Resting Heart Rate and the Risk of Atrial Fibrillation A Dose-Response Analysis of Cohort Studies

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Summary

In a previous meta-analysis, it was demonstrated that the resting heart rate (RHR) is a potential risk factor for atrial fibrillation (AF). However, the results of that meta-analysis were conflicting, and the relationship between the RHR and AF is still not well established. In the current meta-analysis, our aim is to update evidence with a better statistical model. We searched the Cochrane Library, PubMed, and Embase databases for relevant studies and used a “one-stage approach” with a restricted cubic spline model to summarize the dose-specific relationships between the RHR and AF. Relative risk (RR) was used to measure the effects. In total, 10 studies were included, with a total of 18,630 cases of AF among 431,432 participants. In the dose-response analysis, there was evidence of a nonlinear association between the RHR and the risk of AF (nonlinearity, $P < 0.0001$), which exhibited a significant J-shaped association between the two factors. An RHR between 68 and 80 bpm had the lowest risk of AF. Among people who had RHR < 70 bpm, the summary RR was 1.09 per 10-RHR decrease (95% confidence interval [CI] = 1.06-1.12; $P < 0.001$). The results were similar for participants with RHR > 70 bpm (per 10 bpm increase) (RR = 1.06, 95% CI = 1.03-1.08; $P < 0.001$). Our dose-response meta-analysis revealed a significant J-shaped association between the RHR and AF. Both low RHR and high RHR were associated with an increased risk of AF compared with a modest RHR of 68-80 bpm.

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Key words: Risk Factor

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, which affects 1-2% of the general population.¹⁾ AF is associated with an increased risk of stroke, heart failure, and mortality.^{2,3)} Although the etiology of AF is not fully understood, in a population-based prospective study in Norway, it was reported that individuals with a higher resting heart rate (RHR) (> 60 bpm) had a reduced risk of AF compared with those with a lower RHR (< 50 bpm) in both sexes.⁴⁾ In another large prospective study, no relation was found between an increased RHR (> 72 bpm) and a decreased risk of AF. In a previous meta-analysis, data were summarized from some already existing observational studies, and it was concluded that a slight J-shaped association existed between the RHR and AF in the nonlinear model (dose-specific effect).⁵⁾ However, that meta-analysis did not report a significant increased risk per 10 bpm using a linear model (average effect). These data provide valuable information for clinical decisions. However, the arguments were as follows: (1) several published studies were miss-

ing in the meta-analysis;^{4,6-8)} (2) the results of the dose-specific effect and average effect of increased or decreased RHR were conflicting the meta-analysis; and (3) the evidence was confusing. This problem is likely due to the use of improper methods where a simple linear function is insufficient for detecting the “average effect” for a J-shaped relationship.⁹⁾ A more appropriate method is to use a piecewise linear model by dividing the J-shaped trend into two segments at the threshold of 70 bpm. The reference dose was set at 70 bpm because we assumed that an RHR of approximately 70 bpm had the lowest AF risk, according to previous studies.⁵⁻⁷⁾

Based on the results summarized above, the association between the RHR and the risk of AF must be further clarified. Here, we conducted an updated meta-analysis to summarize all of the available evidence on the association between the RHR and the risk of AF.

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Table 1. Quality Assessment of the Included RCTs and Cohort Studies

Author, publication year	NOS										Average score
	Selection			Comparability			Outcome			Total	
	A	B	C	D	E	F	G	H	I		
Aladin, 2018	1	1	1	0	1	1	1	1	0	7	7.8
Morseth, 2016	1	1	1	1	1	1	1	1	1	9	
Sharashova, 2016	1	1	1	1	1	1	1	1	0	8	
Skov, 2016	1	1	1	1	1	1	1	1	0	8	
Bohm, 2015	0	1	1	1	1	1	1	1	0	7	
Hai, 2015	1	1	1	1	1	1	1	0	1	7	
O’Neal, 2015	1	1	1	1	1	1	1	0	1	8	
Grundvold, 2013	1	1	1	1	1	1	1	1	1	9	
Thelle, 2013	1	1	1	1	1	1	0	1	0	7	
Wilhelmsen, 2001	1	1	1	1	1	1	1	1	1	9	
Okin, 2008	1	1	1	1	1	1	0	1	1	7	

