Low Heart Rates Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men

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Background—Low resting heart rate (HR) has been associated with atrial fibrillation (AF) in athletes. We aimed to study whether low HR at rest or during exercise testing was a predictor of AF in initially healthy middle-aged men.

Methods and Results—A total of 2014 healthy Norwegian men participated in a prospective cardiovascular survey, including a standardized bicycle exercise test in 1972 to 1975. During ≤35 years of follow-up (53 000 person-years of observation), 270 men developed incident AF, documented by scrutiny of health charts in all Norwegian hospitals. Risk estimation was analyzed with Cox proportional hazard models. Low exercise HR after 6 minutes exercise on the moderate workload of 100 W (HR100W) was a predictor of incident AF. Men with HR100W <100 beats per minute (n=260) were characterized by high physical fitness, low resting and low maximum HR, and they had 1.60-fold AF risk (95% confidence interval, 1.11–2.26) compared with men with HR100W ≥100 beats per minute when adjusted for age, systolic blood pressure, and physical fitness. Additional adjustment for relative heart volume slightly reduced the association. The subgroup of men (n=860) with hypertensive blood pressure measurements at baseline had the highest risk difference between low and high HR100W with hazard ratio 2.08 (1.19–3.45).

Conclusions—Our data indicate that low exercise HR on a moderate workload is a long-term predictor of incident AF in healthy middle-aged men. Elevated baseline blood pressure substantially amplifies this risk. The present results suggest a relationship between increased vagal tone, high stroke volumes and incident AF, and particularly so in physically fit men. **(*Circ Arrhythm Electrophysiol*. 2013;6:726-731.)**

Key Words: atrial fibrillation ■ heart rate ■ exercise test ■ epidemiology ■ men

The incidence of atrial fibrillation (AF) is increasing in the general population warranting further knowledge about pathophysiological factors. Elevated resting heart rate (HR) has been established as an independent risk factor for cardiovascular mortality and morbidity, but still there is sparse knowledge about the relation to incident AF.[1–3] In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, an increased AF risk was associated with higher in-treatment resting HR independent of blood pressure (BP) lowering.[4] There is growing evidence that long-standing endurance training may increase the risk of AF in middle-aged populations, and a Norwegian study in master cross-country skiers found that low resting HR was the sole long-term predictor of AF.[5]

Clinical Perspective on p 731

In our study cohort of >2000 initially healthy men, we have recently shown that systolic and diastolic BP in the upper normal range are long-term predictors of AF.[6] In the present study, we aim to examine whether low HR at rest or during exercise testing predicts incident AF in healthy middle-aged men. We also explore the influence of associated conditions related to AF risk, in terms of diabetes mellitus and acute myocardial infarction.

Methods

Study Cohort

From 1972–1975, 2014 apparently healthy men aged 40 to 59 years from 5 governmental institutions in Oslo were included in a prospective cardiovascular survey. The participants were defined as healthy if they had no evidence of heart disease or diagnosed hypertension requiring drug treatment, no diabetes mellitus, thyroid disorder, cancer, advanced pulmonary, renal or liver diseases, or other serious disorders. In all, 2341 men fulfilled the health criteria, and 2014 (86%) agreed to participate. All underwent a full clinical examination, blood tests, chest x-ray, resting ECG, and bicycle exercise test. Detailed descriptions of the inclusion process and examination procedures are given elsewhere.[7] The study was approved by the Norwegian Health Authorities, and informed consent was obtained from all the participants.

Measurements and Definitions

The examinations took place between 7.00 and 11.00 AM, and the participants were requested to abstain from smoking and eating for ≥8

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hours. Resting BP was measured thrice manually to the nearest even 2 mm Hg with a calibrated mercury sphygmomanometer after 5 minutes in the supine position in a quiet room. We defined hypertensive BP measurements as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. Resting HR was measured by auscultation for exactly 1 minute using a stopwatch. After another 5-minute rest a standard supine 12-lead ECG was taken. The exercise ECG test was performed with an electrically braked bicycle (Siemens-Elema, Sweden) with initial load of 100 W (600 kpm/min), increasing by 50 W every 6 minutes, until exhaustion or termination by the investigator for safety reasons. Submaximal termination—mainly because of chest pain, ST-depression, brief arrhythmias, or patient unwilling to continue—occurred in 91 men (4.5%), described in detail elsewhere.[8] Total work capacity was calculated as the sum of work at all workloads, and physical fitness as total work capacity in kilojoules divided by body weight. Because echocardiography was not an established clinical method in 1972–1975, relative heart volume (mL/m^2 body surface area) was measured on chest x-ray films by a trained radiologist as described elsewhere (not available in 30 men).[9] Further details of the study population and definitions are found in the online-only Data Supplement.

