Received: 13 February 2017 | Revised: 25 April 2017 | Accepted: 1 May 2017

DOI: 10.1002/clc.22736

WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

The association of QRS duration with atrial fibrillation in a heart failure with preserved ejection fraction population: a pilot study

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Background: Heart failure is a significant cause of morbidity and mortality, yet patient risk stratification may be difficult. Prevention or treatment of atrial fibrillation (AF) may be an important strategy in these patients that could positively affect their outcome. It has been demonstrated that in patients with systolic dysfunction, prolonged QRS duration (QRSd), an easily measured electrocardiographic parameter, is associated with AF.

Hypothesis: Prolonged QRSd is associated with an increase in prevalence of AF in patients with heart failure with preserved ejection fraction(HFPEF).

Methods: Between February 2006 and February 2009, 718 patients were discharged with a diagnosis of HF from the Dartmouth-Hitchcock Medical Center. Of these, 206 had EF ≥50% by echocardiography performed within 72 hours of admission. After exclusions, 82 patients remained, of which 25 had AF and 57 had sinus rhythm. Characteristics of the AF and sinus-rhythm patients were compared in this pilot study.

Results: After adjustment for age, prior diagnosis of HF, and left atrial area, there was a nonsignificant trend (odds ratio: 2.2, 95% CI of 0.3-17.2) for a QRSd >120 ms to be associated with AF.

Conclusions: Similar to results in patients with systolic dysfunction, patients with preserved EF may have an association between a prolonged QRSd and AF.

KEYWORDS

Atrial Fibrillation, Heart Failure, Diastolic Heart Failure, Heart Failure With Preserved Ejection Fraction, QRS Duration

1 | INTRODUCTION

Patients hospitalized for heart failure with reduced or preserved ejection fraction (HFrEF or HFpEF, respectively) have been shown to have similarly high rates of rehospitalization and mortality.[1] Electrocardiographic (ECG) parameters are readily available and inexpensive, and may thus be useful indicators of future morbidity and mortality in HF patients. For instance, it has been demonstrated that QRS duration (QRSd) is an independent risk factor for mortality in patients with either HFrEF or HFpEF.[1–3] In patients with HFpEF, QRSd has also been shown to predict a composite of adverse outcomes.[4,5]

Atrial fibrillation (AF) is another ECG finding that has important prognostic information in HF, increasing mortality[6,7] or a combined endpoint of mortality/rehospitalization,[8] regardless of EF. QRSd and AF may interrelate with regard to the development of AF, and also to prognosis once AF develops. In a study of 25,268 patients with left ventricular (LV) systolic dysfunction, 42% had a QRSd >120 ms, and QRSd was independently associated with AF.[9] In addition, irrespective of HF status, QRSd has been shown to be an independent predictor of morbidity and mortality among patients with AF.[10]

To our knowledge, there are no studies where the primary objective was to examine ECG findings in patients with HFpEF, with

and without AF. The purpose of this study was to examine whether QRSd is associated with AF prevalence in patients with HFpEF.

2 | METHODS

We performed a retrospective data collection and analysis. Between February 2006 and February 2009, 718 patients were discharged with the diagnosis of HF from the Dartmouth-Hitchcock Medical Center. Of these, 206 patients had EF ≥50% by echocardiography performed within 72 hours of admission.

After excluding patients with paced rhythm, atrial flutter, and severe valvular disease, and patients who did not meet Framingham criteria for HF, 82 patients remained and became our study cohort. Of these, 25 had AF on the admission ECG and 57 had sinus rhythm (SR). Clinical, echocardiographic, and ECG data were collected. QRSd, QRS axis, heart rate (HR), and corrected QT interval (QTc) were obtained from the automated measurement algorithm of the General Electric MUSE version 7 ECG system (GE Healthcare, Wauwatosa, WI).

2.1 | Statistical analysis

Characteristics of the AF and SR patients were compared using the χ^2 test, Student *t* test, and Wilcoxon rank-sum test where appropriate.

The primary variable, QRSd, was assessed as a dichotomous variable (QRSd > or <120 ms) for its association with AF, using multivariate logistic analysis. Age, prior diagnosis of HF, and left atrial (LA) area have been shown to be correlated with AF[11,12] and were adjusted for in our analysis. Additionally, we included HR, as it was significantly different in the baseline analysis and may mechanistically be associated with AF and QRSd (aberrant conduction). Creatinine, although statistically different between the SR and AF groups (lower in the AF group), was not adjusted for, as a low normal creatinine has not previously been recognized as a risk factor for AF.

This was an exploratory analysis of a well-defined cohort of patients with HFpEF. It was underpowered to prove the hypothesis that QRSd was a risk factor for AF, as this would have required a combined total of 3,592 patients with and without AF (assuming 90% power and 2-tailed α of 0.05).

