Association of resting heart rate and hypertension stages on all-cause and cardiovascular mortality among elderly Koreans: the Kangwha Cohort Study

Mikyung Ryu1,2, Gombojav Bayasgalan3, Heejin Kimm4, Chung Mo Nam5, Heechoul Ohrr5

1Institute on Aging, Ajou University Medical Center, Suwon, South Korea
2College of Physical Education, Kyonggi University, Suwon, South Korea
3Department of Public Health, the Graduate School, Yonsei University, Seoul, South Korea
4Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, South Korea
5Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea

Abstract

Background Elevated resting heart rate and hypertension independently increase the risk of mortality. However, their combined effect on mortality in stages of hypertension according to updated clinical guidelines among elderly population is unclear. Methods We followed a cohort of 6100 residents (2600 males and 3500 females) of Kangwha County, Korea, ranging from 55 to 99 year-olds as of March 1985, for all-cause and cardiovascular mortality for 20.8 years until December 31, 2005. Mortality data were collected through telephone calls and visits (to 1991), and were confirmed by death record matching with the National Statistical Office (1992–2005). Hazard ratios were calculated for all-cause and cardiovascular mortality by resting heart rate and hypertension defined by Eighth Joint National Committee criteria using the Cox proportional hazard model after controlling for confounding factors. Results The hazard ratios associated with resting heart rate > 80 beats/min were higher in hypertensive men compared with normotensives with heart rate of 61–79 beats/min, with hazard ratios values of 1.43 (95% CI: 1.00–1.92) on all-cause mortality for prehypertension, 3.01 (95% CI: 1.07–8.28) on cardiovascular mortality for prehypertension, and 8.34 (95% CI: 2.52–28.19) for stage 2 hypertension. Increased risk (HR: 3.54, 95% CI: 1.16–9.21) was observed among those with both a resting heart rate ≥ 80 beats/min and prehypertension on cardiovascular mortality in women. Conclusions Individuals with coexisting elevated resting heart rate and hypertension, even in prehypertension, have a greater risk for all-cause and cardiovascular mortality compared to those with elevated resting heart rate or hypertension alone. These findings suggest that elevated resting heart rate should not be regarded as a less serious risk factor in elderly hypertensive patients.

J Geriatr Cardiol 2016; 13: 573–579. doi:10.11909/j.issn.1671-5411.2016.07.003

Keywords: Cardiovascular diseases; Heart rate; Hypertension; Mortality; Prehypertension

1 Introduction

Elevated resting heart rate (ERHR) has been reported as a major risk factor for cardiovascular diseases (CVDs),[1–3] sudden death,[4] heart failure[1] and all-cause mortality[12,5] in the general population. Heart rate has been implicated as a prognostic factor of CVDs like myocardial infarction,[6] coronary heart disease,[7] or chronic heart failure (CHF).[8]

The predictive value of heart rate was even higher than that of blood pressure (BP) in some reports.[9] The significant role of heart rate among hypertension patients has been reported. Heart rate is an independent risk factor of mortality in hypertension patients after adjusting β-blocker use or other combined risk factors.[10] Heart rate and BP may have synergistic effects on CVD complications.[10,11] Heart rate of hypertensive patients has been highlighted in several studies.[11–14] The risk of CVDs was 1.48 (95% CI: 1.22–1.78) in hypertensive patients with tachycardia exceeding 80 beats/min.[14] The combined risk of ERHR and systolic BP has also been reported in chronic heart failure patients.[15]

The 2014 Eighth Report of the Joint National Committee (JNC-8) expert panel, as a foundation of the standardized treatment based on evidences, restructured the stages of hypertension: prehypertension, stage 1, and stage 2.[16] Prehypertension suggested in the recent clinical guideline raise the all-cause mortality.[17] However, previous studies on heart rate in hypertensive cases defined hypertension as
systolic BP > 140 mmHg or diastolic BP > 90 mmHg\cite{11,14} controlled or uncontrolled hypertension,\cite{12} or as a continuous variable.\cite{13}

Therefore, these previous reports provide insufficient information for clinical decision based on JNC-8 guideline. The information on the predictive risk of the each hypertension stage combined with heart rate might have more clinical value. In particular, the JNC-8 expert panel recommended an increased BP target in patients ≥ 60 years of age,\cite{16} for whom the achievement of BP target should require close monitoring because the new target might be more permissive for higher CVD risk.\cite{18} Therefore, information for risk assessment in each stage of hypertension is needed in these age group.

