Impact of Atrial Fibrillation on Exercise Capacity and Mortality in Heart Failure With Preserved Ejection Fraction: Insights From Cardiopulmonary Stress Testing

Mohamed B. Elshazly, MD; Todd Senn, MD; Yuping Wu, PhD; Bruce Lindsay, MD; Walid Saliba, MD; Oussama Wazni, MD; Leslie Cho, MD

Background—Atrial fibrillation (AF) has been objectively associated with exercise intolerance in patients with heart failure with reduced ejection fraction; however, its impact in patients with heart failure with preserved ejection fraction has not been fully scrutinized.

Methods and Results—We identified 1744 patients with heart failure and ejection fraction ≥50% referred for cardiopulmonary stress testing at the Cleveland Clinic (Cleveland, OH), 239 of whom had AF. We used inverse probability of treatment weighting to balance clinical characteristics between patients with and without AF. A weighted linear regression model, adjusted for unbalanced variables (age, sex, diagnosis, hypertension, and β-blocker use), was used to compare metabolic stress parameters and 8-year total mortality (social security index) between both groups. Weighted mean ejection fraction was 58±5.9% in the entire population. After adjusting for unbalanced weighted variables, patients with AF versus those without AF had lower mean peak oxygen consumption (18.5±6.2 versus 20.3±7.1 mL/kg per minute), oxygen pulse (12.4±4.3 versus 12.9±4.7 mL/beat), and circulatory power (2877±1402 versus 3351±1788 mm Hg·mL/kg per minute) (P<0.001 for all comparisons) but similar submaximal exercise capacity (oxygen consumption at anaerobic threshold, 12.0±5.1 versus 12.4±6.0 mL/kg per minute; P=0.3). Both groups had similar peak heart rate, whereas mean peak systolic blood pressure was lower in the AF group (150±35 versus 160±51 mm Hg; P<0.001). Moreover, AF was associated with higher total mortality.

Conclusions—in the largest study of its kind, we demonstrate that AF is associated with peak exercise intolerance, impaired contractile reserve, and increased mortality in patients with heart failure with preserved ejection fraction. Whether AF is the primary offender in these patients or merely a bystander to worse diastolic function requires further investigation. (J Am Heart Assoc. 2017;6:e006662. DOI: 10.1161/JAHA.117.006662.)

Key Words: atrial fibrillation • exercise physiology • exercise testing • heart failure

Atrial fibrillation (AF) is the most common arrhythmia worldwide, with significant morbidity, mortality, and economic implications. It is estimated to affect >6 million Europeans1 and between 2.7 and 6.1 million US adults,2 increasing cost of care by 1.5-fold.1,2 AF is associated with a 5-fold increase in stroke, a 3-fold increase in heart failure, and a 2-fold increase in mortality and dementia.2,3 Moreover, patients with AF are more likely to have impaired social and physical functioning, impaired mental and general health, and reduced quality of life and exercise tolerance comparable to patients with heart failure or post–myocardial infarction.3 Although several studies have demonstrated improvement in symptoms, quality of life, and exercise capacity of patients with AF after restoration of sinus rhythm,4–6 large randomized trials have failed to show survival benefit of a rhythm control strategy.7 Hence, it is imperative to understand the physiologic and hemodynamic consequences associated with AF in individual patients before considering a rhythm versus rate control strategy of treatment.

From the Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH (M.B.E., Y.W., B.L., W.S., O.W., L.C.); Division of Cardiology, Department of Medicine, Weill Cornell Medical College–Qatar, Education City, Doha, Qatar (M.B.E.); Department of Cardiovascular Medicine, Columbia Heart, Columbia, SC (T.S.); and Department of Mathematics, Cleveland State University, Cleveland, OH (Y.W.).

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Correspondence to Leslie Cho, MD, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave, Desk JB-1, Cleveland, OH 44195. E-mail: choll@ccf.org

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Exercise Capacity and Mortality in HFpEF and AF

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Clinical Perspective

What Is New?

- In the largest study of its kind and after using inverse probability of treatment weighting, we found that atrial fibrillation (AF) is associated with impaired peak exercise capacity, but not submaximal exercise capacity, in patients with heart failure with preserved ejection fraction (HFpEF).
- AF is associated with impaired contractile reserve during exercise in patients with HFpEF, evident by lower peak exercise systolic blood pressure.
- AF is associated with increased total mortality in HFpEF, regardless of good heart rate control.

