0]. The multivariable risks of AF associated with each echocardiographic parameter are shown in Table 2. Increasing values of the E/A ratio [per 0.1 increase: hazard ration (HR) = 1.11, 95% CI = 1.06–1.17], left atrial volume (per 5 mL increase: HR = 1.13, 95% CI = 1.03–1.23), and left atrial area (per 5 cm^2 increase: HR = 1.51, 95% CI = 1.03–2.22) were associated with an increased risk of AF. The risk of AF was shown to decrease with higher peak A wave velocities (per 10 cm/s increase: HR = 0.83, 95% CI = 0.72–0.96). When we excluded region of enrolment from our multivariable model, the results were not materially altered (data not shown).

Table 1 Baseline characteristics (*N* = 573)

Characteristic	Incident AF (*n* = 40)	No incident AF (*n* = 533)	*P*-value[a]
Age, years	74 ± 8.9	67 ± 9.4	<0.001
Male (%)	24 (60)	252 (47)	0.14
White (%)	31 (78)	424 (79)	0.69
Current smoker (%)	2 (5)	59 (11)	0.30
Diabetes (%)	20 (50)	224 (424)	0.33
Coronary heart disease (%)	15 (38)	226 (42)	0.62
Stroke (%)	3 (8)	39 (7)	1.0
Systolic blood pressure, mean ± SD, mmHg	130 ± 16	130 ± 15	0.77
Body mass index, mean ± SD, kg/m^2	33 ± 6.8	33 ± 7.6	0.41
Serum creatinine, mean ± SD, mg/dL	1.15 ± 0.30	1.10 ± 0.34	0.14
New York Heart Association Class III-IV (%)	15 (38)	183 (34)	0.73
Prior heart failure hospitalization (%)	24 (60)	373 (70)	0.21
Aspirin use (%)	28 (70)	390 (73)	0.71
Beta blockers (%)	33 (83)	432 (81)	1.0
ACEi/ARB (%)	31 (78)	443 (83)	0.39
Statin (%)	30 (75)	324 (61)	0.091
Spironolactone (%)	21 (53)	271 (51)	0.87
Russia/Georgia	5 (13)	197 (37)	0.0017

ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF, atrial fibrillation; HDL, high-density lipoprotein; SD, standard deviation.
[a]Statistical significance for continuous data was tested using the Wilcoxon rank sum and categorical data was tested using the Fisher's exact test.

When peak A wave velocity was further adjusted for left atrial volume and area, the multivariable risk of AF was not materially altered (Table 3). However, the associations of left atrial volume and area with AF were no longer significant when accounting for peak A wave velocity.

Discussion

In this analysis from TOCPAT, echocardiographic markers of diastolic dysfunction and left atrial structure and function were associated with AF in patients with HFpEF. Overall, the findings of this analysis suggest that diastolic parameters of left atrial function are more important markers of AF risk than left atrial dilation in HFpEF. Additionally, these data alert clinicians to a subset of HFpEF patients who are high risk for AF development.

Several reports have examined the association between echocardiographic measurements of diastolic dysfunction and AF. An examination of 840 patients in Olmstead County, Minnesota ≥ 65 years of age with echocardiographic data demonstrated that diastolic dysfunction (e.g. restrictive, pseudonormal, and abnormal relaxation) and increased left atrial volume were associated with incident AF.[2] An examination of 1655 patients also from Olmstead County, Minnesota reported an increased risk of AF with higher levels of left atrial volume.[3] Additionally, a report of 4480 participants from the community-based Cardiovascular Health Study linked higher Doppler E wave velocity and left atrial diameter with incident AF.[4]

The aforementioned reports clearly demonstrated that echocardiographic measurements of diastolic dysfunction and left atrial enlargement are associated with an increased risk for AF. However, the aforementioned studies were not limited to patients with HFpEF, and were unable to explore the potential for these measurements to vary in their prognostication of AF risk in this high-risk population. The current analysis demonstrated that measures of diastolic dysfunction and elevated left atrial pressure are associated with AF occurrence in HFpEF. Presumably, the increased left atrial pressure results in left atrial dilation, and prolonged exposure to high left atrial pressure results in remodelling to provide the necessary substrate for AF development.[12] Our findings also implicate left atrial function as an important predictor of AF in HFpEF patients, as higher peak A wave velocities were protective for AF development. Furthermore, peak A wave velocity remained a significant predictor of AF after accounting for left atrial volume and area, suggesting that left atrial function is a more important marker of AF risk than markers of left atrial dilation in patients with HFpEF.

Several reports have demonstrated that AF portends a poor prognosis among patients who have HFpEF.[13–15] An increased risk for hospitalization for worsening heart failure, cardiovascular death, and all-cause mortality has been reported in HFpEF patients who have AF.[13,14] Additionally, AF increases the risk of 30-day mortality after admission for decompensated HFpEF.[15] Therefore, the development of strategies to reduce the occurrence of AF in HFpEF is of paramount importance for the practicing clinician. The findings in this analysis provide practitioners with important information regarding AF risk in HFpEF. Possibly, aggressive strategies to reduce left ventricular filling pressure and left atrial hypertension among HFpEF patients will reduce the occurrence of AF, and decrease the likelihood of adverse events. Also, careful attention to persons with HFpEF who report clinical symptoms of AF (e.g. palpitations, rapid heart rate), especially among those with worsening diastolic parameters, potentially will warrant focused diagnostic efforts to identify AF events earlier to provide therapies that are known to prolong survival (e.g. anticoagulation). However, the clinical implications for our findings are