The purpose of this study was to examine the effect of ERHR in stages of hypertension according to JNC-8 on all-cause and cardiovascular mortality in a large cohort of Koreans over a 20.8-year follow-up.

2 Methods

2.1 Study population

This study used the data of the Kangwha cohort that have been collected since March 1985. Kangwha County consists of several islands located approximately 50 km west of Seoul. Its population was 71,116 in 1993.\cite{19,20} In February 1985, 9378 residents in Kangwha County ≥ 55 years of age. Among these residents, 67.9% (6372 residents) participated in the interviews and measurements of heart rate, BP, and body weight. Those who had a stroke or coronary heart disease (n = 135) or had no information on heart rate (n = 137) were excluded. The final study population recruited was 6100 (2600 males and 3500 females). The Institutional Review Board of Human Research of Yonsei University approved the study (Approval No. 4-2007-0182).

2.2 Baseline data collection and follow-up

The primary survey for the Kangwha cohort was conducted over one month in March 1985 by 26 trained interviewers after one week of training. Each participant was interviewed using a structured questionnaire for demographic data comprising education, occupation, health conditions at entry, health behaviors, diet, and other factors (smoking and drinking). Height and weight were measured by trained investigators. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m²). Concerning chronic conditions, the study participants were asked to answer yes or no to the question “Do you have any chronic disease or past accident or injury due to which you feel uncomfortable in your daily life including work?” The study participants were followed up until December 31, 2005, for a maximum period of follow-up for mortality of 20.8 years.

2.3 Heart rate and BP measurements

BP was measured in a seated position by a trained investigator using a standard mercury sphygmomanometer.\cite{20} The first and fifth Korotkoff sounds were recorded as systolic and diastolic BP, respectively. The cut-off point defined in previous studies was used to categorize the resting heart rate.\cite{17,21,22} Participants were categorized into three groups based on resting heart rate: < 61 beats/min, 61–79 beats/min, and ≥ 80 beats/min. BP was classified into four categories using JNC-8 on Detection, Evaluation, and Treatment of High Blood Pressure classification.\cite{16}

2.4 Mortality data

Data for those who died from March 15, 1985 to December 31, 1991 were collected either through telephone calls and visits by trained surveyors twice a year or from records of burial and death certificates from the Eup and Myeon administrative branch offices of the local government in Korea. Deaths among subjects from January 1, 1992 to December 31, 2005 were confirmed by matching the information to death records from the National Statistical Office. The main outcome variables for this study were death from all causes and CVD as defined by the International Classification of Disease, 10th edition.

2.5 Statistical analyses

Continuous variables were shown as means ± SD and were compared using one-way analysis of variance. Categorical variables were shown as counts and percentages and were compared using Chi-square tests for association. The Cox proportional hazard model was used to test the relationship among resting heart rate status, BP level at baseline and subsequent risk for all-cause and cardiovascular mortality. In the model of combined effect, we created twelve different categories of resting heart rate status and BP level with all the different combinations. The combination of heart rate (61–79 beats/min) and normal level of BP was considered as the reference group. Variables adjusted for in the model were age (as a continuous variable), BMI (as a continuous variable), education status (no education/elementary/high), smoking status (never/former/current), alcohol use (non-drinker/drinker), occupation (agriculture/other), and chronic disease (ever/never). The analyses were performed for men and women separately due to the gender differences in all-cause and CVD-related mortality. The outcome of interest was vital status. Hazard ratios and 95% confidence intervals (CIs) were expressed for the results. A
significance level of $P \leq 0.05$ was used for all tests. Analyses were performed using SAS Windows Version 9.3.

3 Results

The mean age of men and women was 66.2 ± 7.2 years and 66.9 ± 8.5 years, respectively. The average resting heart rate for men was 73.3 ± 9.7 beats/min compared to 71.8 ± 9.1 beats/min for women. Men were more likely to be cigarette smokers and alcohol users. Almost all subjects (98.8%) had received no formal education or had been educated only at an elementary school level. During the 20.8 years of follow up, 4065 (66.6%) people comprising 1990 men and 2075 women died.

General characteristics of the study participants according to resting heart rate categories are presented in Table 1. Those who had a heart rate $\geq 80$ beats/min displayed a higher BP, higher proportions of smoking and alcohol drinking, and a higher death rate.

