The beneficial effect of exercise on most aspects of cardiovascular disease is well established with a salutary effect on the incidence of coronary artery disease (CAD), congestive heart failure, and premature death in those who participate in regular physical activity.12 This effect becomes apparent with moderate increases in activity without a defined upper limit of toxicity. For cardiac arrhythmias, atrial fibrillation (AF) in particular, the story appears more complex. In fact, only limited studies have been published on the beneficial effect of physical activity on AF, whereas a number of case-control studies have emphasized the deleterious effect of exercise on the incidence of coronary artery disease (CAD), congestive heart failure, and premature death in those who participate in regular physical activity.1,2 This effect becomes apparent with moderate increases in activity without a defined upper limit of toxicity. For cardiac arrhythmias, atrial fibrillation (AF) in particular, the story appears more complex. In fact, only limited studies have been published on the beneficial effect of physical activity on AF, whereas a number of case-control studies have emphasized the deleterious effect of exercise when performed at sustained high levels.3,4

The pathophysiology of AF is highly heterogeneous and complex. Among the contributing clinical factors that lead to the development and progression of AF are advanced age, left ventricular dysfunction, valvular disease, CAD, diabetes mellitus, and hypertension.1 These physiological stressors alter the normal electrophysiological substrate of a small, rapidly conducting, uniformly repolarizing medium through fibrosis, inflammation, oxidation, and altered ion channel physiology to one adversely remodeled to support re-entry and repetitive pulmonary vein and atrial firing.5,6

The extent of structural and electric remodeling of the atria generally becomes apparent only once AF is clinically established. By that point, risk factor (RF) modification may reduce the frequency and duration of AF paroxysms and theoretically may slow the progression to a more persistent pattern, but maintenance of sinus rhythm requires an ablative or pharmacological approach to make the atrial milieu less favorable for AF. Promising developments in imaging and therapeutic energy delivery to target the atrial substrate supporting AF have recently advanced the former, whereas antiarrhythmic drug development has been highly disappointing for longer than the last 2 decades. Despite these advances in mechanism-directed approaches for AF ablation, the long-term durability remains suboptimal, given progressive adverse remodeling.7,8

The realization that structural and electric remodeling was responsible for the majority of AF fueled the investigation of agents that could attenuate or prevent atrial inflammation and fibrosis such as statins, angiotensin blockade, aldosterone blockade, and antioxidants, collectively labeled upstream therapies.9–11 Although each drew support from animal models of AF models and substudy analyses of large human trials, enthusiasm waned with the results of prospective studies focused on AF as an end point. At the same time, there has been an emerging body of evidence that several cardiometabolic RFs for AF, including obstructive sleep apnea (OSA), obesity, and sedentary lifestyle, are associated with adverse atrial electric and structural remodeling that supports AF:

1. The role of OSA role in the development of AF is likely related to atrial stretch, autonomic imbalance, oxidative stress, and inflammation. Dimitri et al12 demonstrated that OSA is associated with volumetric and electric atrial remodeling. OSA has been clinically associated with a 25% greater risk of recurrent AF after catheter ablation.13 Furthermore, continuous positive airway pressure for OSA is associated with significantly improved AF-free survival after ablation comparable to that of individuals without OSA; ablation in untreated OSA has success rates comparable to those of medical therapy alone.14

2. Obesity is similarly associated with atrial stretch, autonomic imbalance, oxidative stress, and inflammation, as well as increased pericardial fat, an emerging marker of cardiovascular risk. The difficulty in evaluating the role of obesity in AF is confounded by the coexistence of other cardiometabolic RFs for AF. Abed et al15 demonstrated that in sheep excessive caloric intake leading to weight gain was associated with adverse atrial remodeling marked by increased left atrial mass, fibrosis, inflammation, slower and more heterogeneous atrial conduction, and greater burden of AF. When the sheep were subjected to caloric restriction leading to weight reduction, this resulted in favorable structural and electric atrial changes, that is, reverse remodeling.16 Similar beneficial changes have recently been reported with weight reduction in humans.17

3. It is well documented that regular and moderate physical activity improves various parameters of cardiometabolic health and prevents the development of RFs or cardiovascular disease through its beneficial effects on endothelial function, inflammation, and oxidative stress. Several observational studies found that increased physical activity was associated with a reduction in AF.1,2 On the other hand, high-level competitive endurance training in marathon runners, cyclists, and elite cross-country skiers has been associated with an increased risk of AF.3,4 The mechanisms for this association are related to repetitive and extreme hemodynamic loads, heightened vagal tone, fibrosis, and left atrial enlargement.3,4

The Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation
classification, modulates treatment of AF has not been determined.