Table 2 Risk of atrial fibrillation

Echo parameter	*n*	Events	Model 1[a] HR (95% CI)	*P*-value	Model 2[b] HR (95% CI)	*P*-value
Left ventricular mass (per 10 unit increase)	535	39	1.02 (0.98–1.07)	0.29	1.01 (0.96–1.07)	0.69
Ejection fraction (per 5 unit increase)	573	40	1.23 (0.98–1.54)	0.077	1.18 (0.94–1.49)	0.15
Left ventricular end-diastolic volume (per 5 mL increase)	529	37	0.96 (0.92–1.02)	0.17	0.97 (0.91–1.04)	0.41
Left ventricular end-systolic volume (per 5 mL increase)	529	37	0.92 (0.83–1.01)	0.078	0.93 (0.83–1.04)	0.20
E/A ratio (per 0.1 increase)	423	35	1.10 (1.05–1.14)	<0.001	1.11 (1.06–1.17)	<0.001
Peak E wave velocity (per 10 cm/s increase)	435	37	1.10 (0.99–1.21)	0.082	1.10 (0.98–1.24)	0.11
Peak A wave velocity (per 10 cm/s increase)	423	35	0.86 (0.74–0.99)	0.041	0.83 (0.72–0.96)	0.011
Diastolic dysfunction grade						
Normal	69	5	Ref	—	Ref	—
Mild	92	4	0.46 (0.16–2.27)	0.46	0.48 (0.11–2.12)	0.33
Moderate	140	12	1.04 (0.37–2.95)	0.95	0.95 (0.30–2.96)	0.93
Severe	25	6	4.12 (1.25–13.57)	0.020	3.19 (0.82–12.39)	0.094
Left atrial volume (per 5 mL increase)	505	36	1.15 (1.07–1.25)	<0.001	1.13 (1.03–1.23)	0.0080
Left atrial width (per 1 cm increase)	535	39	1.86 (1.15–3.03)	0.012	1.52 (0.85–2.72)	0.16
Left atrial area (per 5 cm^2 increase)	486	35	1.69 (1.21–2.37)	0.0022	1.51 (1.03–2.22)	0.035

CI, confidence interval; HR, hazard ratio.
[a]Unadjusted.
[b]Adjusted for age, sex, race, smoking, systolic blood pressure, diabetes, body mass index, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, randomization group, New York Heart Association Class, coronary heart disease, and region of enrolment (Americas vs. Russia/Georgia).

Table 3 Risk of atrial fibrillation associated with left atrial structure and function

Echo parameter	Model[a] with left atrial volume HR (95% CI)	*P*-value	Model[a] with left atrial area HR (95% CI)	*P*-value
Peak A wave velocity (per 10 cm/s increase)	0.83 (0.71–0.96)	0.012	0.83 (0.71–0.96)	0.012
Left atrial volume (per 5 mL increase)	—	—	1.10 (0.99–1.22)	0.060
Left atrial area (per 5 cm^2 increase)	1.48 (0.96–2.28)	0.077	—	—

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, race, smoking, systolic blood pressure, diabetes, body mass index, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, beta blockers, randomization group, New York Heart Association Class, coronary heart disease, region of enrolment (Americas vs. Russia/Georgia).

speculative and further research is needed before changes in clinical practice are recommended.

The current study should be interpreted in the context of certain limitations. Some of the echocardiograms obtained in TOPCAT were clinical studies. Therefore, certain views or measures were missing for some patients. Additionally, it is possible that cases of AF were missed due to the time-dependent nature of certain events (e.g. paroxysmal vs. chronic). We also attempted to account for baseline differences in our multivariable models, but acknowledge the possibility of residual confounding.

In conclusion, diastolic parameters of left atrial function possibly are more important predictors of AF than left atrial dilation in HFpEF. Prolonged exposure to elevated left atrial pressure possibly results in the abnormal electrical remodelling necessary for AF development. Further studies are needed to determine if these diastolic parameters are able to be used to develop aggressive strategies to reduce the likelihood of AF development among patients who have HFpEF.

Acknowledgements

This article was prepared using Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) Research Materials obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the TOPCAT Study or the National Heart, Lung, and Blood Institute.

Conflict of interest: None declared.

Funding

Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under award number F32-HL134290. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Quinones MA. Assessment of diastolic function. *Prog Cardiovasc Dis* 2005;**47**:340–55.
2. Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR *et al*. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;**40**:1636–44.
3. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y *et al*. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 2001;**76**:467–75.
4. Rosenberg MA, Gottdiener JS, Heckbert SR, Mukamal KJ. Echocardiographic diastolic parameters and risk of atrial fibrillation: the Cardiovascular Health Study. *Eur Heart J* 2012;**33**:904–12.
5. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B *et al*. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–92.
6. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R *et al*. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J* 2011;**162**:966–72.e910.
7. Shah SJ, Heitner JF, Sweitzer NK, Anand IS, Kim HY, Harty B *et al*. Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail* 2013;**6**:184–92.
8. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF *et al*. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. *Circ Heart Fail* 2014;**7**:104–15.
9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al*. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;**7**:79–108.
10. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976;**37**:7–11.
11. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N *et al*. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
12. Iwasaki YK, Nishida K, Kato T, Nattel S. Atrial fibrillation pathophysiology: implications for management. *Circulation* 2011;**124**:2264–74.
13. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ *et al*. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;**47**:1997–2004.
14. McManus DD, Hsu G, Sung SH, Saczynski JS, Smith DH, Magid DJ *et al*. Atrial fibrillation and outcomes in heart failure with preserved versus reduced left ventricular ejection fraction. *J Am Heart Assoc* 2013;**2**:e005694.
15. Eapen ZJ, Greiner MA, Fonarow GC, Yuan Z, Mills RM, Hernandez AF *et al*. Associations between atrial fibrillation and early outcomes of patients with heart failure and reduced or preserved ejection fraction. *Am Heart J* 2014;**167**:369–75.e362.