Table 2 showed the hazard ratios for all-cause and cardiovascular mortality according to resting heart rate categories. heart rate 61–79 beats/min served as the reference group. On univariate analyses for both genders, resting heart rate $\geq 80$ beats/min was significantly associated with increased all-cause and CVD mortality. The magnitude of the risk for all-cause mortality was slightly higher in women than men, but less strong for CVD mortality. On multivariate analyses, the hazard ratios were reduced only slightly, but remained significant for all-cause and CVD mortality both in men and women.

The hazard ratios for all-cause mortality associated with prehypertension was 1.01 (95% CI: 0.63–1.60) for resting heart rate $< 61$ beats/min, 1.15 (95% CI: 0.88–1.55) for resting heart rate 61–79 beats/min, and 1.43 (95% CI: 1.00–1.92) for resting heart rate $\geq 80$ beats/min among men. The results indicated that the combined effect of resting heart rate and hypertension on risk of all-cause mortality increased slightly with the increasing resting heart rate. Compared to the reference group, men with a resting heart rate $\geq 80$ beats/min and stage 2 hypertension had the highest hazard ratios for CVD mortality, 8.34 (95% CI: 2.52–28.19; Table 3).

Table 1. General characteristics of the study population in the Kangwha cohort study categorized by heart rate.

| Variable          | Heart rate category, beats/min                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------|
|                   | < 61 ($n = 554$)                                                                 | 61–79 ($n = 4260$) | $\geq 80$ ($n = 1286$) | $P$ value |
| Age, yrs          | 66.6 ± 8.3                                                                                     | 66.4 ± 7.9         | 67.3 ± 7.9               | 0.0023    |
| SBP, mmHg         | 144.7 ± 32.3                                                                                   | 147.0 ± 31.0       | 152.8 ± 33.1             | < 0.0001  |
| DBP, mmHg         | 68.5 ± 21.4                                                                                   | 71.0 ± 19.3        | 70.9 ± 21.3              | 0.0824    |
| BMI, kg/m²        | 22.0 ± 3.2                                                                                    | 22.0 ± 3.4         | 21.6 ± 3.3               | 0.0445    |
| Gender            |                                                                                                 |                    |                          |           |
| Men               | 222 (40.0%)                                                                                   | 1754 (41.1%)       | 624 (48.5%)              | < 0.0001  |
| Women             | 332 (59.9%)                                                                                   | 2506 (58.8%)       | 662 (51.4%)              |           |
| Education         |                                                                                                 |                    |                          |           |
| No                | 361 (65.1%)                                                                                   | 2704 (63.4%)       | 809 (62.9%)              | 0.7021    |
| Elementary        | 176 (31.7%)                                                                                   | 1376 (32.3%)       | 421 (32.7%)              |           |
| High              | 17 (3.0%)                                                                                     | 180 (4.2%)         | 56 (4.3%)                |           |
| Smoking           |                                                                                                 |                    |                          |           |
| Never             | 296 (53.4%)                                                                                   | 2277 (53.4%)       | 548 (42.6%)              | < 0.0001  |
| Former            | 28 (5.0%)                                                                                     | 180 (4.2%)         | 54 (4.2%)                |           |
| Current           | 230 (41.5%)                                                                                   | 1803 (42.3%)       | 684 (53.1%)              |           |
| Drinking          |                                                                                                 |                    |                          |           |
| Non-drinking      | 383 (69.1%)                                                                                   | 2912 (68.3%)       | 746 (58.0%)              | < 0.0001  |
| Drinking          | 171 (30.7%)                                                                                   | 1348 (31.7%)       | 540 (42.0%)              |           |
| Occupation        |                                                                                                 |                    |                          |           |
| Agriculture       | 458 (82.6%)                                                                                   | 3520 (82.6%)       | 1074 (83.5%)             | 0.7581    |
| Other             | 96 (17.3%)                                                                                    | 740 (17.3%)        | 212 (16.4%)              |           |
| Chronic disease   |                                                                                                 |                    |                          |           |
| Ever              | 302 (54.5%)                                                                                   | 1915 (44.9%)       | 655 (50.9%)              | < 0.0001  |
| Never             | 252 (45.4%)                                                                                   | 2345 (55.0%)       | 631 (49.1%)              |           |
| Death             | 371 (66.9%)                                                                                   | 2753 (64.6%)       | 941 (73.2%)              | < 0.0001  |

