ORIGINAL RESEARCH

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±6.0mL/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 Europeans[1] 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.).

A moderated oral abstract was presented at the American College of Cardiology Scientific Session, April 2 to 6, 2016, in Chicago, IL.

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

Received May 11, 2017; accepted September 19, 2017.

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,[8,9] and some studies have suggested they benefit from a rhythm control strategy.[4,6,10] Although the prevalence of AF in patients with heart failure with preserved ejection fraction (HFpEF) is similar to that in HFrEF,[11] 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.[12] 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. β 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 CO_2 production (VCO_2), oxygen consumption (VO_2), and minute ventilation. We calculated the ventilatory equivalent of CO_2 or ventilatory efficiency (VE/VCO_2) at peak exercise.[12,13] VO_2 at anaerobic threshold was measured by V-slope method[14] or by the inspection of ventilatory equivalents.[15] The respiratory exchange ratio was defined as the value of VCO_2/VO_2 at peak exercise.[13] Circulatory power, a surrogate for cardiac power, was calculated as the product of peak VO_2 and peak SBP (mm Hg·mL/kg per minute).[16] Peak oxygen pulse, a surrogate for stroke volume, was calculated as peak VO_2 (mL/min) divided by peak HR (mL/beat).[17]

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 χ^2 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.[18] 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.[19] All the variables were balanced after IPTW, except for age, sex, HFpEF 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 HFpEF 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 HFpEF (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 HFpEF, 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 VO_2 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/VCO_2 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, VO_2 at anaerobic threshold was similar between both groups (12.0±5.1 versus 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).

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/m^2	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
Medications, n (%)				
α Blocker	31 (1.8)	25 (1.7)	6 (2.5)	0.424
ACE inhibitor	431 (24.7)	363 (24.1)	68 (28.6)	0.164
β blocker	1080 (62.1)	916 (61)	164 (68.9)	0.023
Digitalis	129 (7.4)	80 (5.3)	49 (20.5)	<0.001
Diuretic	447 (25.6)	345 (22.9)	102 (42.9)	<0.001
Other inotropes	17 (1)	12 (0.8)	5 (2.1)	0.071
Metabolic stress parameters				
Peak VO_2, mL/kg per minute	21.6±7.5	22.1±7.6	18.5±6.2	<0.001
VE/VCO_2	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	13.6±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, VO_2 at anaerobic threshold; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption; Δ, change.

Discussion

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 VO_2, 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/VCO_2) and increased total mortality at 8 years, with early

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 (%)				
α Blocker	12 (2.5)	6 (2.5)	6 (2.5)	0.965
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 χ^2 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.

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.[5,8,17,20–23] 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.[9,17,21,22] 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.[9,23–25] Some studies have shown that peak VO_2, a surrogate of maximal aerobic capacity,[12] is 10% to 20% lower in patients with HFrEF with AF.[6,8,9,25] 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.[8,9,20,26] Although the prevalence of AF in patients with HFrEF and HFpEF is similar,[10] the impact of AF on exercise capacity in patients with HFpEF has not been examined, except in small studies.[4,21,25] 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 VO_2, oxygen pulse, and circulatory power at peak exercise; however, AF did not have an effect on VO_2 at anaerobic threshold. Thus, our findings suggest that peak exercise capacity, but not submaximal exercise capacity, is impaired in patients with

Table 3. Exercise Parameter Comparison Using Inverse Probability Weighting

Variable	All (N=1744)	Non-AF (n=1505)	AF (n=239)	*P* Value
Peak VO_2, mL/kg per minute	19.3±6.7	20.3±7.1	18.5±6.2	<0.001
VE/VCO_2	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, VO_2 at anaerobic threshold; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption; Δ, change.

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

AF and Ventilatory Inefficiency During Exercise

The VE/VCO_2 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 CO_2.[12,27] Many studies have confirmed the prognostic impact of VE/VCO_2 in patients with heart failure, in whom a value >35 has been associated with worse prognosis, and have argued for its superiority over peak VO_2.[13,27] However, the value of VE/VCO_2 in AF is contentious, with some studies showing AF association with a higher VE/VCO_2[23] and others showing no association.[9] In our study, we show that AF in patients with HFpEF is associated with significantly higher VE/VCO_2. 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 CO_2, largely determines impaired ventilatory efficiency in patients with AF and HFpEF.

