Predictors of atrial ectopy and their relationship to atrial fibrillation risk

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Aims

Premature atrial contractions (PACs) are known to trigger and predict atrial fibrillation (AF). We sought to identify the determinants of PACs and the degree to which PACs mediate the effects of established risk factors for AF.

Methods and results

Predictors of baseline PAC frequency were examined using a Holter Study among 1392 participants in the Cardiovascular Health Study, a community-based cohort of individuals aged ≥ 65 years. Participants were then followed for their first diagnosis of AF. Independent predictors of PACs were identified, and the extent to which PACs might mediate the relationship between those predictors and AF was determined. The median hourly frequency of PACs was 2.7 (interquartile range 0.8–12.1). After multivariable adjustment, increasing age, increasing height, decreasing body mass index, and a history of myocardial infarction were each associated with more PACs. Regarding modifiable predictors, participants using beta-blockers had 21% less [95% confidence interval (95% CI) 9–30%, $P = 0.001$] and those performing at least moderate intensity exercise vs. lower intensity exercisers had 10% less (95% CI 1–18%, $P = 0.03$) PACs. Higher PAC frequency explained 34% (95% CI 22–57%, $P < 0.0001$) of the relationship between increasing age and AF risk and 27% (95% CI 10–75%, $P = 0.004$) of the relationship between taller height and AF risk.

Conclusion

Enhancing physical activity and use of beta-blockers may represent fruitful strategies to mitigate PAC frequency. A substantial proportion of the excess risk of AF due to increasing age and taller height may be explained by an increase in PAC frequency.

Keywords

Age • Atrial ectopy • Atrial fibrillation • Beta-blockers • Height • Physical exercise • Premature atrial contractions

Introduction

Premature atrial contractions (PACs) are known to trigger atrial fibrillation (AF). Pulmonary vein isolation, the most effective treatment strategy for suppressing AF episodes, eliminates the influence of PACs arising from the pulmonary veins, demonstrating a causal relationship in some patients.¹ Our group has shown that a higher PAC frequency, ascertained using Holter monitoring, is an especially potent predictor of incident AF,² and that even a single PAC recorded on a single 12-lead electrocardiography (ECG) reliably predicts a subsequent new diagnosis of AF.³

The causes of PACs, and particularly varying frequencies of PACs, remain largely unknown. Identifying modifiable behaviours or exposures that might influence the burden of atrial ectopy may be useful. In addition, the mechanism(s) by which many established risk factors for AF lead to AF remains unknown,¹ and identifying those risk factors mediated by an increase in PAC frequency might help better understand those relationships. We therefore sought to leverage data collected from participants in the Cardiovascular Health Study (CHS), in order to identify predictors of PAC frequency. Once identified, we used the information to identify established risk factors for AF that might be explained by an increase in PAC frequency.

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What's new?

- After multivariable adjustment, increasing age, increasing height, decreasing body mass index, and a history of myocardial infarction were each associated with more premature atrial contractions (PACs).
- Regarding readily modifiable predictors, participants using beta-blockers and those performing at least moderate intensity exercise vs. lower intensity exercisers had significantly less PACs; therefore, beta-blockers and enhancing physical activity may represent fruitful strategies to mitigate PAC frequency.
- A substantial proportion of the excess risk of atrial fibrillation due to both increasing age and taller height may be explained by an increase in PAC frequency.

Methods

Study design

The CHS is a prospective, community-based cohort study sponsored by the National Heart, Lung, and Blood Institute. Details regarding eligibility, enrolment, and follow-up have been previously published.^{4,5} Briefly, 5201 subjects 65 years of age or older were recruited between 1989 and 1990 from a random sample of Medicare beneficiaries by four academic centres (Johns Hopkins University, Wake Forest University, University of Pittsburgh, and University of California, Davis). The institutional review board at each centre approved the study, and each participant gave informed consent. An additional 687 black patients were recruited between 1992 and 1993. All participants underwent a medical history, measurement of anthropometrics and vital signs, laboratory testing, and 12-lead ECG at enrolment. Participants were then followed with annual clinic visits and semi-annual telephone contact for 10 years, with telephone contact continued every 6 months thereafter.

