Exercise Capacity and Atrial Fibrillation Risk in Veterans: A Cohort Study

Charles Faselis, MD; Peter Kokkinos, PhD; Apostolos Tsimpoulis, MD; Andreas Pittaras, MD; Jonathan Myers, PhD; Carl J. Lavie, MD; Fiorina Kyritsi, MD; Dragan Lovic, MD; Pamela Karasik, MD; and Hans Moore, MD

Abstract

Objective: To assess the association between exercise capacity and the risk of developing atrial fibrillation (AF).

Patients and Methods: A symptom-limited exercise tolerance test was conducted to assess exercise capacity in 5962 veterans (mean age, 56.8±11.0 years) from the Veterans Affairs Medical Center, Washington, DC. None had evidence of AF or ischemia at the time of or before undergoing their exercise tolerance test. We established 4 fitness categories based on age-stratified quartiles of peak metabolic equivalent task (MET) achieved: least fit (4.9±1.1 METs; n=1446); moderately fit (6.7±1.0 METs; n=1490); fit (7.9±1.0 METs; n=1585), and highly fit (9.3±1.2 METs; n=1441). Multivariable Cox proportional hazards regression models were used to compare the AF-exercise capacity association between fitness categories.

Results: During a median follow-up period of 8.3 years, 722 (12.1%) individuals developed AF (14.5 per 1000 person-years; 95% CI, 13.9-15.9 per 1000 person-years). Exercise capacity was inversely related to AF incidence. The risk was 21% lower (hazard ratio, 0.79; 95% CI, 0.76-0.82) for each 1-MET increase in exercise capacity. Compared with the least fit individuals, hazard ratios were 0.80 (95% CI, 0.67-0.97) for moderately fit individuals, 0.55 (95% CI, 0.45-0.68) for fit individuals, and 0.37 (95% CI, 0.29-0.47) for highly fit individuals. Similar trends were observed in those younger than 65 years and those 65 years or older.

Conclusion: Increased fitness is inversely and independently associated with the reduced risk of developing AF. The decrease in risk was graded and precipitous with only modest increases in exercise capacity. These findings counter previous suggestions that even moderate increases in physical activity, as recommended by national and international guidelines, increase the risk of AF, with marked protection against AF noted with increasing levels of fitness.

Atrial fibrillation (AF) is associated with increased morbidity and mortality. Its prevalence increases with advancing age, hypertension (HTN), diabetes mellitus (DM), thyroid disease, and structural heart disease. Recent evidence from observational studies suggests a higher prevalence of AF in middle-aged and older elite athletes and those participating in long-term high-intensity physical activity (PA), as compared with the general population. This association appears to be directly related to intensity as well as number of hours or days spent per week engaged in vigorous PA. Potential mechanisms suggested for the higher risk of AF secondary to vigorous PA include a disruption in the balance between sympathetic and parasympathetic activity and an increase in left atrial size, leading to atrial fibrillation, myocardial injury, and inflammation. Although these structural and electrophysiological cardiac changes are observed with excessive exercise or physical exertion, not all studies support such an association.

There are also limited data suggesting that regular moderate-intensity exercise, as recommended by national and international guidelines on PA and health, may increase the risk of developing AF. This has not been a consistent finding. However, an increase, decrease, and no association between low- to moderate-intensity PA and the incidence of AF have been reported. This, along with...
the well-documented health benefits of exercise regardless of age and other comorbidities,\textsuperscript{10-26} reduce support for the concept that engaging in regular PA increases the risk of developing AF. Nonetheless, the inconsistency of the evidence and the potential public health and clinical significance of the AF-fitness association merit further exploration. In addition, although PA and fitness are certainly linked and PA is the greatest determinant of fitness, these 2 measurements may provide independent associations with cardiovascular disease (CVD) risk, including for AF.\textsuperscript{27,28} Thus, the aim of the present study was to assess the association between cardiorespiratory fitness (CRF) assessed objectively by a standard exercise test and the incidence of AF in a cohort of middle-aged and older US veterans.

