Maximal Exercise Testing and Gas Exchange in Patients With Chronic Atrial Fibrillation

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To evaluate the response of patients with chronic atrial fibrillation to exercise, 50 men (mean age 65 ± 8 years) with atrial fibrillation underwent a maximal exercise test using respiratory gas exchange techniques. Patients were classified by the presence (n = 29) or absence ("lone atrial fibrillation," n = 21) of underlying heart disease. Responses were evaluated at a standard submaximal work load (3.0 mph, [4.8 km/h] 0% grade), at the gas exchange anaerobic threshold and at maximal exercise. For all 50 patients, the mean maximal oxygen uptake was 20.6 ml/kg per min, which approximates 85% of the aerobic capacity predicted for age-matched normal individuals.

Patients with lone atrial fibrillation demonstrated normal exercise capacity in contrast to patients with atrial fibrillation and known heart disease (22.7 ± 5 versus 19.1 ± 5.0 ml/kg per min, p < 0.05). The mean maximal heart rate (176 ± 30 beats/min) was approximately 20 beats/min higher than that expected for age, was extremely variable and accounted for only 8% of the variance in maximal

oxygen uptake. Maximal heart rate in subjects with lone atrial fibrillation was higher than that of subjects with atrial fibrillation and known heart disease (189 ± 32 versus 166 ± 24 beats/min, p < 0.01). Stepwise regression analysis revealed that maximal systolic blood pressure accounted for 19% of the variance in maximal oxygen uptake ($\dot{V}O_2$ max), suggesting that systolic function is an important determinant of exercise performance in atrial fibrillation.

It is concluded that 1) the exercise response in patients with lone atrial fibrillation differs markedly from the typical heterogeneous group of patients with atrial fibrillation and underlying heart disease, 2) the higher maximal heart rate observed in patients with lone atrial fibrillation may be a compensation for the loss of atrial function, and 3) exercise impairment in patients with atrial fibrillation is due to underlying heart disease and not the arrhythmia itself.

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Chronic atrial fibrillation is one of the most common arrhythmias (1–3), but it remains poorly understood (4). In normal sinus rhythm, atrial contraction is known to augment cardiac output by roughly 19% (5), and several investigators (6–8) have reported compromised cardiac function in the presence of atrial fibrillation. However, few data are available regarding maximal exercise capacity in patients with chronic atrial fibrillation. Previous investigations (9–11) have noted a more

rapid heart rate response early during exercise or a higher maximal heart rate, or both, when compared with that of age-matched normal subjects. To our knowledge, gas exchange techniques have not been utilized to describe the exercise response of patients with stable atrial fibrillation. Given the heterogeneity of intrinsic heart disease in patients with chronic atrial fibrillation (that is, congestive heart failure, valvular and ischemic heart disease), we hypothesized that patients with lone atrial fibrillation would respond differently to exercise than would the typical heterogeneous atrial fibrillation population.

The purpose of the present study was, therefore, to describe the hemodynamic and gas exchange response to maximal exercise in 50 consecutively tested patients with chronic atrial fibrillation, and to compare patients with lone atrial fibrillation with those with accompanying clinical manifestations of heart disease.

Methods

Study patients. Fifty consecutive male volunteers, ranging in age from 49 to 87 years, with chronic atrial fibrillation (≥ 3 months' duration) were included in the study. Acutely ill patients, those with congestive heart failure or symptomatic with angina, patients unable to walk on a treadmill, those taking a beta-adrenergic blocking agent or a calcium-channel antagonist, or both, and those with severe lung disease or thyroid dysfunction were excluded. They were categorized by their history as those with lone atrial fibrillation (n = 21) and those with underlying heart disease (n = 29) including regurgitant valvular heart disease (n = 8), dilated cardiomyopathy (n = 8), history of congestive heart failure (n = 7), ischemic heart disease (n = 3), moderate lung disease (n = 2) and sick sinus syndrome (n = 1).

Forty-one of the 50 patients were taking digoxin (81% of those with lone atrial fibrillation and 83% of the others); continued administration of digoxin was left to the discretion of their physician. Mean digoxin doses were not different between groups. Seventeen patients were taking an antihypertensive medication (33% of those with lone atrial fibrillation and 34% of the others) and none were taking a beta-adrenergic blocking agent. All patients were in New York Heart Association functional class I or II. Thirty-eight of the 40 patients who had M-mode and two-dimensional echocardiography performed had left atrial enlargement. Of these, all had normal left ventricular function except those with the diagnosis of dilated cardiomyopathy.