What Are the Clinical Implications?

- Patients with HFpEF with AF have worse peak exercise capacity and prognosis.
  - Whether AF is in itself responsible for these worse outcomes or merely a sign of worse diastolic function needs to be further investigated.
- A precision medicine approach using cardiopulmonary stress testing may be beneficial to objectively assess the physiologic and hemodynamic consequences of restoring normal sinus rhythm in patients with HFpEF with AF.
- This may be valuable in complex patients with a myriad of coexisting cardiopulmonary diseases, where aggressive rhythm control can be directed only to those who show objective evidence of improved exercise capacity in sinus rhythm.

In patients with heart failure with reduced ejection fraction (HFrEF), AF has been associated with worse exercise capacity, and some studies have suggested they benefit from a rhythm control strategy. Although the prevalence of AF in patients with heart failure with preserved ejection fraction (HFpEF) is similar to that in HFrEF, the impact of AF on exercise capacity in HFpEF has not been well scrutinized. In this study, we sought to compare exercise parameters of patients with HFpEF with and without AF undergoing cardiopulmonary stress testing (CPX) and to assess whether AF is associated with increased mortality.

Methods

Study Population

We identified 1744 consecutive adult patients with EF ≥50%, measured within 6 months, and a clinical diagnosis of heart failure (<85% were referred from heart failure clinics) referred for CPX at the Cleveland Clinic (Cleveland, OH) from January 1, 1995, through January 15, 2013. Data were extracted from the CPX Laboratory database. Cleveland Clinic’s institutional review board approved the study, and informed consent was waived.

Patients were divided into 2 groups: (1) patients with AF, defined as those with a documented history of AF, and the presenting rhythm at the time of CPX had to be AF; and (2) patients without a history of AF and without AF at the time of CPX (non-AF). Patients were divided into 3 subgroups based on the cause of their HFpEF: (1) coronary artery disease, (2) nonischemic, and (3) valvular heart disease. Coronary artery disease was defined as having >70% obstruction of a major epicardial vessel or history of a myocardial infarction. Valvular heart disease was defined as having severe valvular disease thought to be the cause of the patient’s symptoms by the ordering physician. Nonischemic cause was defined as having HFpEF that could not be explained by coronary or valvular heart disease, which included patients with hypertrophic cardiomyopathy.

Exercise Protocol

Patients underwent maximal, symptom-limited metabolic testing with either treadmill or exercise bike using the Bruce, modified Bruce, Cornell, Naughton, or modified Naughton protocol. The choice of protocol was based on an estimation of the patient’s capacity, and tailored to have the patient undergo a fatigue-limited exercise duration of 8 to 12 minutes. All patients were clinically stable at the time of testing, fasted for a minimum of 4 hours before testing, and completed the stress test protocol. Blockers were routinely held 12 hours before testing, whereas no other medications were routinely held unless specified by the prescribing physician.

The gas exchange data were collected throughout the test with a metabolic cart. Patients were encouraged to exercise until limited by symptoms, and the use of handrails was allowed for balance only. Blood pressure, heart rate (HR), respiratory rate, electrocardiogram changes, symptoms, and any arrhythmias were recorded at baseline and during each stage of exercise and recovery. We also examined change in HR, calculated as follows: peak HR—resting HR. We also examined change in systolic blood pressure, calculated as follows: peak SBP—resting SBP. Gas exchange variables were measured after steady state at rest and every 30 seconds during exercise and included CO2 production (VCO2), oxygen consumption (VO2), and minute ventilation. We calculated the ventilatory equivalent of CO2 or ventilatory efficiency (VE/VCO2) at peak exercise. VO2 at anaerobic threshold was measured by V-slope method or by the inspection of ventilatory equivalents. The respiratory exchange ratio was defined as the value of VCO2/VO2 at peak exercise. Circulatory power, a surrogate for cardiac power, was calculated as the product of peak VO2 and peak SBP (mm Hg·mL/kg per minute). Peak oxygen pulse, a surrogate for stroke volume, was calculated as peak VO2 (mL/min) divided by peak HR (mL/beat).
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Statistical Analysis
Patient characteristics and medications, chosen on the basis of known clinical association with AF and availability in our database, and stress test parameters were compared between the AF and non-AF patient groups. Patient characteristics included age, sex, weight, body mass index, left ventricular ejection fraction (LVEF), cause of heart failure, history of hypertension, diabetes mellitus, hypercholesterolemia, and history of cigarette smoking. Medications included α blockers, β blockers, angiotensin-converting enzyme inhibitors, digitalis, diuretics, and inotropes (dobutamine or milrinone). The Student t test was used to compare continuous normally distributed variables, reported as mean±SD. The χ² test was used to compare categorical data. P<0.05 was considered statistically significant.