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 HFpEF,[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

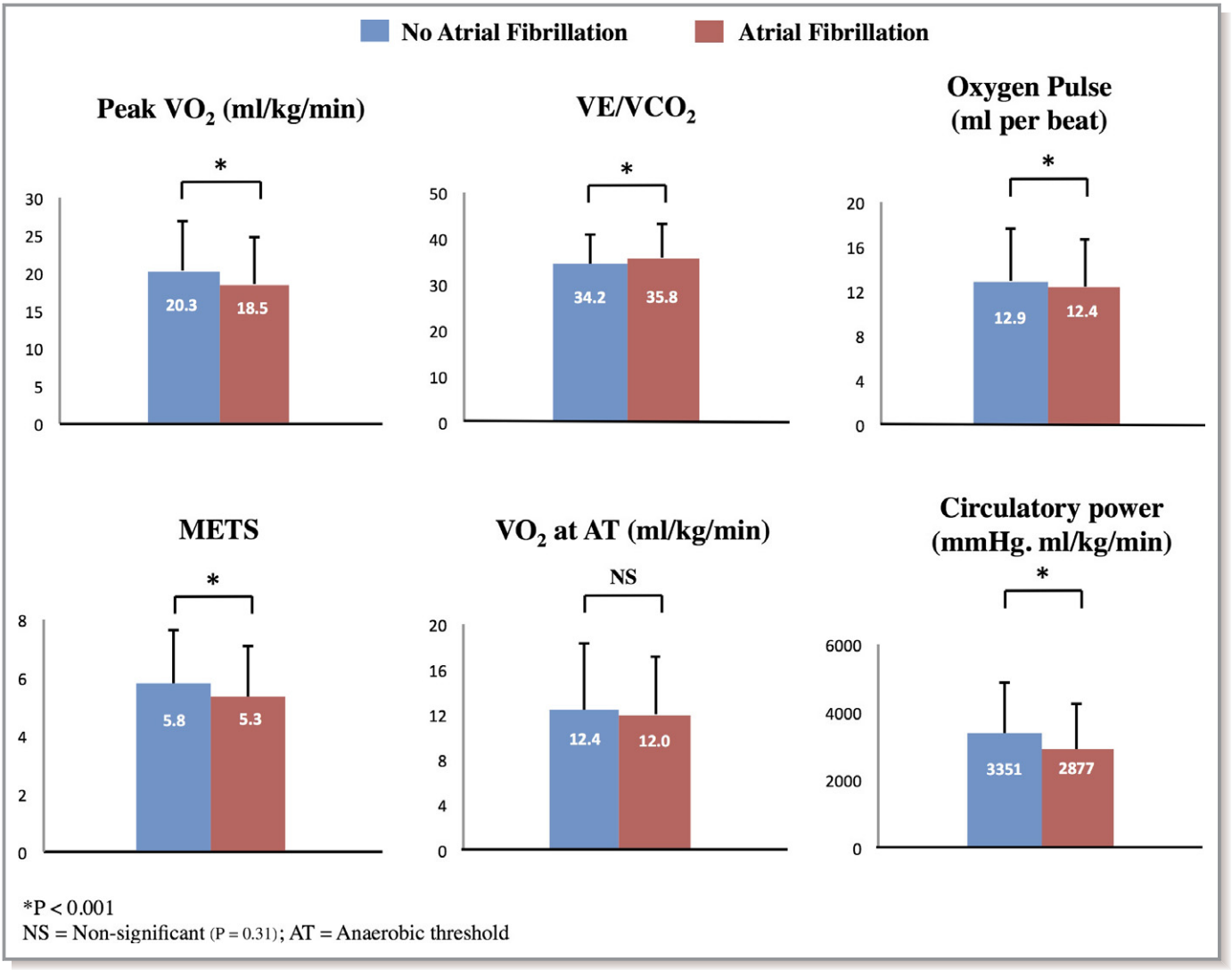

Figure 1. Exercise parameters reflecting circulatory efficiency and ventilatory efficiency in patients with heart failure with preserved ejection fraction with vs without atrial fibrillation (AF) after inverse probability weighting. AT indicates anaerobic threshold; METS, metabolic equivalent; NS, nonsignificant (P = 0.31); VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.

