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Association between within-visit blood pressure variability, stroke, coronary heart disease, and cardiovascular mortality

Bhrugun Anisetti, Hossam Youssef, Ahamed M. Elkhair, Michelle P. Lin

Department of Neurology, Mayo Clinic, Jacksonville, Florida, USA

ABSTRACT

Introduction. Long-term variability in systolic blood pressure (SBP) is associated with a higher risk of cardiovascular events. Little is known about any association between within-visit SBP variability, stroke, coronary heart disease (CHD), and cardiovascular (CV) death.

Material and methods. Participants included adults ≥ 18 years who participated in the US National Health and Nutrition Examination Surveys from 1999 to 2012 linked to the national death index in 2012. Stroke was self-reported. SBP was obtained up to four times by a physician, using a manual sphygmomanometer according to standard procedures. Within-visit SBP variability was defined as the standard deviation of the BP measurements, stratified into quartiles. We evaluated the relationship between within-visit SBP variability and the odds of stroke or CHD using multivariable logistic regression, and with CV mortality, using multivariable Cox regression.

Results. Of the 27,987 adults, 16.4% were aged ≥ 65 years, 51.3% were female, 71.2% were white, and 10.7% were black. Factors associated with higher mean SBP variability included older age, hypertension, chronic kidney disease, peripheral artery disease, and smoking (all $p < 0.05$). The prevalence of stroke significantly increased across SBP variability quartiles, from 2.1% for quartile 1 to 3.7% for quartile 4 ($p < 0.001$). High SBP variability was associated with higher odds of stroke [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.4–2.2], coronary heart disease (OR 2.0, 95% CI 1.6–2.4), and increased risk of CV mortality [hazard ratio (HR) 2.7, 95% CI 2.3–3.1]. The relationships were not observed after adjusting for covariables.

Conclusions. Within-visit variability in SBP is associated with increased risks of stroke, coronary heart disease, and cardiovascular mortality, but the relationship is confounded by age and covariates.

Key words: blood pressure variability, stroke, coronary heart disease, cardiovascular mortality

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Introduction

Blood pressure (BP) variability has been recognised as a potential risk factor for stroke and coronary heart disease (CHD) [1, 2]. With hypertension being the most prevalent treatable risk factor for stroke and other vascular events [3, 4], its diagnosis and treatment should be of primary importance. The role of hypertension and the incidence of stroke and CHD have been investigated in several major prospective studies [5, 6]. Most of these studies have relied on a single blood pressure reading, but the prognostic value of visit-to-visit and within-visit variability and episodic hypertension has not been reliably established.

This prompted us to hypothesise that higher within-visit systolic blood pressure (SBP) variability is associated with higher odds of a stroke. In this study, we conducted a retrospective study using data from the National Health and Nutrition Examination Survey (NHANES) from 1999–2012 to evaluate the relationship between within-visit SBP variability and the risk of stroke, coronary heart disease, and CV mortality.

Address for correspondence: Michelle P. Lin, MD MPH, Department of Neurology, Mayo Clinic School of Medicine and Sciences, 4500 San Pablo Rd., Jacksonville, Florida 32224, USA; e-mail: lin.michelle@mayo.edu

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Material and methods

Study population

The National Health and Nutritional Examination Survey (NHANES) is a series of cross-sectional, stratified surveys of the non-institutionalised civilian population in the United States. Individuals selected for inclusion in NHANES undergo an interview followed by a physical examination and laboratory testing administered by trained personnel. A detailed description of the plan and operations of each survey has been published [7]. Our study received approval from the National Centre for Health Statistics Research Ethics Review Board, and participants were asked to sign an informed consent form. For this study, we used the survey data from NHANES 1999–2012, including only individuals ≥ 18 years of age, and where there was available data on blood pressure, stroke, and CHD.

Blood pressure measurement and variability

Each person had 1–4 blood pressure measurements within the same visit. After at least five minutes of rest in the sitting position, brachial BP was measured by using either a sphygmomanometer or an oscillometer with a cuff of appropriate size monitored by a trained clinician based on the Seventh Joint National Committee recommendations [8]. We defined within-visit systolic blood pressure (SBP) variability using the standard deviation (SD) of the up to four SBP measurements, stratified into quartiles (Q1-4), with Q1 being the group with the lowest SBP variability and Q4 being the group with the highest SBP variability.

