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Association of resting heart rate with carotid and aortic arterial stiffness: Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Resting heart rate is an easily measured, non-invasive vital sign that is associated with cardiovascular disease events. The pathophysiology of this association is not known. We investigated the relationship between resting heart rate and stiffness of the carotid (a peripheral artery) and the aorta (a central artery) in an asymptomatic multi-ethnic population. Resting heart rate was recorded at baseline in the Multi-Ethnic Study of Atherosclerosis (MESA). Distensibility was used as a measure of arterial elasticity, with a lower distensibility indicating an increase in arterial stiffness. Carotid distensibility was measured in 6,484 participants (98% of participants) using B-mode ultrasound and aortic distensibility was measured in 3,512 participants (53% of participants) using cardiac MRI. Heart rate was divided into quintiles and we used progressively adjusted models that included terms for physical activity and AV-nodal blocking agents. Mean resting heart rate of participants (mean age 62 years, 47% male) was 63 beats per minute (SD 9.6 beats per minute). In unadjusted and fully adjusted models, carotid distensibility and aortic distensibility decreased monotonically with increasing resting heart rate (p for trend <0.001 and 0.009 respectively). The relationship was stronger for carotid versus aortic distensibility. Similar results were seen using the resting heart rate taken at the time of MRI scanning. Our results suggest that a higher resting heart rate is associated with an increased arterial stiffness independent

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of AV-nodal blocker use and physical activity level, with a stronger association for a peripheral (carotid) compared to a central (aorta) artery.

Keywords

heart rate; cardiovascular disease; stiffness; ultrasound; cardiac magnetic resonance imaging

Introduction

Resting heart rate is an attractive variable for risk stratification because it is a routinely collected, non-invasive vital sign that requires no special equipment for measurement. Several previous studies have demonstrated an association between an elevated resting heart rate and adverse cardiovascular disease events, cardiovascular death, and all-cause mortality[1–5].

It is still uncertain if resting heart rate is a causative risk factor in cardiovascular disease. Cardiorespiratory fitness is a potential confounder because it is closely associated with both resting heart rate and cardiovascular mortality.[6] However, many studies have shown that resting heart rate predicts adverse events even after adjustment for physical activity.[3, 5, 7] In addition, the use of AV-nodal blocking agents such beta-blockers and non-dihydropyridine calcium channel blockers can pharmacologically lower heart rate and may also decrease cardiovascular disease.

An elevated resting heart rate is a common finding in patients with hypertension and those with subclinical diastolic dysfunction.[8, 9] We hypothesized that resting heart rate would be directly associated with a measure of stiffness in the carotid (peripheral) and aortic (central) arteries, and that this association would be independent of physical activity level and AV-nodal blocker medication use.

Methods

Study Design and Study Participants

We used participant data from the baseline visit (2000–02) of the Multi-Ethnic Study of Atherosclerosis (MESA).[10] Participants were excluded if they did not have a resting heart rate value (n=49) or did not have a measurement of distensibility by either carotid ultrasound or cardiac MRI (n=143). Of these 6,623 participants carotid distensibility was not measured 139 (2%) participants. Cardiac MRI was not performed in 1,526 participants (23%) and aortic distensibility was not calculated in 1,585 (24%) participants. After exclusions, there were 6,484 participants with a measurement of carotid distensibility and 3,512 participants with a measurement of aortic distensibility that were included in the analysis.

Resting Heart Rate and Distensibility Measurement

Participant resting heart rate was recorded from a resting 12 lead ECG performed at the baseline examination. Participants who underwent cardiac MRI scanning also had a separate heart rate measurement at the time of the scan. A separate heart rate was not recorded at the time of the carotid ultrasound.

Distensibility was calculated separately for the carotid and aortic arteries, with a larger distensibility coefficient indicating a more elastic artery and a lower distensibility coefficient indicating a stiffer artery. Carotid distensibility was measured using B-mode ultrasound with

a Logiq 700 machine (General Electric Medical Systems) at the baseline visit. Using these measurements carotid distensibility was calculated from the following equation[11]:

$$DC = 2\Delta D / \Delta P D_s$$

where ΔD is the change in systolic/diastolic diameter, ΔP is the brachial pulse pressure, and D_s is the systolic diameter. Three seated blood pressure measurements were performed at rest using a Dinamap Pro 100 automated sphygmomanometer and the mean of the second and third values were recorded.

Aortic distensibility was measured using 1.5T MRI scanners (3 sites used a Siemens Medical Solutions Symphony or Sonata and 3 sites used a General Electric Medical Systems CV/I or LX) with images of the descending thoracic aorta that were obtained at the level of the right pulmonary artery during mid-diastole. Aortic distensibility was evaluated using gradient-echo phase-contrast cine MRI with ECG gating and calculated using the following equation[12]

$$AD = [(\max \text{ aortic area} - \min \text{ aortic area}) / \min \text{ aortic area}] / \text{pulse pressure}$$

Pulse pressure was calculated using the mean blood pressure value from immediately before and after MRI scanning while the participant was supine.