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,[7] 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.[28] In addition to the detrimental effects of AF on exercise capacity, our study also found a significant survival difference in patients with HFpEF 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.[29] 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

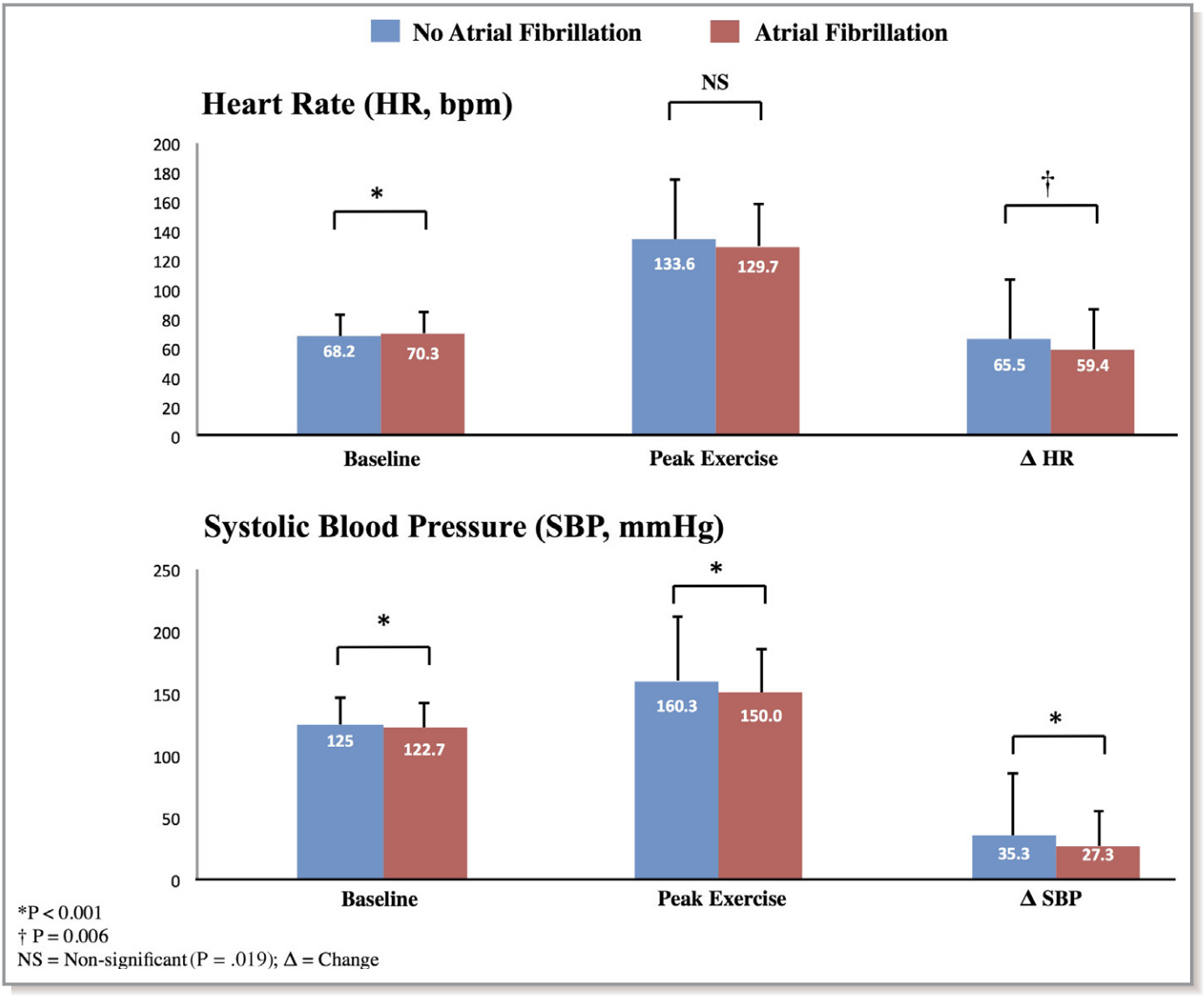

Figure 2. Heart rate (HR) and systolic blood pressure (SBP) response to exercise in patients with heart failure with preserved ejection fraction with vs without atrial fibrillation (AF) after inverse probability weighting. bpm indicates beats per minute; NS, nonsignificant (P = 0.19).