Given significant variability in clinical characteristics, LVEF, and medications between the AF and non-AF groups, we performed inverse probability of treatment weighting (IPTW) to balance both groups. IPTW is a well-validated propensity score method of reducing bias when performing comparative analyses of patient groups in retrospective studies. This propensity score method is available in the R package twang (twang: Toolkit for Weighting and Analysis of Nonequivalent Groups) and was used to estimate inverse probability of treatment weights. All the variables were balanced after IPTW, except for age, sex, HFrEF cause, hypertension, and β blocker use. Subsequently, we adjusted for these unbalanced variables in a weighted linear regression model to compare CPX exercise parameters between the AF and non-AF patient groups.

We used weighted Kaplan-Meier curves with log-rank P values to compare 8-year total mortality between the matched AF and non-AF groups in patients in whom mortality data were available. Mortality status was obtained using the Social Security Death Index. Because of limitations to the current database, patients’ mortality status was censored through November 1, 2011.

All analyses, as described above, were performed using SAS System version 9.2 and R version 2.15.1. P<0.05 is considered statistically significant.

Results
Study Population Characteristics
A summary of baseline demographics, medications, LVEF, and cause of heart failure in our study population is shown in Table 1. Patients with HFrEF with AF were older and had a higher prevalence of hypertension, higher use of β blockers and digitalis, and lower LVEF compared with patients without AF.

CPX Parameters in AF Versus Non-AF Propensity-Matched Cohorts
After IPTW, 61% of the entire population were men, weighted mean age was 57.6±14 years, and weighted mean LVEF was 58±5.9%. Nonischemic cause was the most common cause of HFrEF (68%). The prevalence of comorbidities and medication use after weighting is shown in Table 2.

After adjusting for unbalanced variables from IPTW (age, sex, cause of HFrEF, hypertension, and β blocker use), a weighted linear regression model was used to compare CPX parameters between AF and non-AF patient groups. There were significant differences in the CPX parameters between the 2 patient groups (Table 3). Mean respiratory exchange ratio was ≥1.1 and similar in the AF and non-AF groups (P=0.053), suggesting that the differences in CPX parameters were not attributable to submaximal peak exercise and that all patients reached peak exercise capacity regardless of protocol. Weighted mean±SD of peak VO₂ was 18.5±6.2 mL/kg per minute in the AF group versus 20.3±7.1 mL/kg per minute in the non-AF group (P<0.001) (Table 3 and Figure 1). We also found VE/VCO₂ to be higher in patients with AF versus patients without AF (35.8±7.2 versus 34.2±6.9; P<0.001) (Table 3 and Figure 1). Moreover, patients with AF had lower peak metabolic equivalents (5.3±1.8 versus 5.8±2.0; P<0.001), peak oxygen pulse (12.4±4.3 versus 12.9±4.7 mL/beat; P<0.001), and peak circulatory power (2877±1402 versus 3351±1788 mm Hg·mL/kg per minute; P<0.001) (Table 3 and Figure 1). On the other hand, VO₂ at anaerobic threshold was similar between both groups (12.4±6.0 mL/kg per minute; P=0.3 in AF versus non-AF, respectively), suggesting similar submaximal exercise capacity.

HR and SBP responses to exercise were also examined. Although the resting HR was higher in patients with AF (70±14 versus 68±14 beats per minute [bpm]; P<0.001), peak HR was similar in both groups (130±29 versus 134±42 bpm; P=0.2), thus yielding lower change in HR (59±27 versus 66±42 bpm; P=0.006) in patients with AF (Table 3 and Figure 2). Patients with AF had a lower SBP than patients without AF, both at rest (122.7±20.5 versus 125.0±21.5 mm Hg; P<0.001) and peak exercise (150±35.4 versus 160.3±51.3 mm Hg; P<0.001), yielding a lower change in SBP (27.3±28.1 versus 35.3±49.4 mm Hg; P<0.001) (Table 3 and Figure 2).