Consent

Participants provided written informed consent, and the study protocol was approved by the institutional review board of each centre.

Study population

Our analysis was restricted to the subset of 1392 participants free of prevalent AF, a paced rhythm, and wandering atrial rhythm randomly assigned to 24-h ambulatory ECG (Holter) monitoring during their initial assessment and who were part of the initial recruitment cohort (those recruited between 1989 and 1990).

Holter assessment

Holter data was analysed at the Washington University School of Medicine Heart Rate Variability Laboratory using a MARS 8000 Holter scanner (GE Medical Systems, Milwaukee, WI, USA). All PACs were identified and manually reviewed to ensure accuracy. PAC frequency was characterized as PACs per hour, defined as the total number of PACs divided by the duration of the Holter recording.

Covariate ascertainment

Demographics and anthropometric measurements

Self-identified race was categorized as white, black, Asian/Pacific Islander, and other. Due to the small number of non-white participants, race was dichotomized as white vs. non-white for the regression analyses. Level of education was determined according to self-reported number of

educational years. Measurements of height, weight, waist and hip circumferences, and blood pressure were obtained as previously described.⁴

Cardiovascular comorbidities

Hypertension was defined as either a reported history of physician-diagnosed hypertension combined with the use of antihypertensive medications or a baseline study visit systolic blood pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg. Diabetes was defined as use of an anti-hyperglycaemic medication at baseline or a fasting glucose level ≥ 126 mg/dL (7.0 mmol/L). Congestive heart failure (CHF) and myocardial infarction (MI) were identified by participant self-report and confirmed by medical record review.⁵ Coronary heart disease (CHD) was defined as angina, previous MI, previous coronary artery bypass graft surgery, or previous angioplasty identified by participant self-report and confirmed by medical record review.⁵

Physical activity

Usual leisure-time activity was assessed using a modified, validated Minnesota Leisure-Time activity questionnaire.⁶ The questionnaire evaluated frequency and duration of 15 different activities during the prior 2 weeks, including gardening, mowing, raking, swimming, hiking, aerobics, tennis, jogging, racquetball, walking, golfing, bicycling, dancing, calisthenics, and exercise cycling. Each activity was defined as having an intensity value in metabolic equivalent task (MET) units, and participant responses regarding types, frequency, and duration of each activity were used to calculate weekly energy expenditure (kcal/week) from leisure-time activity. Usual exercise intensity was also separately assessed: based on the highest intensity leisure-time activity reported over the prior 2 weeks, participants were categorized as having engaged in high, moderate, or low-intensity activity or none. High-intensity activity was estimated to require >6 METs.⁶ To ascertain the association of at least moderately intensive exercise with PAC frequency, exercise intensity was dichotomized into no and low exercisers vs. moderate and high-intensity exercisers for regression analyses.

Medications

Baseline angiotensin converting enzyme-inhibitor, beta-blocker, and calcium channel blocker use were ascertained using an in-home medication inventory. Use of a particular medicine required a current prescription filled by a pharmacist or physician that was taken by the patient in the previous 2 weeks.

Habits

Self-reported usual consumption of the number of alcoholic drinks (one drink was defined as a 12-ounce can or bottle of beer, a 6-ounce glass of wine, or a shot of liquor) was used to estimate weekly alcohol consumption. Smoking status was dichotomized as ever (current and former) vs. never smokers.⁴

Echocardiography

The echocardiographic assessment of participants in the CHS has been previously described.⁷ Left ventricular (LV) function was qualitatively assessed from the 2D imaging views, where at least 80% of the myocardium was visualized. Function was categorized as qualitatively normal, borderline or abnormal, with 94% inter-reader agreement and 98% intra-reader agreement of paired studies.⁷ Due to the small number of participants with ejection fraction classified as 'abnormal', qualitative ejection fraction was dichotomized for regression analyses into (i) borderline or abnormal vs. (ii) normal.