3 | RESULTS

In this population of HFpEF patients, 30.5% had AF. Those with AF were notably older (mean age, 79 vs 69 years; $P = 0.001$; Table 1) and more likely to have a history of HF (80% vs 35%, $P < 0.001$; Table 1). Unexpectedly, AF patients also had lower creatinine on average (1.13 vs 1.91 μmol/L, $P = 0.023$; Table 1). Echocardiographically, AF patients had larger LA areas (30.0 vs 21.2 cm^2, $P < 0.001$; Table 1), but there was no significant difference in E/e′ or deceleration time.

Before adjustment (Figure 1, Table 2), there was no significant difference between the SR and AF groups in mean QRSd (SR 103.0 vs AF 99.1 msec, $P = 0.48$; Table 2) or in the proportion of patients with a QRSd >120 ms (SR 15.8% vs AF 20.0%, $P = 0.64$; Table 2). QTc was similar in the 2 groups (SR 442.8 ms vs AF 447.3 ms, $P = 0.58$). HR was greater in the AF group, and this approached statistical significance (SR 77.7 bpm vs AF 86.6 bpm, $P = 0.053$). A box plot of QRS duration for patients in both groups demonstrated overlap of the middle 50% and 95% ranges ($P = 0.59$; Figure 1).

After adjustment for age (odds ratio [OR]: 1.2), history of HF (OR: 31.5), LA area (OR: 1.6), and HR (OR 1.2), there was a nonsignificant trend towards the association of a QRSd >120 ms with AF (OR: 2.2, 95% CI: 0.3-17.2, Table 3).

TABLE 1 Baseline clinical and echocardiographic characteristics

Characteristics	Patients With HFpEF and SR	Patients With HFpEF and AF	*P* Value[a]
N	57 (69.5)	25 (30.5)	—
Age, y	68.9 ± 12.7	78.5 ± 9.5	0.001
Male sex	24 (42.1)	11 (44.0)	0.873
History of HF	20 (35.1)	20 (80.0)	<0.001
History of HTN	46 (80.7)	18 (72.0)	0.381
History of CAD	31 (54.4)	16 (64.0)	0.418
sCr, μmol/L	1.9 ± 1.7	1.1 ± 0.4	0.023
GFR, mL/min	51.4 ± 31.6	61.1 ± 23.1	0.172
Hgb, mmol/L	11.6 ± 2.3	11.9 ± 1.7	0.556
History of DM	32 (56.1)	11 (44.0)	0.311
BMI, kg/m^2	36.6 ± 22.5	30.4 ± 10.6	0.344
E/e′	13.6 ± 6.0	14.4 ± 6.5	0.594
LA area, cm^2	21.2 ± 5.3	30.0 ± 8.7	<0.001
DT, ms	213.0 ± 61.8	195.0 ± 59.7	0.225
Pro-BNP, pg/mL	4951 ± 7576	6019 ± 5789	0.598
SBP, mm Hg	135.3 ± 24.8	124.5 ± 22.0	0.065

Abbreviations: AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CAD, coronary artery disease; DM, diabetes mellitus; DT, deceleration time; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heat failure with preserved ejection fraction; Hgb, hemoglobin; HTN, hypertension; LA, left atrial; SBP, systolic blood pressure; sCr, serum creatinine; SD, standard deviation; SR, sinus rhythm.

Data are presented as n (%) or mean ± SD.

[a] Unadjusted.

TABLE 2 Electrocardiographic characteristics

Parameter	SR	AF	*P* Value, *t* Test
Mean QRSd, ms	99.1 ± 22.9	103.0 ± 23.3	0.476
% Patients with QRS >120 ms	15.8	20.0	0.641
QTc, ms	442.8 ± 32.8	447.3 ± 35.3	0.583
HR, bpm	77.7 ± 16.1	86.6 ± 24.2	0.053

Abbreviations: AF, atrial fibrillation; HR, heart rate; QRSd, QRS duration; QTc, corrected QT interval; SR, sinus rhythm.

4 | DISCUSSION

HF is a significant cause of morbidity and mortality, and accurate risk assessment is essential for improving patient outcomes.[13] AF is associated with an increased risk of mortality in HF patients,[6,7] and prevention or

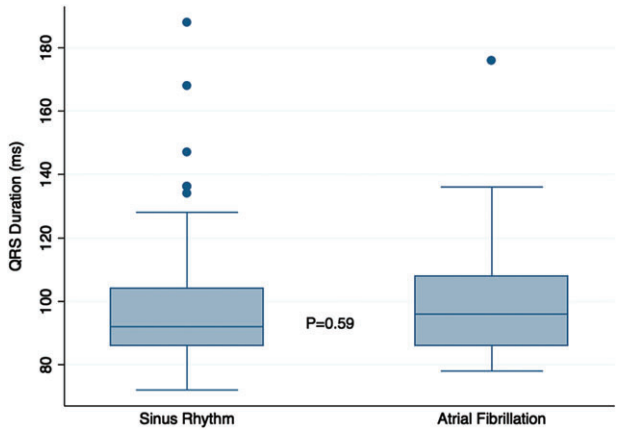

FIGURE 1 Box plot of QRSd, SR vs AF, with 50% and 95% ranges shown. Abbreviations: AF, atrial fibrillation; QRSd, QRS duration; SR, sinus rhythm.

