

Heart Rate Predicts the Risk of New-Onset Peripheral Arterial Disease in a Community-Based Population in China

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Introduction: Elevated heart rate is linked with poor prognosis and has been shown to accelerate the progress of atherosclerosis. However, the association between heart rate and new-onset PAD is unknown.

Methods: A total of 3463 participants without PAD at baseline from a community-based cohort in Beijing were included and followed up for 2.3 years. PAD was defined as ankle-brachial index (ABI) ≤ 0.9 . We used multivariate logistic regression models to investigate the association of heart rate and the risk of new-onset PAD.

Results: Participants were 56.67 ± 8.54 years old, and 36.12% were men. The baseline ABI was 1.11 ± 0.08 , and the incidence of new-onset PAD was 2.97%. Multivariate regression models, adjusted for sex, age, risk factor of atherosclerosis, medications, and baseline ABI, showed that heart rate was significantly associated with incidence of PAD (odds ratio [OR] = 1.22, 95% confidence interval [CI]: 1.03–1.43, $P = 0.020$); every increase of 10 heart beats per minute (bpm) was associated with a 22% increase in the odds of developing new-onset PAD. Respondents in the higher-heart rate group (≥ 80 bpm) had an increased risk of new-onset PAD, compared with those in the lower-heart rate group (< 80 bpm) (OR = 1.73, 95% CI: 1.14–2.63, $P = 0.010$). Subgroup analyses revealed no significant heterogeneity among the analyzed subgroups.

Conclusion: Elevated heart rate was independently associated with the risk of new-onset PAD in a community-based population in Beijing. Heart rate management should be considered for the purpose of PAD prevention.

Keywords: cohort studies, heart rate, peripheral arterial disease, ankle-brachial index

Introduction

Peripheral arterial disease (PAD) is defined as ankle-brachial index (ABI) ≤ 0.9 based on the 2016 American Heart Association/American College of Cardiology guideline concerning the management of patients with lower-extremity PAD. PAD leads to claudication or critical limb ischemia, significantly reducing quality of life¹ and increasing the possibility of cardiovascular events.^{2,3} Moreover, patients with PAD have a higher prevalence of systemic atherosclerosis, including in the coronary arteries,⁴ carotid arteries,⁵ and renal arteries.⁶ In 1993, the Framingham Study first reported the association between heart rate and mortality,⁷ and many epidemiological studies have demonstrated that elevated heart rate is associated with poor prognosis among patients with hypertension,^{8–10} coronary artery disease,^{11,12} and heart failure.^{13,14} Studies have revealed that elevated heart rate could accelerate the progress of atherosclerosis.^{15–17}

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Moreover, several cross-sectional studies have previously revealed an inverse correlation between heart rate and the ABI.^{18–21} However, the association between heart rate and new-onset PAD is unknown, including among populations in China. Therefore, in this longitudinal cohort study with a 2.3-year follow-up, we investigated whether heart rate predicted the risk of new-onset PAD in a community-based population in China without PAD at baseline.

Patients and Methods

Study Population

Participants were drawn from an atherosclerosis cohort survey in Gucheng community and Pingguoyuan community of Shijingshan District of Beijing, China.²² First, we recruited 9540 residents aged ≥ 40 years either through study recruitment posters or phone call invitations if they had health records in community health centers from December 2011 to April 2012. Among the survey participants, we invited 5962 with gene chip data for a follow-up visit from May 2014 to July 2014. A total of 3659 participants

(61.4% of the 5962 invited participants) attended the onsite follow-up visit with baseline or follow-up ABI date. Among these 3659 participants, we excluded 89 participants who had an ABI ≤ 0.9 at baseline. Moreover, we further excluded 51 participants who did not complete the questionnaire and 56 participants with a self-reported history of atrial fibrillation in 2012 and 2014 as well. Ultimately, the analysis consisted of 3463 eligible participants. The schematic diagram of recruitment and excluding procedure is shown in Figure 1. This study obtained approval by the ethics committee of Peking University First Hospital, and we obtained written informed consent from each participant. We adhered to the principles of the Declaration of Helsinki.