Study Covariates

All other covariates were obtained from the baseline MESA clinical examination. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90mmHg, or the use of a blood pressure lowering medication, diabetes was defined as a fasting blood glucose ≥126 mg/dL or self-report of diabetes or self-report of taking glucose lowering medications. Smoking status was defined as never, former, and current. Heavy drinkers were classified as men who consume >14 drinks per week and women who consume >7 drinks per week. Physical activity was measured in MESA using the Typical Week Physical Activity Survey, which assessed the frequency and time spent engaging in various physical activities. There were 28 questions about the typical weekly time spent and frequency engaged in activities including household chores, yard work, leisure time, sports, and occupational activity. This included questions about light, moderate, and vigorous physical activity. Time spent in each activity was multiplied by the metabolic equivalent level to obtain MET-hours/week. We divided participants into approximate quartiles based on reported moderate and vigorous physical activity.[13] Socio-economic status was based upon total household income and the highest attained level of education. Family history of CHD was defined as a positive history of CHD in a parent, sibling, or child.

Statistical Analysis

We divided participants into resting heart rate quintiles to facilitate comparison with the previous heart rate literature. Distensibility was examined as a continuous variable using robust linear regression models. In addition, we performed secondary analysis using prevalence ratio regression models after dividing distensibility into quartiles. Results of these models were interpreted as the prevalence risk ratio of being in the least distensible quartile (stiffest group), with the most distensible quartile as the reference.

We used progressively adjusted models for these analyses. Model 1 included age, sex, and ethnicity. Model 2 added body mass index, waist circumference, total household income, highest attained level of education, SBP, DBP, pulse pressure, anti-hypertensive medication use, smoking status, LDL-C, HDL-C, triglycerides, lipid lowering medication use, hs-CRP, and family history of CHD. Model 3 added physical activity level and AV-nodal medication use.

We then performed sub-group sensitivity analyses modeling the prevalence ratio regression of being in the least distensible quartile per standard deviation change (7.9 bpm) in distensibility. In addition, to determine the relative impact of baseline clinical resting heart rate versus heart rate taking at the exact time of scanning, we modeled the association of heart rate difference (heart rate at time of MRI – resting heart rate at baseline clinical assessment) and arterial distensibility. The group of participants with minimal change in heart rate (+/− 2 bpm) between the two measurements was considered as the reference. Participants with an absolute change in heart rate of 3–5bpm and 6–20bpm were defined as the comparison groups; we excluded the small group of individuals with an absolute heart rate change of 20 (outside of 2 standard deviations) from this analysis.

Results

At the baseline examination participants with higher resting heart rates were more likely to be older, diabetic, have higher blood pressure, BMI, hs-CRP, and have calcification of the thoracic aorta on cardiac CT (Table 1). Participants with lower resting heart rates were more likely to be male, take an AV-nodal blocker medication, have a higher total household income, have more than a high school education, and have a higher reported physical activity level. Overall, the baseline characteristics of the 3,512 participants with an aortic distensibility measurement were similar (Supplemental Table 1).

Participants with lower resting heart rates had more distensible carotid and aortic arteries (Figure 1). There was a significantly graded decrease in distensibility for both the carotid and aortic arteries (p for trend <0.001 and 0.004 respectively). The absolute difference in distensibility between resting heart rate quintiles 1 and 5 was greater for the carotid artery (2.7mmHg$^{10\text{-}3}$ to 2.2mmHg$^{10\text{-}3}$) compared to the aortic artery measurements (1.9mmHg$^{10\text{-}3}$ to 1.71mmHg$^{10\text{-}3)}$.

Carotid and aortic distensibility decreased with increasing heart rate even after adjustment for physical activity and AV nodal blocker use (p for trend <0.001 and 0.009 respectively) (Tables 2 and 3). These beta-coefficients represent small to moderate changes in stiffness. The relationship was stronger and more statistically significant for carotid artery distensibility.

Participants with higher resting heart rates also had an increased risk of being in the least distensible carotid and aortic quartiles (p for trend <0.001 and 0.017 respectively) (Tables 4 and 5). The graded increased risk of being in the least distensible quartile was similar for both measurements, although the association was more robust for the carotid artery compared to the aorta (Figure 2). Moreover, for carotid distensibility the association was significant for all heart rate groups, while for aortic distensibility it was only significant for the highest heart rate group.

In subgroup analyses, elevated resting heart rate was more predictive of being in the least distensible quartile for participants older than 65 years and those without hypertension for carotid distensibility (Table 6). Elevated resting heart rate was more predictive of aortic distensibility for participants who were female, black, had hypertension, or diabetes. However, the differences in sub-group associations were not consistent between carotid and

aortic distensibility. In addition, we performed all analyses for carotid ultrasound restricted to only those 3,512 participants who had a measurement of aortic distensibility; there was no significant difference in the results. Due to concern for potential over adjustment we performed analyses adjusting for hypertension, but not anti-hypertensive medication use in model 2. We also performed analyses adjusting for pack-years of smoking. There was no significant change in the results for these analyses.

We also performed all analyses using heart rate as measured at the time of cardiac MRI and the overall results were similar. Participants whose heart rate was much lower (6–20 bpm) at the time of MRI compared to the clinical resting heart rate assessment were approximately 30% more likely to be in the least distensible aortic quartile compared to those with a minimal change in heart rate between exams (Supplemental Tables S2 and S3). There was no significant association between change in heart rate and aortic distensibility for participants whose heart rate was higher at the time of MRI scanning.