TABLE 3 Multivariate analysis with discrete QRSd

Parameter	OR	95% CI	*P* Value
QRSd >120 ms	2.2	0.3-17.2	0.463
Age	1.2	1.1-1.3	0.006
History of HF	31.5	1.8-565.4	0.019
LA area	1.6	1.2-2.1	0.001
HR	1.1	1.0-1.2	0.002

Abbreviations: CI, confidence interval; HF, heart failure; HR, heart rate; LA, left atrial; OR, odds ratio; QRSd, QRS duration.

early detection of AF may be an effective way to reduce morbidity and mortality in these patients. However, "silent" AF poses a challenge with regard to early identification of patients for intervention.[14–16]

As our ability to detect asymptomatic AF is suboptimal in the absence of an implanted pacemaker, defibrillator, or loop recorder, QRSd might be a useful parameter to select patients for more aggressive screening. In a large study of patients with LV systolic dysfunction, QRSd was independently associated with AF.[9] Mechanistically, a prolonged QRSd could facilitate the onset of AF by causing ventricular dyssynchrony, which in turn can cause adverse ventricular and atrial remodeling due to a reduction in the peak rate of rise in the LV pressure, reduced diastolic filling time, and increased mitral regurgitation.[17,18] The purpose of our pilot study was to determine if QRSd is associated with AF prevalence in HFpEF.

In this study, age, prior history of HF, LA area, and HR were independent predictors of AF in HFpEF. The first 3 parameters have predicted AF in previous studies in different patient populations.[11,12] Though more patients with AF had a QRSd >120 ms (20.0%, vs 15.8% of those in SR), this trend did not reach statistical significance. Interestingly, the 17% prevalence of QRS prolongation >120 ms in our cohort is similar to the 18% prevalence in larger cohorts of HFpEF,[2,5] and it is a higher prevalence than in the general population.[2] This suggests that the pathophysiology of HFpEF (potentially via LV hypertrophy, ischemia, or other causes of fibrosis) contributes to QRS prolongation by causing fibrosis in the conduction system and/or myocardium.[19] QRSd as a surrogate for myocardial fibrosis might explain in part the graded risk for cardiovascular mortality for every 10-ms increase in QRSd, as observed in a cohort of 46,933 consecutive patients.[20]

We are aware of no other studies with a primary goal of assessing the relationship between QRSd and AF in HFpEF. In a study of 25,171 patients in the Swedish Heart Failure Registry, ≥4,783 patients had an EF of ≥50%, and 18% had a QRSd of ≥120 ms. In this study, AF prevalence was less frequent in those with a wide QRS—42% with a QRSd of ≥120 ms, vs 47% with a QRSd of <120 ms ($P < 0.001$). In this analysis of AF, patients with preserved and reduced EFs were combined and not separated by HF type.[2] In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial of 3,426 patients, the proportion of patients with a QRSd of ≥120 ms was again 18%. In this study, AF prevalence was more frequent in those with a QRSd of ≥120 ms (45%) vs those with a QRSd of <120 ms (33%; $P < 0.0001$).[5]

There are a number of differences between our patient population and the patients enrolled in TOPCAT, besides sample size. We identified patients at the time of hospitalization, whereas TOPCAT enrolled outpatients—although 72% of the TOPCAT patients had been hospitalized in the prior year. The EF cutoff was ≥50% in our study and ≥45% in TOPCAT, and TOPCAT excluded patients with AF and a mean ventricular rate >90 bpm.

4.1 | Study limitations

Our analysis is a retrospective, observational pilot study without the ability to establish a causal relationship. The lack of longitudinal data is also a limitation. The study was not powered to allow a definitive determination of an association between QRSd and AF in the HFPEF population. The limited sample size does also not allow for subset analysis or stratification by QRSd to study a threshold effect (e.g., >120 ms vs >140 ms).

We used retrospective application of the Framingham criteria for HF to validate the initial index diagnosis of HF. This relies on the accuracy of documentation of subjective and objective data at the time of admission. We controlled for known, measurable confounders, but there may be other confounders in this population for which we were unable to control.

5 | CONCLUSION

In this cohort of patients with HFpEF, we observed a nonsignificant trend for QRS prolongation (>120 ms) to be associated with AF. This finding is consistent with a large registry of patients with reduced EF and a smaller trial of HFpEF.[5,9] A large prospective trial is warranted to better understand whether ECG parameters including QRSd can predict the development of AF in HFPEF patients.

Conflicts of interest

The authors declare no potential conflicts of interest.

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How to cite this article: Gigliotti JN, Sidhu MS, Robert AM, et al. The association of QRS duration with atrial fibrillation in a heart failure with preserved ejection fraction population: a pilot study. *Clin Cardiol.* 2017;40:861–864. https://doi.org/10.1002/clc.22736