Association between resting heart rate and cardiovascular mortality: evidence from a meta-analysis of prospective studies

Yuechun Li

Department of Cardiology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Received April 13, 2015; Accepted September 6, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: The results from published studies on resting heart rate (RHR) and risk of cardiovascular mortality are not consistent. We therefore conducted a meta-analysis to quantitatively summarize the evidence from prospective studies about the association of RHR with risk cardiovascular mortality. Pertinent studies were identified by a search of Pubmed and Web of Knowledge to January 2015. The random effect model was used. Sensitivity analysis and publication bias were conducted. Dose-response relationship was assessed by restricted cubic spline and variance-weighted least squares regression analysis. Twenty prospective articles were included in this meta-analysis. Pooled results suggested that highest RHR level versus lowest levels was significantly associated with the risk of cardiovascular mortality [summary relative risk (RR) = 1.69, 95% CI = 1.42-2.00, I² = 87.5%]. Subjects with RHR levels of > 80 bites per minute (bpm) had a RR of 1.49 (1.24-1.79) for cardiovascular mortality. The results for subgroups analysis of geographic locations, sex and duration of follow-up are consistent with the overall results. The linear dose-response analysis indicated that an increase in RHR of 10 bpm was statistically significantly associated with a 6% increase in the risk of developing cardiovascular mortality (summary RR = 1.06, 95% CI = 1.04-1.08). Thus, we conclude that elevated RHR was significantly associated with an increased risk of cardiovascular mortality.

Keywords: Resting heart rate, cardiovascular mortality, meta-analysis

Introduction

A higher heart rate has been associated with worse clinical outcomes [1], particularly in individuals with existing cardiovascular disease [2, 3]. The underlying mechanism of this association is not well understood: higher heart rates may reflect underlying autonomic dysfunction and sympathetic overactivity [4, 5], although direct effects of heart rate on atherosclerosis [6] and myocardial energetics may also contribute [7]. In addition, several biologically plausible mechanisms for the effect of elevated resting heart rate (RHR) have been proposed including the anti-ischemic and antiarrhythmic benefits of a low heart rate and the atherogenic hemodynamic effects of an elevated heart rate; a faster heart rate will necessarily impose more shear stresses than a slow one [8, 9].

Up to date, a number of epidemiologic studies have been published to explore the relationship between RHR and cardiovascular mortality risk. However, the results are not consistent. Therefore, we conducted a meta-analysis of prospective cohort studies to (1) first assess the cardiovascular mortality risk for the highest vs. lowest categories of RHR; (2) assess the cardiovascular mortality risk for those RHR > 80 bits per minute (bpm) vs. reference (the lowest category in each study); (3) assess the dose-response association of cardiovascular mortality for every 10 bpm increment in RHR; (3) assess the heterogeneity among studies and publication bias.

Methods

Search strategy

Studies were identified by a literature search of PubMed and Web of Knowledge up to January 2015 and by hand-searching the reference lists of the computer retrieved articles. The following
Association of RHR with cardiovascular mortality

Data extraction

Two researchers independently extracted the following data from each study that met the criteria for inclusion: the first author’s last name, geographic locations, year of publication, the age range of study participants, sample source, the number of cases and participants (person-years), duration of follow-up, and RR (95% CI) for each category of RHR were also extracted. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders.

Quality assessment

The quality of studies was examined and controlled in accordance with checklists of Preferred Reporting Items for Systematic reviews and Meta-Analyses for randomized trials (PRISMA) [10]. To determine the quality score of included studies, two reviewers independently performed the quality assessment by using the Newcastle-Ottawa Scale, which is a validated scale for non-randomized studies in meta-analyses [11]. The Newcastle-Ottawa Scale is a nine-point scale that allocates points based on the selection process of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the identification of the exposure and the outcomes of study participants (0-3 points). We assigned scores of 0-3, 4-6, and 7-9 for low, moderate, and high quality of studies, respectively.

Statistical analysis

We carried out a random-effect dose-response meta-analysis using the method proposed by Greenland and Longnecker [12] and Orsini et al. [13], which takes into account the correlation between the log RR estimates across categories of RHR. We also explored the possibility of nonlinear relationships by modeling RHR

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

search terms were used: ‘heart rate’ or ‘pulse rate’ AND ‘cardiovascular’ AND ‘death’ or ‘mortality’. Two investigators searched articles and reviewed all retrieved studies independently.