A: representativeness of the exposed cohort; B: selection of the nonexposed cohort; C: ascertainment of exposure; D: demonstration that the outcome of interest was not present at the start of the study; E: comparability of cohorts on the basis of the design or analysis (adjusted for age); F: comparability of cohorts on the basis of the design or analysis (adjusted for any other factor); G: assessment of outcome; H: follow-up long enough for outcomes to occur (more than five years); I: adequacy of follow-up of cohorts.

Methods

Literature search: We systematically searched the Cochrane Library, PubMed, and Embase databases through February 1, 2018, for studies published in any language, using the following search terms in the “title/abstract” search fields: heart rate, resting pulse, atrial fibrillation, atrial flutter, atrial tachycardia, and supraventricular tachycardia. Supplemental Table 1 provides a detailed description of the search strategy. Our study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number 42018091692.

Study selection: Studies were considered eligible if they met the following criteria: (1) if they investigated the association between the RHR and the risk of AF; (2) if they reported the relative risk (RR) and the corresponding 95% confidence interval (CI) or provided data to calculate these factors; and (3) if they were designed as randomized controlled trials (RCTs) or cohort studies. Studies where RHR was not analyzed as a categorical variable were excluded. Post hoc analysis of RCTs was treated as a cohort study to achieve quality assessment.¹⁰ For multiple publications/reports created from the same data, we used the estimates from the most informative or recent study. We contacted the authors of one study¹¹ to obtain more detailed results so that their study could be included in the dose-response analysis. We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist for reporting meta-analyses.¹²

Data extraction and quality assessment: Two researchers (X. Liu and N. Guo) independently assessed the eligibility of the literature according to the aforementioned inclusion criteria. All discrepancies were resolved through discussion or by a third researcher (K. Hong) as necessary. For each study, basic characteristics were extracted, including the first author, publication year, geographical location, participants (sex, mean age, and sample size), duration of follow-up, adjusted covariates, and RRs with 95% CIs for each category of RHR.

We used the Newcastle-Ottawa Scale (NOS) for quality assessment in order to evaluate the quality of the studies,¹³ and we developed the evaluation criteria with a score ranging from 0 to 9 points for cohort studies, with a higher score (NOS ≥ 7) indicating higher study quality.^{13,14}

Statistical analysis and risk-of-bias assessment: We used random-effects models to calculate summary RRs and 95% CIs for the highest versus the lowest levels of RHR. Effect measures were transformed to their natural logarithms (log RR), and the standard errors (SElog [RR]) were calculated from the corresponding 95% CIs. Summary RRs for the highest versus the lowest levels of RHR were estimated by pooling the study-specific estimates using random-effects models. In order to assess the heterogeneity of RRs across studies, the I^2 (95% CI) statistic was calculated with the following interpretation: low heterogeneity, defined as $I^2 < 50\%$; moderate heterogeneity, defined as I^2 between 50% and 75%; and high heterogeneity, defined as $I^2 > 75\%$.¹⁰

We used the robust error meta-regression method (REMR) described by Xu, *et al.*¹⁵ to fit the model. This method is based on a “one-stage approach” that treats each included study as a cluster as a solution for handling the correlation between estimates (log RRs) within each study while applying weighted least squares to obtain the regression coefficients. The method requires known levels of RHR and RRs with variance estimates for at least two quantitative exposure categories. For studies that did not set the lowest RHR group as a reference, data were transformed using a method described by Hamling, *et al.*,¹⁶ which requires the number of cases and participants in each category (for detailed calculations, see the Supplemental Figure 1).

If the median or mean RHR was not provided and reported in ranges, we estimated the midpoint of each category by averaging the lower and upper boundaries of that category.¹⁷ If the highest or lowest category was open-ended, we assumed that the open-ended interval length was the same as the adjacent interval.^{18,19} Dose-response meta-analyses (linear and nonlinear) were per-

Figure 1. Forest plot for the meta-analysis of the association between the RHR and the risk of AF, analyzing the highest-versus-lowest RHR groups. AF: atrial fibrillation; RHR: resting heart rate.