Data Collection

Trained research staff was responsible for collecting baseline data according to standard operating procedures. A standardized questionnaire, including sociodemographic status, occupation, lifestyle, education, health behavior, diet, and medical history, was used to acquire basic

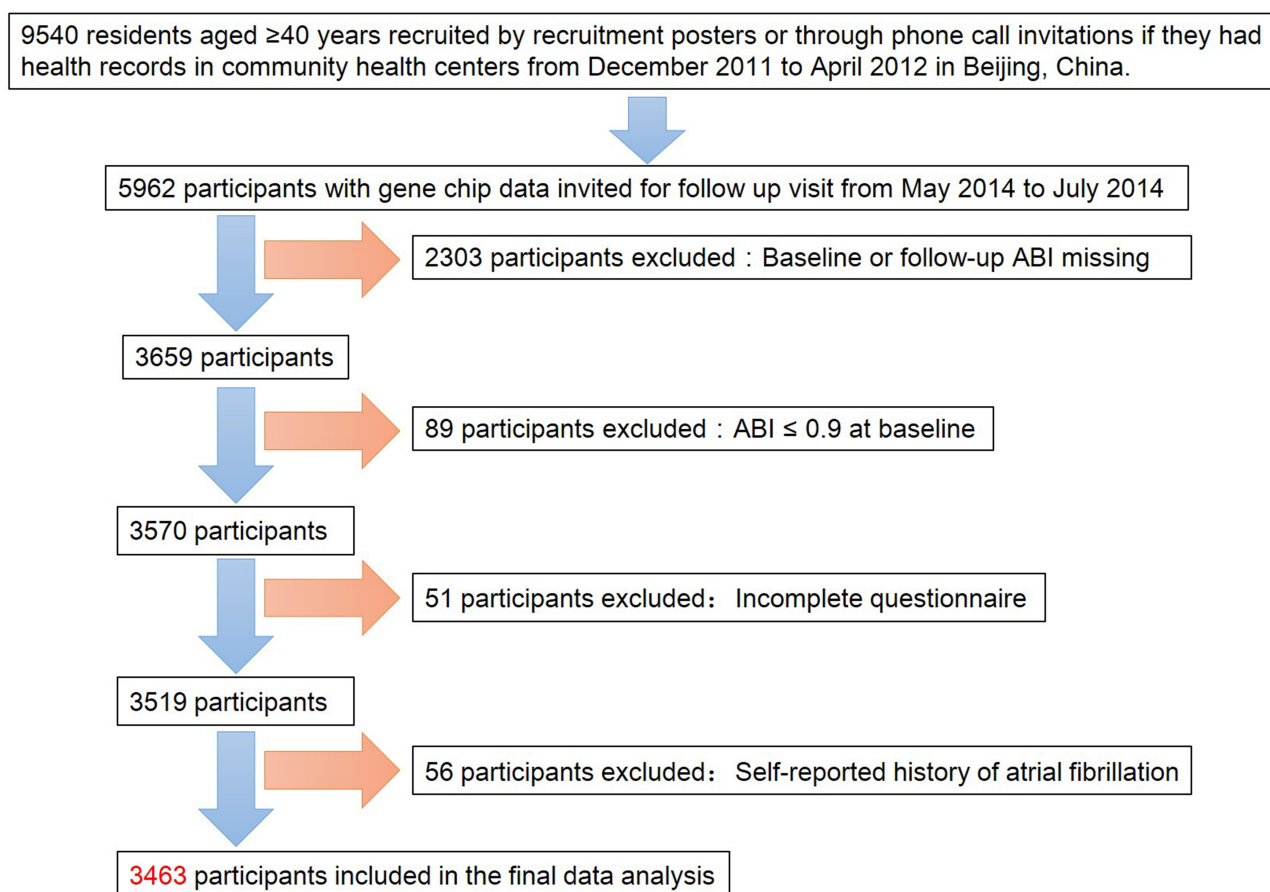


Figure 1 The schematic diagram of recruitment and excluding procedure.

information. We used an Omron HEM-7117 electronic sphygmomanometer, with the standard method of calibration and appropriate-sized cuffs to obtain the seated brachial blood pressure (BP) and pulse rate for each participant after a 5-minute rest. Triplicate measurements were taken on the right arm with intervals ≥ 1 minute between successive readings. For the measurement of each participant's heart rate in the analysis, we calculated the mean pulse rate from the three consecutive measurements. In the same way, each participant's systolic BP and diastolic BP were the mean of three consecutive measurements. Body mass index (BMI) was assessed as weight (kg) divided by height (m) squared.

After an overnight fast of 12 hours at minimum, we obtained a venous blood sample from each participant's forearm. All laboratory variables at baseline, including fasting blood glucose, a standard 75 g oral glucose tolerance test, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, triglycerides, and creatinine, were measured on the Roche C8000 Automatic Analyzer (Basel, Switzerland).