Additional echocardiographic measurements were available in only 927 participants: left atrium diameter, LV mass index, and fractional shortening were derived from M-mode measurements.

Ascertainment of atrial fibrillation

Prevalent AF was defined as a reported history of AF at the first study encounter, on baseline 12-lead ECG, or on baseline Holter monitoring. Incident AF was ascertained from the serial 12-lead ECGs conducted at each annual clinic visit through 1999 and medical records (discharge diagnosis codes supplemented by Medicare claims data) for all hospitalizations after enrolment. The date of incident AF was defined as the time that AF by any of these measures was first identified. Follow-up ended at the time of AF diagnosis, time of death, or end of the year 2008.

Statistical analysis

Continuous variables with a normal distribution are presented as mean $\pm$ standard deviation (SD) and were compared using the Student's *t*-tests. Non-normally distributed continuous variables are presented as medians with interquartile ranges (IQR) and were compared using the Mann–Whitney *U* test. Categorical variables are presented as numbers and percentages and were compared using the χ^2 test.

Linear regression was used to estimate the associations between covariates and PAC frequency, which was log base 2 transformed to meet normality assumptions. Most continuous covariates were expressed in units of SD, and their regression coefficients (β s) were back-transformed using the standard formula $100*[\exp(\beta*\ln(2)) - 1]$ in order to obtain estimates of the percentage difference in PAC frequency per SD increase (or presence vs. absence) in the predictor. Given the skewed distribution of kilocalories of activity, a log base 2 transformation was applied to meet model linearity assumptions; back transformation, using the same formula yielded the percentage increment in PAC frequency for each doubling of the kilocalories of physical activity.

Multivariate models included covariates associated with the outcome with $P < 0.10$ in unadjusted analysis; age and sex were then forced into the model and retention of other covariates was determined by backwards selection until all *P*-values were < 0.10 . Multivariable-adjusted predictors were categorized as immutable (e.g. age and height), potentially modifiable (e.g. ejection fraction), and directly modifiable (such as conditions that could be modified with available medicines or habits that could, at least theoretically, change).

The covariates independently associated with baseline PAC frequency were carried forward to mediation analyses. Cox proportional hazards models adjusted for age, sex, history of hypertension, diabetes, MI, and CHF were used to assess the crude and adjusted association between the predictors and incident AF before and after inclusion of log base 2-transformed PAC frequency in the model. The proportional hazards assumption was assessed using scaled Schoenfeld residuals, and the assumption of linearity was assessed with inclusion of cubic-spline terms for continuous predictors. The assumptions of proportional hazards and linearity were met in all Cox models. The 'percent treatment effect' methodology was used to assess the degree of mediation by PACs. Confidence intervals (CIs) for mediation statistics were obtained using bootstrap resampling with 500 repetitions.

Data were analysed using SPSS® Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). A two-tailed $P < 0.05$ was considered statistically significant.

Results

The mean length of Holter recording was 21.8 ± 2.5 h, yielding a median hourly frequency of PACs of 2.7 (IQR 0.8–12.1). The baseline

characteristics of the participants are presented in the Table 1. Individuals exhibiting above the median PAC frequency were older, more often male, taller, had a lower body mass index (BMI), more often presented with a history of MI, and had a lower ejection fraction (Table 1). Unadjusted predictors of PAC frequency are shown in Table 2. After multivariable adjustment, older age, taller height, lower BMI, and a history of MI were each statistically significantly associated with increasing PAC frequency. Regarding modifiable predictors, use of beta-blockers and performing at least moderate intensity exercise predicted lower PAC frequency (Figure 1).

In the subpopulation with fractional shortening, LV mass index, and left atrium diameter measurements available, an increased LV mass index was additionally independently associated with a higher PAC frequency while a history of MI lost its statistical significance (Figure 1).