Figure 2. Dose-response relationship (nonlinear) of the RHR and the risk of AF using a restricted cubic spline model. The solid and dashed lines represent the estimated RR and the 95% CI, respectively. RR: relative risk; AF: atrial fibrillation; bpm: beats per minute.

Table II. RRs from the Nonlinear Dose-Response Analysis

RHR (bpm)	Outcome AF (RR, 95% CI)
50	1.15 (1.10-1.21)
60	1.06 (1.04-1.08)
70	Ref.
80	1.01 (1.01-1.02)
90	1.07 (1.04-1.09)
100	1.15 (1.10-1.19)
110	1.24 (1.18-1.31)
$P_{\text{nonlinearity}}$	< 0.0001

RHR indicates resting heart rate; RR, relative risk; CI, confidence interval; and AF, atrial fibrillation.

formed to examine the potential relationships between the RHR and AF. A restricted cubic spline with three knots of the distribution was used in the dose-response model to generate a potential nonlinear dose-response curve in order to investigate the dose-specific effects.¹⁸⁾ A linear relationship typically acts as the main analysis when the nonlinear trend is insignificant or as an additional analysis when the nonlinear trend is significant. Thus, we first used a piecewise linear regression model in the meta-analysis to establish the “average” trends between different RHRs and AF by treating the slope as two piecewise points greater than and less than 70 bpm to demonstrate the linear trends.^{9,20)} The reference dose was set at 70 bpm because we assumed that an RHR of approximately 70 bpm had the lowest risk of AF, according to previous studies.⁵⁻⁷⁾

Possible publication bias was assessed using Begg’s test²¹⁾ and Egger’s test.²²⁾ All statistical analyses were performed using Review Manager (RevMan) software (Version 5.30; Nordic Cochrane Center, Rigshospitalet, Copen-

hagen, Denmark) and Stata software (Version 14.0; StataCorp LP, College Station, TX, USA). A P -value < 0.05 was considered statistically significant.

Results

Study selection: As shown in Supplemental Figure 2, we identified a total of 6,441 studies in our initial database search. After removing duplicates and studies with inadequate information on heart rate (HR) and AF, 33 studies were reviewed in more detail. Out of these 33 studies, 23 were excluded for the following reasons: (1) they were letters, case reports, or comments ($n = 4$), (2) they had no relevant outcomes ($n = 16$), (3) they did not analyze RHR as a categorical variable ($n = 2$), and (4) they contained duplicate data from other studies ($n = 1$). In total, 10 studies^{4,6-8,11,23-26)} were included in the final analysis.

Study characteristics and quality: Detailed characteristics of the included studies are presented in Supplemental Table II. Overall, these studies were published between 2001 and 2017. The sample size of the included studies varied from 438 to 281,451, with a total of 18,630 AF cases and 431,432 participants. The mean age ranged from 39.1 to 66.6 years. Among the 10 articles, one⁸⁾ was a post hoc analysis of RCTs, eight^{4,6-8,11,23,25,26)} were prospective cohort studies, and one²⁴⁾ was a retrospective co-

Figure 3. Dose-response relationship (linear) of the RHR and the risk of AF using a piecewise linear regression model. RR: relative risk; AF: atrial fibrillation; RHR: resting heart rate; bpm: beats per minute.

hort study. Four studies^{8,23,24,26} were conducted in the USA, six^{4,6,11,25,26} were conducted in Europe, and only one⁷ was based in Asia. As shown in Table I, the reporting quality of the included articles was high. All observational studies obtained an NOS of ≥ 7 points.

Risk of AF with the highest-versus-lowest RHRs: A total of 10 studies^{4,6-8,11,23-27} with 431,432 participants and 18,630 incident cases were included. The pooled RR for the highest-versus-lowest RHR group was 0.95 (95% CI = 0.81-1.12, $P = 0.57$), but there was a substantial heterogeneity in the RRs across the included studies ($I^2 = 84\%$, $P < 0.001$) (Figure 1). The pooled RRs ranged from 0.89 (95% CI = 0.74-1.08, $P = 0.23$) to 1.01 (95% CI = 0.86-1.19, $P = 0.89$) when one study was excluded at each time, which indicated the result is stable.