Discussion

Individuals with higher a resting heart rate are more likely to have decreased cardiorespiratory fitness, engage in less physical activity, and have an increased sympathetic tone and autonomic instability.[2, 6] Increased resting heart rate has been associated with traditional cardiovascular risk factors, adverse cardiovascular events, and cardiovascular mortality in many studies.[7, 14]

Stiffening of both the medium-sized and large elastic arteries is associated with aging, hypertension, diastolic dysfunction, and other traditional risk factors for atherosclerosis.[15–20] Arterial stiffness itself is also associated with coronary artery calcium and has been demonstrated to predict the severity of atherosclerosis.[21–25] In addition, it is associated with adverse clinical events such as stroke[26], myocardial infarction[27], heart failure[28], and cardiovascular mortality.[29]

Similar to other studies, our results demonstrate that a higher resting heart rate is associated with cardiovascular risk factors including blood pressure, obesity, and decreased physical activity. In this analysis we have also demonstrated that an increased resting heart rate is associated with a decreased arterial distensibility, which is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall.[30] This robust association persisted after adjustment for traditional cardiovascular risk factors and AV nodal blocker medication use.

There are a number of biological mechanisms that may explain why individuals with higher resting heart rates are more likely to develop cardiovascular disease. Previous animal and human studies have suggested a casual association between resting heart rate and stiffness; however these have not been fully replicated on a larger scale using modern imaging modalities.[31, 32] These results demonstrate that an increased heart rate is associated with a decreased dynamic compliance and increased mechanical stress that ultimately may lead to an increased stiffening of the arterial wall. This may be due to the progressively shorter amount of time available for arterial wall recoil as heart rate increases.[33] An increased heart rate also exerts a greater number of pulsatile strain cycles on the arterial wall, leading to an increased fatigue and fracture of the elastic fibers in the arterial wall, which is an important cause of age-related arterial stiffening.[34] There is also an increase in arterial pulsatile flow and shear stress, which can promote atherosclerotic lesion formation.[35, 36] Furthermore, a higher heart rate increases mean arterial pressure, due to a reduction in the time spent in diastole and may physiologically be a compensatory mechanism for a decreased cardiac function due to myocardial damage.[36]

The autonomic nervous system may also be an important common pathway that can influence both resting heart rate and arterial stiffness. Increased sympathetic activity has been shown to decrease arterial compliance in both medium and large muscular arteries.[37–39] This increase in arterial stiffness may be partially due to an increase in vasomotor tone. Vascular re-modeling also occurs through the sympathetic nervous system's effect on the renin-angiotensin-aldosterone system, which results in smooth muscle hypertrophy, fibrosis, and reduced elastin synthesis.[40, 41]

The significant association between increased heart rate and cardiovascular mortality has created interest in heart rate reduction as a potential therapeutic target. A reduction in heart rate by beta-blockers has been demonstrated to reduce infarct size, decrease mortality after myocardial infarction, and reduce mortality in heart failure patients. [42,43] However, in Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), there was no suggestion of increased relative benefit of atenolol over amlodipine in patients with increased heart rate.[44] Results from a meta-analysis of over 68,000 individuals by Bangalore et al. also suggested that heart rate lowering with beta-blockers in hypertensive patients was associated with increased mortality.[45] The Morbidity-mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction trial (BEAUTIFUL) investigated heart rate reduction using Ivabradine, which decreases heart rate by directly acting upon the sinoatrial node and unlike beta-blockers does not have other cardiac effects.[46] There was no significant change in the composite primary outcome of cardiovascular death, admission for myocardial infarction, or admission for heart failure. In a follow-up study the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT) used Ivabradine to lower heart rate beyond that achieved with beta-blockers for participants with a resting heart rate of at least 70bpm and found a 26% reduction in mortality from heart failure.[47]

One explanation for the lack of an observed benefit within some of these trials is the inverse relationship between heart rate and central aortic pressures.[48] The Conduit Artery Function Evaluation (CAFÉ) trial investigated the effect of brachial blood pressure reduction with or without beta-blockers on central aortic pressures and measured central aortic pressures using Augmentation Index. In a sub-study investigating the association of heart rate reduction and Augmentation Index there was a strong inverse association between heart rate and central aortic systolic and pulse pressure.[49] The increase in aortic stiffness may be due to pharmacologic heart rate reduction leading to an increased wave reflection and subsequently increased central aortic pressure. A decreased heart rate also results in increased filling and stroke volume, which when ejected into stiffened arteries that have a reduced compliance causes an increased in central aortic and pulse pressures.

Strengths of this study include the multi-ethnic cohort, detailed measurement of anthropometric covariates, physical activity levels, and AV nodal blocker medication use. However, our results should be considered in light of certain limitations including the cross-sectional nature of our data. We were not able to assess the temporal relationship between resting heart rate and arterial distensibility, which precludes any conclusions with regard to causality. There were also significantly fewer participants with a measure of aortic distensibility compared to carotid distensibility. However, there were still 3,512 participants with a measurement of aortic distensibility and when we limited our analyses to these participants there were no significant differences in the results. Our measurements of distensibility were performed using two different imaging techniques (ultrasound and cardiac MRI) which may limit the comparability of results. The two measurement sites also represent peripheral-muscular (carotid) and central-elastic (aortic) arteries, which have inherent differences that must be remembered when interpreting our findings. However, Lenard et al demonstrated that when measured using ultrasound there is strong correlation

between carotid and aortic distensibility (r=0.81).[50] Similarly, Harloff et al showed excellent agreement between ultrasound and MRI measurement of common carotid distensibility.[51] In addition, the physical activity measurement quantified the participant reported weekly intensity and duration of physical activity, but may not accurately reflect cardiovascular fitness as this was not directly measured in MESA.