Current smoking in this analysis was smoking ≥ 1 cigarette per day for half a year at minimum. Current drinking in this analysis was drinking alcohol ≥ 1 time per week for half a year at minimum. Hypertension in this analysis was any self-reported history of hypertension, systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of any antihypertensive drugs. Diabetes mellitus in this analysis was any self-reported history of diabetes, fasting blood glucose (FBG) ≥ 7.0 mmol/L or a 2-hour plasma glucose value ≥ 11.1 mmol/L in an oral glucose tolerance test (OGTT), or use of any hypoglycemic drugs. Dyslipidemia in this analysis was any self-reported history of dyslipidemia, triglycerides (TG) >1.7 mmol/L (150mg/dL), total cholesterol (TC) >5.18 mmol/L (200 mg/dL), low-density lipoprotein cholesterol (LDL-C) >3.37 mmol/L (130 mg/dL), high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L (40 mg/dL), or use of any lipid-lowering drugs. Cardiovascular disease (CVD) in this analysis was any self-reported history of stroke or coronary heart disease.

Participants' systolic BP was measured simultaneously in both arms and both ankles (brachial artery and posterior tibial arteries) using a BP-203RPE III device (Omron Healthcare) immediately after the participant had rested in a supine position for a minimum of 5 minutes. The instrument calculated the ABI; and the left and right ABI values were calculated as the ankle systolic BP for each side divided by the highest brachial systolic BP. We measured ABI twice during the study: once at baseline and once during

the follow-up in 2014. New-onset PAD in this analysis was the lowest ABI value being ≤ 0.9 at the 2014 follow-up.

Statistical Analysis

Continuous variables were expressed as means \pm standard deviations for data with normal distributions and median (interquartile range) for that with non-normal distributions. Categorical variables were presented as frequency (percentage). A heart rate threshold of 80 beats per minute (bpm) was used as the cut-off value based on several previous cohort studies.^{8,23–26} Therefore, all eligible participants were divided into two groups by heart rate (≥ 80 bpm vs <80 bpm) for further analysis. We used the Student's *t*-test to compare differences for normally distributed continuous variables and Kruskal–Wallis test for data with non-normal distribution. Pearson's χ^2 test was used to compare differences for categorical variables.

We applied a spline smoothing function to examine the relationship between heart rate and the risk of new-onset PAD using a generalized additive model. Then, piecewise linear regression was conducted to fit the smoothing curve, with adjustment for potential confounders.

We used multivariate logistic regression models to investigate the effect of heart rate (as a continuous variable and as a categorical variable) on the risk of new-onset PAD. We applied three sets of models to examine the association of heart rate with new-onset PAD risk. Model 1 was not adjusted for any other variables, model 2 was adjusted for age as well as sex, and model 3 was additionally adjusted for BMI, baseline ABI, current smoking and drinking, diabetes mellitus, hypertension, dyslipidemia, CVD, and use of lipid-lowering agents, antihypertensive agents, and hypoglycemic agents.

Interactions were also tested, to examine the relationships between heart rate and PAD risk among the analyzed subgroups including sex, age, BMI, current smoking and drinking status, diabetes mellitus, hypertension, dyslipidemia, CVD, and use of lipid-lowering agents, antihypertensive agents, and hypoglycemic agents.

All analyses were performed using Empower(R) (www.empowerstats.com, X&Y Solutions, Boston, MA, USA) and R (R 3.4.3; <http://www.R-project.org>). A P-value of 0.05 (two-sided) was considered statistically significant for all tests.

Results

Baseline Characteristics of Participants

Baseline characteristics of all participants are shown overall and divided into two groups by heart rate (≥ 80 bpm vs <80 bpm) in Tables 1–3. In total, 60.0% of participants had heart

Table 1 Baseline Characteristics of All Eligible Participants

Variable	Total	HR<80bpm	HR≥80bpm	P
N	3463	2079	1384	
Heart rate, bpm	78.15 ± 11.26	70.96 ± 6.11	88.95 ± 8.16	<0.001
Age, years	56.67 ± 8.54	56.43 ± 8.26	57.04 ± 8.93	0.039
Male, n (%)	1251 (36.12%)	766 (36.84%)	485 (35.04%)	0.280
BMI, kg/m ²	26.00 ± 3.33	25.86 ± 3.18	26.22 ± 3.52	0.002
Current smoking, n (%)	643 (18.57%)	416 (20.01%)	227 (16.40%)	0.007
Current drinking, n (%)	802 (23.16%)	508 (24.43%)	294 (21.24%)	0.029
ABI	1.11 ± 0.08	1.12 ± 0.08	1.10 ± 0.08	<0.001

Note: Data presented as percentage for dichotomous variables and as means ± standard deviations for continuous variables.

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; HR, heart rate.

