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ORIGINAL ARTICLE

Poor Heart Rate Recovery Is Associated With the Development of New-Onset Atrial Fibrillation in Middle-Aged Adults

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Abstract

Objective: To investigate the association between heart rate recovery (HRR) and new-onset atrial fibrillation (AF) in middle-aged adults.

Patients and Methods: Heart rate recovery was calculated using the exercise stress test in 15,729 apparently healthy self-referred men and women who attended periodic health screening examinations between January 2000, and December 2015. All participants completed the maximal exercise stress test according to the Bruce protocol and were followed clinically on a yearly basis for a median of 6.4±4 years. The primary end point was new-onset AF. Participants were grouped according to HRR at 5 minutes, dichotomized at the median value (<73 beats/min).

Results: Participants with low HRR were older, were more commonly men, had a higher rate of comorbidities, and were less fit. Kaplan-Meier survival analysis revealed that the cumulative probability of AF at 6 years was higher in participants with low HRR (2.1%) than in those with high HRR (0.6%) (log-rank, $P<.001$). Older age, male sex, obesity resting heart rate, and ischemic heart disease were all associated with increased AF risk in a univariate Cox regression model ($P<.05$ for all). Multivariate Cox regression analysis revealed that low HRR was independently associated with increased AF risk (hazard ratio, 1.92; 95% CI, 1.3-2.8; $P<.001$) after adjustment for multiple confounders.

Conclusion: Lower HRR is independently associated with the development of new-onset AF during long-term follow-up in middle-aged adults.

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Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting 1% to 2% of the general population.[1] Atrial fibrillation is associated with a considerable risk of stroke and an increased risk of mortality.[2] The exact pathophysiological processes leading to the initiation and perpetuation of the arrhythmia are not yet fully understood; however, autonomic dysregulation has been postulated as an important factor.[3] Heart rate recovery (HRR), a simple, readily available marker of autonomic dysfunction has been established as a powerful and independent predictor of the risk of all-cause mortality,[4,5] sudden cardiac death,[6] and cardiovascular events.[7] It has also been shown to predict the development of malignant arrhythmias after myocardial infarction[8] or in patients referred to the evaluation of chest pain.[9] Moreover, HRR predicted emergence of new-onset heart failure or AF in patients with diabetes mellitus.[10] However, only limited data exist on the association between HRR and cardiac arrhythmias in apparently healthy adults. Therefore, the purpose of the present study was to investigate the association between HRR and new-onset AF in middle-aged adults.

PATIENTS AND METHODS

The study population was described previously.[11,12] The Institute for Medical Screening of the Chaim Sheba Medical Center performs approximately 9000 annual examinations of asymptomatic, apparently healthy adults. A computerized database established in 2000

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was used as the source of data for the present study. All participants were self-referred asymptomatic adults, attending periodic health screening examinations as private individuals or as part of health executive programs. The annual evaluation included a questionnaire composed of their demographic characteristics, medical history, lifestyle, and health-related habits, as well as any unusual medical event that might have occurred since the previous meeting. At each visit the height and weight of all participants were measured and patients underwent a physical examination, blood pressure measurement, and laboratory blood tests that were analyzed in the center's laboratory. In addition, all participants underwent baseline electrocardiography followed by a standard exercise stress test (EST) according to the Bruce protocol. The Institutional Review Board of Sheba Medical Center approved this study on the basis of strict maintenance of participants' anonymity during database analyses. No individual consent was obtained.

Inclusion and Exclusion Criteria

The complete database includes 25,890 patients. Inclusion criteria for the present study included at least 2 visits with baseline EST with HRR documented. An adequate EST was defined as lasting ≥60 seconds with the subject reaching 85% of age-adjusted target heart rate (220−age). Exclusion criteria included attending only 1 visit (n=7036), missing EST data (n=2427), incomplete or inadequate EST data (n=423), AF at baseline (n=48), and long-term treatment with β-blockers (n=127). The final study sample comprised 15,729 individuals (Figure 1).

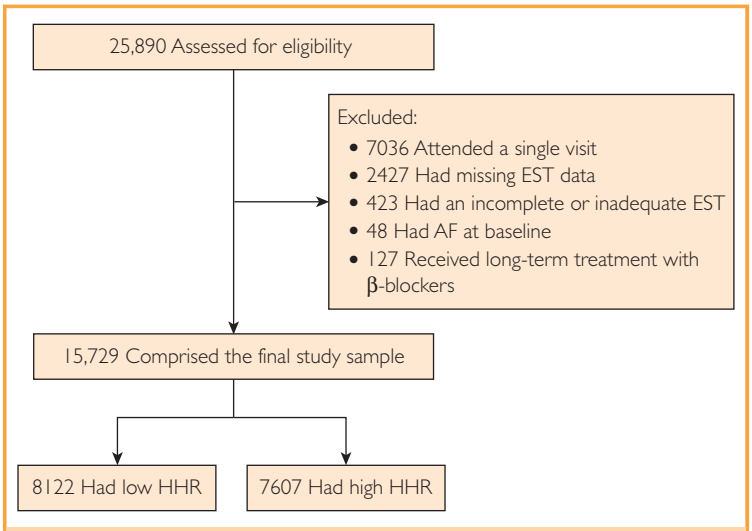

FIGURE 1. Study population. AF = atrial fibrillation; EST = exercise stress test; HRR = heart rate recovery.

Exercise Stress Test and HRR

A maximal EST according to the Bruce protocol was performed under the supervision of, and interpreted by, a board-certified cardiologist at each annual visit.[13] Participants were encouraged to reach their maximal age-specific target heart rate, and the test was terminated early because of exhaustion, angina, or other medical reasons. Using a standardized cuff sphygmomanometer, blood pressure was recorded at rest, at peak exercise, and during recovery. Heart rate measurements were based on electrocardiographic monitoring. Three predefined measurements were recorded: resting heart rate, maximal heart rate, and recovery heart rate (defined as heart rate after 5 minutes of recovery).[14] Heart rate recovery was calculated by subtracting the heart rate at 5 minutes of recovery from the maximal heart rate. Exercise stress test duration time was used to calculate metabolic equivalents (METs) with well-characterized regression equations.[15] *Low fitness level* was defined as the lowest age- and sex-specific quantile of exercise duration time, as previously described.[16]

Study Design

The study population was divided at baseline into 2 groups on the basis of the median HRR of the final study population. The risk of developing new AF was compared between the 2 groups. The following parameters from the baseline visit were also documented for all participants: age, sex, low-density lipoprotein level, high-density lipoprotein level, total cholesterol level, triglycerides level, and fasting glucose level. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease Study equation,[17] with *chronic kidney disease* defined as estimated glomerular filtration rate below 60 mL/min per 1.73 m^2. Smoking status was extracted from the survey questionnaire, and for the

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