**PATIENTS AND METHODS**

**Design and Sampling**

This prospective cohort study included individuals from the Veterans Affairs (VA) Medical Center, Washington, DC. The cohort was taken from a database of 11,456 that comprises the results of the Exercise Testing and Health Outcomes Study. This is a prospective observational study designed to assess the association between cardiorespiratory fitness (CRF) assessed objectively by a standard exercise test and the incidence of AF in a cohort of middle-aged and older US veterans. Patients who developed AF and the development of AF during the exercise test (n=989); history of an implanted pacemaker or the development of left bundle branch block during the test (n=438); inability to complete the test because of musculoskeletal pain or impairments; exercise capacity less than 2 metabolic equivalents (METs); instability, evidence of ischemia based on American Heart Association criteria;\textsuperscript{29} or need for emergency intervention; impaired chronotropic response to exercise (n=556); body mass index (BMI); calculated as the weight in kilograms divided by the height in meters squared) less than 15.5 kg/m\textsuperscript{2} or HIV/AIDS; lung disease (n=521); CVD defined as documented coronary artery disease, myocardial infarction, coronary artery bypass graft, and stroke (n=1791); and missing data (n=156).

Clinical and demographic characteristics and drug information were obtained from the patients’ electronic medical record before the ETT. Each individual was asked to verify the information, including history of chronic disease, current treatments, and smoking habits. Body weight and height were assessed by a standard scale and recorded before the test and used to determine BMI. The study was approved by the VA Central Institutional Review Board, and all participants gave written informed consent before undergoing their ETT.

**Exercise Assessments**

Exercise capacity was assessed by a standard treadmill test using the Bruce protocol. Peak exercise time was recorded in minutes. Peak exercise capacity (in METs) was estimated using standard equations based on peak exercise time.\textsuperscript{30} Participants were encouraged to exercise until volitional fatigue in the absence of symptoms or other indications for stopping.\textsuperscript{29} Handrails were used in all participants for balance and safety. Medications were not altered before testing.

**Determination of Fitness Categories**

We stratified the cohort into 4 age categories—less than 50, 50 to 59, 60 to 69, and 70 years and more—and identified those with an exercise capacity of 25% or less, 26% to 50%, 51% to 75%, and greater than 75% of METs achieved within their respective age category, as described previously.\textsuperscript{23,26} We then established the following 4 fitness categories based on age-stratified quartiles of peak METs achieved: least fit (4.9±1.10 METs; range, 2.0-7.0; n=1446), moderately fit (6.7±1.0 METs; range, 4.4-8.5; n=1490), fit (7.9±1.0 METs; range, 5.5-9.6; n=1585), and highly fit (9.3±1.2 METs; range, 6.6-14.5; n=1441).

**Follow-Up and End Point**

The primary end point was incidence of AF. Vital status was determined as of December 31, 2012. Patients who developed AF and the date of the onset were identified by an electronic search of the medical records (CPRS database).
TABLE 1. Demographic and Clinical Characteristics According to Fitness Categories