Assessment of stroke, CHD and CV mortality

Prevalence of stroke among the subjects was determined by any self-reported history of stroke in the NHANES 1999–2010 survey database. We considered an answer of "Yes" to the question, "Has a doctor or other health professional ever told you that you had a stroke?" in the Medical Conditions (MCQ) section of the NHANES questionnaire, as a positive self-reported history of stroke. The participants were asked if they had been told by a doctor or another health practitioner that they had CHD. If the individuals replied yes to this question, they were considered positive for CHD existence.

We calculated the CV mortality rates. We used data from NHANES III linked mortality file, in which the NHANES III eligible participants were matched, using a probabilistic matching algorithm, to the National Death Index up until the end of 2012 to determine their mortality status. Deaths from cardiovascular diseases were identified by using the International Classification of Disease 10th revision (ICD-10), codes I00-I99. A detailed description of the methodology is described elsewhere [9].

Covariates

Demographic and comorbid covariates included were age, sex, education (≤ 12th grade, > 12th grade), ethnicity (i.e. Caucasian, African-American, Mexican-American, or other), poverty income ratio (≤ 200%, > 200%), smoking status (ever smoker), hypertension, diabetes, hypercholesterolemia, myocardial infarction (MI), and chronic kidney disease (CKD).

Hypertension was defined as a self-reported history of hypertension, being on antihypertensive medication, or a blood pressure recording of > 140/90 mmHg. Diabetes was defined as a self-reported history of diabetes, being on antidiabetic medication, or haemoglobin A1C ≥ 6.5%. Hypercholesterolemia was defined as a history of anti-cholesterol medication or a total serum cholesterol ≥ 240 mg/dL. CKD was defined as a urine albumin to urine creatinine ratio > 30 mg/dL.

Statistical analyses

Baseline characteristics were presented as a percentage for categorical variables and compared across the SBP variability quartiles using the Rao-Scott Chi-Square test. Survey-weighted prevalence rates of self-reported stroke and CHD/MI were calculated and compared across SBP variability quartiles. To evaluate the relationship between the severity of SBP variability and odds of stroke and CHD/MI, univariable and multivariable logistic regression analyses were performed. To evaluate the association between the severity of SBP variability and the risk of CV mortality, the Cox regression model, before and after adjusting for covariables was performed. Model 1 was adjusted for demographic factors including age, sex, education, ethnicity, and poverty index ratio. Model 2 was also adjusted for medical conditions including hypertension, diabetes, myocardial infarction, chronic kidney disease, and smoking. The statistical significance was defined as p for interaction < 0.1 and a 2-side p value of < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Study characteristics

We identified 27,987 patients who met the inclusion criteria from NHANES 1999–2010. The baseline characteristics of the sample population are set out in Table 1. Age distribution was 49.2%, 34.4%, 12.6%, and 3.8% for patients aged 18–44, 45–63, 65–79, and ≥ 80, respectively. The proportion of patients with increased BP variability across severity quartiles decreased in the youngest age group (18–44), while the proportion of patients with increased severity of BP variability increased in the oldest age groups (65–79, ≥ 80; Tab. 1). Participants with the highest BP variability (Q4) were more likely to be Caucasian and to have more prevalent comorbid conditions, including hypertension, diabetes, MI, CKD, and smoking history (p < 0.05).

Risk of stroke and coronary heart disease across within-visit BP variability

Of the 27,987 subjects, 986 had a self-reported history of stroke. The prevalence of stroke in the sample population

Table 1. Patient characteristics across SBP variability quartiles (Q1–4), NHANES 1999–2010