HR Variables

HR at 100 W exercise (HR100W) describes HR measured at 6-minute exercise, just before the next 50-W load increase according to protocol. This workload was of specific interest as we have previously shown that 6-minute exercise systolic BP was a strong and independent predictor of cardiovascular death.[10] For categorical analyses, we chose HR limits applied in previous studies or considered clinically relevant. At submaximal workload, the HR limit of 100 beats per minute has also been applied earlier in the prediction of cardiovascular disease mortality in healthy men.[11] The term HR reserve refers to the difference between maximal and resting HR.

Morbidity and Mortality Data

Morbidity data were consecutively obtained from 3 clinical surveys (1979–1982, 1989–1990, and 1995–1996), 1 questionnaire survey (1987) and 2 nationwide searches by 2 of the investigators (J.B., J.E.) in all patient records in all Norwegian hospitals (1995–1996 and 2005–2008, respectively). Data were obtained from all available sections in the records, including ECG readings. Mortality data were obtained from the database of Statistics Norway, completed up to December 31, 2007 (end of the present study). None was lost to follow-up.

Atrial Fibrillation

Our primary end point AF was registered on the basis of data from the hospital medical records (code I48 in the *International Classification of Diseases-Tenth Revision*). The AF endpoints—including paroxysmal, persistent, and permanent AF and a few cases of atrial flutter—were confirmed by ECG or infrequently by documentation of cardioversion. Episodes of AF related to acute myocardial infarction, recent coronary artery bypass grafting, or valve replacement were not included. Seventeen men with an AF event were excluded from survival analyses, as exact event date was not available.

Statistical Analysis

Differences in baseline data between groups were tested by Student *t* test or Pearson χ^2 test according to data type. Univariable analyses of the risk of developing AF were estimated with Kaplan–Meier plots and tested with log-rank tests. All HR variables were tested both as continuous and categorical variables. Significant predictors in univariable analysis were entered into multivariable analysis, and a prediction model for AF was reached by stepwise forward variable selection. The first Cox regression model (model A) included adjustments for age, systolic BP, and physical fitness on the basis of age and BP as mandatory clinical variables and physical fitness as an essential variable for the specific issue of studying associations between AF and exercise HR. A Directed Acyclic Graph approach was used to identify a final model for assessing the relation between HR variables and AF, where potentially confounding variables were included, whereas intermediate variables were left out.[12] A minimal sufficient adjustment set for estimating the total effect of HR on incident AF by Directed Acyclic Graph were age, systolic BP, physical fitness, and relative heart volume. Accordingly, relative heart volume was included in the final model (model B). In subsequent analyses (model C), we stratified the cohort according to baseline BP measurements with multivariable adjustments as in model B. Supplementary Cox analyses, including competing risk of death on the predictive impact of HR100W, were performed. Finally, we performed separate Cox analyses where AF events were not included if diabetes mellitus, respective acute myocardial infarction occurred before an AF event; these conditions were additionally tested as time-varying covariates. The proportionality assumption for the Cox model was tested by time interaction terms. We calculated 95% confidence intervals throughout the analyses. A 2-sided value of $P<0.05$ was considered statistically significant. Data were analyzed using the statistical packages of JMP9 (SAS Institute Inc, Cary, NC) and STATA12 (StataCorp LP, College Station, TX).