Data are presented as mean ± SD or n (%) unless otherwise specified. BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

http://www.jgc301.com; jgc@mail.sciencep.com | Journal of Geriatric Cardiology
### Table 2. Hazard ratios of all-cause and cardiovascular mortality according to heart rate in the Kangwha cohort.

| Heart rate, beats/min | All-cause mortality | Cardiovascular mortality |
|-----------------------|---------------------|-------------------------|
|                       | Univariate*         | Multivariate*           | Univariate*         | Multivariate* |
|                       | HRs (95% CI)        | HRs (95% CI)            | HRs (95% CI)        | HRs (95% CI)  |
| Men                   |                     |                         |                       |               |
| < 61                  | 1.07 (0.91–1.26)    | 1.08 (0.92–1.27)        | 1.06 (0.88–1.27)     | 1.00 (0.83–1.21) |
| 61–79                 | 1.00 Reference      | 1.00 Reference          | 1.00 Reference       | 1.00 Reference |
| ≥ 80                  | 1.16 (1.04–1.29)    | 1.10 (1.00–1.21)        | 1.35 (1.20–1.51)     | 1.15 (1.02–1.25) |
| Women                 |                     |                         |                       |               |
| < 61                  | 1.07 (0.92–1.25)    | 1.09 (0.94–1.27)        | 0.94 (0.80–1.10)     | 1.04 (0.88–1.22) |
| 61–79                 | 1.00 Reference      | 1.00 Reference          | 1.00 Reference       | 1.00 Reference |
| ≥ 80                  | 1.24 (1.11–1.38)    | 1.20 (1.07–1.33)        | 1.24 (1.11–1.38)     | 1.11 (1.03–1.28) |

*Adjusted for age; #Adjusted for age, education, smoking, drinking, body mass index, occupation, chronic disease and blood pressure. HRs: hazard ratios.

### Table 3. Combined effect of heart rate and hypertension by JNC-8 on all-cause and cardiovascular mortality in the Kangwha cohort.

| Category of heart rate and BP level | All-cause mortality | Cardiovascular mortality |
|-------------------------------------|---------------------|-------------------------|
|                                     | n                   | HRs (95% CI)            | n                   | HRs (95% CI) |
| Men                                 |                     |                         |                       |               |
| Normal (< 120/80 mm Hg)             |                     |                         |                       |               |
| < 61 beats/min                      | 29                  | 1.25 (0.67–2.34)        | 2                   | 2.67 (0.51–13.85) |
| 61–79 beats/min                     | 162                 | 1.00 Reference          | 18                  | 1.00 Reference |
| ≥ 80 beats/min                      | 46                  | 1.69 (0.97–2.93)        | 3                   | 4.32 (1.03–18.28) |
| Prehypertension (120–139/80–89 mmHg)|                     |                         |                       |               |
| < 61 beats/min                      | 89                  | 1.01 (0.63–1.60)        | 11                  | 1.36 (0.32–5.75) |
| 61–79 beats/min                     | 773                 | 1.15 (0.88–1.55)        | 132                 | 2.03 (0.79–5.02) |
| ≥ 80 beats/min                      | 290                 | 1.43 (1.00–1.92)        | 40                  | 3.01 (1.07–8.28) |
| Stage 1 hypertension (140–159/90–99 mmHg) |                     |                         |                       |               |
| < 61 beats/min                      | 23                  | 2.40 (0.96–2.07)        | 4                   | 10.1 (1.97–17.64) |
| 61–79 beats/min                     | 173                 | 1.26 (0.81–1.59)        | 35                  | 5.59 (1.99–10.07) |
| ≥ 80 beats/min                      | 67                  | 0.67 (0.34–1.31)        | 12                  | 0.83 (0.09–7.16) |
| Stage 2 hypertension (≥ 160/≥ 100 mmHg) |                     |                         |                       |               |
| Heart rate < 61 beats/min           | 33                  | 1.23 (0.77–1.93)        | 6                   | 6.76 (1.28–35.98) |
| Heart rate 61–79 beats/min          | 221                 | 1.22 (0.77–1.93)        | 49                  | 5.74 (1.94–17.44) |
| Heart rate ≥ 80 beats/min           | 91                  | 1.48 (0.85–2.55)        | 28                  | 8.34 (2.52–28.19) |
| Women                               |                     |                         |                       |               |
| Normal (< 120/80 mm Hg)             |                     |                         |                       |               |
| < 61 beats/min                      | 20                  | 1.34 (0.55–3.24)        | 2                   | 1.32 (0.15–11.43) |
| 61–79 beats/min                     | 135                 | 1.00 Reference          | 25                  | 1.00 Reference |
| ≥ 80 beats/min                      | 55                  | 2.29 (1.18–4.41)        | 10                  | 3.15 (0.75–13.33) |
| Prehypertension (120–139/80–89 mmHg)|                     |                         |                       |               |
| < 61 beats/min                      | 114                 | 1.80 (1.10–2.97)        | 24                  | 2.72 (0.88–8.32) |
| 61–79 beats/min                     | 783                 | 1.95 (1.33–2.82)        | 155                 | 2.38 (0.90–5.80) |
| ≥ 80 beats/min                      | 199                 | 2.23 (1.31–3.26)        | 36                  | 3.54 (1.16–9.21) |
| Stage 1 hypertension (140–159/90–99 mmHg) |                     |                         |                       |               |
| < 61 beats/min                      | 22                  | 2.96 (1.23–4.74)        | 3                   | 3.25 (0.61–16.71) |
| 61–79 beats/min                     | 212                 | 2.06 (1.30–3.16)        | 50                  | 4.11 (1.41–9.93) |
| ≥ 80 beats/min                      | 75                  | 2.73 (1.76–4.92)        | 16                  | 4.50 (1.59–16.32) |
| Stage 2 hypertension (≥ 160/≥ 100 mmHg) |                     |                         |                       |               |
| < 61 beats/min                      | 39                  | 3.76 (1.45–9.77)        | 6                   | 6.13 (0.71–53.85) |
| 61–79 beats/min                     | 302                 | 3.18 (2.03–5.00)        | 65                  | 7.13 (2.62–19.88) |
| ≥ 80 beats/min                      | 122                 | 3.40 (1.89–6.21)        | 25                  | 5.95 (1.59–22.97) |