Testing procedures. Patients were exercised on a calibrated motor-driven treadmill after abstaining from food, coffee and cigarettes for ≥3 h before testing. Individualized tests were modified from the Balke protocol and designed for each patient such that the exercise test lasted between 8 and 12 min. These protocols conformed to guidelines for optimizing cardiopulmonary assessment as outlined by Buchfuhrer et al.(12). The patient's subjective perception of exertion was evaluated using the Borg 6 to 20 point scale (13). All exercise tests were continued to volitional fatigue or dyspnea, or both, and no patient experienced angina.

Respiratory gas exchange variables were determined continuously throughout the exercise test using the Beckman Horizon MMC or Medical Graphics Corp. 2001 exercise systems. The reproducibility of these exercise systems was documented using techniques outlined by Jones and Campbell (14). Gas exchange variables analyzed were oxygen uptake ($\dot{V}O_2$, ml/mg per min), minute ventilation (liters/min BTPS), oxygen pulse (oxygen uptake divided by heart rate) and respiratory exchange ratio, ($\dot{V}CO_2/\dot{V}O_2$). In addition, estimated oxygen uptake was calculated from the external work ascribed to the highest completed treadmill stage (15).

Twelve lead electrocardiograms (ECG) (16) and blood pressure measurements (using a clinical sphygmomanometer) were obtained at rest and throughout the exercise test

and recovery. The number of ECG complexes multiplied by 10 in a 6 s rhythm strip at the end of each minute was used to determine heart rate.

Points of analysis. Analysis of hemodynamic and pulmonary gas exchange variables was performed at a standard submaximal work load (3.0 mph [4.8 km/h], 0% grade) at the gas exchange anaerobic threshold and at maximal exertion. The gas exchange anaerobic threshold was determined by two independent observers who were unaware of other data, as outlined by Sullivan et al. (17).

Statistics. Descriptive statistics are presented as mean values and standard deviations. Unpaired *t* testing was performed to evaluate patients with lone atrial fibrillation versus those with known heart disease. Analysis of covariance (ANCOVA) with repeated measures was used to evaluate the relation among heart rate, oxygen uptake and group membership during progressive submaximal exercise, and a stepwise regression analysis was performed to estimate predictors of maximal exercise capacity.

Results

Findings in all 50 patients (Table 1). No adverse complications occurred during any of the exercise tests. A summary of the hemodynamic and gas exchange data for all 50 patients at each exercise stage is presented in Table 1. The study group as a whole exhibited a mean maximal perceived exertion of 18 points on the Borg scale and a respiratory exchange ratio of 1.06, values indicative of maximal effort. The mean maximal oxygen uptake of 20.6 ml/kg per min was approximately 85% of that which would be predicted for age-matched normal men (14). Oxygen uptake at the gas exchange anaerobic threshold was 15.4 ml/kg per min or 73% of the maximal oxygen uptake, a percentage somewhat higher than that observed in normal subjects.

Lone atrial fibrillation versus atrial fibrillation and heart disease (Table 2). The mean age was not significantly different between patient groups. Heart rate did not differ between the groups at rest or any of the submaximal stages of exercise. Mean maximal heart rate, however, was significantly higher in the lone atrial fibrillation group (189 ± 32 versus 166 ± 24 beats/min, p < 0.01). Oxygen uptake was significantly higher in the lone atrial fibrillation group at the submaximal work load, 3.0 mph (4.8 km/h), 0% grade (16.0 ± 4 versus 14.0 ± 3 ml/kg per min, p < 0.05), at the gas exchange anaerobic threshold (16.2 ± 4 versus 14.0 ± 3 ml/kg per min, p < 0.05) and at maximal exertion (22.7 ± 5 versus 19.1 ± 5 ml/kg per min, p < 0.05). Minute ventilation was significantly higher among patients with lone atrial fibrillation at the gas exchange anaerobic threshold (40.8 ± 9 versus 34.0 ± 7 liters/min, p < 0.01) and at maximal exertion (76.2 ± 15 versus 61.1 ± 17 liters/min, p < 0.05). Oxygen pulse was roughly 2 ml/beat higher among patients with lone atrial fibrillation at each level of exercise (p < 0.05).

Oxygen uptake and heart rate were significantly though modestly correlated from rest to 8 min of progressive exercise (r = 0.54, p < 0.001) (Fig. 1). However, the variance for heart rate was large (SD ± 28.6 beats/min). An ANCOVA repeated measures design was used to evaluate the relation among group membership (lone atrial fibrillation versus atrial fibrillation and known heart disease), heart rate and oxygen uptake over 8 min of progressive exercise. This analysis revealed that group membership did not affect the relation between heart rate and oxygen uptake over time. However, oxygen uptake covaried significantly with heart rate (F = 27.1, p < 0.001). The interaction between change in heart rate and group membership was not significant.