Mediation analyses

Over a mean follow-up of 11.8 ± 5.7 years, 400 participants (28.7%) developed AF. The mean time to incidence of AF was 8.5 ± 4.9 years. Every doubling in PAC frequency was associated with a 16% (95% CI 13–20%, $P < 0.0001$) increase in the incidence of AF after adjusting for age, sex, history of hypertension, diabetes, MI, and CHF. Of the covariates independently associated with PAC frequency, older age, taller height, a history of MI, and lower exercise intensity, each independently predicted a greater incidence of AF (Table 3). A greater PAC frequency explained approximately one-third of the relationship between older age and incident AF risk and about one-fourth of the association between taller height and incident AF (Table 3).

Discussion

Immutable risk factors for increasing PAC frequency included older age and taller height, and potentially modifiable risk factors included a lower BMI and a history of MI. Regarding directly modifiable predictors, beta-blocker use and a higher intensity of physical exercise were each independently associated with a lower PAC frequency. Pertinent negatives in this cohort included the absence of a detectable statistically significant relationship between PAC frequency and elevated blood pressure, diabetes, CHF, history of smoking, or increasing alcohol use. Finally, in considering the relationship between PAC frequency and established AF risk factors, an increased PAC frequency statistically explained a substantial proportion of the heightened AF risk attributed to greater age and taller height.

To our knowledge, there is only one other community-based study to describe predictors of PAC frequency.⁸ In that study, which included neither echocardiographic data nor information regarding incident AF, older age, a taller stature, a history of cardiovascular disease, and less physical activity were associated with a higher PAC frequency.

Age is known to be one of the most potent risk factors for AF, but the precise mechanism(s) remain unknown. Based on speculation, this may be related to age-related fibrotic changes in the atrial substrate, potentially leading to conduction heterogeneity and other aberrant electrophysiologic properties prone to fibrillation⁹ once triggered by a PAC.¹⁰ In addition to confirming previous observations connecting increasing age and increasing PAC counts,⁸ we showed that a substantial proportion of the risk of AF due to age was itself mediated by an increasing PAC count. Our findings are thus

Figure 1 Multivariable-adjusted predictors of PAC. Multivariable models including all covariates listed for each population (please see the Methods section for selection of covariates); †Percent increase in PACs per hour per SD of continuous covariate or the presence (vs. absence) for each categorical variable; ‡dichotomized into high and intermediate intensity exercisers vs. low intensity and no exercisers. CI, confidence interval; LV, left ventricular; PACs, premature atrial contractions; SD, standard deviation.

consistent with the hypothesis that the age–AF relationship is not only explained by atrial substrate effects but also by increasing the frequency of the triggers that may act on that substrate.

Taller stature has been established as a risk factor for AF,¹¹ but the reason remains unknown. Efforts have failed to identify any cardiovascular risk factors that mediate the height–AF relationship,¹¹ and indeed tall stature is otherwise not associated with traditional cardiovascular comorbidities. We found that taller individuals have more PACs, and that the associated increased PAC frequency may explain the relationship between taller stature and AF. Atrial fibrillation patients are known to have larger pulmonary veins compared to healthy controls.¹² Perhaps the larger pulmonary veins of taller individuals have histological and electrophysiological characteristics that generate more PACs.

Surprisingly, lower BMI arose as an independent predictor of higher PAC frequency, an observation not previously reported. A low BMI has been associated with excess morbidity in the very elderly,¹³ and our finding might be interpreted as related to this phenomenon. It is also possible that those who are less obese have other subtle hormonal or autonomic differences that might more likely promote PACs.