Perspectives

Our analysis demonstrated a direct relationship between resting heart rate and arterial stiffness using modern imaging modalities in an ethnically diverse population free of known cardiovascular disease. Importantly, these results persist after adjustment for known cardiovascular risk factors, physical activity level, and AV-nodal blocking medications. Our results suggest that an increased resting heart rate may be a useful non-invasive tool for inferring arterial stiffness and identifying a population at increased cardiovascular risk. Overall, these results provide evidence for a potential underlying mechanism to explain the association of an increased resting heart rate with adverse cardiovascular outcomes and further study is needed to determine the potential causality of the association and whether resting heart rate reduction as a target of pharmacologic treatment is useful for reducing cardiovascular events in asymptomatic patients.

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References

1. Palatini P, Julius S. Elevated heart rate: A major risk factor for cardiovascular disease. Clin Exp Hypertens. 2004; 26:637–644. [PubMed: 15702618]
2. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, Steg PG, Tardif JC, Tavazzi L, Tendera M. Resting heart rate in cardiovascular disease. Journal of the American College of Cardiology. 2007; 50:823–830. [PubMed: 17719466]
3. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. European heart journal. 2005; 26:967–974. [PubMed: 15774493]
4. Kovar D, Cannon CP, Bentley JH, Charlesworth A, Rogers WJ. Does initial and delayed heart rate predict mortality in patients with acute coronary syndromes? Clinical cardiology. 2004; 27:80–86. [PubMed: 14979625]
5. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. The New England journal of medicine. 2005; 352:1951–1958. [PubMed: 15888695]
6. Jurca R, Jackson AS, LaMonte MJ, Morrow JR Jr, Blair SN, Wareham NJ, Haskell WL, van Mechelen W, Church TS, Jakicic JM, Laukkanen R. Assessing cardiorespiratory fitness without performing exercise testing. American journal of preventive medicine. 2005; 29:185–193. [PubMed: 16168867]
7. Janssen I, Katzmarzyk PT, Church TS, Blair SN. The cooper clinic mortality risk index: Clinical score sheet for men. American journal of preventive medicine. 2005; 29:194–203. [PubMed: 16168868]

8. Palatini P, Casiglia E, Pauletto P, Staessen J, Kaciroti N, Julius S. Relationship of tachycardia with high blood pressure and metabolic abnormalities: A study with mixture analysis in three populations. Hypertension. 1997; 30:1267–1273. [PubMed: 9369286]
9. Kuznetsova T, Herbots L, Lopez B, Jin Y, Richart T, Thijs L, Gonzalez A, Herregods MC, Fagard RH, Diez J, Staessen JA. Prevalence of left ventricular diastolic dysfunction in a general population. Circulation Heart failure. 2009; 2:105–112. [PubMed: 19808325]
10. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: Objectives and design. American journal of epidemiology. 2002; 156:871–881. [PubMed: 12397006]
11. Gamble G, Zorn J, Sanders G, MacMahon S, Sharpe N. Estimation of arterial stiffness, compliance, and distensibility from m-mode ultrasound measurements of the common carotid artery. Stroke; a journal of cerebral circulation. 1994; 25:11–16.
12. Honda T, Yano K, Matsuoka H, Hamada M, Hiwada K. Evaluation of aortic distensibility in patients with essential hypertension by using cine magnetic resonance imaging. Angiology. 1994; 45:207–212. [PubMed: 8129201]
13. Bertoni AG, Whitt-Glover MC, Chung H, Le KY, Barr RG, Mahesh M, Jenny NS, Burke GL, Jacobs DR. The association between physical activity and subclinical atherosclerosis: The multi-ethnic study of atherosclerosis. American journal of epidemiology. 2009; 169:444–454. [PubMed: 19075250]
14. Woodward M, Webster R, Murakami Y, Barzi F, Lam TH, Fang X, Suh I, Batty GD, Huxley R, Rodgers A. The association between resting heart rate, cardiovascular disease and mortality : Evidence from 112,680 men and women in 12 cohorts. European journal of preventive cardiology. 2012 In Press.
15. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The aric study. Atherosclerosis risk in communities study. Circulation. 1995; 91:1432–1443. [PubMed: 7867184]
16. Kupari M, Hekali P, Keto P, Poutanen VP, Tikkanen MJ, Standerstkjold-Nordenstam CG. Relation of aortic stiffness to factors modifying the risk of atherosclerosis in healthy people. Arteriosclerosis and thrombosis : a journal of vascular biology/American Heart Association. 1994; 14:386–394. [PubMed: 8123643]
17. Urbina EM, Srinivasan SR, Kieltyka RL, Tang R, Bond MG, Chen W, Berenson GS. Correlates of carotid artery stiffness in young adults: The bogalusa heart study. Atherosclerosis. 2004; 176:157–164. [PubMed: 15306189]
18. Najjar SS, Scuteri A, Lakatta EG. Arterial aging: Is it an immutable cardiovascular risk factor? Hypertension. 2005; 46:454–462. [PubMed: 16103272]
19. Peralta CA, Adeney KL, Shlipak MG, Jacobs D Jr, Duprez D, Bluemke D, Polak J, Psaty B, Kestenbaum BR. Structural and functional vascular alterations and incident hypertension in normotensive adults: The multi-ethnic study of atherosclerosis. American journal of epidemiology. 2010; 171:63–71. [PubMed: 19951938]
20. Kass DA. Ventricular arterial stiffening: Integrating the pathophysiology. Hypertension. 2005; 46:185–193. [PubMed: 15911741]
21. Hirai T, Sasayama S, Kawasaki T, Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation. 1989; 80:78–86. [PubMed: 2610739]
22. Gatzka CD, Cameron JD, Kingwell BA, Dart AM. Relation between coronary artery disease, aortic stiffness, and left ventricular structure in a population sample. Hypertension. 1998; 32:575–578. [PubMed: 9740629]
23. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis: The rotterdam study. Stroke; a journal of cerebral circulation. 2001; 32:454–460.