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n=5962)</th>
<th>Least fit (n=1446)</th>
<th>Moderately fit (n=1490)</th>
<th>Fit (n=1585)</th>
<th>Highly fit (n=1441)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>56.8±11.0</td>
<td>59.9±10.3</td>
<td>56.7±11.0</td>
<td>55.3±11.0</td>
<td>56.5±11.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7±5.4</td>
<td>31.1±6.5</td>
<td>30.7±5.5</td>
<td>29.2±4.6</td>
<td>27.7±4.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>72±16</td>
<td>77±23</td>
<td>74±13</td>
<td>70±12</td>
<td>67±12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting systolic BP (mm Hg)</td>
<td>126±18</td>
<td>131±20</td>
<td>126±18</td>
<td>123±17</td>
<td>123±17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Resting diastolic BP (mm Hg)</td>
<td>77±11</td>
<td>79±11</td>
<td>77±11</td>
<td>76±11</td>
<td>76±10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exercise capacity (METs)</td>
<td>7.3±1.9</td>
<td>4.9±1.1</td>
<td>6.7±1.0</td>
<td>7.9±1.0</td>
<td>9.3±1.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol level (mg/dL)</td>
<td>188±42</td>
<td>185±45</td>
<td>188±42</td>
<td>191±42</td>
<td>188±41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglyceride level (mg/dL)</td>
<td>144±109</td>
<td>157±117</td>
<td>147±106</td>
<td>144±116</td>
<td>130±94</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-cholesterol level (mg/dL)</td>
<td>115±38</td>
<td>112±39</td>
<td>115±38</td>
<td>117±37</td>
<td>115±36</td>
<td>.052</td>
</tr>
<tr>
<td>HDL-cholesterol level (mg/dL)</td>
<td>47±15</td>
<td>45±15</td>
<td>46±15</td>
<td>47±16</td>
<td>47±15</td>
<td>92</td>
</tr>
<tr>
<td>Glucose level</td>
<td>111±43</td>
<td>118±46</td>
<td>113±44</td>
<td>109±47</td>
<td>104±33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>4085 (68.5)</td>
<td>1015 (70.2)</td>
<td>1062 (71.3)</td>
<td>1089 (68.7)</td>
<td>919 (63.8)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>White</td>
<td>1463 (24.5)</td>
<td>362 (25.0)</td>
<td>316 (21.2)</td>
<td>371 (28.7)</td>
<td>414 (28.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>414 (6.9)</td>
<td>69 (4.8)</td>
<td>112 (7.5)</td>
<td>125 (7.9)</td>
<td>108 (7.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3491 (58.6)</td>
<td>955 (66.0)</td>
<td>933 (62.6)</td>
<td>892 (56.3)</td>
<td>711 (49.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2611 (40.9)</td>
<td>844 (53.5)</td>
<td>714 (44.3)</td>
<td>611 (24.5)</td>
<td>301 (19.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td>1472 (24.7)</td>
<td>399 (27.6)</td>
<td>411 (27.6)</td>
<td>384 (24.2)</td>
<td>278 (19.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1208 (20.3)</td>
<td>292 (20.2)</td>
<td>292 (19.6)</td>
<td>343 (21.6)</td>
<td>281 (19.5)</td>
<td>.42</td>
</tr>
<tr>
<td>Statins</td>
<td>2923 (49.0)</td>
<td>749 (41.8)</td>
<td>773 (51.9)</td>
<td>760 (47.9)</td>
<td>641 (44.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE-I/ARBs</td>
<td>2038 (34.2)</td>
<td>585 (40.5)</td>
<td>544 (36.5)</td>
<td>503 (31.7)</td>
<td>406 (28.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1011 (17.0)</td>
<td>291 (20.1)</td>
<td>268 (18.0)</td>
<td>277 (17.5)</td>
<td>175 (12.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1178 (19.8)</td>
<td>316 (21.9)</td>
<td>327 (21.9)</td>
<td>294 (18.5)</td>
<td>241 (16.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1604 (26.9)</td>
<td>409 (28.3)</td>
<td>419 (28.1)</td>
<td>451 (28.5)</td>
<td>325 (22.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1023 (17.2)</td>
<td>307 (21.2)</td>
<td>245 (16.4)</td>
<td>254 (16.0)</td>
<td>217 (15.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypoglycemic agents</td>
<td>1891 (31.7)</td>
<td>627 (43.4)</td>
<td>520 (34.9)</td>
<td>417 (26.3)</td>
<td>327 (22.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*SI conversion factor: To convert to mmol/L values, multiply by 0.0259.

*Data are presented as means ± SD or as No. (percentage).

using the International Classification of Diseases coding and verified by 2 coinvestigators.

Statistical Analyses

Follow-up time is presented as median (interquartile range [IQR]). Atrial fibrillation rate was calculated as the ratio of AF occurrence to the person-years of follow-up. A 95% CI for the incidence of AF was also calculated. Continuous variables are presented as mean ± SD and categorical variables as frequency (percentage). We tested baseline associations between categorical variables using the chi-square test. A 1-way analysis of variance was used to evaluate differences between fitness categories and continuous variables included in Table 1. Age and BMI were used as covariates in the analyses for resting heart rate, systolic blood pressure (BP), diastolic BP, blood lipid level, blood glucose level, and exercise capacity. We tested the assumption of equality of variances between groups by using Levene’s test.