Predictors of exercise capacity (Table 3). Data from stepwise regression analysis with maximal oxygen uptake as the dependent variable indicated that the significant predictors of maximal oxygen uptake were maximal heart rate and systolic blood pressure. Age and group (lone atrial fibrillation versus atrial fibrillation and known heart disease) were not significant predictors. The proportion of variance in maximal oxygen uptake that could be accounted for by maximal systolic blood pressure was 19%, and 8% of the variance in maximal oxygen uptake could be accounted for by maximal heart rate, the two predictors accounting for a total of 27% of the variance.

Discussion

Exercise capacity. Nine studies (9–11, 18–23) have previously evaluated the response of patients with atrial fibrillation to maximal exercise testing (Table 4). Most of these studies have focused on pharmacologic control of the ventricular response; studies reporting only submaximal exercise responses to pharmacologic therapy have not been included. As is typical in clinical practice, all of these preceding studies estimated maximal oxygen uptake from treadmill time or work load. Numerous studies (24–26) have demonstrated that estimation of oxygen uptake from treadmill time or work load can be misleading because of differences in habituation, gait, oxygen kinetics, fitness and extent of disease. These factors can alter the relation between treadmill time or work load and measured oxygen uptake. Recent advances in technology have provided instruments that allow for more frequent, accurate and convenient gas exchange analysis. Availability of gas exchange instrumentation provides one explanation of why the present study is the first to employ gas exchange analysis in patients with atrial fibrillation.

In previous studies, patients were estimated to have a maximal oxygen uptake of roughly 19 ml/kg per min. Although the present study demonstrates a somewhat higher estimated maximal oxygen uptake (26 ml/kg per min), previous studies included more patients with accompanying cardiac disease. These included patients with intrinsic heart disease, particularly valvular, and often patients in functional class III. The fact that a large number of our patients had both lone atrial fibrillation and normal left ventricular function by echocardiogram may account for the differences in exercise capacity. In light of the relatively high maximal heart rates observed in patients with atrial fibrillation, the decreased exercise performance appears to represent a compromised cardiac output consistent with reduced left ventricular function or lack of atrial contribution to ventricular filling, or both. This suggests that the major limitation in patients with atrial fibrillation may not be the arrhythmia, but rather the associated heart disease.

In the present study, maximal oxygen uptake was greater and oxygen pulse rate was approximately 2 ml/beat greater (p < 0.05) throughout exercise among patients with lone atrial fibrillation (Table 2). The functional capacity of this patient group approached the capacity typical of age-matched normal men, whereas the patients with known heart disease exhibited a deficit of 19% (14). These observations suggest that cardiac performance is normal in subjects with atrial fibrillation who have no evidence of underlying heart disease. The discrepancy between groups in oxygen uptake

Table 1. Hemodynamic and Gas Exchange Results for All 50 Patients With Atrial Fibrillation

	Rest	Submaximal Exercise (3.0 mph, 0% grade)	Gas Exchange Anaerobic Threshold	Maximal Exercise
Heart rate (beats/min)	95 ± 23 (55 to 181)	146 ± 24 (105 to 210)	148 ± 27 (90 to 200)	176 ± 30 (112 to 248)
Blood pressure (mm Hg)				
Systolic	148 ± 70 (100 to 190)	160 ± 22 (108 to 220)	161 ± 23 (98 to 200)	175 ± 27 (110 to 220)
Diastolic	85 ± 10 (70 to 110)	84 ± 13 (58 to 120)	81 ± 13 (50 to 110)	83 ± 14 (60 to 120)
VE (liters/min)		39.8 ± 11 (23.0 to 70.2)	37.2 ± 9 (20.6 to 64.1)	67.4 ± 18 (32.5 to 95.2)
VO_2 (ml/kg per min)		14.9 ± 3 (7.0 to 26.1)	15.1 ± 3 (8.1 to 23.9)	20.6 ± 5 (7.0 to 32.3)
O_2 pulse (ml/beat)		8.5 ± 2 (3.3 to 16.7)	9.0 ± 3 (4.0 to 14.1)	9.7 ± 3 (3.9 to 16.4)
RER		$0.90 \pm .1$ (0.72 to 1.11)	0.85 ± 0.07 (0.68 to 1.04)	1.06 ± 0.10 (0.83 to 1.28)
Perceive 1 exertion		12.6 ± 3 (6 to 20)	12.6 ± 2 (6 to 19)	18.3 ± 2 (13 to 20)

Values in parentheses under each row designate range. O_2 pulse = oxygen uptake (VO_2) divided by heart rate; RER = respiratory exchange ratio (VCO_2/VO_2); VE = minute ventilation; VO_2 = maximal oxygen uptake.