24. Qureshi G, Brown R, Salciccioli L, Qureshi M, Rizvi S, Farhan S, Lazar J. Relationship between aortic atherosclerosis and non-invasive measures of arterial stiffness. Atherosclerosis. 2007; 195:e190–194. [PubMed: 17678931]
25. Rubin J, Blaha MJ, Budoff MJ, Rivera JJ, Shaw LJ, Blankstein R, Mallah MA, Carr JJ, Jones DL, Blumenthal RS, Nasir K. The relationship between resting heart rate and incidence and progression of coronary artery calcification: The multi-ethnic study of atherosclerosis (mesa). Atherosclerosis. 2012; 220:194–200. [PubMed: 21763655]
26. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, Boutouyrie P. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke; a journal of cerebral circulation. 2003; 34:1203–1206.
27. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. Hypertension. 2002; 39:10–15. [PubMed: 11799071]
28. Vaccarino V, Holford TR, Krumholz HM. Pulse pressure and risk for myocardial infarction and heart failure in the elderly. Journal of the American College of Cardiology. 2000; 36:130–138. [PubMed: 10898424]
29. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999; 99:2434–2439. [PubMed: 10318666]
30. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. Hypertension. 2005; 45:1050–1055. [PubMed: 15851625]
31. Mircoli L, Mangoni AA, Giannattasio C, Mancia G, Ferrari AU. Heart rate-dependent stiffening of large arteries in intact and sympathectomized rats. Hypertension. 1999; 34:598–602. [PubMed: 10523333]
32. Sa Cunha R, Pannier B, Benetos A, Siche JP, London GM, Mallion JM, Safar ME. Association between high heart rate and high arterial rigidity in normotensive and hypertensive subjects. Journal of hypertension. 1997; 15:1423–1430. [PubMed: 9431848]
33. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. Journal of hypertension. 1996; 14:897–901. [PubMed: 8818929]
34. Nichols, WVORM. Theoretical, experimental, and principles. London: Edward Arnold; 1990.
35. Palatini P, Julius S. Association of tachycardia with morbidity and mortality: Pathophysiological considerations. Journal of human hypertension. 1997; 11 (Suppl 1):S19–27. [PubMed: 9321736]
36. Palatini P, Julius S. Heart rate and the cardiovascular risk. Journal of hypertension. 1997; 15:3–17. [PubMed: 9050965]
37. Giannattasio C, Failla M, Lucchina S, Zazzeron C, Scotti V, Capra A, Viscardi L, Bianchi F, Vitale G, Lanzetta M, Mancia G. Arterial stiffening influence of sympathetic nerve activity: Evidence from hand transplantation in humans. Hypertension. 2005; 45:608–611. [PubMed: 15699439]
38. Failla M, Grappiolo A, Emanuelli G, Vitale G, Fraschini N, Bigoni M, Grieco N, Denti M, Giannattasio C, Mancia G. Sympathetic tone restrains arterial distensibility of healthy and atherosclerotic subjects. Journal of hypertension. 1999; 17:1117–1123. [PubMed: 10466467]
39. Boutouyrie P, Lacolley P, Girerd X, Beck L, Safar M, Laurent S. Sympathetic activation decreases medium-sized arterial compliance in humans. The American journal of physiology. 1994; 267:H1368–1376. [PubMed: 7943382]
40. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arteriosclerosis, thrombosis, and vascular biology. 2005; 25:932–943.
41. Swierblewska E, Hering D, Kara T, Kunicka K, Kruszewski P, Bieniaszewski L, Boutouyrie P, Somers VK, Narkiewicz K. An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. Journal of hypertension. 2010; 28:979–984. [PubMed: 20408258]
42. Kjekshus JK. Importance of heart rate in determining beta-blocker efficacy in acute and long-term acute myocardial infarction intervention trials. The American journal of cardiology. 1986; 57:43F–49F.
43. Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. Eur Heart J Suppl. 1999; 1:H64–H69.

44. Poulter NR, Dobson JE, Sever PS, Dahlof B, Wedel H, Campbell NR. Baseline heart rate, antihypertensive treatment, and prevention of cardiovascular outcomes in ascot (anglo-scandinavian cardiac outcomes trial). Journal of the American College of Cardiology. 2009; 54:1154–1161. [PubMed: 19761936]
45. Bangalore S, Sawhney S, Messerli FH. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. Journal of the American College of Cardiology. 2008; 52:1482–1489. [PubMed: 19017516]
46. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (beautiful): A subgroup analysis of a randomised controlled trial. Lancet. 2008; 372:817–821. [PubMed: 18757091]
47. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (shift): A randomised placebo-controlled study. Lancet. 2010; 376:875–885. [PubMed: 20801500]
48. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. The Journal of physiology. 2000; 525(Pt 1):263–270. [PubMed: 10811742]
49. Williams B, Lacy PS. Impact of heart rate on central aortic pressures and hemodynamics: Analysis from the cafe (conduit artery function evaluation) study: Cafe-heart rate. Journal of the American College of Cardiology. 2009; 54:705–713. [PubMed: 19679248]
50. Lenard Z, Studinger P, Kovats Z, Reneman R, Kollai M. Comparison of aortic arch and carotid sinus distensibility in humans--relation to baroreflex sensitivity. Autonomic neuroscience : basic & clinical. 2001; 92:92–99. [PubMed: 11570709]
51. Harloff A, Zech T, Frydrychowicz A, Schumacher M, Schollhorn J, Hennig J, Weiller C, Markl M. Carotid intima-media thickness and distensibility measured by mri at 3 t versus high-resolution ultrasound. European radiology. 2009; 19:1470–1479. [PubMed: 19214524]

Novelty and Significance

1) What is new?