In this issue of Circulation, Qureshi et al18 examine the relationship of cardiorespiratory fitness and the development of incident AF after adjusting for cardiometabolic RFs and medications. The investigators report the results of a retrospective cohort analysis of the Henry Ford Exercise Testing (FIT) project enrolling 69,885 subjects between 1991 and 2009 referred for clinically indicated exercise testing. Individuals with pre-existing AF, atrial flutter, or left ventricular dysfunction were excluded. The final study cohort included 64,561 individuals in whom cardiorespiratory fitness, as measured by metabolic equivalents of task (METS), was assessed for development of AF via linkage to International Classification of Disease, Ninth Revision codes in insurance claim files over a mean follow-up of 5.4 years. Cardiorespiratory fitness was stratified into 4 categories of <6, 6 to 9, 10 to 11, and >11 METs. As would be anticipated, there were significant trends toward accumulating cardiometabolic RFs and advancing age as cardiorespiratory fitness declines. A nested Cox proportional hazard model was used to sequentially control for 3 groupings of RFs and medications. The investigators found that the unadjusted 5-year cumulative incidences of AF across the 4 strata of cardiorespiratory fitness were 18.8%, 9.5%, 5.0%, and 3.7%, respectively. For every 1-MET increase, there was an associated 7% decrease in the risk of AF. There was no attenuation of benefit when cardiorespiratory fitness was >10 METs.

The limitations of this study include the retrospective design reliant on coding of clinical characteristics at the time of exercise testing and linkage to billing codes to the subsequent development of AF. An ECG diagnosis of AF would have been more powerful, and the inclusion of atrial flutter as an end point would have been justified given the close pathophysiological underpinnings and clinical relationship.20 A remaining concern is the generalizability of the study. The population is largely a middle-aged cohort referred for stress testing, which presumably has higher prevalence of cardiovascular disease and RFs for AF. Furthermore, the effect of cardiorespiratory fitness on reduction in AF was more pronounced in obese and older individuals, presumed to have higher risk of AF. This limits extrapolation to intermediate- or low-risk groups. It would be reasonable to assume that less fit patients were more likely to be limited by or diagnosed with CAD or heart failure after stress testing. The investigators addressed this concern with adjustment for incident CAD as a time-varying covariate and subgroup analyses of those with incident left ventricular dysfunction or pre-existing CAD; the relationship of cardiorespiratory fitness to AF remained significant. However, incident cardiometabolic RF development over time before the coding of AF was not ascertained and may confound the result.

The fact that blacks are well represented strengthens the conclusion that cardiorespiratory fitness is inversely related to AF for 2 reasons. First, most AF studies enroll a lower proportion of ethnic minorities.1 Second, blacks are known to have a high burden of cardiometabolic RFs but a lower incidence of AF.1 Despite the potential for dilution of the observed effect, the results remain significant.

Overall, this study represents the first cohort to establish a link between cardiorespiratory fitness and incidence of AF, supporting the aforementioned link between physical activity and AF. However, we should recognize that physical activity and cardiometabolic RFs are different physiological markers and that each has a different association with risk of cardiovascular disease.21 It would not be surprising if there were a nonlinear relationship between cardiorespiratory fitness and AF, given this difference and the evident adverse effects in competitive endurance athletes. We should be careful not to overinterpret the results and to intensify the exercise prescription for our patients until several issues are further elucidated: (1) the potential for an upper limit of benefit, given concerns that high-level and sustained exercise training may adversely affect remodeling; (2) the potential benefit of exercise training once AF is established; and (3) the optimal way to improve cardiorespiratory fitness in at-risk populations.

The study is promising in that it suggests further reason to encourage exercise and opens the door to a strategy that complements ARREST-AF and ablation to mitigate the burgeoning epidemic of AF in the future.

Disclosures
None.

References


Fitness and the Development of Atrial Fibrillation
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Circulation. 2015;131:1821-1823; originally published online April 22, 2015; doi: 10.1161/CIRCULATIONAHA.115.016596

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