Results

Baseline characteristics of our study cohort are shown in Table 1. Mean resting HR measured by auscultation was low (61 beats per minute) with almost identical HR obtained from the resting ECGs (r=0.89). Mean maximum exercise HR was 163 beats per minute and both resting and maximum HR decreased with age, 1.3 and 10.2 beats per minute per 10 years, respectively. At 6-minute exercise, representing on average 43% of maximal exercise capacity, mean HR100W was 118

Table 1. Baseline Characteristics

Characteristics	N=2014
Age at baseline, y	49.8 (5.5)
Body height, cm	176.7 (6.2)
Body weight, kg	76.8 (9.9)
BMI, kg/m^2	24.6 (2.8)
Current smoker, n (%)	882 (44)
Alcohol consumption, n (%)	448 (22)
Systolic BP, mm Hg	130 (18)
Diastolic BP, mm Hg	87 (10)
LVH, n (%)	106 (5)
Resting HR, beats per minute	61 (10)
PR-interval, ms	172 (25)
First-degree AV block, n (%)	108 (5)
Relative heart volume, mL/m^2	403 (59)
Total cholesterol, mmol/L	6.7 (1.2)
Exercise data	
HR100W, beats per minute	118 (16)
Low HR100W (<100 beats per minute), n (%)	260 (13)
Maximum HR, beats per minute	163 (14)
Heart rate reserve, beats per minute	101 (14)
Systolic BP100W, mm Hg	182 (24)
Maximum systolic BP, mm Hg	216 (22)
Total work performed, kJ	110 (45)
Total exercise time, min	13.9 (6)

Values are mean±SD or numbers (%). BMI indicates body mass index; BP, blood pressure; HR, heart rate; heart rate reserve, the difference between maximum exercise and resting heart rate; and LVH, left ventricular hypertrophy.

Table 2. Predictors of Atrial Fibrillation (Ranked by χ^2 in Multivariable Analysis)

	Multivariable Analysis			
Univariable Predictors of AF	Hazard Ratio	95% CI	*P* Value	χ^2
Age at baseline (10 y)	1.67	(1.29–2.17)	<0.001	14.7
Systolic BP (1SD)	1.23	(1.07–1.40)	<0.01	8.7
LVH (yes/no)	1.87	(1.17–2.86)	0.01	6.5
Relative heart volume (1SD)	1.18	(1.03–1.35)	0.02	5.8
BMI×relative heart volume			0.03	5.4
HR100W (1SD)	0.85	(0.73–1.0)	0.04	4.0
BMI (1SD)	1.14	(0.99–1.31)	0.06	3.4
Physical fitness (1SD)	0.90	(0.76–1.06)	0.2	1.5

Multivariable analysis performed with all the other variables listed in the final model, including the significant interaction term BMI×relative heart volume. HR100W was not a univariable predictor as a continuous variable but as a categorical variable. BMI indicates body mass index; BP, blood pressure; CI, confidence interval; HR, heart rate; HR100W, HR at 100 W; and LVH, left ventricular hypertrophy.

beats per minute. Subgroup analyses showed that resting HR and HR100W were lower at baseline among men with normal BP and high physical fitness (Table I in the online-only Data Supplement). There was a moderate correlation between HR100W and resting HR, respective maximum HR (r=0.59 and 0.35). Excluding the 91 men with submaximal exercise test did not influence the main results.

Predictors of AF

During median 30 years of follow-up (53 000 person-years of observation), 270 men (13%) developed AF representing an incidence rate of 5.1 per 1000 person-years. The mean age of diagnosis of AF was 71 years (range, 40–88 years). Univariable predictors of AF were age, systolic BP at rest/during exercise, left ventricular hypertrophy, body mass index (BMI), relative heart volume, and with inverse association: maximum HR, HR reserve, HR100W, and physical fitness. Age, resting systolic BP, relative heart volume, left ventricular hypertrophy, and HR100W (inverse) remained significant predictors in multivariable analyses (Table 2). There was a significant interaction between BMI and relative heart volume (P=0.02), and BMI was not a significant predictor with relative heart volume in the model. Physical fitness itself was not a multivariable predictor, neither as a continuous nor as a categorical variable. We did not find substantial collinearity in our prediction model.