Mortality in AF Versus Non-AF Patient Groups
We analyzed total mortality in a subgroup of patients who had mortality data available through the Social Security Death Index. After IPTW, there was higher mortality in the AF versus non-AF group (15.9% versus 12.9%; log-rank P<0.001) at 8 years of follow-up, with early curve separation (Figure 3).
In this well-matched weighted analysis of patients with HFpEF with a mean LVEF of 58%, we demonstrate that patients with AF with controlled HRs (mean resting HR, 70 bpm; and peak HR, 130 bpm) had impaired peak exercise tolerance, reflected in lower VO2, lower oxygen pulse, and lower circulatory power at peak exercise. However, their submaximal exercise capacity was similar to that of patients without AF. Moreover, AF was associated with impaired ventilatory efficiency (higher VE/VCO2) and increased total mortality at 8 years, with early

Table 1. Baseline Demographics, Clinical Characteristics, and Exercise Parameters in the Overall Study Population

| Variable                        | All (N=1744) | Non-AF (n=1505) | AF (n=239) | P Value |
|---------------------------------|--------------|-----------------|------------|---------|
| Age, y                          | 51.2±15.4    | 50±15.4         | 58.7±13.1  | <0.001  |
| Male, n (%)                     | 1029 (59.1)  | 875 (58.3)      | 154 (64.4) | 0.085   |
| Weight, kg                      | 85.9±20      | 85.7±20.1       | 86.8±19.9  | 0.361   |
| BMI, kg/m²                      | 28.9±5.7     | 29±5.7          | 28.7±5.7   | 0.568   |
| Diagnosis, n (%)                |              |                 |            | 0.983   |
| CM-CAD                          | 143 (8.2)    | 123 (8.2)       | 20 (8.4)   | 1       |
| CM-valvular                     | 372 (21.3)   | 322 (21.4)      | 50 (20.9)  | 0.935   |
| CM-nonischemic                  | 1229 (70.5)  | 1060 (70.4)     | 169 (70.7) | 0.991   |
| LVEF, %                         | 59.7±6.2     | 60±6.3          | 57.9±5.5   | <0.001  |
| Hypertension, n (%)             | 872 (50.1)   | 724 (48.2)      | 148 (61.9) | <0.001  |
| Hypercholesterolemia, n (%)     | 768 (44)     | 650 (43.2)      | 118 (49.4) | 0.086   |
| Diabetes mellitus, n (%)        | 182 (10.4)   | 153 (10.2)      | 29 (12.1)  | 0.418   |
| History of smoking, n (%)       | 728 (41.7)   | 621 (41.3)      | 107 (44.8) | 0.342   |
| Metabolic stress parameters     |              |                 |            |         |
| Peak VO2, mL/kg per minute      | 21.6±7.5     | 22.1±7.6        | 18.5±6.2   | <0.001  |
| VE/VCO2                         | 33.6±6.5     | 33.1±6.3        | 35.8±7.2   | <0.001  |
| RER                             | 1.225±1.95   | 1.242±2.098     | 1.121±0.115| 0.354   |
| METS                            | 6.2±2.1      | 6.3±2.2         | 5.3±1.8    | <0.001  |
| Resting HR, bpm                 | 67.9±13.6    | 67.5±13.5       | 70.3±13.9  | 0.001   |
| Peak HR, bpm                    | 139.4±46.4   | 140.9±48.4      | 129.7±29.2 | <0.001  |
| ΔHR, bpm                        | 71.5±46.3    | 73.4±48.3       | 59.4±27.4  | <0.001  |
| Resting SBP, mm Hg              | 123.8±20.6   | 124±20.6        | 122.7±20.5 | 0.314   |
| Peak SBP, mm Hg                 | 159.4±48.9   | 160.9±50.6      | 150±35.4   | <0.001  |
| ΔSBP, mm Hg                     | 35.6±46.9    | 36.9±49.1       | 27.3±28.1  | <0.001  |
| VAT, mL/kg per minute           | 13.4±6.1     | 13.8±6.2        | 12±5.1     | <0.001  |
| Peak oxygen pulse, mL/beat      | 13.319±4.789 | 13.469±4.846    | 12.377±4.308| 0.001   |
| Circulatory power, mm Hg·mL/kg per minute | 3536.2±1828.1 | 3641±1866.1 | 2877.4±1402.2 | <0.001 |

Data are given as mean±SD unless otherwise indicated. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CM, cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; METS, metabolic equivalent; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, VO2 at anaerobic threshold; VE/VCO2, ventilatory efficiency; VO2, oxygen consumption; Δ, change.