Obesity, hypertension, diabetes, alcohol use, and smoking, all known predictors of AF,^{14–16} were not associated with a higher PAC frequency. Left atrial size, known to be enlarged among AF patients,¹² also did not exhibit a relationship with PACs. While these negative findings could be attributed to insufficient power, the point estimates generally did not favour an association, and the study was clearly sufficiently powered to detect several other positive relationships. Indeed, as we consider categorizing mechanisms of AF into those related to the myocardial ‘substrate’ (such as a general

electrophysiologic or structural milieu prone to fibrillation)⁹ vs. triggers manifesting as PACs,¹⁰ it is interesting to consider how AF risk factors might or might not influence each.

We found that those receiving beta-blockers exhibited significantly fewer PACs both before and after multivariable adjustment. While this may not be a surprising finding, there are two points worthy of comment. First, although prescribing beta-blockers for atrial ectopy is commonly performed, there is no existing data that has demonstrated successful suppression of PACs among free-living individuals. Second, although ‘effect-cause’ is a possibility in this cross-sectional analysis, one would expect those prescribed beta-blockers to have a *greater* likelihood of PACs (either due to underlying cardiovascular disease or symptomatic palpitations that may have led to the medicine’s indication), suggesting that the beta-blockers do themselves indeed have a protective effect.

Those who engaged in a higher intensity of physical activity exhibited fewer PACs. Interestingly, consistent with our findings, a recent analysis of recreational athletes demonstrated a relationship between increased lifetime training and left atrial enlargement without any associated increase in atrial ectopy¹⁷—taken together, these data likely suggest that the subtype of AF found in athletes is different than PAC-mediated AF. Given the absence of a clear association between blood pressure and PAC frequency, it appears physical activity may reduce PACs via some other mechanism. Increased physical activity is also known to reduce general inflammation and sympathetic nervous activity, both of which may be related to atrial arrhythmias.^{18,19} It is also possible that the participants with more PACs did not tolerate more physical exertion precisely because of their frequent PACs (another example of effect-cause). If that is indeed the case, the harms of PACs^{2,3} may be in part explained by less physical activity,

Table 1 Baseline characteristics of participants ($n = 1392$) exhibiting below and above the median number of PACs per hour (median = 2.7)

Characteristics	≤Median PACs per hour ($n = 697$)	>Median PACs per hour ($n = 695$)	P-value
Age (years)	70.8 ± 4.3	73.1 ± 5.3	<0.0001
Sex, male	288 (41%)	357 (51%)	<0.0001
Race			0.67
White	662 (95%)	659 (95%)	
Black	31 (4.4%)	32 (5%)	
American Indian/Alaskan	2 (0.3%)	1 (0.1%)	
Asian/Pacific Islander	1 (0.1%)	0 (0%)	
Other	1 (0.1%)	3 (0.4%)	
Educational level (years)	14.2 ± 4.4	14.1 ± 4.6	0.63
Height (cm)	166.9 ± 9.4	169.1 ± 9.5	<0.0001
Weight, kg	72.8 ± 12.8	72.7 ± 13.5	0.93
Body mass index	27.1 ± 4.3	26.2 ± 4.0	<0.0001
Waist to hip ratio	0.92 ± 0.08	0.92 ± 0.09	0.97
Heart rate (b.p.m.)	64.4 ± 10.1	63.1 ± 11.0	0.04
Systolic blood pressure (mmHg)	133.8 ± 20.5	135.2 ± 21.3	0.21
Diastolic blood pressure (mmHg)	70.1 ± 11.2	70.0 ± 11.2	0.81
Hypertension	395 (57%)	367 (53%)	0.12
Diabetes	109 (16%)	98 (14%)	0.41
Coronary heart disease	129 (19%)	169 (21%)	0.19
Congestive heart failure	19 (3%)	23 (3%)	0.54
Myocardial infarction	62 (9%)	92 (13%)	0.01
Physical activity (kcal/week) (IQR)	1290 (540–2730)	1240 (530–2600)	0.27
Exercise intensity			0.19
No exercise	35 (5%)	45 (7%)	
Low	313 (45%)	342 (49%)	
Intermediate	263 (38%)	241 (35%)	
High	83 (12%)	69 (10%)	
ACE-inhibitors	47 (7%)	37 (5%)	0.26
Beta-blockers	119 (17%)	78 (11%)	0.002
Calcium channel blockers	74 (11%)	78 (11%)	0.74
Alcohol consumption (units per week)	2.4 ± 5.6	2.5 ± 5.9	0.79
Smoking status			0.002
Never	332 (48%)	303 (43%)	
Ex-smoker	294 (42%)	332 (48%)	
Current smoker	69 (10%)	61 (9%)	
Left ventricular ejection fraction			0.048
Normal	645 (93%)	614 (89%)	
Borderline	32 (5%)	46 (7%)	
Abnormal	16 (2%)	27 (4%)	
Left ventricular mass index (g/m^2) ^a	81.3 ± 21.2	88.3 ± 27.0	<0.0001
Left ventricular fractional shortening ^a	0.42 ± 0.08	0.41 ± 0.08	0.17
Left atrium diameter (mm) ^a	38.5 ± 6.1	39.1 ± 6.5	0.14