Cox proportional hazards regression models were used to evaluate the association between the development of AF and peak METs (continuous variable) and between the development of AF and fitness categories (defined in the “Patients and Methods” section) for the entire cohort and for those younger than 65 years and 65 years or older. Hazard ratios (HRs) and 95% CIs are presented. We repeated the same analyses by excluding patients treated with β-blockers and/or calcium channel blockers (CCBs). The least fit category was the reference group in all Cox proportional hazards regression models. We adjusted analyses for age, resting...
TABLE 2. Risk of Developing AF According to Fitness Categoriesa

<table>
<thead>
<tr>
<th>Category</th>
<th>Events, n (%)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Fully-adjusted HR (95% CI)b</th>
<th>P valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort (N=5962)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least fit (n=1446)</td>
<td>314 (21.7)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderately fit (n=1490)</td>
<td>185 (12.4)</td>
<td>0.59 (0.49-0.71)</td>
<td>0.66 (0.55-0.79)</td>
<td>0.80 (0.67-0.97)</td>
<td>.021</td>
</tr>
<tr>
<td>Fit (n=1585)</td>
<td>132 (8.3)</td>
<td>0.41 (0.34-0.51)</td>
<td>0.47 (0.39-0.58)</td>
<td>0.55 (0.45-0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Highly fit (n=1441)</td>
<td>91 (6.3)</td>
<td>0.30 (0.24-0.38)</td>
<td>0.33 (0.26-0.42)</td>
<td>0.37 (0.29-0.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Excluding patients treated with β-blockers and/or calcium channel blockers only (n=5067)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least fit (n=1204)</td>
<td>300 (24.9)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderately fit (n=1249)</td>
<td>181 (14.5)</td>
<td>0.61 (0.51-0.73)</td>
<td>0.68 (0.57-0.82)</td>
<td>0.83 (0.69-1.00)</td>
<td>.53</td>
</tr>
<tr>
<td>Fit (n=1361)</td>
<td>126 (9.3)</td>
<td>0.41 (0.34-0.51)</td>
<td>0.49 (0.40-0.60)</td>
<td>0.55 (0.45-0.69)</td>
<td>.001</td>
</tr>
<tr>
<td>Highly fit (n=1253)</td>
<td>89 (7.1)</td>
<td>0.31 (0.24-0.39)</td>
<td>0.34 (0.27-0.43)</td>
<td>0.38 (0.30-0.49)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

aACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; HR = hazard ratio.
bAdjusted for age, BMI, resting BP, ethnicity, sex, β-blockers, calcium channel blockers, ACE-I, ARBs, diuretics, hypoglycemic agents, statins, aspirin, smoking status, alcohol/drug abuse, type 2 diabetes mellitus, dyslipidemia, and hypertension.
cFor fully adjusted model.

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BP, BMI, ethnicity, sex, risk factors (HTN, type 2 DM, dyslipidemia, and smoking status), alcohol/drug abuse, and cardiac medications (β-blockers, CCBs, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aspirin), lipid-lowering agents, and hypoglycemic agents, present at the time of the ETT. An interaction between race and fitness status was tested in the fully adjusted Cox model by using the Wald test in SPSS software version 22.0 (IBM Corp.) by entering the interaction term race by MET (continuous variable) in the fully adjusted Cox model.

The assumption of proportionality for the Cox proportional hazards regression models was tested graphically by plotting the cumulative hazards of the logarithms of the covariates. The proportionality assumption was met for each model. All hypotheses were 2-sided, and P values <.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 22.0.