	Overall	Q1	Q2	Q3	Q4	p-value
	N%	N%	N%	N%	N%	
Age						< 0.001
18–44	49.2%	58.4%	55.2%	48.3%	32.2%	
45–64	34.4%	30.6%	32.9%	36.2%	38.9%	
65–79	12.6%	8.7%	9.6%	12.3%	21.1%	
≥ 80	3.8%	2.3%	2.3%	3.2%	7.7%	
Sex						0.100
Male	48.7%	48.5%	49.6%	49.6%	47.2%	
Female	51.3%	51.5%	50.4%	50.4%	52.8%	
Ethnicity						< 0.001
Mexican-American	7.8%	8.7%	8.3%	7.7%	6.4%	
Caucasian	71.2%	69.5%	70.7%	71.1%	74.0%	
African-American	10.7%	11.1%	11.2%	10.4%	9.9%	
Other	10.3%	10.7%	9.9%	10.8%	9.7%	
Education						0.072
≤ 12th grade	44.6%	44.0%	44.1%	43.9%	46.5%	
> 12th grade	55.3%	55.8%	55.8%	56.0%	53.4%	
Unknown	0.1%	0.2%	0.1%	0.0%	0.1%	
PIR						0.566
≤ 200%	31.5%	32.4%	31.0%	31.4%	31.0%	
> 200%	61.6%	60.6%	61.9%	62.1%	61.8%	
Unknown	6.9%	7.0%	7.1%	6.5%	7.1%	
Medical history						
Hypertension*	35.5%	28.9%	30.9%	33.8%	50.3%	< 0.001
Diabetes†	9.4%	7.4%	8.3%	10.0%	12.3%	< 0.001
Hypercholesterolemia‡	27.6%	24.0%	25.3%	27.9%	34.5%	< 0.001
Myocardial infarction	3.3%	2.5%	2.8%	3.4%	4.7%	< 0.001
Chronic kidney disease§	8.8%	8.2%	6.9%	7.9%	12.4%	< 0.001
Peripheral arterial disease**	16.1%	14.6%	15.8%	16.1%	17.4%	0.102
Ever smoker	48.5%	47.7%	47.1%	49.0%	50.5%	0.040

*BP > 140/90 or on anti-hypertensive medications, or self-report; †Haemoglobin A1C ≥ 6.5% or on diabetes medications, or self-report; ‡Total serum cholesterol ≥ 240 mg/dL or on anti-cholesterol medications; §Urine albumin to urine creatinine ratio > 30 mg/g; ** ABI < 0.9 or ABI > 1.3. Myocardial infarction, ever smoking: self-report

was 2.6% [standard error (SE) 0.12] overall. Those with the highest SBP variability (Q4) had a higher prevalent stroke compared to those with the lowest (Q1) BP variability (3.7% *vs.* 1.8%; p < 0.001).

In our crude analysis, we observed that subjects with the highest BP variability (Q4) had higher odds of stroke compared to another group (OR 1.75, p < 0.001, Tab. 2). After adjusting for covariables, a relationship between BP variability and stroke was no longer observed.

In our study sample, 1,742 reported a history of CHD (Tab. 2). The prevalence of CHD in the overall cohort was 4.8% ± 0.19%. The prevalence increased from 3.6% ± 0.25% in the lowest quartile of SBP variability (Q1) to 6.9% ± 0.40% in the highest quartile of SBP variability (Q4) (p < 0.001, Tab. 2). In our crude analysis, the risk of having a MI/CHD was 1.99--fold in the subjects in the highest quartile of SBP variability (p < 0.001, Tab. 2). On further adjustment with demographics (Model 1) and vascular risk factors (Model 2), there was no significance seen for both stroke and CHD/MI.

CV-mortality across BP variability

CV mortality was highest in the patients with the highest quartile of BP variability (2.9%, SE 0.39, p < 0.001). The HR in our unadjusted model was also highest in the Q4 group (HR 2.73, SE 0.39, p < 0.001). After adjustment, these associations were no longer statistically significant; the adjusted HR in the highest quartile (Q4) compared to the lowest quartile (Q1) was 0.87 (p = 0.937, Model 2) for CV-related mortality.

Table 2. Rate and odds ratio (OR) of stroke, coronary heart disease/myocardial infarction, and cardiovascular mortality across within-visit SBP variability quartiles, NHANES 1999–2010