Adjusted for age, education, smoking, drinking, body mass index, occupation and chronic disease. BP: blood pressure; HRs: hazard ratios; JNC-8: eighth report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure.
Women with resting heart rate \( \geq 80 \) beats/min with
pre-hypertension had significantly higher hazard ratio for
all-cause and CVD mortality \((2.23\) and \(3.54\), respectively) than those in the reference group, as well as in stage 1 or
stage 2 hypertension. The hazard ratios for CVD mortality
associated with the stage 1 hypertension increased from
3.25 (95% CI: 0.61–16.71) for resting heart rate \(< 61
beats/min to 4.11 (95% CI: 1.41–9.93) for resting heart
rate 61–79 beats/min, and 4.50 (95% CI: 1.59–16.32) for resting
heart rate \(\geq 80\) beats/min among women. With a
resting heart rate \(\geq 80\) beats/min and stage 2 hypertension
had the highest hazard ratios for CVD mortality, 5.95 (95%
CI: 1.59–22.97; Table 3).

The association seemed to be stronger in the JNC-8 hy-
pertension groups. In JNC-7 stage 2 hypertension and the
resting heart rate faster than 80 group, the highest hazard
ratios were for cardiovascular mortality 4.23 (95% CI:
2.21–9.58) in men and 3.52 (95% CI: 2.01–5.88) in women
(Online data Table S1, Table S2).

4 Discussion

We report the findings of survival analysis examining the
combined effect of resting heart rate and hypertension on
all-cause and CVD mortality among Korean men and
women over a 20.8-year follow-up period in the Kangwha
cohort. ERHR alone and in combination with hypertension
increased the risks of all-cause and CVD mortality. These
associations remained evident for both men and women
after controlling for the confounding effects of other poten-
tial risk factors including age, BMI, education, occupation,
chronic disease, cigarette smoking, and alcohol consump-
tion. The hazard ratio for mortality due to CVDs was par-
ticularly high in patients with both ERHR and hypertension.

The association between resting heart rate and high syl-
tolic BP is consistent with previous studies where resting
heart rate was associated with high BP.\[^{10,23–25}\] In this study,
resting heart rate \(\geq 80\) beats/min was associated with a high
risk of all-cause mortality, compared to a heart rate of 61–79
beats/min for both genders. This was consistent with previous
studies that showed evidence of the highest risk of
all-cause mortality for people with ERHR.\[^{32}\] Further, al-
though the relationship between ERHR and CVD mortality
varied,\[^{17}\] it was associated with an increased risk of CVD
mortality in both men and women.