Data are presented as means (SD), medians (IQR) or numbers (percentage). P-values are based on Student's t-test, Mann–Whitney U test and χ^2 -test.

P values < 0.05 are shown in bold.

ACE, angiotensin converting enzyme; IQR, interquartile range; PAC, premature atrial contraction; SD, standard deviation.

^aAvailable for 927 participants.

itself an important predictor of cardiovascular morbidity and mortality.⁶

Our study has several strengths and limitations that should be acknowledged. First, we utilized 24 h Holter monitoring, considered

the reference standard in quantification of PACs. This was performed in a community-based population not prone to referral bias inherent to medical record-based analyses. All participants underwent echocardiography as part of the research study using the same protocol

Table 2 Unadjusted associations of the variables and frequency of premature atrial contractions

Characteristic, unit (SD)	Percent increase ^a	(95% CI)	P-value
Immutable			
Age, years (4.9)	25	(19 to 30)	<0.0001
Male	34	(22 to 47)	<0.0001
White race vs. non-white	−5	(−23 to 18)	0.66
Height, cm (9.5)	16	(11 to 22)	<0.0001
Potentially modifiable			
Educational level, years (4.5)	−3	(−7 to 2)	0.24
Weight, kg (13.2)	2	(−3 to 7)	0.49
Body mass index (kg/m ²) (4.2)	−9	(−14 to −5)	<0.0001
Waist to hip ratio (0.08)	2	(−3 to 7)	0.39
Heart rate, b.p.m. (10.5)	−4	(−8 to 1)	0.11
Hypertension	−5	(−14 to 4)	0.29
Diabetes	−5	(−17 to 9)	0.49
Coronary heart disease	4	(−8 to 17)	0.52
Congestive heart failure	16	(−12 to 53)	0.29
Myocardial infarction	28	(10 to 49)	0.002
Ejection fraction, reduced ^b	20	(1 to 42)	0.04
Left ventricular (LV) mass index, g/m ² (24.5) ^c	18	(12 to 26)	<0.0001
LV fractional shortening, % (8.1) ^c	−8	(−14 to 3)	0.003
Left atrium diameter, mm (6.3) ^c	2	(−3 to 7)	0.40
Directly modifiable			
Systolic blood pressure, mmHg (20.1)	4	(−1 to 8)	0.14
Diastolic blood pressure, mmHg (11.2)	0	(−5 to 5)	0.98
Leisure-time physical activity, kcal/week ^d	−1	(−2 to 0)	0.20
Exercise intensity ^e	−11	(−19 to −2)	0.02
ACE-inhibitors	−5	(−22 to 17)	0.65
Beta-blockers	−20	(−30 to −8)	0.001
Calcium channel blockers	−1	(−15 to 15)	0.86
Alcohol consumption, units/week (5.8)	3	(−2 to 8)	0.30
Smoking status ^f	10	(0 to 21)	0.051

P values < 0.05 are shown in bold.