An increased resting heart rate is associated with cardiovascular disease and mortality. However, the underlying pathophysiologic mechanism for this association is unclear. This manuscript investigates arterial stiffness as an underlying mechanism that may help to explain why resting heart rate is associated with adverse cardiovascular events.

2) What is relevant?

A number of trials including ASCOT, BEAUTIFUL, SHIFT, and CAFÉ have investigated the effects of medically lowered resting heart rate, but have found differing results. Therefore, a better understanding of the underlying pathophysiologic mechanism for the association between an increased resting heart rate and cardiovascular disease may help with interpretation of these trial results and may inform future research.

3) Summary

Our analysis demonstrated a strong association between resting heart rate and arterial stiffness that persisted after adjustment for known cardiovascular risk factors, physical activity level, and AV-nodal blocking medications. These results provide evidence for a potential underlying mechanism to explain the association of an increased resting heart rate with adverse cardiovascular outcomes.

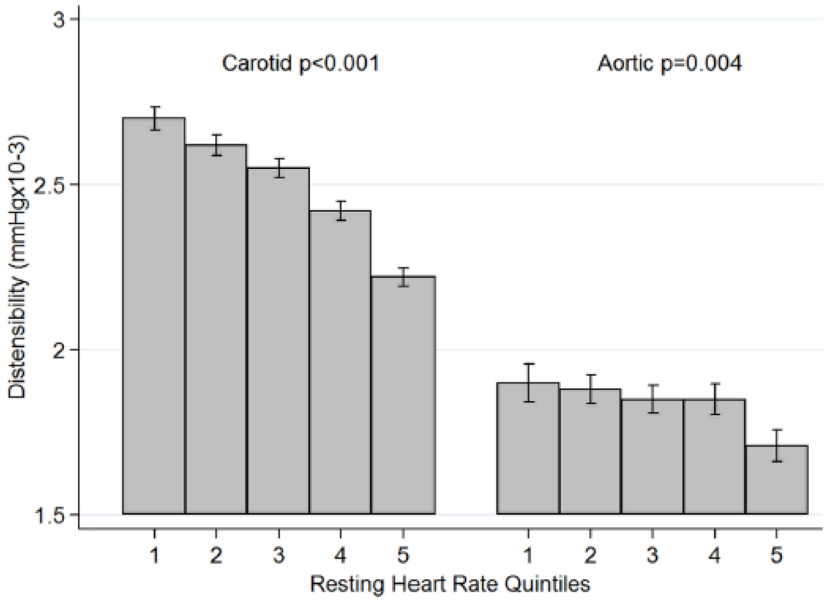

Figure 1.
Distensibility of the carotid and aorta stratified by increasing baseline heart rate quintiles with standard error bars, unadjusted

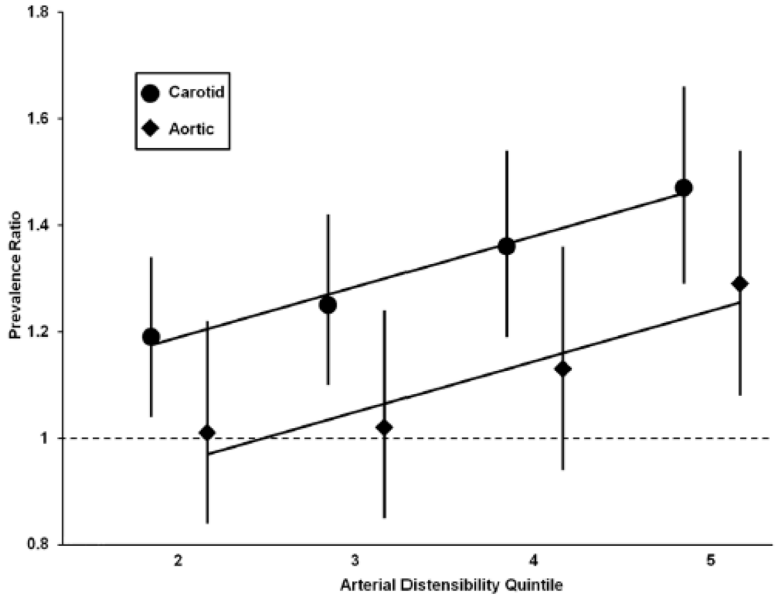

Figure 2.
Prevalence ratio for being in the stiffest carotid or aortic distensibility quartile based on baseline resting heart rate quintile