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[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

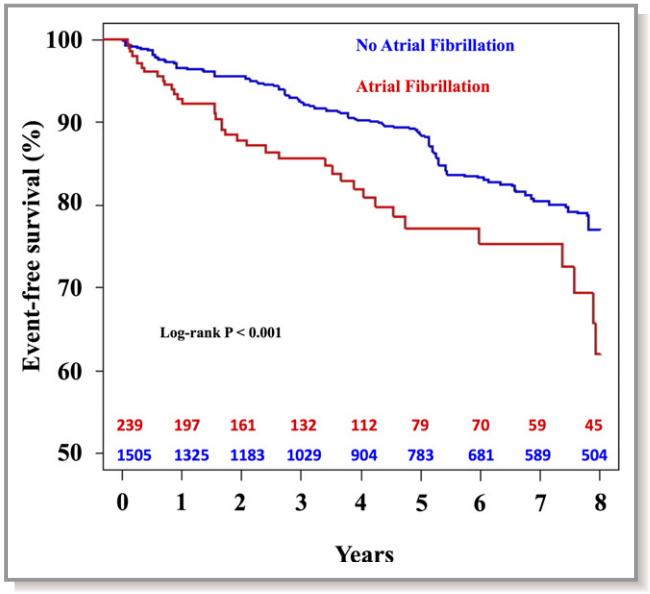

Figure 3. Weighted survival analysis in patients with vs without atrial fibrillation (AF). Mortality data were gathered from the Social Security Death Index. Log-rank $P<0.01$ was considered statistically significant.

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.

Acknowledgments

We acknowledge the Cleveland Clinic Women's Cardiovascular Research Center and the Karos Chair for Women's Cardiovascular Research fund.

Sources of Funding

Funding was provided by the Cleveland Clinic Women's Cardiovascular Research Center and the Karos Chair for Women's Cardiovascular Research Fund.

Disclosures

None.