ACE, angiotensin converting enzyme; CI, confidence interval; PAC, premature atrial contraction; SD, standard deviation.

^aPercent increase in PACs per hour per SD in continuous covariate/presence vs. absence of dichotomous covariate.

^bDichotomized into abnormal and borderline ejection fraction vs. normal ejection fraction.

^cAvailable for 927 participants.

^dPercent increase in PACs per every doubling of leisure-time physical activity.

^eDichotomized into high and intermediate intensity exercisers vs. low intensity and no exercisers.

^fDichotomized into ever smokers vs. never smokers.

and interpreted by a single, core laboratory. The population was subsequently followed for decades for incident AF, allowing for several novel mediation analyses.

As the study was conducted in an elderly, mainly Caucasian population, extrapolation of the results to other groups should be done with caution. The observational nature of our study does not allow any conclusions to be made about the causality between the cardiovascular risks observed and PAC frequency nor between PACs and incident AF. We cannot distinguish between acute and chronic effects of the covariates involved and certainly cannot exclude the possibility that the acute effects of some of these potential predictors yet remain important. For example, although neither smoking nor alcohol exhibited significant relationships with PAC frequency, it remains possible that binge drinking or discrete smoking episodes

may yet increase PAC frequencies in more immediate time-frames. Neither diurnal distribution of PACs nor their coupling intervals, both of which may be relevant to AF pathogenesis,²⁰ were available for the current analyses. Finally, as with any observational study, although we adjusted for relevant covariates, we cannot exclude residual confounding or confounding due to unmeasured factors.

Conclusions

Several independent predictors of an increased frequency of PACs were observed, including older age, a taller height, a lower BMI, and a history of MI. Directly modifiable predictors included beta-blocker use and a higher intensity of physical exercise, serving as potential

Table 3 Covariates independently associated with PAC frequency examined as predictors of AF with emphasis on the mediator effect of PAC frequency

Covariate (SD)	Unadjusted models			Multivariate adjusted models			Multivariate models adjusted for PACs			Proportion of associated AF risk explained by PACs		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	%	95% CI	P-value
Age, years (4.9)	1.47	1.33–1.62	<0.0001	1.42	1.28–1.57	<0.0001	1.26	1.14–1.39	<0.0001	34	22 to 57	<0.0001
Height, cm (9.5)	1.31	1.20–1.45	<0.0001	1.29	1.12–1.49	0.001	1.21	1.03–1.40	0.01	27	10 to 57	0.004
Body mass index, kg/m ² (4.2)	1.01	0.92–1.12	0.80	–	–	–	–	–	–	–	–	–
Use of beta-blockers	0.97	0.72–1.29	0.81	–	–	–	–	–	–	–	–	–
Myocardial infarction	2.13	1.61–2.82	<0.0001	1.60	1.19–2.15	0.002	1.51	1.12–2.03	0.01	13	–20 to 76	0.29
Exercise intensity ^a	0.78	0.64–0.95	0.02	0.81	0.66–0.99	0.04	0.84	0.69–1.03	0.09	19	–16 to 122	0.22

Each HR represents separate Cox regression model. Covariates in adjusted models include age, sex, history of hypertension, diabetes, MI, heart failure (and the observed covariate if not already included). Hazard ratios interpreted as a hazard for the presence (vs. absence) of each categorical covariate or for the increase of 1 SD for continuous covariate. P values < 0.05 are shown in bold.

AF, atrial fibrillation; HR, hazard ratio; MI, myocardial infarction; PAC, premature atrial contraction; SD, standard deviation.

^aDichotomized into high and intermediate intensity exercisers vs. low intensity and no exercisers.

strategies to consider if a reduction in PAC frequency is desirable. The relationships between older age and taller height and incident AF may be explained in part by increasing PAC frequency, while other characteristics (such as hypertension, diabetes, and obesity) may lead to AF by affecting the general atrial myocardial substrate rather than by increasing PAC triggers.

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