Table 1

Participant characteristics by baseline heart rate quintile

Baseline HR Quintile	1	2	3	4	5	p-value for trend
Heart rate *	50.9 (36–55)	58.1 (56–60)	62.9 (61–65)	68.3 (66–71)	78.1 (72–130)	<0.001
Age	62.9 (10.1)	62.0 (10.3)	61.8 (10.2)	61.6 (10.1)	62.5 (10.2)	0.088
% Male	60.1	47.0	43.3	43.0	41.1	<0.001
Ethnicity						
% White	38.9	38.4	39.1	37.5	37.2	0.837
% Black	31.0	26.5	25.3	27.3	29.2	0.005
% Hispanic	19.9	22.7	22.5	22.3	23.0	0.226
% Chinese	10.2	12.5	13.2	12.9	10.5	0.051
% Current Smoker	12.2	13.6	12.2	14.2	13.2	0.586
% Family history CHD	41.7	42.7	40.2	41.7	48.1	0.001
SBP (mmHg)	126.8 (23.8)	124.8 (21.4)	126.2 (21.2)	126.0 (20.0)	129.7 (20.3)	<0.001
DBP (mmHg)	70.3 (10.0)	70.7 (10.2)	71.9 (10.1)	72.9 (10.2)	74.2 (10.4)	<0.001
Pulse Pressure (mmHg)	56.5 (19.7)	54.0 (17.2)	54.3 (16.8)	53.1 (15.7)	55.5 (16.3)	0.933
LDL (mg/dL)	115.7 (29.7)	118.9 (30.4)	116.7 (32.5)	116.8 (31.5)	118.0 (33.4)	0.259
HDL (mg/dL)	50.9 (14.5)	51.5 (15.1)	51.2 (15.0)	50.7 (14.7)	50.4 (14.7)	0.188
Triglycerides † **(mg/dL)**	100 (72,146)	105 (76,151)	114 (79,161)	118 (80,170)	123 (85,180)	<0.001
BMI (kg/m^2)	27.5 (4.9)	28.0 (5.2)	28.2 (5.3)	28.7 (5.8)	29.6 (6.0)	<0.001
Waist Circ. (cm)	96.1 (13.3)	97.1 (14.2)	97.6 (14.0)	98.8 (14.8)	101.7 (15.3)	<0.001
CRP‡ **(mg/L)**	1.4 (0.7, 3.1)	1.7 (0.7, 3.9)	2.0 (0.9, 4.3)	2.2 (1.0, 4.7)	2.8 (1.2, 5.7)	<0.001
% Anti-HTN med use	40.3	33.8	34.1	36.6	41.6	<0.001
% AV-blocker use	20.6	12.8	11.7	9.6	8.0	<0.001
% Lipid lowering med	15.0	14.1	16.1	16.6	19.0	0.026
% Diabetes	7.5	8.9	10.5	14.9	23.2	<0.001
Mod. and Vigorous PA‡	105 (101)	101 (103)	94 (102)	92 (92)	84 (88.9)	<0.001
% with Thoracic Aorta Calcium	27.1	26.3	27.6	28.2	30.9	0.023
% ≥$40,000 Income	55.5	51.5	53.3	48.6	47.2	<0.001
% ≥ High School	68.7	65.6	64.2	60.5	59.3	<0.001
Education						

Data presented as mean and SD, unless otherwise indicated

[*] Mean and minimum-maximum values

[†] Median and Inter-quartile range

[‡] MET-hours/week

Table 2

Linear regression of carotid distensibility (continuous) and baseline resting heart rate quintile

	B-coefficient					
HR Quintile	**1**	**2**	**3**	**4**	**5**	**p for trend**
Unadjusted	Reference	-0.08×10^{-4}	$\mathbf{-1.50 \times 10^{-4}}$	$\mathbf{-2.80 \times 10^{-4}}$	$\mathbf{-4.80 \times 10^{-4}}$	<0.001
Model 1	Reference	$\mathbf{-1.16 \times 10^{-4}}$	$\mathbf{-2.02 \times 10^{-4}}$	$\mathbf{-3.34 \times 10^{-4}}$	$\mathbf{-4.87 \times 10^{-4}}$	<0.001
Model 2	Reference	$\mathbf{-1.10 \times 10^{-4}}$	$\mathbf{-1.59 \times 10^{-4}}$	$\mathbf{-2.79 \times 10^{-4}}$	$\mathbf{-3.69 \times 10^{-4}}$	<0.001
Model 3	Reference	$\mathbf{-1.14 \times 10^{-4}}$	$\mathbf{-1.67 \times 10^{-4}}$	$\mathbf{-2.88 \times 10^{-4}}$	$\mathbf{-3.82 \times 10^{-4}}$	<0.001

Model 1 – age, gender, ethnicity

Model 2 – Model 1 + BMI, waist circumference, SBP, DBP, pulse pressure, anti-hypertensive use, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering use, hsCRP, family history of CHD, household income, educational attainment, heavy alcohol use

Model 3 – Model 2 + physical activity level, AV nodal blocker use

Table 3

Linear regression of aortic distensibility (continuous) and baseline resting heart rate quintile

	B-coefficient					
HR Quintile	**1**	**2**	**3**	**4**	**5**	**p for trend**
Unadjusted	Reference	-0.23×10^{-4}	-0.54×10^{-4}	-0.58×10^{-4}	$\mathbf{-1.99 \times 10^{-4}}$	0.035
Model 1	Reference	-0.64×10^{-4}	$\mathbf{-1.52 \times 10^{-4}}$	-1.30×10^{-4}	$\mathbf{-2.25 \times 10^{-4}}$	0.012
Model 2	Reference	-0.70×10^{-4}	$\mathbf{-1.51 \times 10^{-4}}$	-1.45×10^{-4}	$\mathbf{-2.35 \times 10^{-4}}$	0.015
Model 3	Reference	-0.74×10^{-4}	$\mathbf{-1.55 \times 10^{-4}}$	$\mathbf{-1.51 \times 10^{-4}}$	$\mathbf{-2.42 \times 10^{-4}}$	0.009