Table 2 Baseline Prevalence of Disease of All Eligible Participants

Variable	Total	HR<80bpm	HR≥80bpm	P
Prevalence of disease, n (%)				
Hypertension	1685(48.66%)	979 (47.09%)	706 (51.01%)	0.024
Diabetes mellites	822 (23.74%)	446 (21.45%)	376 (27.17%)	<0.001
Dyslipidemia	2482 (71.67%)	1462 (70.32%)	1020 (73.70%)	0.031
CVD	421 (12.16%)	256 (12.31%)	165 (11.92%)	0.730
Medication, n (%)				
Antihypertensive agents	1066 (30.78%)	645 (31.02%)	421 (30.42%)	0.705
Hypoglycemic agents	347 (10.02%)	202(9.72%)	145 (10.48%)	0.465
Lipid-lowering agents	356 (10.28%)	210 (10.10%)	146 (10.55%)	0.671

Note: Data presented as percentage for dichotomous variables.

Abbreviations: CVD, cardiovascular disease; HR, heart rate.

Table 3 Baseline Laboratory Variable of All Eligible Participants

Laboratory Variable	Total	HR<80bpm	HR≥80bpm	P
TC, mmol/L	5.31 ± 1.00	5.29 ± 1.01	5.33 ± 1.00	0.283
TG, mmol/L	1.30 (0.92–1.87)	1.26(0.89–1.81)	1.37(0.96–1.97)	<0.001
HDL-C, mmol/L	1.44 ± 0.38	1.44 ± 0.37	1.43 ± 0.39	0.206
LDL-C, mmol/L	3.24 ± 0.84	3.24 ± 0.84	3.23 ± 0.85	0.806
FBG, mmol/	6.16 ± 1.76	6.00 ± 1.51	6.35 ± 1.95	<0.001
OGTT, mmol/	8.55 ± 4.05	8.15 ± 3.73	9.10 ± 4.30	<0.001

Note: Data presented as means ± standard deviations for continuous variables with the exception of TG which presented as median (interquartile range).

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; OGTT, a standard 75 g oral glucose tolerance test; HR, heart rate.

rate <80 bpm and 40.0% had heart rate ≥80 bpm. The mean age of participants was 56.67 ± 8.54 years, among which 36.12% were men. The mean heart rate was 78.15 ± 11.26 bpm, mean BMI was 26.00 ± 3.33 kg/m², and mean ABI was 1.11 ± 0.08. The sample was made up of 18.57% (n = 643) current smokers and 23.16% (n = 802) current drinkers. A total 48.66% (n = 1685) of participants had hypertension, 23.74% (n = 822) had diabetes, 71.67% (n = 2482) had dyslipidemia, and 12.16% (n = 421) had a history of CVD. Participants in the higher-heart rate group were significantly

older, had significantly higher BMI, TG, FBG, OGTT, lower ABI, and higher prevalence rates of diabetes, hypertension, and dyslipidemia than those in the lower-heart rate group. There was no significant difference in the prevalence of CVD between the two groups.

Predictors of New-Onset PAD

The incidence of PAD among all participants was 2.97% (n = 103) after a 2.3-year (median: 2.34 years; 25th percentile–75th percentile: 2.28–2.39 years) follow-up.

Figure 2 shows the smoothing curve of heart rate and new-onset PAD adjusted for sex, BMI, age, baseline ABI, current smoking and drinking status, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and use of lipid-lowering agents, antihypertensive agents, and hypoglycemic agents. The curve showed that the risk of PAD increased with elevated heart rate with no inflection points.

The results of the multivariate regression models estimating the association of heart rate with new-onset PAD are shown in Table 4. Heart rate was significantly linked to the incidence of PAD (OR = 1.41, 95% confidence interval (CI): 1.20–1.64, $P < 0.001$), with every increase of 10 bpm associated with a 41% increase in the odds of developing new-onset PAD (Model 1). The relationship remained significant (OR = 1.22, 95% CI: 1.03–1.43, $P = 0.020$) after adjusting for sex, BMI, age, baseline ABI, current smoking and drinking status, diabetes mellitus, hypertension, dyslipidemia, CVD, and use of lipid-lowering agents, antihypertensive agents, and hypoglycemic agents. When participants were divided into two groups by heart rate (≥ 80 bpm vs < 80 bpm), the incidence of new-onset PAD was consistently dose-dependently related to heart rate group in the multivariate regression models. The OR of being in the higher-heart rate group (≥ 80 bpm) for new-onset PAD was 2.24 (95% CI: 1.50–3.33, $P < 0.001$), compared with the lower-heart rate group (< 80

bpm). In Model 3, after adjusting for various confounders and baseline ABI, this effect declined somewhat but remained significant (OR = 1.73, 95% CI: 1.14–2.63, $P = 0.010$).