Dose-response association between the RHR and AF incidence: Dose-response analysis is more efficient than the highest-versus-lowest approach because it uses all of the exposure-disease information, including the intermediate categories. Nine studies^{4,6-8,11,23-26} were included in the dose-response analysis of RHR and AF incidence, for a total of 16,904 AF cases among 406,934 participants. The meta-analysis revealed a significant J-shaped association between the RHR and AF ($P < 0.001$ for the nonlinear test) (Figure 2). RHRs between 68 and 80 bpm exhibited the lowest risk for AF. Both low and high RHRs were associated with an increased risk of AF when we used 70 bpm as the reference group (50 bpm: RR = 1.16, 95% CI = 1.10-1.22; 60 bpm: RR = 1.06, 95% CI = 1.03-1.09; 80 bpm: RR = 1.01, 95% CI = 1.00-1.02; 90 bpm: RR = 1.07, 95% CI = 1.05-1.09; 100 bpm: RR = 1.15, 95% CI = 1.11-1.19; 110 bpm: RR = 1.24, 95% CI = 1.18-1.31) (Table II).

Importantly, we first used a piecewise linear regression model to detect linear trends between the RHR and AF given that simple linear functions were insufficient to detect the J-shaped association. Among individuals who had an RHR of < 70 bpm, an associated increase in the risk of AF was noted for every 10 bpm decrease in the RHR (RR = 1.09, 95% CI = 1.06-1.12; $P < 0.001$). An

increased risk of AF was also observed among people with RHR > 70 bpm (per 10 bpm increase) (RR = 1.06, 95% CI = 1.03-1.08; $P < 0.001$) (Figure 3).

Publication bias: Egger's test ($P = 0.37$) and Begg's test ($P = 0.22$) revealed no evidence of publication bias (Supplemental Figure 3).

Sensitivity analysis: A sensitivity analysis was conducted, and the following groups were excluded: studies with short follow-up durations (less than 5 years),⁸ special populations (hypertensive patients),^{4,8} small sample sizes ($< 5,000$ individuals),⁷ studies not adjusted for cardiovascular disease²⁴ and retrospective studies.²⁴ No important changes were observed in any of the sensitivity analyses (Table III).

Discussion

Our dose-response meta-analysis revealed a J-shaped association between the RHR and AF despite the nonsignificant RR between the highest and the lowest RHR groups. A modest RHR between 68 and 80 bpm exhibited the lowest risk of AF. Moreover, we first demonstrated that a decrease or increase in the RHR per 10 bpm was associated with a 9% or a 6% increase in the risk of AF, respectively, compared with the modest 70 bpm RHR group.

Low RHR is generally associated with improved physical fitness and prognoses.²⁸ It has been demonstrated in previous studies that a 10 bpm increase in the RHR was associated with a 7-12% increased risk for coronary heart disease, a 9-12% increased risk for sudden cardiac death, an 18-40% increased risk for heart failure, and a 6% increased risk for total stroke.^{5,29,30} High RHRs can increase hemodynamic stress and shorten the diastolic phase, thereby increasing the blood pressure, cardiac workload, and oxygen consumption, which can eventually result in coronary atherosclerosis and myocardial ischemia.³¹⁻³³ However, the relationship between the RHR and AF incidence remains controversial. It was found in two large independent cohort studies from the Copenhagen Electrocardiographic Study and the Tromsø Study that a low RHR is considered an independent predictor of AF.^{4,11} In contrast, results from another study showed that a low RHR is not a significant risk factor for AF.²⁴ Moreover, in a few studies, a U-shaped association has been suggested between the RHR and AF.^{11,24} The present dose-response analysis revealed a nonlinear relationship between RHR and AF. Moreover, our data revealed a J-shaped association between the RHR and AF. Compared with a modest RHR of 68-80 bpm, a decrease or an increase in the RHR per 10 bpm was associated with a 9% or a 6% increase in the risk of AF, respectively. These results suggest that a simple linear regression model is not sufficient to establish the "average" changing trend between the RHR and AF. This result may also explain (1) why no association was observed between the RHR and AF in the highest-versus-lowest approach used in our study and previous meta-analyses and (2) the nonsignificant RR per 10 bpm change in the RHR for risk of AF in cohort studies and previous meta-analyses, such as the Framingham Heart Study³⁴ and the Rotterdam Study.³⁵