Study selection

For inclusion, studies had to fulfill the following criteria: (1) have a prospective design; (2) the exposure of interest was RHR; (3) the outcome of interest was cardiovascular mortality; (4) relative risk (RR) with 95% confidence interval (CI) was provided; and (5) for dose-response analysis, the RHR for each category must also be provided. Accordingly, the following exclusion criteria were also used: (1) reviews; (2) the RR with 95% CI was not available and (3) repeated or overlapped publications.
Association of RHR with cardiovascular mortality using restricted cubic splines with three knots at fixed percentiles (25%, 50% and 75%) of RHR distribution. A $P$-value for nonlinearity was calculated by testing against the null hypothesis that the coefficient of the second spline transformation was equal to 0 [14]. The method requires that the distribution of cases and person-years or noncases and the RR with the variance estimates for at least three quantitative exposure categories are known. When this information was not available, we estimated the slopes (linear trends) by using variance-weighted least squares regression analysis [15, 16]. The median or mean level of RHR each category was assigned to the corresponding RR for every study. If the upper boundary of the highest category was not provided, we assumed that the boundary had the same amplitude as the adjacent category. Statistical heterogeneity across studies was assessed using the Q and $I^2$ statistics [17]. $I^2$ describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, and $I^2$ values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity, respectively [18]. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [19]. A study of influence analysis [20] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. Publication bias was estimated using Egger’s regression asymmetry test [21]. In this study, we combined the RHR and cardiovascular mortality risk into 3 groups: highest vs. lowest, > 80 bpm vs. reference (the lowest category in each study), and 10 bpm increment of RHR and cardiovascular mortality risk. All statistical analyses were conducted with STATA version 10.0 (StataCorp LP, College Station, Texas, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Search results and study characteristics

The search strategy identified 6369 articles from Pubmed and 8634 from the Web of Knowledge. Twenty articles [22-41] were included in this meta-analysis. The detailed steps of our literature search are shown in Figure 1. Ten studies come from Europe, 5 from United States and 5 from Asia. The characteristics of these studies are presented in Table 1. The quality of studies was generally good, with results of study quality assessment yielded a score of 6 or above for all included studies, with an average score of 7.70.

High versus low analyses

Data from 18 articles including 25 studies were used in the highest vs. lowest analysis. Seventeen of these studies reported that highest RHR could increase the risk of cardiovascular mortality, while no significant associations were reported in 8 studies. The combined RR (95% CI) of cardiovascular mortality was 1.69 (1.42-2.00) for highest RHR levels vs. lowest levels (Figure 2).

When the studies were stratified by geographic locations, the associations were also found in the Europe [summary RR = 1.66, 95% CI = 1.23-2.25], America [summary RR = 1.67, 95% CI = 1.41-1.98] and Asia [summary RR = 1.50, 95% CI = 1.28-1.77]. In subgroup analyses for sex, a positive association of RHR with risk of cardiovascular mortality was found both in the men and women. Furthermore, with stratification for duration of follow-up, associations were also found in duration of > 10 years and those ≤ 10 years. Details results are summarized in Table 2.

In addition, we also did the analysis for those > 80 bpm vs. reference (the lowest category in each study), and the RR (95% CI) of cardiovascular mortality was 1.49 (1.24-1.79) (Figure 3).

The results for subgroups analysis of geographic locations, sex and duration of follow-up are consistent with the highest vs. lowest analysis.

Dose-response analysis

For dose-response analysis, data from 19 articles [22-40] including 26 studies were used for RHR and cardiovascular mortality risk. The departure from a linear relationship was not significant ($P$ for nonlinearity = 0.29). The dose-response analysis indicated that an increase in RHR of 10 bpm was statistically significantly associated with a 6% increase in the risk of
Association of RHR with cardiovascular mortality

