Journal of Geriatric Cardiology (2016) 13: 573–579

Research Article · Open Access ·

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

Mikyung Ryu[1,2], Gombojav Bayasgalan[3], Heejin Kimm[4], Chung Mo Nam[5], Heechoul Ohrr[5]

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

Correspondence to: Heejin Kimm, MD, PhD, Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, South Korea. E-mail: heejink@yuhs.ac
Telephone: +82-2-2228-1531 **Fax:** +82-2-365-5118
Received: March 21, 2016 **Revised:** July 11, 2016
Accepted: July 19, 2016 **Published online:** July 28, 2016

systolic BP > 140 mmHg or diastolic BP > 90 mmHg,[11,14] controlled or uncontrolled hypertension,[12] or as a continuous variable.[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,[16] for whom the achievement of BP target should require close monitoring because the new target might be more permissive for higher CVD risk.[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.[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/m^2). 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.[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.[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.[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 ≥ 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 ≥ 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 ≥ 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 ≥ 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			*P* value
	< 61 (*n* = 554)	61–79 (*n* = 4260)	≥ 80 (*n* = 1286)	
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/m^2	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.

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	(0.75–13.3)
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 ≥ 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 ≥ 80 beats/min among women. Women with a resting heart rate ≥ 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 hypertension 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 potential risk factors including age, BMI, education, occupation, chronic disease, cigarette smoking, and alcohol consumption. The hazard ratio for mortality due to CVDs was particularly high in patients with both ERHR and hypertension.

The association between resting heart rate and high systolic BP is consistent with previous studies where resting heart rate was associated with high BP.[10,23–25] In this study, resting heart rate ≥ 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.[22] Further, although the relationship between ERHR and CVD mortality varied,[7] 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[8,26,27] and BP.[27] ERHR measured in the supine position reflected a heightened sympathetic tone that in the long- term could cause deleterious cardiovascular alterations.[28] ERHR was frequently associated with high BP; however, 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 adjustment 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 normotensive 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 combined with higher heart rate in men and women, respectively. In women, the hazard ratios of the stage 2 hypertension group were higher than those of stage 1 hypertension group, which had higher hazard ratios than the prehypertension group. The hazard ratios of stage 2 hypertensive individuals 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 hypertension group concerning all-cause mortality. This is difficult to explain but we cannot exclude the possibility of the influence from several unidentified chronic heart failure patients 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_f channel inhibitor that lowers ERHR, which improves cardiovascular mortality in chronic heart failure patients[30] and symptoms associated with inappropriate 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 unexplored. 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 examination, the use of these drugs was > 10% in Korea.[32] Secondly, 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.

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