Model 1 – age, gender, ethnicity

Model 2 – Model 1 + BMI, waist circumference, SBP, DBP, pulse pressure, anti-hypertensive use, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering use, hsCRP, family history of CHD, household income, educational attainment, heavy alcohol use

Model 3 – Model 2 + physical activity level, AV nodal blocker use

Table 4

Prevalence ratio for stiffest carotid distensibility quartile by baseline resting heart rate quintile

HR Quintile	1	2	3	4	5	p for trend
Unadjusted	Reference	1.04 (0.90–1.21)	1.12 (0.97–1.29)	**1.25 (1.09–1.44)**	**1.67 (1.46–1.90)**	<0.001
Model 1	Reference	1.08 (0.95–1.24)	**1.18 (1.03–1.34)**	**1.25 (1.10–1.42)**	**1.45 (1.29–1.64)**	<0.001
Model 2	Reference	**1.18 (1.04–1.33)**	**1.24 (1.10–1.40)**	**1.33 (1.17–1.51)**	**1.44 (1.27–1.62)**	<0.001
Model 3	Reference	**1.19 (1.05–1.35)**	**1.26 (1.11–1.42)**	**1.36 (1.19–1.54)**	**1.47 (1.29–1.66)**	<0.001

Model 1 – age, gender, ethnicity

Model 2 – Model 1 + BMI, waist circumference, SBP, DBP, pulse pressure, anti-hypertensive use, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering use, hsCRP, family history of CHD, household income, educational attainment, heavy alcohol use

Model 3 – Model 2 + physical activity level, AV nodal blocker use

Table 5

Prevalence ratio for stiffest aortic distensibility quartile by baseline resting heart rate quintile

HR Quintile	1	2	3	4	5	p for trend
Unadjusted	Reference	0.95 (0.79–1.14)	0.95 (0.79–1.14)	1.02 (0.85–1.22)	**1.27 (1.06–1.51)**	0.006
Model 1	Reference	0.96 (0.80–1.14)	1.01 (0.85–1.21)	1.07 (0.90–1.27)	**1.19 (1.00–1.40)**	0.115
Model 2	Reference	1.00 (0.83–1.21)	1.01 (0.84–1.22)	1.11 (0.92–1.33)	**1.26 (1.07–1.50)**	0.027
Model 3	Reference	1.02 (0.84–1.22)	1.03 (0.85–1.24)	1.13 (0.94–1.36)	**1.29 (1.08–1.54)**	0.020

Model 1 – age, gender, ethnicity

Model 2 – Model 1 + BMI, waist circumference, SBP, DBP, pulse pressure, anti-hypertensive use, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering use, hsCRP, family history of CHD, household income, educational attainment, heavy alcohol use

Model 3 – Model 2 + physical activity level, AV nodal blocker use

Table 6

Prevalence ratio regression for being in the stiffest quartile (carotid and aortic) per SD (9.7bpm) change in baseline heart change compared to the most elastic quartile.

Subgroup variable	Number of participants	Stiffest Quartile Carotid Distensibility	Stiffest Quartile Aortic Distensibility
Heart Rate		**Per SD**	**Per SD**
Age			
<65	3,722	1.08 (0.99–1.19)†	1.15 (1.04–1.26)
≥65	2,901	1.18 (1.13–1.22)	1.10 (1.03–1.17)
Gender			
Male	3,139	1.16 (1.09–1.23)	1.02 (0.94–1.11)†
Female	3,484	1.13 (1.08–1.18)	1.13 (1.05–1.21)
Ethnicity			
White	2,541	1.16 (1.07–1.27)	1.01 (0.92–1.12)
Black	1,828	1.12 (1.06–1.18)	1.15 (1.05–1.27)
Chinese	793	1.10 (0.96–1.27)	1.26 (0.92–1.73)
Hispanic	1,461	1.17 (1.09–1.25)	1.06 (0.93–1.22)
Hypertension			
Yes	2,958	1.11 (1.07–1.15)†	1.12 (1.05–1.19)†
No	3,665	1.31 (1.20–1.43)	1.00 (0.90–1.12)
Hypertensive Medication			
Yes	2,450	1.10 (1.05–1.16)	1.11 (1.04–1.19)
No	4,170	1.21 (1.14–1.28)	1.07 (0.98–1.17)
Diabetes			
Yes	830	1.15 (1.06–1.23)	1.21 (1.01–1.44)†
No	5,793	1.14 (1.09–1.19)	1.05 (0.99–1.12)
Smoking			
Current	862	1.22 (1.05–1.42)	1.11 (0.92–1.33)
Former	2,415	1.13 (1.06–1.20)	1.05 (0.97–1.14)
Never	3,327	1.15 (1.09–1.21)	1.12 (1.03–1.22)
Presence of TAC			
Yes	1,845	1.12 (1.07–1.18)	1.04 (0.96–1.13)

Subgroup variable	Number of participants	Stiffest Quartile Carotid Distensibility	Stiffest Quartile Aortic Distensibility
Heart Rate		**Per SD**	**Per SD**
No	4,776	1.17 (1.10–1.24)	1.13 (1.04–1.22)
AV nodal blocker use			
Yes	847	1.12 (1.03–1.21)	1.12 (0.98–1.28)
No	5,776	1.15 (1.10–1.20)	1.08 (1.02–1.15)
Physical Activity			
Lowest quintile	1,422	1.15 (1.08–1.22)	0.97 (0.88–1.08)
Highest quintile	1,762	1.26 (1.14–1.39)	1.01 (0.87–1.18)

*Results presented using fully adjusted model

†P for interaction <0.05