It was essential to consider possible mechanisms of the
interaction between ERHR and hypertension, and mortality.
Several studies claimed that over-activity of the sympathetic
nervous system might be responsible for the increase in both
heart rate\[^{6,26,27}\] and BP.\[^{27}\] ERHR measured in the supine
position reflected a heightened sympathetic tone that in the
long-term could cause deleterious cardiovascular altera-
tions.\[^{28}\] ERHR was frequently associated with high BP; how-
ever, these two factors seemed to have additive effects on
CVD risk. Several epidemiological studies have shown that
the risk associated with ERHR persisted even after ad-
justment for BP levels.\[^{29}\] Moreover, other studies have
demonstrated that the increase in CVD risk in individuals
with ERHR could be even higher in hypertensive than nor-
motensive individuals.\[^{11,13,25}\]

Hazard ratios for mortality according to resting heart rate
were 1.10 to 1.24. These were relatively low compared to
the hazard ratios of the combined groups, which were as
high as 8.34 and 5.95 for the cardiovascular mortality com-
bined with higher heart rate in men and women, respec-
tively. In women, the hazard ratios of the stage 2 hyperten-
sion group were higher than those of stage 1 hypertension
group, which had higher hazard ratios than the prehyperten-
sion group. The hazard ratios of stage 2 hypertensive indi-
viduals were even higher, even in low heart rate group (3.76,
6.13) than those of stage 1 hypertension group with higher
heart rate (2.73, 4.50), which implies the impact of BP
might be stronger than that of heart rate. However, in men,
there was no significant difference from the risk of reference
groups in stage 1 hypertension groups and stage 2 hyperten-
sion group concerning all-cause mortality. This is difficult
to explain but we cannot exclude the possibility of the in-
fluence from several unidentified chronic heart failure pa-
tients in those groups. The prognosis of chronic heart failure
has been known to be superior in higher heart rate groups
than lower heart rate groups.\[^{15}\]

Ivabradine is an \(I_{\text{f}}\) channel inhibitor that lowers ERHR,
which improves cardiovascular mortality in chronic heart
failure patients\[^{30}\] and symptoms associated with inap-
propriate sinus tachycardia.\[^{31}\] Presently, there was an increased
risk of cardiovascular mortality in individuals with ERHR
with hypertension. However, therapeutic value of the heart
rate lowering treatment for this risk group remains unex-
plored. Our study had notable strengths. The prospective
study design minimized recall bias. The sample size was
larger and the follow-up period (20.8 years) was longer than
other studies.

Several potential limitations should be noted. We did not
include the use of cardiovascular and antihypertensive drugs
possibly affecting resting heart rate and BP into the group of
confounders. However, at the time of the baseline examina-
tion, the use of these drugs was > 10% in Korea.\[^{32}\] Sec-
ondly, the level of physical activity of participant was not
evaluated. But, 80%–87% of participants were farmers, so
would be expected to have little difference in that regard.\[^{19}\]
Because most of the participants (82.8%) were engaged in agriculture, we adjusted for occupation as a proxy for physical activity.

In conclusion, individuals with coexisting ERHR and hypertension are at the greater risk for all-cause (in women) and cardiovascular mortality (in both men and women) compared to those with either ERHR or hypertension alone. These findings also suggest that ERHR should not be regarded as a less serious risk factor in elderly hypertensive patients than those with normal BP among Koreans.

Acknowledgements

This study was funded by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C2686). The authors declare that they have no competing interests.