HR Variables and Risk of AF

Table 3 summarizes the number of events and incidence rate of AF according to different HR variables. The highest incidence rates were found in men with very low or very high resting HR demonstrating a possible U-shaped relation, and the association with the highest, respectively the lowest physical fitness quartile is evident. Men with low HR100W had a high AF incidence rate of 6.6 per 1000 person-years.

The main results are shown in Table 4. Low resting HR <50 beats per minute found among 9% of the men, showed a nonsignificant trend toward increased AF risk in the subgroup with hypertensive BP measurements at baseline. We found that

Table 3. Incidence Rate of Atrial Fibrillation According to Heart Rate Variables

			Lowest Q PF		Highest Q PF	
Variables	(n of AF)	Incidence Rate	(n of AF/total n in Q)	Incidence Rate	(n of AF/total n in Q)	Incidence Rate
Resting heart rate, beats per minute						
≤45 (n=58)	(10)	6.3	(0/5)	0	(8/31)	9.0
46–49 (n=125)	(15)	4.6	(1/15)	2.9	(7/48)	4.9
50–74 (n=1657)	(225)	5.2	(47/402)	4.8	(53/420)	4.4
75–84 (n=125)	(12)	3.7	(5/56)	3.6	(1/11)	3.2
≥85 (n=49)	(8)	6.1	(5/23)	8.5	(0/4)	0
Heart rate 100 W, beats per minute						
<100 (n=260)	(46)	6.6	(4/21)	9.2	(27/142)	6.5
100–139 (n=1537)	(197)	4.9	(35/354)	4.1	(42/367)	4.0
≥140 (n=217)	(27)	4.8	(19/126)	6.0	(0/5)	0
Maximum heart rate, beats per minute						
<150 (n=268)	(36)	6.2	(16/133)	5.9	(3/28)	3.9
150–179 (n=1511)	(202)	5.0	(32/319)	4.0	(55/411)	4.7
≥180 (n=235)	(32)	4.5	(10/49)	7.0	(11/75)	4.8

Incidence rate (per 1000 person-years) of atrial fibrillation among 2014 men with a total of 270 atrial fibrillation events (incidence rate total cohort, 5.1 per 1000 person-years). AF indicates atrial fibrillation; n, number; and Q PF quartiles of age-adjusted physical fitness at baseline.

Table 4. Relative Risks of Atrial Fibrillation in Hazard Ratios (95% CI) According to Heart Rate Variables

Variables	Unadjusted (n=1997)	Model A (n=1997)	Model B (Model A+rHV; n=1967)	Model C (Model B, Hypertensives; n=846)
Resting HR, beats per minute				
<50 (n=181)	0.99 (0.67–1.59)	1.10 (0.69–1.66)	1.06 (0.66–1.61)	1.69 (0.79–3.21)
≥50 (n=1816)	1	1	1	1
HR100W, beats per minute				
<100 (n=257)	1.40 (1.00–1.92)	1.60 (1.11–2.26)	1.48 (1.02–2.10)	2.08 (1.19–3.45)
≥100 (n=1740)	1	1	1	1
AMI before AF*				
<100 (n=257)	1.28 (0.85–1.87)	1.39 (0.90–2.10)	1.26 (0.80–1.92)	1.95 (1.00–3.51)
≥100 (n=1740)	1	1	1	1
Diabetes mellitus before AF†				
<100 (n=254)	1.52 (1.07–2.09)	1.71 (1.18–2.43)	1.56 (1.07–2.23)	2.49 (1.45–4.09)
≥100 (n=1725)	1	1	1	1
Maximum HR, beats per minute				
<150 (n=265)	1.53 (1.04–2.18)	1.29 (0.87–1.87)	1.17 (0.78–1.70)	1.33 (0.75–2.23)
≥150 (n=1732)	1	1	1	1

AF indicates atrial fibrillation; AMI, acute myocardial infarction; CI, confidence interval; HR, heart rate; HR100W, HR at 100 W; and rHV, relative heart volume. Model A, multivariable adjustments for age, systolic blood pressure, and physical fitness; model B: model A+adjustment for rHV; model C, model B in the subgroup of men with baseline hypertensive blood pressure measurements.

*Not including AF if AMI occurred before an AF incident, 185 AF events remaining.