RESULTS

We assessed 11,456 people for eligibility. We enrolled 5962 veterans (5591 men and 371 women). Of those veterans, 4085 (68.5%) were African American (mean age, 56.4±10.7 years), 1463 (24.5%) were white (mean age, 58.4±11.5 years), and 414 (6.9%) were other (mean age, 54.6±11.0 years). During the median follow-up period of 8.3 years (IQR, 4.2-11.7 years, providing a total of 49,727 person-years), 722 (12.1%) developed AF (no data missing) at an average yearly incidence rate of 14.5 per 1000 person-years (95% CI, 13.9-15.9 per 1000 person-years). Those who developed AF were older than those who did not (mean age, 62.2±10.2 years vs 56.1±10.9 years, respectively; P<.001). Older age was associated with developing AF (HR, 1.04; 95% CI, 1.03-1.05; P<.001). Using those who were not treated with β-blockers and/or CCBs as the reference group, being treated with β-blockers and/or CCBs was protective for developing AF (HR, 0.27; 95% CI, 0.19-0.38; P<.001).

Demographic and clinical characteristics across fitness categories are presented in Table 1. In general, significant differences were observed between fitness categories in all variables examined, with the exception of dyslipidemia, total cholesterol level, low-density lipoprotein level, and high-density lipoprotein cholesterol level. The differences tended to be more pronounced between the least fit and highly fit categories. Specifically, participants in the least fit category were older than those in the highly fit category and had higher BMI, resting heart rate, BP, triglyceride levels, and blood glucose levels. In general, the prevalence of HTN, DM, smoking status, and the use of medications was higher in the least fit individuals than in those with higher fitness levels (when moving from the highest fit category.
to the least fit category; \( P < .001 \). No interaction existed between ethnic origin and METs \( (P = .81) \).

In the fully adjusted model, exercise capacity (in METs), when treated as a continuous variable, was inversely related to the development of AF. For each 1-MET increase in exercise capacity, the risk of developing AF was 21% lower \( (HR, 0.79; 95\% \ CI, 0.76-0.82; P < .001) \). The development of AF was also significantly lower in those treated vs not treated with medications \( (HR, 0.71; 95\% \ CI, 0.58-0.86; P < .001) \). The risk of developing AF increased with age \( (HR, 1.03; 95\% \ CI, 1.02-1.04; P < .001) \), resting diastolic BP \( (HR, 1.03; 95\% \ CI, 1.02-1.04; P < .001) \), DM \( (HR, 1.40; 95\% \ CI, 1.17-1.66; P < .001) \), and dyslipidemia \( (HR, 2.42; 95\% \ CI, 1.96-2.99; P < .001) \).

Table 2 and Figure 1 depict the risk of developing AF across CRF categories for the entire cohort. In the final adjusted model, the risk of developing AF decreased progressively with increase in exercise capacity. Compared with the least fit individuals (reference group), HRs were 0.80 \( (95\% \ CI, 0.67-0.97; P = .02) \) for moderately fit individuals, 0.55 \( (95\% \ CI, 0.45-0.68; P < .001) \) for fit individuals, and 0.37 \( (95\% \ CI, 0.29-0.47; P < .001) \) for highly fit individuals. Similar trends were observed for those younger than 65 years and those 65 years or older, with the exception of individuals in the moderately fit category who were younger than 65 years (Figure 2).

To account for the potential effect of \( \beta \)-blockers and CCBs on AF, we excluded those treated with the aforementioned medications \( (n = 1032) \) and assessed the risk of developing AF in the remaining cohort \( (n = 5067) \). With the exception of individuals in the moderately fit category, the risk of developing AF associated with individuals in the fit and highly fit categories did not vary substantially from the risk observed in the entire cohort (Table 2).

**DISCUSSION**

The present findings support an inverse, independent, and graded association between the risk of developing AF and exercise capacity. The decrease in risk was precipitous with only modest increases in CRF as derived from a maximal ETT. Compared with the least fit individuals (average exercise capacity, 4.9 METs), the risk in those in the next fitness category (average exercise capacity, 6.7 METs) was 20% lower. For fit and highly fit individuals, the risk decreased by 45% and 63%, respectively (Table 2). The effect of fitness was similar in the relatively young (<65 years of age) and older (≥65 years of age) individuals (Figure 2).