References

1. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH; ESC Committee for Practice Guidelines (CPG), Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P; Document Reviewers, Vardas PE, Agladze V, Aliot E, Balabanski T, Blomstrom-Lundqvist C, Capucci A, Crijns H, Dahlof B, Folliguet T, Glikson M, Goethals M, Gulba DC, Ho SY, Klautz RJM, Kose S, McMurray J, Perrone Filardi P, Raatikainen P, Salvador MJ, Schalij MJ, Shpektor A, Sousa J, Stepinska J, Uuetoa H, Zamorano JL, Zupan I. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
2. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1–e76.
3. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res*. 2014;114:1453–1468.
4. Wozakowska-Kapłon B, Opolski G. Effects of sinus rhythm restoration in patients with persistent atrial fibrillation: a clinical, echocardiographic and hormonal study. *Int J Cardiol*. 2004;96:171–176.
5. Hsu L-F, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié J-L, Scavée C, Bordachar P, Clémenty J, Haïssaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med*. 2004;351:2373–2383.
6. Halabi Al S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O, Callahan T, Saliba W, Chung MK. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *JACC Clin Electrophysiol*. 2015;1:200–209.
7. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
8. Pardaens K, Van Cleemput J, Vanhaecke J, Fagard RH. Atrial fibrillation is associated with a lower exercise capacity in male chronic heart failure patients. *Heart*. 1997;78:564–568.
9. Agostoni P, Emdin M, Corra U, Veglia F, Magri D, Tedesco CC, Berton E, Passino C, Bertella E, Re F, Mezzani A, Belardinelli R, Colombo C, La Gioia R, Vicenzi M, Giannoni A, Scrutinio D, Giannuzzi P, Tondo C, Di Lenarda A, Sinagra G, Piepoli MF, Guazzi M. Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J*. 2008;29:2367–2372.
10. Shelton RJ, Clark AL, Goode K, Rigby AS, Houghton T, Kaye GC, Cleland JGF. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFE-II Study). *Heart*. 2009;95:924–930.
11. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA; CHARM Investigators. 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.
12. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225.
13. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, Young JB, Lauer MS. Ventilatory and heart rate responses to exercise: better predictors of heart failure mortality than peak oxygen consumption. *Circulation*. 1999;100:2411–2417.
14. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*. 1986;60:2020–2027.
15. Wasserman K. Breathing during exercise. *N Engl J Med*. 1978;298:780–785.
16. Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A non-invasively determined surrogate of cardiac power ("circulatory power") at peak exercise is a powerful prognostic factor in chronic heart failure. *Eur Heart J*. 2002;23:806–814.
17. Lok NS, Lau CP. Oxygen uptake kinetics and cardiopulmonary performance in lone atrial fibrillation and the effects of sotalol. *Chest*. 1997;111:934–940.
18. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189.
19. Griffin BA, Ridgeway G, Morral AR, Burgette LF, Martin C, Almirall D, Ramchand R, Jaycox LH, McCaffrey DF. *Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG)*. Santa Monica, CA: RAND Corporation; 2014. http://www.rand.org/statistics/twang. Accessed 09/03/2017.
20. Atwood JE, Myers JN, Tang XC, Reda DJ, Singh SN, Singh BN. Exercise capacity in atrial fibrillation: a substudy of the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). *Am Heart J*. 2007;153:566–572.

21. Atwood JE, Myers J, Sullivan M, Forbes S, Friis R, Pewen W, Callaham P, Hall P, Froelicher V. Maximal exercise testing and gas exchange in patients with chronic atrial fibrillation. *J Am Coll Cardiol*. 1988;11:508–513.
22. Ueshima K, Myers J, Ribisl PM, Atwood JE, Morris CK, Kawaguchi T, Liu J, Froelicher VF. Hemodynamic determinants of exercise capacity in chronic atrial fibrillation. *Am Heart J*. 1993;125:1301–1305.
23. Guazzi M. Endothelial dysfunction and exercise performance in lone atrial fibrillation or associated with hypertension or diabetes: different results with cardioversion. *Am J Physiol Heart Circ Physiol*. 2006;291:H921–H928.
24. Gosselink AT, Crijns HJ, van den Berg MP, van den Broek SA, Hillege H, Landsman ML, Lie KI. Functional capacity before and after cardioversion of atrial fibrillation: a controlled study. *Br Heart J*. 1994;72:161–166.
25. Zakeri R, Borlaug BA, McNulty SE, Mohammed SF, Lewis GD, Semigran MJ, Deswal A, LeWinter M, Hernandez AF, Braunwald E, Redfield MM. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail*. 2014;7:123–130.
26. Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L. Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardiol*. 1998;32:197–204.
27. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Gläser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation*. 2000;101:2803–2809.
28. Cleland JGF, Coletta AP, Buga L, Ahmed D, Clark AL. Clinical trials update from the American College of Cardiology meeting 2010: DOSE, ASPIRE, CONNECT, STICH, STOP-AF, CABANA, RACE II, EVEREST II, ACCORD, and NAVIGATOR. *Eur J Heart Fail*. 2010;12:623–629.
29. Gottlieb SS. Dead is dead: artificial definitions are no substitute. *Lancet*. 1997;349:662–663.
30. Streiner DL, Norman GR. The pros and cons of propensity scores. *Chest*. 2012;142:1380–1382.