†Not including AF if diabetes mellitus (excluding cases that do not have exact date of diagnosis) occurred before an AF incident, 213 AF events remaining.

the men who did not exceed 100 beats per minute at the end of 6-minute workload had a significantly increased AF risk; this significance was marginal in the unadjusted analysis but clear in the adjusted model A. The inclusion of relative heart volume (model B) decreased the strength of the association. The strongest association was observed in men with baseline hypertensive BP measurements (model C). Extended analysis with death as competing risk weakened the results marginally. Including additional variables to model B (BMI, interaction term, left ventricular hypertrophy, HR reserve) did not influence the main result. Figure demonstrates the cumulative incidence of AF during follow-up according to low and high HR100W. The 2 curves diverge visually after ≈10 years and thereafter show a proportional risk development. Baseline characteristics according to HR100W showed that low HR100W was associated with bigger men (increased height, weight, and relative heart volume) with low resting HR and long PR-interval. Interestingly, men with low HR100W had high physical fitness, but low maximum HR, and as a group they also had low BP at baseline (Table II in the online-only Data Supplement).

We additionally analyzed tertiles of HR100W, and the lowest tertile (HR100W <110 beats per minute) showed significantly increased AF risk compared with the highest tertile (HR100W ≥125 beats per minute). Neither maximum HR nor HR reserve was a multivariable predictor. *C*-statistics using traditional risk variables for AF showed that the area under the curve was only marginally increased with the new variable HR100W in the model.

Associated Conditions

Among the participants who developed AF, 68 were diagnosed with acute myocardial infarction and 22 with diabetes mellitus before an AF event. Not including the AF events after diabetes mellitus demonstrated even stronger association between HR100W and AF (Table 4). Not including the higher number of AF events after acute myocardial infarction (leaving 185 AF events) showed attenuated results but still significant in adjusted model A in the subgroup of men with above median physical fitness (data not shown). Analyses with these conditions as time-varying covariates had minor impact on the main results.

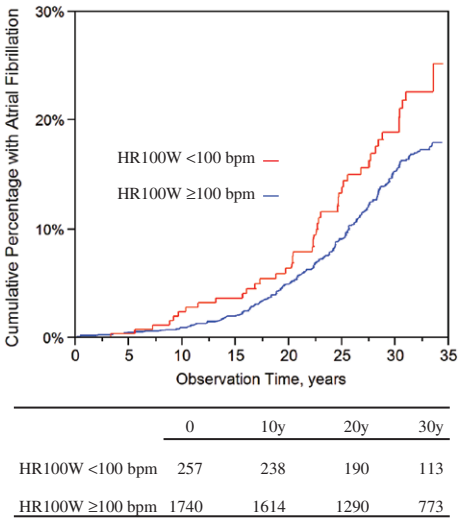

Figure. Kaplan–Meier curves showing cumulative risk of atrial fibrillation (AF %) through 35 years of follow-up among 1997 initially healthy middle-aged men according to heart rate (HR) at 100-W (6 minutes) exercise during standardized bicycle exercise test. Log-rank, *P*=0.04.

Discussion

In our long-term follow-up study of 2014 initially healthy middle-aged men, 13% developed AF. Low HR after 6-minute exercise on 100-W workload was a significant long-term predictor of incident AF. The men with low HR100W comprised a predominantly low-risk group for cardiovascular diseases with low BP and high physical fitness. One might argue that the fit men had low HR100W because this workload was far below their maximum capacity but as a group they also showed significantly decreased maximum exercise HR. This new variable HR100W did not alter established risk prediction scores for AF significantly, but our findings highlight possible mechanisms underlying AF, especially among fit persons.

Comparison With Related Studies

Valid comparison of epidemiological data requires standardized techniques of measurements.[13] The standardized HR measurements used in our study probably, in part, explain our low mean resting HR compared with other cohorts.