Table III. Sensitivity Analyses

	AF (RR, 95% CI)							P-value (nonlinear)
	50 bpm	60 bpm	70 bpm	80 bpm	90 bpm	100 bpm	110 bpm	
Overall analysis	1.16 (1.10-1.22)	1.06 (1.03-1.09)	1	1.01 (1.01-1.02)	1.07 (1.05-1.09)	1.15 (1.11-1.19)	1.24 (1.18-1.31)	< 0.001
Studies of hypertension individuals omitted	1.17 (1.13-1.21)	1.06 (1.04-1.08)	1	1.01 (1.01-1.02)	1.08 (1.06-1.10)	1.17 (1.13-1.20)	1.26 (1.21-1.31)	< 0.001
Short follow-up duration excluded	1.17 (1.13-1.21)	1.06 (1.04-1.08)	1	1.01 (1.01-1.02)	1.08 (1.06-1.10)	1.17 (1.13-1.20)	1.26 (1.21-1.31)	< 0.001
Small size excluded	1.15 (1.10-1.20)	1.06 (1.04-1.08)	1	1.00 (0.99-1.01)	1.06 (1.03-1.09)	1.14 (1.10-1.19)	1.26 (1.20-1.31)	< 0.001
Retrospective cohort study omitted	1.15 (1.09-1.23)	1.06 (1.03-1.08)	1	1.01 (1.00-1.02)	1.07 (1.05-1.09)	1.15 (1.12-1.19)	1.23 (1.16-1.31)	< 0.001
Not adjusted for CVD omitted	1.15 (1.09-1.23)	1.06 (1.03-1.08)	1	1.01 (1.00-1.02)	1.07 (1.05-1.09)	1.15 (1.12-1.19)	1.23 (1.16-1.31)	< 0.001

AF indicates atrial fibrillation; RR, relative risk; CI, confidence interval; bpm, beats per minute; and CVD, cardiovascular disease.

Low RHRs are typically associated with a lower body mass index (BMI), good exercise capacity, and reduced morbidity and mortality.^{36,37)} Therefore, our results raise the question of why lower RHR is associated with a higher incidence of AF, which could be explained by several biological mechanisms. HR regulation is a complex interplay between vagal withdrawal and sympathetic activation during exercise.³⁸⁾ A low HR during exercise might suggest the involvement of a blunted HR response to exercise with prolonged vagal activation.³⁹⁾ Heightened vagal tone enhances acetylcholine-dependent potassium currents, reducing the action potential duration and stabilizing reentrant rotors in the atria supporting AF.⁴⁰⁾ An increased cardiac volume and larger atrial filling volumes promote atrial remodeling and subsequent fibrosis, eventually increasing the susceptibility to AF.⁴⁰⁾ In addition, the positive correlation between sick sinus syndrome (SSS) and AF has long been identified in the elderly population. In SSS, there is presumably an age-related structural change in both the sinus atrial node and the atrial muscle, and such changes could be the functional and anatomical substrate for AF.⁴¹⁾ In a previous study, it was shown that medium- to high-rate atrial pacing significantly reduces episodes of symptomatic AF among patients with paroxysmal AF and sinus bradycardia requiring pacing.⁴²⁾ Although later studies with different designs and pacing algorithms have yielded inconsistent results,^{43,44)} it is possible that, in certain patients, sinus bradycardia initiates or perpetuates AF.