		Overall cohort	Q1	Q2	Q3	Q4	p-value
Stroke	No. of stroke/No. at risk	986/27,987	214/7,890	162/6,393	238/6,688	372/7,016	–
	Prevalence rate – % (SE)	2.6 (0.12)	2.1 (0.20)	1.8 (0.20)	2.7 (0.24)	3.7 (0.24)	< 0.001
	Crude OR	–	1.00	0.82	1.27	1.75	< 0.001
	Model 1 OR*	–	1.00	0.77	1.03	0.90	0.854
	Model 2 OR**	–	1.00	0.77	1.03	0.84	0.407
CHD/MI	No. of CHD and MI/No. at risk	1,742/27,987	381/7,890	329/6,393	427/6,688	605/7,016	–
	Prevalence rate – % (SE)	4.8 (0.19)	3.6 (0.25)	4.1 (0.28)	5.1 (0.26)	6.9 (0.40)	< 0.001
	Crude OR	–	1.00	1.13	1.42	1.99	< 0.001
	Model 1 OR*	–	1.00	1.06	1.13	0.99	0.940
	Model 2 OR**	–	1.00	1.07	1.11	0.95	0.620
CV-mortality	No. of CV deaths / No. person-years	305/118,447	63/34,256	50/27,403	63/27,697	129/29,089	
	Rate – CV deaths per 1,000 person-yrs (SE)	1.5 (0.14)	1.0 (0.23)	1.1 (0.26)	1.1 (0.29)	2.9 (0.39)	<0.001
	Crude HR	–	1.00	1.08	1.05	2.73	<0.001
	Model 1 HR*	–	1.00	1.02	0.77	0.94	0.640
	Model 2 HR**	–	1.00	1.09	0.72	0.87	0.937

CHD — coronary heart disease; CV — cardiovascular; MI — myocardial infarction; OR — odds ratio; *Model 1 (demographic): adjusted for age, sex, race, poverty index ratio, education; **Model 2 (demographic + comorbidities): model 1 + hypertension, diabetes, hypercholesterolemia, chronic kidney disease, peripheral artery disease, smoking

Discussion

In our study, we demonstrated that subjects with high within-visit SBP variability had a higher risk of stroke, CHD, and CV mortality. However, the relationship was not observed after adjusting for age and risk factors. We also noticed that those with the highest quartile of SBP variability (Q4) had the highest prevalent vascular risk factors.

This study addressed for the first time the prognostic implications of within-visit blood pressure variability.

In our study, we observed that the proportion of older age groups increased with each quartile. This can be explained in part by ageing, and chronic hypertension, which both lead to stiffening of the arteries. This stiffening of the large arterial wall results in an attenuation of the baroreflex function, which then causes a larger BP variability [10]. With ageing, the elastin-rich medial layer of the arteries undergoes damage or degradation of the elastic fibres (elastin and elastin-associated glycoproteins such as fibrillin-1) and increased aggregation glycosaminoglycans or collagen fibres, or both [11]. Other conditions such as diabetes which lead to increased crosslinking of the collagen via glycosylation have also been associated with increased stiffness of arteries [12]. Sasaki et al. [13] and Lacolley et al. [14, 15] demonstrated that an increase in BP variability induced by arterial baroreceptor denervation in rats, without an increase in mean blood pressure, was linked to aortic atherosclerosis, decreased arterial distensibility, and increased collagen content and density in arterial walls.

Another possible explanation could be conditions such as autonomic dysfunction that can also cause swings in haemodynamic variables [16], particularly in conditions such as diabetes, synucleinopathy, and Alzheimer's Disease which are known to cause autonomic dysfunction and have been associated with BP variability [17, 18]. Thus, high SBP variability may serve as a marker, rather than an independent risk factor, for these conditions. In our study, we similarly observed that the prevalence of diabetes mellitus increased with every quartile, concurring with the results of other studies [19, 20] showing that diabetes is associated with autonomic dysfunction manifested as high BP variability.

The presence of untreated hypertension, along with common behaviours such as smoking, low physical activity levels, and high obesity rates among young individuals, has a notable impact on the prevalence of cardiovascular diseases like myocardial infarction and atrial fibrillation [21]. It is widely acknowledged by clinicians that these conditions increase the risk of cerebrovascular events in the young population. Considering the known association between blood pressure variability and cardiovascular outcomes, it is plausible to suggest that the high prevalence of cardiovascular diseases and risk factors in young individuals, as mentioned above, may also contribute to variations in blood pressure readings.

It should be noted that a previous study (conducted in Poland) revealed a higher prevalence of arterial hypertension and peripheral arterial disease in the lower limbs among patients with DM [22]. This could lead to a compromised

bloodflow and vascular function in peripheral arteries that may lead to fluctuations in blood pressure readings. While DM and other systemic vascular risk factors could also cause baroreceptor denervation resulting in blood pressure variability, the causal pathway may also be reversed. Hyperglycaemia could directly harm the ischaemic brain by causing the build-up of lactate and intracellular acidosis. Additionally, the inflammatory response triggered by stress might elevate the levels of circulating free fatty acids in individuals with acute illnesses, which can negatively affect the ability of the endothelium to dilate blood vessels. Moreover, hyperglycaemia can contribute to reperfusion injury by intensifying oxidative stress and inflammation [22].

