Preplanned Studies

Effect of Heart Rate on Major Adverse Cardiovascular Events in Hypertensive Patients with Different Ages and Genders

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Summary

What is already known on this topic?

The increase of heart rate will increase blood pressure, and the cardiovascular risk will increase when heart rate >80 beats/min (bpm) in patients with hypertension.

What is added by this report?

Compared with patients who were female, <65 years old, and with hypertension, patients who were male, ≥ 65 years old, and with hypertension had the lowest risk of major adverse cardiovascular events (MACE) at baseline heart rate (HR) of 70–74 bpm.

What are the implications for public health practice?

Patients with hypertension should control their blood pressure well, and the HR of male and elderly patients should be managed well at the same time.

The previous follow-up study of the Kailuan cohort in Tangshan City, Hebei Province found that resting heart rate (HR) was associated with all-cause death; the risk of all-cause death was the lowest when heart rate was 68–72 beats/min (bpm) and was the highest when heart rate exceeded 82 bpm (*1*). Compared with the normal population, the related risk was higher in hypertensive population when heart rate was > 80 bpm (*2*). The gender and age of patients with hypertension affected the prognosis of cardiovascular events (*3*), but whether it was related to heart rate was not clear. This study conducted cohort follow-up of patients with hypertension and analyzed the impact of baseline heart rate level on major adverse cardiovascular events (MACE) in patients with different ages and genders.

The HR, blood pressure (BP), systolic blood pressure (SBP), and diastolic blood pressure (DBP) of the patients were measured by Omron medical automatic electronic sphygmomanometers (model: hem-8102a). According to the baseline HR, patients were divided into 4 groups: <70 bpm, 70–74 bpm, 75–79 bpm, and ≥80 bpm. All patients with hypertension were treated with calcium antagonist (amlodipine). If the target BP was not met, other antihypertensive drugs would be added until the target BP was <140/90 mmHg. After 24 months of follow-up, the effects of baseline HR on MACE were analyzed in hypertensive patients of different ages (<65 years old/≥65 years old) and genders (male/female). The definition of MACE includes death, non-fatal stroke, non-fatal myocardial infarction, unstable angina pectoris, coronary intervention, coronary artery bypass grafting, newly onset atrial fibrillation, heart failure, and aortic dissection aneurysm, one of which criteria is enough for patient to be defined as MACE. All statistical analysis was performed by SAS (version 9.4, SAS Institute Inc., Cary, USA).

A total of 9,991 patients with hypertension from 110 hospitals in 21 cities* were enrolled in this study, including 5,045 males, 4,946 females, 5,400 patients aged <65 years, and 4,591 patients aged ≥65 years. The mean age was 64.46±10.65 years. The results showed that faster HR, younger age, and higher baseline SBP and DBP were all significant (all $P<0.001$) (Supplementary Table S1, available in http://weekly.chinacdc.cn/). After 24 months of antihypertensive drug treatment, SBP, DBP of hypertensive patients with different ages and genders were significantly lower than those at baseline ($P<0.001$). HR of female patients after treatment was significantly lower than that of baseline ($P<0.001$), but there was no significant difference in HR of male patients before and after treatment (Table 1).

The results showed that after adjusting for baseline BP, smoking, drinking, hyperlipidemia, diabetes, coronary heart disease, cerebrovascular disease, and taking beta blockers, the relative risk of MACE at baseline HR of 70–74 bpm in male and ≥65 years old patients decreased by 41% and 40% [HR=0.593 (95%CI: 0.401–0.876), $P=0.009$; HR=0.603 (95%CI: 0.422–0.861), $P=0.005$] (Table 2).

* 21 cities: Beijing, Hangzhou, Shanghai, Xuzhou, Nanjing, Guangzhou, Shenzhen, Changsha, Yinchuan, Jilin, Xi'an, Wuhan, Shenyang, Dalian, Tianjin, Zhengzhou, Chongqing, Chengdu, Jinan, Shijiazhuang, Handan.

TABLE 1. Blood pressure and heart rate at baseline and 24 months follow-up in hypertensive patients with different ages and genders.

Item	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)		Heart rate (bpm)	
	Baseline	24 months follow-up	Baseline	24 months follow-up	Baseline	24 months follow-up
≥65 years old (n=4,591)	145.03±17.27	130.97±7.28	82.41±10.31	77.00±6.19	72.90±8.67	71.52±5.81
<65 years old (n=5,400)	145.78±17.52*	130.27±6.99†	87.21±10.52†	78.21±5.75†	74.08±7.93†	71.81±5.42†
Male (n=5,045)	145.40±17.09	130.67±7.09	85.52±10.74	77.86±6.04	71.73±8.28	71.72±5.57
Female (n=4,946)	145.47±17.73	130.51±7.18	84.27±10.57§	77.45±5.94§	73.33±8.32§	71.63±8.32

Abbreviation: bpm=beats/min.

Note: Compared before and after 24 months treatment, except heart rate of male patients, *P* values were <0.001; compared with ≥65 years old, *P<0.05, †P<0.01; compared with male patients, §P <0.01.

TABLE 2. Effects of different baseline heart rate levels on MACE in hypertensive patients with different ages and genders.