Figure 3 displays the results of the stratification and interaction analyses using a forest map. There was no significant heterogeneity among the analyzed subgroups in terms of sex, age (< 60 vs ≥ 60 years), BMI (< 25 vs ≥ 25 kg/m²), current drinking, current smoking, hypertension, dyslipidemia, diabetes mellitus, CVD, or use of lipid-lowering agents, antihypertensive agents, or hypoglycemic agents.

Discussion

Studies have confirmed that increased heart rate is of prognostic importance for all-cause mortality and cardiovascular mortality.²⁷ The main result of our study is that a higher heart rate was associated with a higher incidence of new-onset PAD in a community-based population. Consequently, these findings indicate we can use heart rate to predict new-onset PAD in the future.

Several studies have previously revealed an inverse correlation between heart rate and ABI,^{18–21} where ABI was decreased when the heart rate was accelerated through pacing among patients without significant organic heart disease. However, the studies above were all cross-sectional. To the best of our knowledge, our study is the first to report that increased heart rate was associated with the risk of new-onset PAD without inter-subgroup heterogeneity in a Chinese community-based population that did not have PAD at baseline after a 2.3-year follow-up, which further supports their potential association.

The incidence of new-onset PAD among all participants in our study was 3.07%. A cohort study in Taiwan enrolled 723,750 patients with no past history of PAD, rheumatic heart disease, or AF. The mean age of participants was 41.7 ± 16.8 years and the incidence of new-onset PAD was 3.4% after a 9-year-follow-up.²⁸ The participants in our study were older and had more risk factors of atherosclerosis, so the incidence of new-onset PAD was higher than that in other studies.

Based on clinical experience, beta blockers are contraindicated in severe PAD owing to the presumed peripheral hemodynamic consequences of beta blockers. However, there is no proof suggesting that beta blockers adversely affect PAD in current studies.²⁹ Moreover, studies have shown that the use of beta blockers was associated with better outcome in patients with coronary heart disease,³⁰ especially those with myocardial infarction.^{31,32} Our study found a correlation between heart rate and new-onset PAD,

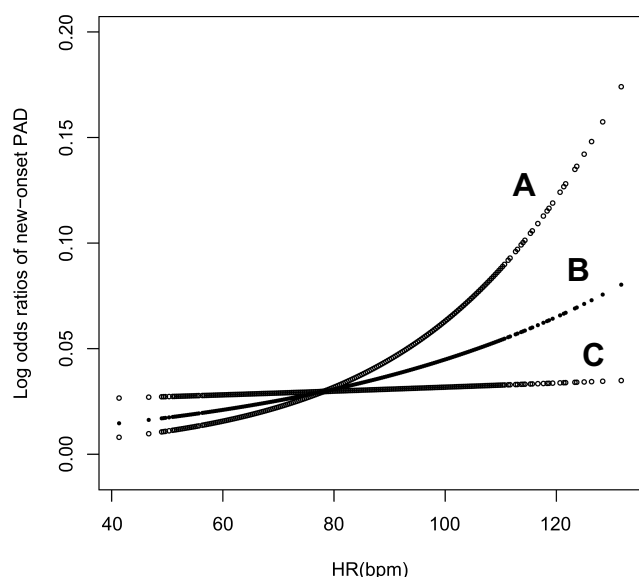


Figure 2 Smoothing curve of the risk of new-onset PAD by heart rate. Line B represents the smoothing curve for the association of heart rate and new-onset PAD. Lines A and C represent the 95% confidence interval for the risk of new-onset PAD. This relationship was adjusted for sex, age, body mass index, baseline ankle-brachial index, current smoking and drinking status, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, and use of antihypertensive agents, lipid-lowering agents, and hypoglycemic agents.

Abbreviations: PAD, peripheral arterial disease; HR, heart rate.

Table 4 Logistic Regression Analysis of the Association of Heart Rate with New-Onset PAD

			Model 1		Model 2		Model 3	
	N	PAD, n (%)	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
HR, per 10bpm	3463	103(2.97%)	1.41 (1.20, 1.64)	<0.001	1.20 (1.0, 1.41)	0.026	1.22 (1.03, 1.43)	0.020
HR<80bpm	2079	42(2.02%)	1.0		1.0		1.0	
HR≥80bpm	1384	61(4.41%)	2.24 (1.50, 3.33)	<0.001	1.70 (1.12, 2.56)	0.012	1.73 (1.14, 2.63)	0.010

Notes: Model 1: not adjusted; Model 2: adjusted for sex, age, and baseline ankle–brachial index; Model 3: adjusted for sex, age, body mass index, baseline ankle–brachial index, current smoking and drinking status, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, and use of antihypertensive agents, lipid-lowering agents, and hypoglycemic agents.