Brain injury such as stroke is known to cause central autonomic dysfunction, particularly lesions affecting the bilateral insular cortex, anterior cingulate gyrus, amygdala, and hypothalamus [23]. Previous studies have shown an association between an excessive drop in nocturnal blood pressure and silent cerebrovascular lesions [24, 25]. The explanation for this could be pre-existing cerebral ischaemia that could lead to both altered central autonomic control of blood pressure [26, 27] and an increased risk of stroke. Furthermore, BP variability is also known to associate with pro-inflammatory cytokine production, hyperglycaemia, and increased blood-brain-barrier permeability [28–31], all of which can contribute to an increased risk of stroke. Haemodynamic instability caused by high BP variability can also increase shear stress, resulting in small vessel disease, cerebral hypoperfusion, and neuronal cell damage [32].

Blood pressure variability may have a different effect on different vascular beds (cerebrovascular *vs.* cardiovascular). For instance, Hata et al. [33] demonstrated that the coefficient of variation between clinic SBP was slightly greater in 138 patients with stroke than in healthy controls [34], but not in patients with myocardial infarction, suggesting that the mechanism involved in larger office BP variability and the incidence of a stroke may be different from the mechanism that links 24-h BP variability and cardiovascular complications. A previous study found that home BP variability, as measured by SD of SBP, was related to CVD events in 2,455 individuals from a typical Japanese community who did not have a CVD risk [35]. These studies have indicated that environmental factors (mental and physical stress), poor compliance of arteries, and adherence to drug therapy by the patients were thought to be the possible reasons for causing BP variability leading to increased risks of MI and CV mortality [33]. However, another reasonable explanation is that the relatively quick BP variations assessed by this method have a traumatic impact on the CV system, encouraging the formation and progression of atherosclerosis.

Similar to our study, Verdecchia et al. [36] were unable to show an independent association between baseline BP variability, which was defined as the SD of ambulatory BP, and cardiovascular morbidity after adjusting for associated confounding factors such as ageing, diabetes mellitus, and severity of hypertension. Also in another study there was no significant association seen between the excessive circadian amplitude of BP and the occurrence of CHD [37]. This suggests the prognostic significance of 24h BP variability may have organ specificity.

Our study has several strengths, including a nationally representative sample of US adults with a long follow-up for mortality, rigorous and validated survey and examination procedures, adjustment for numerous possible confounders, and robust estimations of absolute mortality and cumulative 10-year mortality rates, with multiple models adjusting for various potential confounders. An advantage of using the NHANES data to explore a mechanistic hypothesis is that the results apply to the US population. By utilising within-visit blood pressure measurements, we successfully accounted for significant potential confounding factors, specifically mean blood pressure levels and the influence of antihypertensive medications. Our blood pressure measurements were conducted by extensively trained staff using a validated electronic device and standard protocols, thereby minimising any potential imprecision and bias in the data collection process.

This study also has several limitations. The available data on risk factor prevalence, including both our study and the NHANES, rely on self-reporting. However, it is important to acknowledge the limitations of self-reporting, such as potential biases associated with telephone surveys and the exclusion of individuals with health conditions. Additionally, in our population survey, we did not collect data on body mass index (BMI), preventing us from assessing the impact of obesity within our population over time.

The assessment of stroke relied on self-reporting, and crucial details such as stroke type, duration since stroke, severity, and functional status were not available. These factors, which could potentially impact upon mortality, were not accounted for in our study. Moreover, the absence of CT or MRI findings in the patients may have led to the inclusion of individuals with asymptomatic cerebrovascular lesions as control patients. However, it is important to note that the limitations arising from self-reported illness are probably mitigated to some extent. A previous study has demonstrated the validity of using self-reported illness as a measure of objective health [38]. NHANES only captures non-institutionalised individuals and those who can comprehend and respond to surveys, resulting in a possible bias towards a healthier population. This study used only four BP readings to calculate the variability.

In conclusion, the findings of this study provide evidence of significant associations between within-visit SBP variability and an increased risk of stroke, coronary heart disease, and CV mortality. Our results indicate that patients with the highest quartile of blood pressure variability are particularly susceptible to these adverse health outcomes. These findings underline the need for vigilant monitoring and management of blood pressure to minimise the risk of stroke.

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