To test whether individuals treated with \( \beta \)-blockers and/or CCBs had lower CRF and were consequently aggregated into a lower fitness category, we investigated the association between exercise capacity and the risk of developing AF in patients treated and not treated with \( \beta \)-blockers and/or CCBs. Exercise capacity was not significantly different between the 2 subgroups \( (7.1 \pm 1.9 \text{ METs vs } 7.2 \pm 1.9 \text{ METs}; P = .249) \), and the distribution of patients treated with these medications was also similar for all CRF categories \( (P = .453) \). Nevertheless, because the incidence of AF was significantly lower in those treated with \( \beta \)-blockers and/or CCBs, we excluded those treated with the aforementioned medications and examined the risk of developing AF only in those not treated with \( \beta \)-blockers and/or CCBs. Again, the AF-fitness association remained robust and the findings, with the exception of individuals in the moderately fit category, were similar to those observed in the entire cohort (Table 2).

Collectively, these findings strengthen the concept that along with other potentially modifiable risk factors, increased CRF...
independently lowers the risk of developing AF, which supports the evidence from 2 recent studies. However, the effect of fitness (higher exercise capacity) was substantially greater in the present study. The risk of developing AF was 21% lower for each 1-MET increase in exercise capacity in the present study as compared with 7% and 9% in the aforementioned studies. Although the reasons for the marked differences in the risk of developing AF per increment in exercise capacity are not apparent, population differences are likely to, at least in part, account for the different findings.

Previous studies have reported an increased incidence of AF in athletes competing in endurance sports, and some studies have suggested similar increases in the incidence of AF even with low- to moderate-intensity PA, although there is also evidence of a U-shaped relationship between exercise intensity and AF. Proposed mechanisms for this phenomenon include disruption in the balance between sympathetic and parasympathetic activity and an increase in left atrial size, leading to atrial fibrosis, myocardial injury, or transient inflammation that may occur with excessive exercise. Others, however, have reported no association or a significantly lower risk of AF incidence with such PA.

The aforementioned structural and electrophysiological cardiac changes have been observed in highly trained athletes. It is also reasonable to assume that a threshold exists beyond which long-term demands imposed by excessively high exercise intensity or volume can lead to maladaptive changes of the involved systems. However, it is unlikely that such a threshold is exceeded with moderate levels of PA. This is suggested by at least 1 study involving more than 22,000 male physicians. After adjusting for several factors, a higher risk of AF was associated with frequency of jogging (≥5 times/wk) and distance (>4 mi/session), but not exercise duration. The risk of developing AF remained elevated in those younger than 50 years who engaged in high levels of exercise, but decreased in those 50 years or older and when joggers were excluded from the analysis. Because jogging is considered a vigorous PA and older individuals are less likely to engage in such vigorous activities, these findings suggest an association between exercise intensity and the incidence of AF. Collectively, the aforementioned findings suggest that chronic demands imposed by excessively high exercise volume or intensity may lead to cardiac maladaptation that fosters the genesis of AF.

In the present study, we assessed exercise capacity but did not quantify PA patterns of the cohort. Although CRF is affected by many factors, including a non-PA inherited component, increased PA is the factor that...
most strongly affects CRF.\textsuperscript{38,39} Nevertheless, CRF and PA, especially considering their intensities, appear to have variable effects on CVD.\textsuperscript{10,27,28,37} In our cohort, the risk of AF was progressively lower with increased CRF, with no evidence of a nadir. Although the precise mechanisms that underlie this effect are not known, a number of potential mechanisms may be involved. Regular exercise of low to moderate intensity fosters left ventricular compliance and improves diastolic function, leading to improved left ventricular filling.\textsuperscript{40,41} Consequently, the workload of the left atrium decreases, and the stimulus for left atrial structural changes is reduced.

The possibility that high-intensity exercise increases the risk of AF in older individuals, as suggested by some studies,\textsuperscript{3,10,17} warrants mention. In the present study, approximately 24% (n=344) of the participants 65 years or older were in the highly fit category. The mean MET level of these individuals was 8.0±0.9, suggesting that at least some proportion of these individuals were likely engaging in regular moderate- to high-intensity exercise. In this subgroup of older and highly fit individuals, 12.8% developed AF as compared with 16.1% in the subgroup of the least fit individuals younger than 65 years. The incidence of AF in these 2 subgroups was not different (HR, 0.76; 95% CI, 0.48-1.22; \( P = .89 \)), suggesting the possibility that increased CRF, probably because of higher PA, may not increase the risk of developing AF.