Abbreviations: PAD, peripheral arterial disease; CI, confidence interval; HR, heart rate; OR, odds ratio.

which leads to the question of whether beta blockers would affect the incidence of new-onset PAD. Unfortunately, there were too few patients who used beta blockers in our study to be able to reach any conclusions. However, we found no significant heterogeneity among the analyzed subgroups in terms of the use of antihypertensive agents. Future investigations are needed to answer that question.

There are several hypotheses describing the mechanism in the impact of heart rate on atherosclerosis. First, as early as 1998, increased heart rate was confirmed to

be associated with sympathetic activity.³³ Sympathetic activation may mediate the vascular remodeling process.³⁴ Adrenergic receptors, a biomarker of the sympathetic reaction, are crucial in the regulation of vascular stiffness by influencing myocyte volume, the replication of smooth muscle cells, and collagen synthesis in peripheral arteries.³⁵ Second, separately from the effect of sympathetic activation, the pulsatile frequency alone can lead to endothelial function injury³⁶ and inflammatory factor upregulation.³⁷ Additionally, increased heart rate causes vascular smooth muscle cells to create more

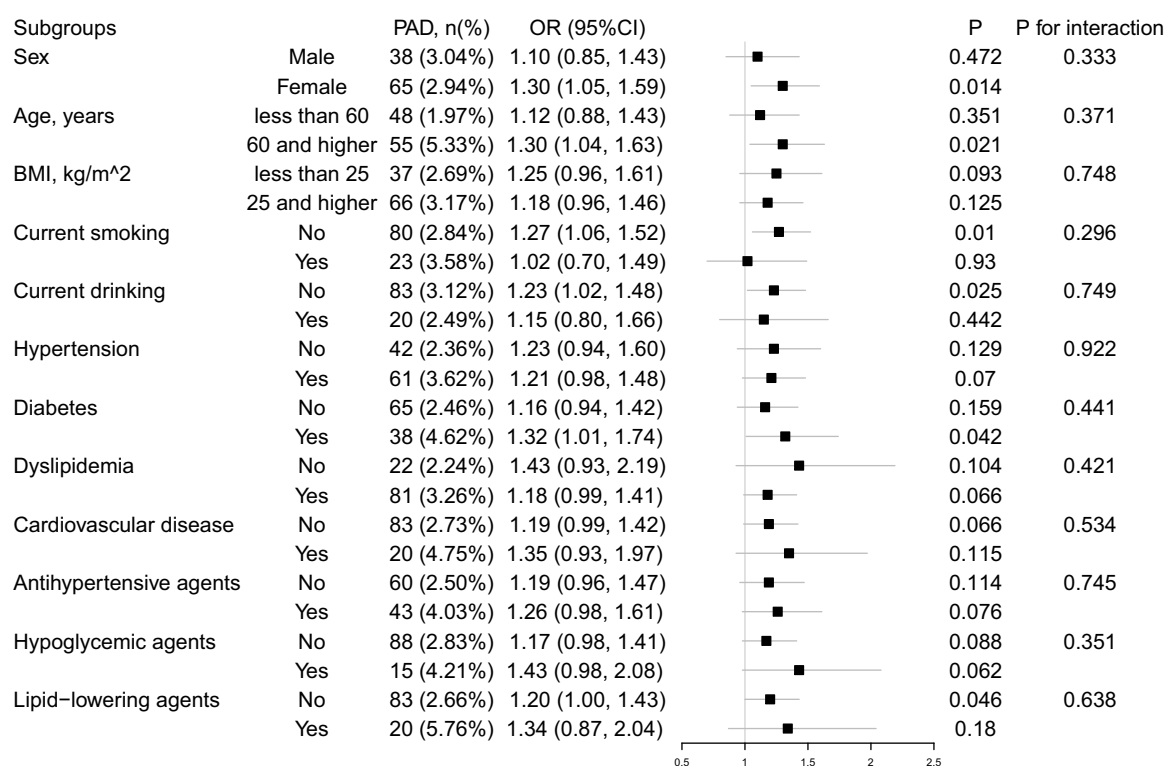


Figure 3 Subgroup analyses and interaction tests in different populations. The subgroup analyses were adjusted for sex, age, body mass index, baseline ankle–brachial index, current smoking and drinking status, hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, and use of antihypertensive agents, lipid-lowering agents, and hypoglycemic agents.