Several large epidemiological studies have shown that high resting HR is associated with increased morbidity and mortality.[1–3] Low resting HR is generally associated with better physical fitness and good prognosis.[14] In the present study, we confirm the association between low resting HR and high physical fitness and, moreover, demonstrate a trend toward an increased AF risk among fit men with low HR at rest. This is in accordance with a small study in male athletes demonstrating a high prevalence of AF among middle-aged and old endurance trained skiers after long-term follow-up, where the only predictors of AF were long PR-interval and resting bradycardia (mean HR, 44 beats per minute).[5] There might be a U-shaped curve relating AF to resting HR, however not confirmed in our cohort, although the small proportion of men with resting HR ≥85 beats per minute demonstrated increased crude event rate of AF. Our findings might thus be in accordance with the results from the patients with hypertension in the LIFE study, where resting HR >84 beats per minute was predictive of AF.[4]

Stroke Volume, HR, and Exercise

Long-term endurance exercise training, related to increased AF risk in several smaller studies, is known to lower resting HR and to increase maximal cardiac output, both effects eventually increasing stroke volume.[15] In our study, the association between low HR and AF risk was attenuated when adjusting for relative heart volume, which might indicate that elevated heart volumes accounted for at least part of the observed risk association with AF. This bears a resemblance to results from Wang et al[16] where the association between high BMI and AF risk became insignificant after adjustments for left atrium size concluding that left atrium enlargement accounted for the entire observed risk association.

During moderate exercise, the increase in cardiac output will be mediated by a larger increase in stroke volume by the ones who show a modest increase in HR, and thus physical training might further contribute to increased cardiac volumes. Our results fit well within the hypothesis that increased stroke volumes—and larger atrial filling volumes causing elevated wall tension—may be associated with increased susceptibility to AF.[17]

Low HRs and Elevated Blood Pressure

The finding that the combination of elevated baseline BP and low HR was associated with considerably increased AF risk was not present in the LIFE results, but the substantial differences in the study populations complicate a direct comparison.[4] Extra large stroke volumes because of low HR might even contribute to higher BP if assuming that aorta is unable to expand fast enough to absorb the larger blood volumes without a BP increase. An imbalance in the autonomic nervous system between sympathetic and vagal influence, as discussed below, might also be an explanation. HR100W is not a very strong predictor of AF by itself, but our present findings might supplement the well-known association between hypertension and AF, especially in fit men. Men with hypertensive BP measurements at baseline compared with normotensive men had, as expected, a considerably higher AF risk, but particularly interesting; the predictive impact of high BP was stronger with concomitant low HR.

The Autonomic Nervous System

The initial HR increase during exercise is considered mainly to be caused by vagal withdrawal and the subsequent HR increase by sympathetic activation.[18] The balance between parasympathetic and sympathetic activity is considered to be involved in both the initiation and the maintenance of AF.[19] The present main results—an increased AF risk associated with low HR at moderate exercise in healthy men—might suggest involvement of an inappropriate HR response to exercise with prolonged parasympathetic activation. Vagally mediated paroxysmal AF may be particularly important in athletic men without apparent heart disease.[20] Elucidating the possible pathophysiological mechanisms of the present findings is, however, complicated. Some of the men with low HR100W, particularly those with low fitness, might have a subclinical heart disease and thereby impaired autonomic function. Alterations in autonomic balance may partly explain the opposite effects related to diabetes mellitus, respective acute myocardial infarction, diagnosed before an AF event. We found an amplified association between low HR100W and AF risk when AF events after diabetes mellitus were not included. This is consistent with a study reporting decreased vagal activity and hence higher sympathetic activity among diabetic subjects.[21] In contrast, prior myocardial infarction attenuated the association between low HR100W and AF, particularly in unfit men. This observation is also in accordance with previous studies suggesting that reduced HR response to exercise, labeled chronotropic incompetence, may be an appropriate compensatory parasympathetic hyperactivity to latent ischemic heart disease.[22,23]

In conclusion, low HR at moderate exercise, associated with high physical fitness and elevated heart volumes, seems to predict AF in healthy middle-aged men, possibly because of a relative predominance of parasympathetic activity. Baseline elevated BP amplifies the risk substantially. The present study supports the view that even the best fit, healthy persons may be at increased risk of developing AF.