Discussion

In this well-matched weighted analysis of patients with HFpEF and AF, we demonstrate that patients with AF with controlled HRs (mean resting HR, 70 bpm; and peak HR, 130 bpm) had impaired peak exercise tolerance, reflected
curve separation. Our study, the largest of its kind, provides preliminary evidence that patients with HFpEF with AF represent a sicker substrate with worse exercise capacity and higher mortality. These results open the door for future studies to examine whether these findings are primarily attributable to AF or attributable to worse diastolic function, where AF serves as a bystander to a sicker substrate. This will eventually help us determine whether patients with HFpEF may benefit from a rhythm control strategy and if CPX may assist in identifying those who could benefit the most.

**AF and Circulatory Inefficiency at Peak Exercise**

During the past few decades, several invasive and noninvasive hemodynamic studies have shed light on the role played by atrial systole and normal sinus rhythm in maintaining adequate cardiac output, particularly during exercise and in patients with heart failure. Inadequate cardiac output during AF has been attributed to several mechanisms, including loss of atrial systole, irregular ventricular rhythm with beat-to-beat variability, and impaired ventricular filling time. Each of these mechanisms is of particular importance at peak exercise when maximal contractile reserve is used. As such, AF has been associated with exercise intolerance in patients with lone AF and more notably in those with associated heart disease. Some studies have shown that peak VO2, a surrogate of maximal aerobic capacity, is 10% to 20% lower in patients with HFrEF with AF. In addition, surrogates of cardiac output at peak exercise, such as oxygen pulse (a surrogate for stroke volume), circulatory power (a surrogate for cardiac power), and SBP, have been shown to be lower in patients with HFrEF with AF. Although the prevalence of AF in patients with HFrEF and HFpEF is similar, the impact of AF on exercise capacity in patients with HFpEF has not been examined, except in small studies. In these studies, there were significant differences in the clinical characteristics of the AF versus non-AF patient groups, and multivariable adjusted analyses were not routinely performed. In this large well-matched propensity analysis, we demonstrate that AF in patients with HFpEF is associated with lower peak VO2, oxygen pulse, and circulatory power at peak exercise; however, AF did not have an effect on VO2 at anaerobic threshold. Thus, our findings suggest that peak exercise capacity, but not submaximal exercise capacity, is impaired in patients with

| Table 2. Comparison of Baseline Demographics and Clinical Characteristics Using Inverse Probability of Treatment Weighting |
|---------------------------------------------------------------|
| **Variable** | **All (N=1744)** | **Non-AF (n=1505)** | **AF (n=239)** | **P Value** |
| Age, y | 57.6±13.9 | 56.4±14.5 | 58.7±13.1 | 0.013 |
| Male, n (%) | 284 (60.8) | 130 (57) | 154 (64.4) | 0.002 |
| BMI | 28.7±5.6 | 28.8±5.6 | 28.7±5.7 | 0.938 |
| Cause | | | | |
| CM-CAD, n (%) | 48 (10.3) | 28 (12.4) | 20 (8.4) | 0.006 |
| CM-valvular, n (%) | 100 (21.5) | 50 (22.2) | 50 (20.9) | 0.512 |
| CM-nonischemic, n (%) | 318 (68.1) | 149 (65.4) | 169 (70.7) | 0.017 |
| LVEF, % | 58.2±5.9 | 58.6±6.2 | 57.9±5.5 | 0.058 |
| Hypertension, n (%) | 277 (59.4) | 129 (56.7) | 148 (61.9) | 0.028 |
| Hypercholesterolemia, n (%) | 228 (48.8) | 110 (48.2) | 118 (49.4) | 0.628 |
| Diabetes mellitus, n (%) | 60 (12.9) | 31 (13.7) | 29 (12.1) | 0.333 |
| History of smoking, n (%) | 208 (44.6) | 101 (44.4) | 107 (44.8) | 0.873 |
| Medications, n (%) | | | | |
| β Blocker | | | | |
| ACE inhibitor | 139 (29.8) | 71 (31.3) | 68 (28.5) | 0.212 |
| β Blocker | 307 (65.8) | 143 (62.9) | 164 (68.6) | 0.01 |
| Digitalis | 88 (18.9) | 39 (17.3) | 49 (20.5) | 0.088 |
| Diuretic | 198 (42.4) | 96 (42.1) | 102 (42.7) | 0.744 |
| Other inotropes | 8 (1.8) | 3 (1.5) | 5 (2.1) | 0.328 |