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>Follow-up (years)</th>
<th>Cases, age</th>
<th>Quality score</th>
<th>RR (95% CI) for highest versus lowest category</th>
<th>Adjustment or matched for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillum et al. 1991</td>
<td>United States</td>
<td>10.1</td>
<td>Men: 373, 45-74 Women: 265, 45-74</td>
<td>7</td>
<td>1.52 (0.86-2.70) for men 3.03 (1.46-6.28) for women</td>
<td>Age, smoking, systolic blood pressure, serum total cholesterol, and history of diabetes</td>
</tr>
<tr>
<td>Benetos et al. 1999</td>
<td>France</td>
<td>18.2</td>
<td>Men: 664, 51.1 Women: 180, 52.1</td>
<td>7</td>
<td>3.09 (2.04-4.70) for men 1.06 (0.42-2.68) for women</td>
<td>Age, SBP, DBP, BMI, history of myocardial infarction, antihypertensive treatment, total cholesterol, physical activity, and tobacco consumption</td>
</tr>
<tr>
<td>Kristal-Boneh et al. 2000</td>
<td>Israel</td>
<td>8</td>
<td>Men: 57, 45-69</td>
<td>8</td>
<td>2.02 (1.40-4.00)</td>
<td>Age, education, BMI, cholesterol, smoking, and sport</td>
</tr>
<tr>
<td>Reunanen et al. 2000</td>
<td>Finland</td>
<td>23</td>
<td>Men: 1033, 30-59 Women: 426, 30-59</td>
<td>7</td>
<td>1.40 (1.11-1.77) for men 1.40 (1.00-1.96) for women</td>
<td>Age, smoking, blood pressure, and serum cholesterol, diabetes, BMI, perceived health and job and leisure time physical activity</td>
</tr>
<tr>
<td>Seccareccia et al. 2001</td>
<td>Italy</td>
<td>8.5</td>
<td>Men: 133, 40-69</td>
<td>8</td>
<td>2.54 (1.25-5.16)</td>
<td>Age, SBP, serum cholesterol, cigarettes smoked per day, BMI, arm circumference, adjusted forced expiratory volume, diabetes, and preexisting cardiovascular disease</td>
</tr>
<tr>
<td>Cheng et al. 2002</td>
<td>United States</td>
<td>13</td>
<td>Men: 166, 46.7</td>
<td>8</td>
<td>0.8 (0.3-1.6)</td>
<td>Age, cardiorespiratory fitness, resting SBP, SBP difference, cholesterol, triglycerides, BMI, smoking, and alcohol consumption</td>
</tr>
<tr>
<td>Hozawa et al. 2004</td>
<td>Japan</td>
<td>10</td>
<td>Men: 1780, 60.3</td>
<td>8</td>
<td>2.61 (1.29-5.31)</td>
<td>Age, sex, smoking status, overweight, use of antihypertensive medication, history of CVD, diabetes, hypercholesterolemia</td>
</tr>
<tr>
<td>Okamura et al. 2004</td>
<td>Japan</td>
<td>16.5</td>
<td>Men: 291, 49.6</td>
<td>7</td>
<td>2.55 (1.22-5.31)</td>
<td>Age, serum albumin, BMI, hypertension, hypercholesterolemia, diabetes, cigarette smoking and drinking</td>
</tr>
<tr>
<td>Kizilbash et al. 2008</td>
<td>United States</td>
<td>32</td>
<td>Men: 370, 48.4 Women: 467, 49.1</td>
<td>8</td>
<td>1.89 (1.48-2.40) for men 1.69 (1.35-2.13) for women</td>
<td>Age, race, educational level, SBP, cigarette smoking, diabetes, and total cholesterol</td>
</tr>
<tr>
<td>Tverdal et al. 2008</td>
<td>Norway</td>
<td>12</td>
<td>Men: 1283, 41.4 Women: 460, 41.4</td>
<td>8</td>
<td>1.51 (1.21-1.87) for men 0.78 (0.53-1.15) for women</td>
<td>Calendar year, total cholesterol, triglycerides, diastolic blood pressure, smoking, physical activity, and family history</td>
</tr>
<tr>
<td>Cooney et al. 2010</td>
<td>Finland</td>
<td>12</td>