Limitations

Our study included healthy white men in their middle-age in the early 1970s, and the present results cannot necessarily be generalized to men of today, with different ethnicity or

concomitant diseases, neither to women. Only 18 men reported competition sports, and the findings cannot be generalized to athletes. The AF data were collected from the hospital records, and if a participant had never been hospitalized or consulted an outpatient clinic (however, very rare in the Norwegian health care system), the diagnosis of AF could have been missed. We were not able to differentiate between various types of AF in our cohort. Heart size was measured by chest x-ray, which is a less precise method compared with echocardiography, but the latter was not an established method at baseline of our study.

The strengths of the present study, however, are the prospective study design, comprehensive clinical examination at baseline, long follow-up time, and complete end point registrations. The long time-course between baseline examinations and clinical end points is considered both a limitation and a strength in classical epidemiological studies. For instance, 40 years ago the diagnosis and treatment of hypertension differed from today, and despite high BP values the men were not diagnosed with hypertension.

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Disclosures

Three of the authors (Drs Gjesdal, Kjeldsen, and Arnesen) have received honoraria for ad hoc lectures and advisory board meetings. Dr Bodegard holds a position as an epidemiologist at AstraZeneca. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Low resting heart rate has been associated with increased atrial fibrillation risk in athletes. In the present observational study, including 2014 initially healthy middle-aged Norwegian men, we found that baseline low exercise heart rate after 6-minute exercise on the moderate workload of 100 W was a predictor of incident atrial fibrillation after ≤35 years of follow-up. The majority of men with low heart rate (<100 beats per minute) at 100-W exercise had above median age-adjusted physical fitness but concurrently below median maximum heart rate during exercise. Our data indicate that the best fit, healthy persons may be at increased risk of atrial fibrillation possibly because of a relatively predominance of vagal activity. Concomitant high blood pressure strengthens this association probably because of additive influence of pathophysiological factors, such as increased stroke volumes and enlarged cardiac chambers. We warrant additional studies that might explore further the supposed relation between increased vagal response, at rest and during exercise, and increased risk of atrial fibrillation, particularly in fit persons.

Low Heart Rates Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men

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SUPPLEMENTAL MATERIAL

Methods

Study population

Men aged 40-59 years working in five Governmental agencies in Oslo, Norway, were recruited for a cardiovascular health survey that took place between August 28, 1972 and March 21, 1975. Only employees working in agencies practicing annual or biennial health examinations of all their employees were chosen for the study. Eligibility of each man was decided, after a joint scrutiny of his health records, by the Chief Medical Officer of each agency and the survey leader (JE). Presence of any of the following diseases caused primary exclusion: Known or suspected coronary heart disease, diagnosed hypertension requiring drug treatment, diabetes mellitus, thyroid disorders, cancer, advanced pulmonary, renal, or liver diseases, or other serious disorders. Subjects on any chronic drug regimen were also excluded, as were those who for various reasons were judged unable to properly conduct a symptom limited bicycle exercise ECG test (e.g. for orthopedic, neurological, or muscular reasons). In all 2341 men fulfilled these health criteria, and 2014 (86%) agreed to participate.

Men who at arrival for the study reported that any of the above mentioned diseases/disorders had been diagnosed elsewhere after their last visit to the company health office underwent a full survey examination, but were later excluded from our files. Accordingly our study population was judged to represent a group of apparently healthy men aged 40-59 years.

Current and former smoking habits were registered, and the participants were asked if they had consumed alcohol the last two days before examination. All men were employed and

none reported alcohol abuse.

Blood pressure measurements

The fifth phase of Korotkoff sounds established diastolic BP. BP was measured three times, where the first measurement established approximately the pressure level. The second measurement was a very careful procedure with first elevating the arm for venous draining, and then lowering the arm with measurements during inspiration followed by relaxed expiration. The third measurement was identical to the second. There was a systematic minimal fall in BP from the first to the second reading, and then on average a minimal rise in BP (<1 mm Hg) from the second to the third reading. The second reading was therefore considered the most basic recording, and has therefore been used as baseline value.