Numerical data were summarized as weighted mean±weighted SD. Categorical data were presented as weighted sample size (weighted percentage). Weighted 2-sample t test or χ² test was used to compare numerical data or categorical data between AF and non-AF groups. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CM, cardiomyopathy; LVEF, left ventricular ejection fraction.
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Table 3. Exercise Parameter Comparison Using Inverse Probability Weighting

| Variable                          | All (N=1744) | Non-AF (n=1505) | AF (n=239) | P Value |
|-----------------------------------|-------------|-----------------|------------|---------|
| Peak VO₂, mL/kg per minute        | 19.3±6.7    | 20.3±7.1        | 18.5±6.2   | <0.001  |
| VE/VCO₂                           | 35.1±7.1    | 34.2±6.9        | 35.8±7.2   | <0.001  |
| RER                               | 1.2±1.5     | 1.2±2.1         | 1.1±0.1    | 0.0528  |
| METS                              | 5.5±1.9     | 5.8±2           | 5.3±1.8    | <0.001  |
| HR, bpm                           |             |                 |            |         |
| At rest                           | 69.3±13.9   | 68.2±13.9       | 70.3±13.9  | <0.001  |
| At peak                           | 131.6±35.7  | 133.6±41.5      | 129.7±29.2 | 0.1919  |
| Δ HR, bpm                         | 62.4±35.2   | 65.5±41.7       | 59.4±27.4  | 0.0063  |
| SBP, mm Hg                        |             |                 |            |         |
| At rest                           | 123.8±21    | 125±21.5        | 122.7±20.5 | <0.001  |
| At peak                           | 155±44.1    | 160.3±51.3      | 150±35.4   | <0.001  |
| Δ SBP, mm Hg                      | 31.2±40.1   | 35.3±49.4       | 27.3±28.1  | <0.001  |
| VAT, mL/kg per minute             | 12.2±5.6    | 12.4±6          | 12±5.1     | 0.312   |
| Peak oxygen pulse, mL/beat        | 12.6±4.5    | 12.9±4.7        | 12.4±4.3   | <0.001  |
| Circulatory power, mm Hg/mL/kg per minute | 3108.1±1617.3 | 3351.4±1787.9 | 2877.4±1402.2 | <0.001 |

Data were expressed as weighted mean±weighted SD. P values were calculated using a weighted linear regression model. The model was adjusted for age, sex, diagnosis, hypertension, and β blocker, which were not balanced after inverse probability weighting. AF indicates atrial fibrillation; bpm, beats per minute; HR, heart rate; METS, metabolic equivalent; RER, respiratory exchange ratio; SBP, systolic blood pressure; VAT, VO₂ at anaerobic threshold; VE/VCO₂, ventilatory efficiency; VO₂, oxygen consumption; Δ, change.

HFrEF who have AF compared with those who do not have AF, despite adequate rate control.

AF and Ventilatory Inefficiency During Exercise
The VE/VCO₂ slope is a measure of ventilatory efficiency during exercise that evaluates the degree of increase in minute ventilation in relation to the metabolic and anaerobic production of CO₂.²⁻¹²,²⁷ Many studies have confirmed the prognostic impact of VE/VCO₂ in patients with heart failure, in whom a value >35 has been associated with worse prognosis, and have argued for its superiority over peak VO₂.¹³,²⁷ However, the value of VE/VCO₂ in AF is contentious, with some studies showing AF association with a higher VE/VCO₂²³ and others showing no association.⁹ In our study, we show that AF in patients with HFrEF is associated with significantly higher VE/VCO₂. This suggests that these patients have more physiologic pulmonary dead space as a product of the interaction of many complex cardiac and pulmonary factors.¹² This, coupled with an increase in metabolic and anaerobic production of CO₂, largely determines impaired ventilatory efficiency in patients with AF and HFrEF.