Abbreviations: BMI, body mass index; PAD, peripheral arterial disease; OR, odds ratio; CI, confidence interval.

fibronectin and collagen.³⁸ In summary, increased heart rate accelerates atherosclerosis via a few known pathophysiological mechanisms.

There were several limitations in our study. First, the measure of heart rate used here was the mean pulse rate. Pulse rate is not entirely equivalent to heart rate, especially for patients with atrial fibrillation. However, the relationship between pulse rate and new-onset PAD remained after participants with a self-reported history of atrial fibrillation were excluded. Although we were unable to exclude patients who were unaware of the existence of asymptomatic atrial fibrillation, the incidence of atrial fibrillation in our study should be small, according to the epidemiology of atrial fibrillation.³⁹ Thus, the difference between pulse rate and heart rate is unlikely to influence the results of our study. Second, we obtained measures of ABI at only two time points. The accuracy of PAD diagnosis would be enhanced if based on measurements collected at multiple follow-up time points. Third, our study was based on a large community-based population in China who did not have PAD at baseline. Thus, it is difficult to generalize our findings to other populations.

Conclusions

Elevated heart rate was independently associated with the risk of new-onset PAD in a community-based population in Beijing. This indicates that heart rate may be crucial in PAD and supports the hypothesis that elevated heart rate accelerates the progression of atherosclerosis. Greater attention is needed to heart rate management for the purpose of PAD primary prevention.

Disclaimer

The views in the article belong to the authors and are not an official position of any institution or funder.

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Disclosure

The authors declare that they have no competing interests.

References

1. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive Summary: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e686–e725. doi:10.1161/CIR.0000000000000470
2. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381–386. doi:10.1056/NEJM199202063260605
3. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206. doi:10.1001/jama.297.11.1197
4. Lee JY, Lee SW, Lee WS, et al. Prevalence and clinical implications of newly revealed, asymptomatic abnormal ankle-brachial index in patients with significant coronary artery disease. *JACC Cardiovasc Interv*. 2013;6:1303–1313. doi:10.1016/j.jcin.2013.08.008
5. Kurvers HAJM, van der Graaf Y, Blankensteijn JD, et al. Screening for asymptomatic internal carotid artery stenosis and aneurysm of the abdominal aorta: comparing the yield between patients with manifest atherosclerosis and patients with risk factors for atherosclerosis only. 1 Competition of interest: none. *J Vasc Surg*. 2003;37:1226–1233. doi:10.1016/S0741-5214(02)75140-9
6. Leertouwer TC, Pattinama PM, van den Berg-huysmans A. Incidental renal artery stenosis in peripheral vascular disease: a case for treatment? *Kidney Int*. 2001;59:1480–1483. doi:10.1046/j.1523-1755.2001.0590041480.x
7. Mw G, Wb K, Belanger A, et al. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. *Am Heart J*. 1993;125:1148–1154. doi:10.1016/0002-8703(93)90128-V
8. King D, Everett C, Mainousiii A, Liszka H. Long-term prognostic value of resting heart rate in subjects with prehypertension. *Am J Hypertens*. 2006;19:796–800. doi:10.1016/j.amjhyper.2006.01.019
9. Okin PM, Kjeldsen SE, Julius S, et al. All-cause and cardiovascular mortality in relation to changing heart rate during treatment of hypertensive patients with electrocardiographic left ventricular hypertrophy. *Eur Heart J*. 2010;31:2271–2279. doi:10.1093/eurheartj/ehq225
10. 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. doi:10.1016/j.amjcard.2011.10.025
11. Kolloch R, Legler UF, Champion A, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the International Verapamil-SR/trandolapril Study (INVEST). *Eur Heart J*. 2008;29:1327–1334. doi:10.1093/eurheartj/ehn123
12. Lonn EM, Rambihar S, Gao P, et al. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clin Res Cardiol*. 2014;103:149–159. doi:10.1007/s00392-013-0644-4