Item	Baseline heart rate (bpm)	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)*	*P*
Male					
	<70	0.996 (0.685−1.447)	0.981	0.871 (0.593−1.279)	0.480†
	70−74	0.639 (0.436−0.935)	0.021	0.593 (0.401−0.876)	0.009†
	75−79	0.756 (0.506−1.130)	0.173	0.751 (0.500−1.127)	0.167†
	≥80	Ref		Ref	
Female					
	<70	1.063 (0.719−1.570)	0.760	1.007 (0.676−1.501)	0.973†
	70−74	0.860 (0.584−1.266)	0.445	0.891 (0.601−1.321)	0.567†
	75−79	0.713 (0.461−1.104)	0.130	0.791 (0.509−1.230)	0.298†
	≥80	Ref		Ref	
<65 years old					
	<70	1.094 (0.696−1.720)	0.697	1.028 (0.644−1.641)	0.909§
	70−74	0.941 (0.611−1.450)	0.784	0.963 (0.620−1.496)	0.866§
	75−79	0.741 (0.458−1.199)	0.222	0.769 (0.473−1.249)	0.288§
	≥80	Ref		Ref	
≥65 years old					
	<70	0.892 (0.637−1.248)	0.505	0.853 (0.604−1.205)	0.369§
	70−74	0.612 (0.432−0.867)	0.006	0.603 (0.422−0.861)	0.005§
	75−79	0.751 (0.516−1.092)	0.134	0.784 (0.537−1.146)	0.209§
	≥80	Ref		Ref	

Abbreviation: MACE=major adverse cardiovascular events.

* Adjusted for age/gender, baseline blood pressure, smoking, drinking, hyperlipidemia, diabetes, coronary heart disease, cerebrovascular disease, taking beta blockers.

† Adjusted for age, baseline blood pressure, smoking, drinking, hyperlipidemia, diabetes, coronary heart disease, cerebrovascular disease, and taking beta blockers.

§ Adjusted for gender, baseline blood pressure, smoking, drinking, hyperlipidemia, diabetes, coronary heart disease, cerebrovascular disease, and taking beta blockers.

DISCUSSION

The increase of HR is a common clinical phenotype of hypertension. A cross-sectional survey of 115,229 patients with hypertension in 21 cities in China showed that 38.2% of the patients with hypertension had a HR of ≥80 bpm (*4*). In European systolic hypertension trial, compared with patients with baseline HR <80 bpm, patients with baseline HR ≥80 bpm had an 89% increase in all-cause mortality risk after an average follow-up of 24 months (*5*). The previous studies in Chinese and Swedish suggested that there were age and gender differences in the prevalence, awareness, treatment, and control of

hypertension (*6*). However, there are few studies on the optimal HR range of hypertensive patients of different ages and genders (*7*).

The study compared baseline HR of patients with hypertension before treatment. The results showed that patients with faster baseline HR had higher baseline blood pressure and lower age. Previous studies have shown that increased HR is a biomarker of increased sympathetic activity (*8*). This study further suggested that the sympathetic activity was higher in younger patients with hypertension.

Previous studies have shown that estrogen affects the cardiovascular system, including inducing vasodilation, inhibiting vascular remodeling, regulating renin-angiotensin-aldosterone system, and sympathetic nervous system. However, these protective effects can be significantly reversed in postmenopausal women (*9*). The mean age of hypertensive patients in this study was 64.46±10.65 years old, and the female patients at this age were lacking estrogen. The disappearance of estrogen's protective effect in postmenopausal elderly women, which is closely related to increases in blood pressure variability, nocturnal blood pressure load, and cardiovascular events, is likely not related to MACE decreases in hypertensive patients with HR of 70–74 bpm. In addition, previous studies have suggested that elderly age is closely related to the occurrence of MACE, especially in patients with stage 2 hypertension, and the increased risk of MACE was only observed in ≥70 years old patients (*10*). The study showed that the relative risk of MACE was lower when HR was 70–74 bpm in hypertensive patients ≥65 years. Strengthening the management of HR may reduce risk of MACE.

Furthermore, enrolled patients had been treated with standard antihypertensive drugs, which probably was one of the reasons that there was not much difference in systolic blood pressure between men and women and between younger and older people at baseline.

This study was subjected to some limitations. First, 24-hour Holter was not used to evaluate HR variability, which was the deficiency of heart rate analysis in this study. Second, this study was not a prospective study, further studies were needed to confirm the relationship between HR and MACE.

In summary, major adverse cardiovascular events increased when HR was ≥80 bpm in patients with hypertension. To better control the cardiovascular risk of male and elderly hypertensive patients over 65 years old, the HR should be controlled in the range of 70–74 bpm while the blood pressure is properly managed.

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SUPPLEMENTARY TABLE S1. Baseline characteristics of hypertensive patients with different baseline heart rates [($\bar{x}$±s), n (%)].

Baseline HR (bpm)	Age (years)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	Diabetes (%)	Hyperlipidemia (%)
Total (n=9,991)	64.46±10.65	24.61±2.82	145.43±17.41	84.90±10.67	1,477(14.78)	858(8.59)
<70 (n=2,655)	65.74±10.73	24.59±2.81	143.23±17.07	82.75±10.87	422(15.89)	250(9.42)
70–74 (n=3,589)	64.47±10.47 *	24.53±2.78	143.59±16.65	84.13±10.16 *	507(14.13)	294(8.19)
75–79 (n=2,305)	63.28±10.37 *, †	24.72±2.78	146.35±16.83*, †	85.99±10.10*, †	320(13.88)	188(8.16)
≥80 (n=1,442)	63.94±11.17 *	24.66±2.99	152.62±18.73*, †, §	89.04±11.10 *, †, §	228(15.81)	126(8.74)
	F=23.409	*F*=2.355	*F*=115.527	*F*=126.957	χ^2=6.525	χ^2=3.627
P value	<0.001	0.070	<0.001	<0.001	0.089	0.305

Abbreviation: SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; bpm=beats/min.
* compared with <70 bpm, *P*<0.05.
† compared with 70–74 bpm, *P*<0.05.
§ compared with 75–79 bmp, *P*<0.05.