HR and SBP Response During Exercise in AF
In our study, patients with AF had a higher resting HR but similar peak HR, despite adjusting for rates of medication use, suggesting adequate rate control in our AF patient population. Most prior studies have shown that patients with AF have a higher peak HR, which is likely a result of activation of sympathetic compensatory mechanisms to low cardiac output.⁸,⁹,¹⁷ In contrast, only 1 study showed that peak HR was not different between AF and non-AF in patients with HFrEF,²⁵ similar to our study, suggesting that the implementation of a strict rate control strategy in these patients may inhibit the essential normal compensatory response required to maintain adequate perfusion at peak exercise.

The increase in SBP during exercise is a normal physiologic process in healthy individuals, reflecting an increase in cardiac output for the most part and peripheral vascular resistance to a lesser extent.¹² Although most studies have shown AF association with lower peak SBP attributable to loss of atrial contractility,⁹,²¹,²⁵ some have shown no association.⁸ Some have also suggested that peak exercise SBP may account for up to 20% of the variance in maximal oxygen uptake in patients with AF.²¹ In our study, mean peak SBP was lower in patients with AF compared with patients without AF by 10 mm Hg, despite having similar resting SBP; this finding suggests impaired contractile reserve during exercise.

Applying a precision medicine approach that uses CPX to objectively compare exercise capacity during rate-controlled AF with that during sinus rhythm after cardioversion may be more effective in identifying those unique patients who benefit from rhythm control. This may be particularly valuable in complex patients with a myriad of coexisting
cardiopulmonary diseases, in whom AF burden may be either contributing significantly to exercise intolerance or merely a bystander to a sicker substrate. This approach may allow for better targeting of patients who would benefit most from maintaining sinus rhythm versus those in whom rate control may be sufficient.

**AF and Total Mortality**

For many years, we have wondered if a rhythm control strategy is associated with survival benefit. Although the largest trial to date in the preablation era, the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial, has shown no survival benefit, we are still waiting for long-term results of more contemporary trials that examine this question in the era of ablation. In addition to the detrimental effects of AF on exercise capacity, our study also found a significant survival difference in patients with HfP EF with versus without AF with early curve separation. Although the lack of data on the cause of mortality is a limitation of our study, total mortality is the ultimate outcome of clinical significance. Whether this mortality difference is related primarily to AF or is a reflection of worse diastolic function, where AF is a bystander, is a question that needs to be addressed in future studies and trials.

**Limitations**

This is a retrospective, single-center study using a database registry. Patients referred for CPX at a tertiary referral hospital are not representative of the community at large, and may
represent a referral bias. We performed propensity matching using IPTW to adjust for baseline variables; however, IPTW is also subject to bias of the variables in the database. Propensity matching will certainly miss any unmeasured variables\textsuperscript{18,30} that may be of importance, such as history of pulmonary disease, kidney disease, anemia, and cancer. Although our study lacked imaging and hemodynamic data on diastolic function, we have matched for many diastolic function associated clinical variables, LVEF, and medications. This would make the matched groups in our study more comparable in terms of diastolic function, particularly compared with prior studies looking at this patient population. Data on the duration of HFpEF, AF, and the type of AF (paroxysmal versus persistent versus permanent) were also not available in our database. We also lack data on the use of antiarrhythmic medications, such as amiodarone; however, patients in the AF group were required to be in AF at the time of CPX, thus decreasing the likelihood that a significant proportion of them were taking long-standing antiarrhythmic therapy. The difference in total mortality between the AF and non-AF patient groups appears to be larger than the absolute difference in CPX exercise variables, suggesting that it may be slightly exaggerated by a noncardiovascular cause.

Conclusions
AF is independently associated with peak exercise intolerance and mortality in patients with HFpEF, regardless of good rate control. Whether AF is the primary offender in these patients or merely a bystander to a worse diastolic function requires

\textbf{Figure 2.} Heart rate (HR) and systolic blood pressure (SBP) response to exercise in patients with heart failure with preserved ejection fraction with vs without atrial fibrillation (AF) after inverse probability weighting. bpm indicates beats per minute; NS, nonsignificant (P = 0.19).
Figure 3. Weighted survival analysis in patients with vs without atrial fibrillation (AF). Mortality data were gathered from the Social Security Death Index. Log-rank P<0.01 was considered statistically significant.

Further investigation. Furthermore, implementing a personalized medicine approach using CPX to examine the physiologic and hemodynamic consequences of AF in individual patients may help identify those who may benefit more from a rhythm control strategy, where AF is the primary offender for worse exercise capacity.

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Disclosures
None.

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