13. McAlister FA, Wiebe N, Ezekowitz JA, et al. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med.* 2009;150:784–794. doi:10.7326/0003-4819-150-11-200906020-00006
14. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet.* 2010;376:875–885. doi:10.1016/S0140-6736(10)61198-1
15. Benetos A, Adamopoulos C, Bureau J-M, et al. Determinants of accelerated progression of arterial stiffness in normotensive subjects and in treated hypertensive subjects over a 6-year period. *Circulation.* 2002;105:1202–1207. doi:10.1161/hc1002.105135
16. Tomiyama H, Hashimoto H, Tanaka H, et al. Synergistic relationship between changes in the pulse wave velocity and changes in the heart rate in middle-aged Japanese adults: a prospective study. *J Hypertens.* 2010;28:687–694. doi:10.1097/HJH.0b013e3283369fe8
17. Grassi G, Seravalle G, Quarti-Trevano F. The 'neuroadrenergic hypothesis' in hypertension: current evidence. *Exp Physiol.* 2010;95:581–586. doi:10.1113/expphysiol.2009.047381
18. Abraham P, Desvaux B, Colin D, et al. Heart rate-corrected ankle-to-arm index in the diagnosis of moderate lower extremity arterial disease. *Angiology.* 1995;46:673–677. doi:10.1177/000331979504600805
19. Su HM, Lee KT, Chu CS, et al. Effects of heart rate on brachial-ankle pulse wave velocity and ankle-brachial pressure index in patients without significant organic heart disease. *Angiology.* 2007;58:67–74. doi:10.1177/0003319706295481
20. Hsu PC, Lee WH, Chu CY, et al. Heart rate significantly influences the relationship between atrial fibrillation and ankle-brachial index. *J Cardiol.* 2015;66:143–147. doi:10.1016/j.jcc.2014.10.011
21. Schroll M, Munck O. Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population study of 60-year-old men and women. *J Chronic Dis.* 1981;34:261–269. doi:10.1016/0021-9681(81)90031-X
22. Fan F, Qi L, Jia J, et al. Noninvasive central systolic blood pressure is more strongly related to kidney function decline than peripheral systolic blood pressure in a Chinese community-based population. *Hypertension.* 2016;67:1166–1172. doi:10.1161/HYPERTENSIONAHA.115.07019
23. Thomas F, Bean K, Provost J-C, et al. Combined effects of heart rate and pulse pressure on cardiovascular mortality according to age. *J Hypertens.* 2001;19:863–869. doi:10.1097/00004872-200105000-00005
24. 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. doi:10.1001/archinte.162.20.2313
25. Saxena A, Minton D, Lee DC, et al. Protective role of resting heart rate on all-cause and cardiovascular disease mortality. *Mayo Clin Proc.* 2013;88:1420–1426. doi:10.1016/j.mayocp.2013.09.011
26. Paul L, Hastie CE, Li WS, et al. Resting heart rate pattern during follow-up and mortality in hypertensive patients. *Hypertension.* 2010;55:567–574. doi:10.1161/HYPERTENSIONAHA.109.144808
27. Courand PY, Lantelme P. Significance, prognostic value and management of heart rate in hypertension. *Arch Cardiovasc Dis.* 2014;107:48–57. doi:10.1016/j.acvd.2013.11.003
28. Hsu PC, Chiu CA, Chu CY, et al. CHADS2 score and risk of new-onset peripheral arterial occlusive disease in patients without atrial fibrillation: a nationwide cohort study in Taiwan. *J Atheroscler Thromb.* 2015;22:490–498. doi:10.5551/jat.27284
29. Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev.* 2013;CD005508. doi:10.1002/14651858.CD005508.pub3
30. Fihn SD, Gardin JM, Abrams J, et al. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2012;2012(60):e44–e164.
31. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. *Am J Cardiol.* 1986;57:43F–9F. doi:10.1016/0002-9149(86)90888-X
32. Cucherat M. Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. *Eur Heart J.* 2007;28:3012–3019. doi:10.1093/eurheartj/ehm489
33. Grassi GVS, Bertinieri G, Seravalle G, Stella ML, Dell'Oro R, Mancia G. Heart rate as marker of sympathetic activity. *J Hypertens.* 1998;16:1635–1639. doi:10.1097/00004872-199816110-00010
34. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. *Hypertension.* 2009;54:690–697. doi:10.1161/HYPERTENSIONAHA.108.119883
35. Mancia G, Grassi G, Giannattasio C, et al. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension.* 1999;34:724–728. doi:10.1161/01.HYP.34.4.724
36. Custodis F, Schirmer SH, Baumhakel M, et al. Vascular pathophysiology in response to increased heart rate. *J Am Coll Cardiol.* 2010;56:1973–1983. doi:10.1016/j.jacc.2010.09.014
37. Himburg HA, Dowd SE, Friedman MH. Frequency-dependent response of the vascular endothelium to pulsatile shear stress. *Am J Physiol Heart Circ Physiol.* 2007;293:H645–53. doi:10.1152/ajpheart.01087.2006
38. Stegmann JP, Hong H, Nerem RM. Mechanical, biochemical, and extracellular matrix effects on vascular smooth muscle cell phenotype. *J Appl Physiol.* (1985). 2005;98:2321–2327. doi:10.1152/japplphysiol.01114.2004
39. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation.* 2014;129:837–847. doi:10.1161/CIRCULATIONAHA.113.005119

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