Hypertensive BP values refer to standard definitions (≥140 mm Hg and/or ≥90 mm Hg). During bicycle exercise-testing BP was measured at 1, 3 and 5 min on each workload and immediately prior to test termination. ECG was recorded at 2, 4 and 6 min on all loads while sitting on the bicycle, immediately prior to test termination, and thereafter recumbent at 1 min after exercise.

Definitions

Left ventricular hypertrophy (LVH) was defined by the Minnesota Code classification system for ECG (codes 3.1 and 3.3). First-degree AV block was classified as PR- (or PQ-) interval above 210 milliseconds.

Morbidity and Mortality data

With permissions from Norwegian health authorities and Data Inspectorate all 2014 subjects were linked to the patient record system using a unique personal identification number (Norwegian social security number).

Supplemental Table I. Heart Rate According to Baseline Subgroups

Baseline subgroups	Resting HR (bpm)	HR100W (bpm)	Maximum HR (bpm)
All participants (n=2014)	61 (10)	118 (17)	163 (14)
Age <50 y (n=970)	62 (10)*	118 (16)	167 (13)‡
≥50 y	61 (9)	118 (17)	158 (13)
Smoking, current (n=882)	61 (9)†	116 (16)†	159 (14)‡
non-smoker	62 (10)	119 (17)	166 (12)
Baseline BP ≥140/90 mm Hg (n=860)	64 (10)‡	122 (17)‡	163 (14)
<140/90 mm Hg	59 (9)	115 (15)	163 (13)
Age-adjusted PF above median, kJ/kg (n= 1000)	59 (9)‡	111 (13)‡	166 (11)‡
below median, kJ/kg	63 (10)	125 (17)	160 (15)
BMI ≥28 kg/m² (n=213)	63 (10)*	116 (15)*	159 (15)‡
<28 kg/m²	61 (10)	118 (17)	163 (13)
Relative heart volume ≥450 ml/m² (n=470)	60 (9)‡	114 (16)‡	161 (14)†
<450 ml/m²	62 (10)	119 (16)	164 (13)

Values are mean ± SD (standard deviation). HR indicates heart rate; BP, blood pressure; bpm, beats per minute; PF, physical fitness; BMI, body mass index. *p-value <0.05, †p-value <0.001, ‡p-value <0.0001 comparing HR within subgroups.

Supplemental Table II. Baseline Characteristics According to Heart Rate at 6 min (100W) Exercise

Characteristics	HR100W <100 bpm n = 260		HR100W ≥100 bpm n = 1754		P-value
Age at baseline, y	50	(5)	50	(5)	0.8
Body height, cm	179	(6)	176	(6)	<0.001
Body weight, kg	80	(10)	76	(10)	<0.001
BMI, kg/m²	24.9	(3)	24.5	(3)	<0.001
Current smoker, n (%)	119	(46)	763	(44)	0.5
Systolic BP, mm Hg	124	(16)	131	(18)	<0.001
Diastolic BP, mm Hg	84	(10)	88	(10)	<0.001
LVH, n (%)	5	(2)	101	(6)	0.01
Resting HR, bpm	52	(6)	63	(9)	<0.001
PR-interval, ms	179	(27)	170	(24)	<0.001
First-degree AV-block, n (%)	28	(11)	80	(5)	<0.001
Relative heart volume, ml/m²	425	(62)	400	(58)	<0.001
Total cholesterol, mmol/l	6.5	(1.1)	6.7	(1.2)	<0.01
Exercise data					
HR100W, bpm	94	(5)	121	(14)	—
Maximum HR, bpm	155	(15)	164	(13)	<0.001
Heart rate reserve, bpm	102	(16)	101	(14)	0.4
Systolic BP100W, mm Hg	166	(18)	184	(24)	<0.001
Maximum systolic BP, mm Hg	217	(21)	216	(23)	0.5
Total work performed, kJ	146	(56)	105	(41)	<0.001
Total exercise time, min	18.4	(7)	13.3	(5)	<0.001

Values are mean ± SD (standard deviation) or numbers (%). HR indicates heart rate; BMI, body mass index; BP, blood pressure; LVH, left ventricular hypertrophy; bpm, beats per minute and heart rate reserve, the difference between maximum exercise and resting heart rate. P-values comparing groups.