Table 2. Patients With Lone Atrial Fibrillation Contrasted With
Those With Atrial Fibrillation and Known Heart Disease

	Lone AF (n = 21)	AF and Known Heart Disease (n = 29)	p
Rest			
Age (yr)	63 ± 5	66 ± 9	NS
Weight (kg)	88.2 ± 14.1	76.5 ± 8.9	<0.01
HR (beats/min)	96 ± 26	94 ± 21	NS
SBP (mm Hg)	136 ± 21	139 ± 20	NS
DBP (mm Hg)	89 ± 10	82 ± 9	<0.05
Submaximal exercise (3.0 mph, 0% grade)			
HR (beats/min)	151 ± 26	142 ± 21	NS
SBP (mm Hg)	162 ± 21	159 ± 23	NS
DBP (mm Hg)	88 ± 13	81 ± 13	NS
VE (liters/min)	42.2 ± 10.4	38.0 ± 12.6	NS
VO₂ (ml/kg-min)	16.0 ± 3.8	14.0 ± 2.6	<0.05
O₂ pulse (ml/beat)	9.7 ± 3.0	7.7 ± 1.6	<0.01
RER	0.89 ± 0.09	0.91 ± 0.10	NS
PE	12 ± 3	13 ± 3	NS
Gas exchange anaerobic threshold			
HR (beats/min)	152 ± 26	139 ± 26	NS
SBP (mm Hg)	166 ± 19	157 ± 26	NS
DBP (mm Hg)	86 ± 12	77 ± 12	<0.05
VE (liters/min)	40.8 ± 8.9	34.0 ± 7.3	<0.01
VO₂ (ml/kg-min)	16.2 ± 3.7	14.0 ± 2.9	<0.05
O₂ pulse (ml/beat)	9.9 ± 2.8	8.1 ± 2.2	<0.05
RER	0.85 ± 0.08	0.85 ± 0.05	NS
PE	13 ± 2	13 ± 3	NS
Maximal exercise			
HR (beats/min)	189 ± 32	166 ± 24	<0.01
SBP (mm Hg)	183 ± 23	168 ± 28	<0.05
DBP (mm Hg)	87 ± 15	79 ± 13	NS
VE (liters/min)	76.2 ± 14.6	61.1 ± 17.4	<0.05
VO₂ (ml/kg-min)	22.7 ± 4.6	19.1 ± 5.0	<0.05
O₂ pulse (ml/beat)	10.8 ± 3.0	9.0 ± 2.9	<0.05
RER	1.08 ± 0.09	1.05 ± 0.10	NS
PE	19 ± 1	18 ± 2	NS

AF = atrial fibrillation; DBP = diastolic blood pressure; HR = heart rate; PE = perceived exertion; RER = respiratory exchange ratio; SBP = systolic blood pressure. Other abbreviations as in Table 1.

submaximally is curious, however, and is perhaps attributable to differences in treadmill experience.

Hemodynamics. Digoxin administration has long been considered standard therapy for atrial fibrillation although, by itself, digoxin is of limited effectiveness in controlling the ventricular response in these patients (27,28). That 41 (82%) of all 50 patients in our study were taking digoxin is generally consistent with studies reported in Table 4.

Several of these studies have reported that patients with atrial fibrillation have an inordinately rapid ventricular response to the first stage of exercise (9,10,22,29) and that this response is greater than in normal subjects at a given stage of
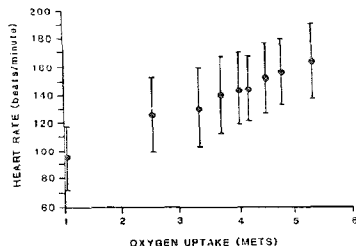

Figure 1. Relation between maximal heart rate and oxygen uptake for all 50 patients with atrial fibrillation during progressive exercise (0 to 8 min). Heart rate and oxygen uptake were significantly correlated (r = 0.54, p < 0.001) despite a large variance in heart rate (SD ± 28 beats/min) and they covaried significantly over time (F = 27.1, p < 0.001). Group membership (lone versus atrial fibrillation with heart disease) did not affect these relations. METS = multiples of oxygen consumption at rest.

exercise (9). Hornsten and Bruce (9), for example, reported that 74% of the total change in heart rate occurred in the first stage of exercise. Roth et al. (29) demonstrated that 66% of the total change in heart rate occurred after the first minute of exercise in 12 patients with atrial fibrillation who were receiving digoxin. These findings contrast the linear response observed among subjects with normal sinus rhythm (30). However, these studies have failed to recognize that changes in heart rate closely follow changes in oxygen uptake (30).