References

1. Ho JE, Larson MG, Ghorbani A, et al. Long-term cardiovascular risks associated with an elevated heart rate: the Framingham Heart Study. J Am Heart Assoc 2014; 3: e000668.
2. Wang A, Chen S, Wang C, et al. Resting heart rate and risk of cardiovascular diseases and all-cause death: the Kailuan study. PLoS One 2014; 9: e110985.
3. Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: A 12 year follow-up study of 379,843 men and women aged 40-45 years. Eur Heart J 2008; 29: 2772–2781.
4. Jouven X, Zureik M, Desnos M, et al. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. Cardiovasc Res 2001; 50: 373–378.
5. Kristal-Boneh E, Silber H, Harari G, et al. The association of resting heart rate with cardiovascular, cancer and all-cause mortality. Eight year follow-up of 3527 male israeli employees (the cordis study). Eur Heart J 2000; 21: 116–124.
6. Perski A, Olsson G, Landou C, et al. Minimum heart rate and coronary atherosclerosis: Independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. Am Heart J 1992; 123: 609–616.
7. Dyer AR, Persky V, Stamler J, et al. Heart rate as a prognostic factor for coronary heart disease and mortality: Findings in three chicago epidemiologic studies. Am J Epidemiol 1980; 112: 736–749.
8. Guo YF, An Y. Is heart rate reduction more important than target dose in chronic heart failure therapy with a beta-blocker? J Geriatr Cardiol 2011; 8: 260–262.
9. Palatini P, Benetos A, Grassi G, et al. Identification and management of the hypertensive patient with elevated heart rate: Statement of a european society of hypertension consensus meeting. J Hypertens 2006; 24: 603–610.
10. Palatini P. Role of elevated heart rate in the development of cardiovascular disease in hypertension. Hypertension 2011; 58: 745–750.
11. Gillman MW, Kannel WB, Belanger A, et al. Influence of heart rate on mortality among persons with hypertension: The framingham study. Am Heart J 1993; 125: 1148–1154.
12. Julius S, Palatini P, Kjeldsen SE, et al. Usefulness of heart rate to predict cardiac events in treated patients with high-risk systemic hypertension. Am J Cardiol 2012; 109: 685–692.
13. Pal P, Hastie CE, Li WS, et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. Hypertension 2010; 55: 567–574.
14. Thomas F, Rudnichi A, Bacri AM, et al. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. Hypertension 2001; 37: 1256–1261.
15. Miura M, Sakata Y, Miyata S, et al. Usefulness of combined risk stratification with heart rate and systolic bloodpressure in the management of chronic heart failure. A report from the CHART-2study. Circ J 2013; 77: 2954–2962.
16. James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the management of high blood pressure in adults report from the panel members appointed to the Eighth Joint National Committee (JNC-8). JAMA 2014; 311: 507–520.
17. King DE, Everett CJ, Mainous AG 3rd, et al. Long-term prognostic value of resting heart rate in subjects with prehypertension. Am J Hypertens 2006; 19: 796–800.
18. Borden WB, Maddox TM, Tang F, et al. Impact of the 2014 expert panel recommendations for management of high blood pressure on contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. J Am Coll Cardiol 2014; 64: 2196–2203.
19. Sull JW, Yi SW, Nam CM, et al. Binge drinking and hypertension on cardiovascular disease mortality in korean men and women: A Kangwha cohort study. Stroke 2010; 41: 2157–2162.
20. Sull JW, Yi SW, Nam CM, et al. Binge drinking and mortality from all causes and cerebrovascular diseases in korean men and women: A Kangwha cohort study. Stroke 2009; 40: 2953–2958.
21. Perk G, Stessman J, Ginsberg G, et al. Sex differences in the effect of heart rate on mortality in the elderly. J Am Geriatr Soc 2003; 51: 1260–1264.
22. Jouven X, Empana JP, Escolano S, et al. Relation of heart rate at rest and long-term (> 20 years) death rate in initially healthy middle-aged men. Am J Cardiol 2009; 103: 279–283.
23. Gilliam RF. The epidemiology of resting heart rate in a national sample of men and women: Associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. Am Heart J 1988; 116: 163–174.
24. Simpson FO, Waal-Manning HJ, Bolli P, et al. The milton survey. 2. Blood pressure and heart rate. N Z Med J 1978; 88: 1–4.
25. Palatini P, Thijs L, Staessen JA, et al. Predictive value of clinic and ambulatory heart rate for mortality in elderly
subjects with systolic hypertension. Arch Intern Med 2002; 162: 2313–2321.

26 Grassi G, Vailati S, Bertinieri G, et al. Heart rate as marker of sympathetic activity. J Hypertens 1998; 16: 1635–1639.

27 Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc 2009; 84: 822–830.

28 Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 2001; 104: 1477–1482.

29 Benetos A, Rudnichi A, Thomas F, et al. Influence of heart rate on mortality in a french population: Role of age, gender, and blood pressure. Hypertension 1999; 33: 44–52.

30 Böhm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010; 376: 886–894.

31 Cappato R, Castelvecchio S, Ricci C, et al. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. J Am Coll Cardiol 2012; 60: 1323–1329.

32 Hatano S, Kim JS, Guzman SV, et al. Personal attributes related to blood pressure in a community population in Japan, Korea and Philippines: an international cooperative study. Magnesium 1982; 1: 185–195.