<td>Men: 266, 43.3 Women: 96, 43.0</td>
<td>8</td>
<td>4.5 (3.8-5.4) for men 1.6 (1.2-2.1) for women</td>
<td>Age, smoking status, SBP, total cholesterol, self-reported diabetes, BMI, HDL cholesterol, and physical activity</td>
</tr>
<tr>
<td>Nauman et al. 2010</td>
<td>Norway</td>
<td>18.2</td>
<td>Men: 2566, 46 Women: 1814, 46</td>
<td>7</td>
<td>1.22 (0.97-1.55) for men 1.40 (1.03-1.89) for women</td>
<td>Age, BMI, physical activity index, marital status, education, alcohol consumption, and smoking status</td>
</tr>
</tbody>
</table>
### Association of RHR with cardiovascular mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Follow-up (years)</th>
<th>Male: Age, Cases, Systolic Blood Pressure</th>
<th>RR (95% CI) for Highest versus Lowest Category</th>
<th>Adjustments or Matched for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen et al. 2011</td>
<td>Denmark</td>
<td>21.2</td>
<td>3821, 49.8</td>
<td>0.86 (0.99-1.13)</td>
<td>Age, leisure time physical activity, BMI, SBP, pulmonary function, alcohol consumption and triglycerides</td>
</tr>
<tr>
<td>Jouven et al. 2011</td>
<td>France</td>
<td>25</td>
<td>Men: 435, 48.0</td>
<td>2.0 (1.5-2.7)</td>
<td>Age and smoking</td>
</tr>
<tr>
<td>Legeai et al. 2011</td>
<td>France</td>
<td>6</td>
<td>110, 73.9</td>
<td>1.87 (0.96-3.58)</td>
<td>Age, gender, study centre, SBP, smoking status, wine consumption, regular fish consumption, BMI, total cholesterol, HDL cholesterol, diabetes status, previous cardiovascular disease, living alone, disability status, beta-blocker use and calcium antagonist use</td>
</tr>
<tr>
<td>Leistner et al. 2012</td>
<td>Germany</td>
<td>5</td>
<td>22, 55.9</td>
<td>0.84 (0.22-3.31)</td>
<td>Age, gender, atrial fibrillation, rate control medication, diabetes mellitus, hypertension, smoking status, family history of CAD, hyperlipidaemia, and BMI</td>
</tr>
<tr>
<td>Woodward et al. 2012</td>
<td>Asia</td>
<td>7.4</td>
<td>2055, 51</td>
<td>1.45 (1.28-1.64)</td>
<td>Age, SBP, anti-hypertensive medication use, total cholesterol, smoking status, BMI and diabetes</td>
</tr>
<tr>
<td>Saxena et al. 2013</td>
<td>United States</td>
<td>15</td>
<td>1081, 44.0</td>
<td>1.51 (1.22-1.87)</td>
<td>Age, sex, examination year, BMI, smoking status, heavy alcohol drinking, physical activity, parental cardiovascular disease, abnormal electrocardiographic findings, diabetes, measured high blood pressure, self-reported hypertension, and hypercholesterolemia, maximal metabolic equivalents</td>
</tr>
<tr>
<td>Ho et al. 2014</td>
<td>United States</td>
<td>19</td>
<td>252, 55</td>
<td>1.18 (1.04-1.33)</td>
<td>Age, sex, SBP, use of antihypertensive treatment, BMI, diabetes, smoking status, physical activity index, valvular heart disease, electrocardiographic left ventricular hypertrophy, total/HDL cholesterol ratio, minor cardiovascular disease, and QRS duration</td>
</tr>
<tr>
<td>Ryu et al. 2014</td>
<td>Korea</td>
<td>20.8</td>
<td>337, 66.2</td>
<td>1.33 (1.18-1.49)</td>
<td>Age, hypertension, BMI, education, smoking, occupation, chronic disease and antihypertensive medication</td>
</tr>
</tbody>
</table>