Notably, in the present study, it was demonstrated that an increased RHR was associated with an increased hazard ratio of AF. Some publications could help in elucidating the reason. It has been reported in recent studies that higher RHRs are associated with an increased risk of coronary artery disease, hypertension, stroke, heart failure, and type 2 diabetes, which are all risk factors for AF.^{5,45,46)} Furthermore, a high RHR is a marker of sympathetic overactivity and subclinical reductions in left ventricle function. The role of the sympathetic nervous system in the initiation and maintenance of AF has been assessed extensively.^{47,48)} Increased sympathetic tone may promote automaticity, reduce the atrial effective refractory period, and thereby contribute to AF, particularly in patients with

structural heart diseases.^{49,50)} Additionally, increased RHRs caused by subclinical left ventricle dysfunction or early heart failure can increase the left atrial pressure and stretch over time, thereby facilitating the induction of AF.⁵¹⁾ Further work is needed to help identify the key underlying biological mechanisms through which RHRs may play a role in the development of AF. Regardless of whether RHR plays a causal role in the etiology of AF, its potential utility for AF risk assessment warrants consideration, particularly as its measurement involves a simple, noninvasive, routine procedure in clinical practice.⁵²⁾

Comparisons with other studies: A previous report⁵⁾ revealed some indication of a slight J-shaped association between the RHR and AF in a nonlinear model in seven articles^{11,23,25-27,35,53)} (nine cohorts) with 20,474 cases/649,188 participants. Among these nine articles, two studies^{35,53)} (five cohorts) that did not report RHR as a categorical variable were not available for the nonlinear model. Eventually, only 11,120 cases among 294,172 individuals were analyzed for a dose-response analysis of a nonlinear model in a previous meta-analysis. We excluded these two studies^{33,48)} (five cohorts) given that the association between the RHR and AF was expected to be nonlinear. Moreover, we added another six studies^{4,6-8,24,26)} containing 5,784 cases among 137,300 participants in our dose-response model. We observed a significant J-shaped association between the RHR and AF, which is consistent with the previous meta-analysis in the nonlinear model. However, the previous study did not identify a significant RR (0.97, 95% CI: 0.92-1.02) of AF per 10 bpm increase because the simple linear function is insufficient for detecting J-shaped or U-shaped associations.⁵⁾ In order to solve this problem, we first applied a piecewise linear regression model in the meta-analysis described by Xu, *et al.* and Gould, *et al.*,^{20,54)} which demonstrated that a 10 bpm decrease or increase in the RHR was associated with a 9% or a 6% risk of AF, respectively, compared with RHRs of 70 bpm.

Strengths and limitations: Our meta-analysis has several strengths. First, this is the first study using a piecewise linear regression model in a meta-analysis that exhibited a different linear trend with a cutoff of 70 bpm. Second, both linear and nonlinear dose-response analyses were

used to clarify the strength and the shape of the dose-response relationships between the RHR and AF because a well-established dose response should consider both linear and nonlinear models. The nonlinear results were used to measure the dose-specific effects, whereas the linear result was used to measure the average trend. Thus, it is useful and reasonable to provide the results to physicians and patients to form an informed decision. Finally, we used an REMR model for the dose-response meta-analysis, which is expected to generate a more conservative CI, thus making the results more conservative.¹⁵⁾

Several limitations should also be considered. A modest heterogeneity was observed in the studies included in this meta-analysis, which was adjusted for known confounding factors, including age, BMI, CVD, drug-related HR reduction, and physical activity. This heterogeneity may be partially attributable to differences in the study design, analysis strategy, participant characteristics, and the method of ascertaining AF among the included studies. Although sex is an independent risk factor for AF,^{55,56)} the scarcity of data precluded us from performing a subgroup analysis on sex.

Conclusions

Our dose-response meta-analysis revealed a significant J-shaped association between the RHR and AF. A 10-bpm increase or decrease in RHR was associated with a 9% or a 6% increased risk of AF, respectively, compared with those with modest RHRs of 70 bpm. Large-scale, well-designed, observational studies with analyses stratified by confounders of interest are needed to further explore the association between the RHR and the risk of AF.

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Disclosure

Conflicts of interest: None.

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Supplemental Files

Supplemental Tables I, II

Supplemental Figures 1-3

Please see Supplemental Files: <https://doi.org/10.1536/ihj.18-470>