The present study has several unique strengths and limitations. First, the strengths include the fact that it was a relatively large study with nearly 6000 individuals without evidence of existing AF at baseline. Second, AF incidence was established during a follow-up period spanning approximately 22 years (median, 8.3 years [IQR, 3.2-26.4 years]). Third, CRF status of all participants was assessed objectively by an ETT and estimated METs. Fourth, we had access to longitudinal data and adjusted for important covariates including medications and established CVD risk factors. Finally, the equal access to care independent of a patient’s financial status provided by the Veterans Health Administration is noteworthy. This permits epidemiologic evaluations while minimizing the effect of disparities in medical care.\textsuperscript{42,43} This, along with the existence of electronic health records within the VA health care system (CPRS), enables detailed observation of history and alterations in health status. These attributes minimize the likelihood of reverse causality and support of the validity of the CRF-related health benefits.

The study also has limitations inherent to most epidemiological studies. The precise cause of AF was not ascertained. Fitness levels were based on 1 assessment, PA was not accessed, and follow-up data on changes in CRF or PA of the participants over time were not available.

We also considered that the rate of AF detection may be lower for fit vs unfit individuals. To account for this, we examined the number of electrocardiograms recorded in AF-free individuals during the last 3 years of the follow-up period. The proportion of individuals with at least 1 electrocardiogram was 46.7% for the least fit category, 49.9% for the moderately fit category, 48.0% for the fit category, and 46.7% for the highly fit category (\( P = .31 \)). These findings suggest that AF detection was not affected by CRF status.

We have no information on PA patterns of the participants and cannot make associations between frequency, intensity, duration, or volume of PA and AF incidence. This also precludes inferences of our findings to elite athletes. The onset of chronic diseases, their severity, and duration of therapy were not evaluated. In addition, because all participants in the cohort were referred for ETT for a clinical reason, a bias could exist that would limit the generalizability of these findings. We also did not perform an echocardiographic assessment of the participants for the evaluation of valvular disease or left ventricular hypertrophy, a strong contributor to AF.

Finally, our findings apply mostly to male veterans. Future studies are needed to document the effects of CRF on the incidence of AF for other cohorts, including female participants.

**CONCLUSION**

The present findings support an inverse, independent, and graded association between CRF determined by estimated METs and the risk of developing AF. The relatively moderate exercise capacity necessary to achieve these health benefits is similar to what has been shown to lower all-cause mortality in previous studies. This level of fitness is achievable by many middle-aged and older men by daily exercise and PA, such
as brisk walking. Thus, increased CRF may provide a potential intervention for men at risk of developing AF. Future studies are warranted to establish regular PA and PA/exercise-induced increases in CRF as an effective intervention to prevent or attenuate the incidence of AF.

Abbreviations and Acronyms: AF = atrial fibrillation; BMI = body mass index; CCB = calcium channel blocker; CPRS = Computerized Patient Record System; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; DM = diabetes mellitus; ETT = exercise tolerance test; HR = hazard ratio; HTN = hypertension; IGR = interquartile range; MET = metabolic equivalent; PA = physical activity; VA = Veterans Affairs

Affiliations (Continued from the first page of this article). P. Karasik); Georgetown University School of Medicine, Washington, DC (P. Kokkinos, P. Karasik, H.M.); Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia (P. Kokkinos); Veterans Affairs Palo Alto Health Care System, Cardiology Division, Palo Alto, CA (JM); Stanford University, Stanford, CA (JM); and Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, LA (CLJ).

Correspondence: Address to Peter Kokkinos, PhD, Cardiology Division, Veterans Affairs Medical Center, 50 Irving St NW, Washington, DC 20422 (peter.kokkinos@va.gov).

REFERENCES