Abbreviations: RR = relative risk; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = Body Mass Index.
Association of RHR with cardiovascular mortality


developing cardiovascular mortality (summary RR = 1.06, 95% CI = 1.04-1.08) (Figure 4).

Sources of heterogeneity and meta-regression

In order to explore the high between-study heterogeneity found in several analysis, univariate meta-regression with the covariates of publication year, sex, location where the study was conducted, number of cases, duration of follow-up, mean age and degree of adjustments of covariates was performed. No significant findings were found in the above-mentioned analysis.

Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the above mentioned pooled effect. Egger test showed no evidence of significant publication bias for the highest vs. lowest RHR and cardiovascular mortality risk (P = 0.47).

Discussion

Finding from this meta-analysis suggested that the higher RHR could increase the risk of cardiovascular mortality. The associations were also significant in the subgroup analysis of country, sex and duration of follow-up. Our dose-response analysis demonstrated a linear relationship between RHR and the risk of cardiovascular mortality, with a 6% increase in the risk of developing cardiovascular mortality for every 10 bpm increases in RHR.

An elevated heart rate has been linked to increased risks of cardiovascular diseases, through a multitude of actions including its detrimental effects on the progression of coronary atherosclerosis, on the occurrence of myocar-
Association of RHR with cardiovascular mortality

Table 2. Summary risk estimates of the association between resting heart rate and risk of cardiovascular mortality

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Highest vs. Lowest</th>
<th>80 bpm</th>
<th>10 bpm increment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>All</td>
<td>1.69 (1.42-2.00)</td>
<td>87.5</td>
<td>1.49 (1.24-1.79)</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1.66 (1.23-2.25)</td>
<td>91.6</td>
<td>1.47 (1.05-2.06)</td>
</tr>
<tr>
<td>America</td>
<td>1.67 (1.41-1.98)</td>
<td>33.4</td>
<td>1.67 (1.41-1.98)</td>
</tr>
<tr>
<td>Asia</td>
<td>1.50 (1.28-1.77)</td>
<td>48.3</td>
<td>1.37 (1.23-1.53)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.85 (1.26-2.74)</td>
<td>93.5</td>
<td>1.60 (1.03-2.50)</td>
</tr>
<tr>
<td>Women</td>
<td>1.43 (1.13-1.80)</td>
<td>63.6</td>
<td>1.41 (1.12-1.78)</td>
</tr>
<tr>
<td>Both</td>
<td>1.57 (1.37-1.79)</td>
<td>43.1</td>
<td>1.40 (1.30-1.52)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>1.65 (1.34-2.03)</td>
<td>90.2</td>
<td>1.51 (1.21-1.89)</td>
</tr>
<tr>
<td>≤ 10 years</td>
<td>1.71 (1.34-2.19)</td>
<td>25.2</td>
<td>1.45 (1.29-1.63)</td>
</tr>
</tbody>
</table>

bpm, bites per minute.

Figure 3. The forest plot for subjects with RHR levels of > 80 bpm and the risk of cardiovascular mortality.

dial ischemia and ventricular arrhythmias, on left ventricular function, and on circulating levels of inflammatory markers [8]. The main discussed mechanism is that the elevated RHR is a marker of an imbalance between the vagal and the sympathetic tone, and dysfunctional

Association of RHR with cardiovascular mortality

Autonomic nervous activity likely plays a central role in the pathogenesis of numerous adverse health conditions [42].

Munafo and Flint reported that between-study heterogeneity is common in meta-analyses [43], and exploring potential sources of between-study heterogeneity is an essential component of meta-analysis. We found a high degree of heterogeneity in our pooled results. This might have arisen from publication year, sex, location where the study was conducted, number of cases, duration of follow-up, mean age and degree of adjustments of covariates. Thus, we used meta-regression to explore the causes of heterogeneity for covariates. However, no covariate having a significant impact on between-study heterogeneity was found among those mentioned above. We then performed subgroup analyses by geographic locations, sex and duration of follow-up to explore the source of heterogeneity. However, between-study heterogeneity persisted in some of the subgroups, suggesting the presence of other unknown confounding factors.

A major strength of this study was the large number of participants included from prospective studies, allowing a much greater possibility of reaching reasonable conclusions. And prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case-control studies. Furthermore, this is the first comprehensive dose-response meta-analysis of RHR and cardiovascular mortality risk based on high versus low analysis and dose-response meta-analysis. Also, no significant publication bias was found, indicating that our results are stable. However, there were some limitations in this meta-analy-

FIGURE 4. The forest plot of every 10 bpm increased in RHR and the risk of cardiovascular mortality risk. Squares represent study-specific RR, horizontal lines represent 95% CI and diamonds represent summary relative risks.
sis. First, although we extracted the RR that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and the possibility that the observed association was due to unmeasured or residual confounding should be considered. Second, between-study heterogeneity was found in some analysis in this meta-analysis, but the between-study heterogeneity was not successfully explained by the subgroup analysis and meta-regression. However, other genetic and environment variables, as well as their possible interaction may be potential contributors to this disease-effect unconformity.

In summary, this meta-analysis found that an elevated RHR was a risk factor of cardiovascular mortality in general population. Dose-response analysis indicated that the estimated risk increased in cardiovascular mortality is 6% for every 10 bpm increase in RHR.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yuechun Li, Department of Cardiology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Kongjiang Road No. 1665, Shanghai 200092, China. Tel: +8613482697118; E-mail: yuechunli1@163.com

References

Association of RHR with cardiovascular mortality


Association of RHR with cardiovascular mortality