The relation between changes in heart rate and oxygen uptake for the 50 patients in the present study is presented in Figure 1. Despite its wide scatter, heart rate was a significant covariate of oxygen uptake during progressive submaximal exercise. This relation was not influenced by group membership (lone atrial fibrillation versus atrial fibrillation with known heart disease). Although 64% of the total change in heart rate occurred from rest to 3.0 mph (4.8 km/h), 0% grade, 66% of the change in oxygen uptake also occurred.

Table 3. Stepwise Regression Analysis for the Prediction of Maximal Oxygen Uptake*

	R^2	Change in R^2	F to Enter	Step No.
Maximal systolic blood pressure	0.19	0.19	11.7	1
Maximal heart rate	0.28	0.08	5.4	2

*Age and group (lone versus atrial fibrillation and known heart disease) were not significant predictors. F = F ratio; R^2 = squared multiple correlation coefficient.

Table 4. Previous Studies of Exercise Testing in Patients With Atrial Fibrillation

Reference Investigator	(9) Hornsten*	(10) Aberg*	(18) Aberg*	(19) Aberg*	(20) Khalsa*	(21) Davidson	(22) Lang*	(23) Molajo*	(11) Di Bianco*	Atwood
Year	1968	1972	1972	1977	1979	1979	1983	1984	1984	1988
No. patients	65	179	24	15	11	11	20	10	20	50
Mean age (yr)	48	47	45	45	56	55	59	52	60	65
Exercise protocol	Bruce	Bike	Bike	Bike	Bike	Bruce	Bike	Bruce	Mod Bruce	Mod B-W
Mean max HR (beats/min)	176	134	157	138	142	176	169	162	175	176
Estimated METs	7	3.5	3.5	4	5.9	6.5	3.5	5	7	7.5
Estimated max VO_2 (ml/kg per min)	25	12	12	13	21	23	12	18	25	26
Measured max VO_2	—	—	—	—	—	—	—	—	—	21

*Study included both men and women. B-W Balke-Ware; HR = heart rate; max = maximal; METs = multiples of oxygen consumption at rest; Mod = modified; VO_2 = oxygen uptake.

Similarly, changes in heart rate and predicted oxygen uptake in the first stage of exercise for the Hornsten and Bruce study (9) were 74 and 70%, respectively. The inordinate rises in heart rate reported in atrial fibrillation are due to the use of testing protocols with excessive work load increments in patients with reduced functional capacity. As in normal sinus rhythm, the heart rate response to exercise in atrial fibrillation is directly related to total body oxygen demand.

The mean maximal heart rate observed in the present study (176 beats/min) is roughly 20 beats/min higher than that expected for age (30). This response was most marked among patients with lone atrial fibrillation (189 beats/min). Because of the loss of atrial contribution to cardiac output, the increased heart rate in atrial fibrillation may provide a compensatory mechanism for subjects to maintain functional capacity. The finding that subjects with lone atrial fibrillation had normal functional capacity and a maximal heart rate roughly 30 beats higher than expected for subjects with normal sinus rhythm would support this conclusion.

The marked variability in maximal heart rate in the present study is evidenced by a large standard deviation (30 beats/min) and range (112 to 248 beats/min). Given the inconsistent heart rate response, it is not surprising that only 8% of the variance in maximal oxygen uptake could be accounted for by maximal heart rate. This contrasts with the 39% variance in exercise capacity accounted for by maximal heart rate among patients who have coronary heart disease and normal sinus rhythm (31). The observation that maximal systolic blood pressure accounted for the greatest variance in maximal oxygen uptake differs from that found in subjects with normal sinus rhythm, and suggests that systolic function may be the most important determinant of exercise capacity in atrial fibrillation.

Conclusion. To our knowledge, this study is the first to directly evaluate oxygen uptake and hemodynamic responses in a large group of patients with atrial fibrillation during exercise. On the basis of our findings, the following conclusions appear warranted: 1) The exercise response of patients with lone atrial fibrillation differs markedly from that of a typical heterogeneous group of patients with atrial fibrillation and underlying heart disease. 2) Maximal heart rate in atrial fibrillation is not controlled by digoxin alone. The higher maximal heart rate observed in patients with lone atrial fibrillation, however, may compensate for the loss of atrial function in order to maintain normal exercise capacity. 3) In contrast to previous suggestions, heart rate in atrial fibrillation is directly related to total body oxygen demand. 4) Exercise capacity in chronic atrial fibrillation is limited by underlying heart disease and not by the arrhythmia itself.

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