



Body Mass Index and Arterial Stiffness Are Associated With Greater Beat-to-Beat Blood Pressure Variability After Transient Ischemic Attack or Minor Stroke

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BACKGROUND AND PURPOSE: Blood pressure variability (BPV) from beat to beat is associated with an increased risk of cardiovascular events and enables rapid assessment of BPV, but the underlying causes of elevated BPV are unclear.

METHODS: In consecutive patients within 4 to 6 weeks of transient ischemic attack or nondisabling stroke (OXVASC [Oxford Vascular Study]), continuous noninvasive blood pressure was measured beat to beat over 5 minutes (Finometer). Arterial stiffness was measured by carotid-femoral pulse wave velocity (Sphygmocor). After automated and manual data cleaning, associations between BPV (residual coefficient of variation), demographic factors, and arterial stiffness were determined for both systolic and diastolic blood pressure, by ANOVA and linear models. Relationships between demographic factors and arterial stiffness were determined by interaction terms and mediation.

RESULTS: Among 1013 patients, 54 (5.3%) were in AF, and 51 (5%) had low-quality recordings. In a general linear model including the remaining 908 participants, systolic BPV (SBPV) was most strongly associated with age ($P=0.00003$), body mass index (BMI; $P=0.003$), and arterial stiffness ($P=0.008$), with weaker independent associations with current smoking ($P=0.01$) and a low diastolic blood pressure ($P=0.046$). However, while there was a linear increase in SBPV with BMI in men, in women, SBPV was lowest for a BMI in the normal range but was greater below 20 or above 30 (ANOVA, $P=0.012$; BMI-sex interaction, $P=0.03$). Although BMI and pulse wave velocity were partially independent, increased pulse wave velocity mediated $\approx 32\%$ of the relationship between increased BMI and SBPV ($P<0.001$).

CONCLUSIONS: Vascular aging, manifest as arterial stiffness, was a strong determinant of increased SBPV and partially mediated the effect of increased BMI. However, although high BMI was independently associated with SBPV in both sexes, a low BMI was associated with increased SBPV only in women. SBPV may partially mediate the relationship between BMI and cardiovascular events, while obesity may provide a modifiable target to reduce SBPV and cardiovascular events.

GRAPHIC ABSTRACT: An online [graphic abstract](#) is available for this article.

Key Words: blood pressure ■ body mass index ■ linear models ■ systole ■ vascular stiffness

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Nonstandard Abbreviations and Acronyms

BMI	body mass index
BP	blood pressure
BPV	blood pressure variability
CV	coefficient of variation
DBP	diastolic blood pressure
DBPV	diastolic blood pressure variability
OXVASC	Oxford Vascular Study
PWV	pulse wave velocity
SBP	systolic blood pressure
SBPV	systolic blood pressure variability

Patients with episodic hypertension after a cerebrovascular event have a high risk of recurrent stroke,^{1,2} residual visit-to-visit variability in blood pressure (BPV) on treatment has a poor prognosis despite good control of mean blood pressure (BP),³ and benefits of some antihypertensive drugs in the prevention of stroke may partly result from reduced variability in systolic BP (SBPV).^{4–6} Strong associations between visit-to-visit BPV, cardiovascular events, renal impairment, and cognitive decline have now been demonstrated in population-based cohorts,^{7,8} patients with diabetes,⁹ renal impairment,¹⁰ cognitive decline,¹¹ and other groups,¹² with similar predictive value of BPV from day to day on home readings,^{13–15} with a significant reduction in BPV with specific antihypertensives.^{4,6} However, both visit-to-visit and home BPV require a prolonged period of assessment, good patient compliance, and follow-up visits, limiting their use in acute assessment or for assessing treatment response in clinical practice and future trials.

BPV from one beat to the next (beat-to-beat BPV) is also associated with an increased risk of recurrent stroke or cardiovascular events in patients with a transient ischemic attack or minor stroke, with a similar physiological profile to home day-to-day BPV,¹⁶ and has at least similar predictive value,¹⁵ while enabling BPV assessment at a single visit. However, the determinants of beat-to-beat BPV in at-risk individuals and its covariance with other major cardiovascular risk factors is unclear. Furthermore, beat-to-beat BPV is itself composed of multiple components contributing to total BPV, from physiological rhythms reflecting breathing and intact autonomic function to increased BPV associated with stiff arteries and impaired baroreceptor function in older patients with impaired compensatory mechanisms.¹⁶ To assess the potential clinical utility of beat-to-beat BPV, and to identify populations at an increased risk of elevated BPV, it is necessary to understand the determinants of beat-to-beat BPV in at-risk populations and how this varies by demographic characteristics.

Therefore, in patients attending a transient ischemic attack and minor stroke clinic, we determined associations

between beat-to-beat BPV with arterial stiffness and major cardiovascular risk factors and which demographic features determine a likely pathological excess of beat-to-beat BPV.

METHODS

Study Population

Consecutive, consenting patients with transient ischemic attack or minor stroke (National Institutes of Health Stroke Scale score, <5) were recruited between September 2010 and October 2019, as part of the Phenotyped Cohort of OXVASC (Oxford Vascular Study).^{15,16} Participants were recruited at the OXVASC daily emergency assessment clinic, following a referral after attendance at the Emergency Department or from primary care, usually within 24 hours. Patients were referred after transient neurological symptoms or symptoms consistent with a minor stroke, not requiring direct admission to hospital. The OXVASC population consists of >92 000 individuals registered with about 100 primary-care physicians in Oxfordshire, United Kingdom.¹⁷ All consenting patients had a standardized medical history and examination, ECG, blood tests, and a stroke protocol brain magnetic resonance imaging and contrast-enhanced magnetic resonance angiography (or computed tomography of the brain and carotid Doppler ultrasound or computed tomography angiogram), an echocardiogram, and 5-day ambulatory cardiac monitor. All patients were assessed by a study physician, reviewed by the senior study neurologist (P.M.R.), and were followed up face to face at 1, 3, 6, and 12 months and 2, 5, and 10 years. Medication is standardly prescribed according to guidelines, most commonly with dual antiplatelets (aspirin and clopidogrel), high-dose statins (atorvastatin, 40–80 mg), and a combination of perindopril and indapamide, with the possible addition of amlodipine, to reach a target of <130/80 on home telemetric BP monitoring.¹⁶ Access to the data will be openly considered on application to the chief investigator (P.M.R.).

As part of the OXVASC Phenotyped Cohort, a routine prospective cardiovascular physiological assessment is performed at the 1-month follow-up visit between September 2010 and September 2019. Participants were excluded if they were under 18 years of age, had severe cognitive impairment, were pregnant, or had autonomic failure, a recent myocardial infarction, unstable angina, heart failure (New York Heart Association class 3–4 or ejection fraction <40%), or untreated bilateral carotid stenosis (>70%). OXVASC is approved by the Oxfordshire Research Ethics Committee.

After 15 to 20 minutes of supine rest, beat-to-beat BPV was measured over 5 minutes in a quiet, dimly lit, temperature-controlled room (21–23°C). Continuous ECG and noninvasive BP were acquired at 200 Hz (Finometer; Finapres Medical Systems, the Netherlands), via a Powerlab 8/30 with LabChart Pro software (ADInstruments). Waveforms were preferentially recorded from the middle phalanx of the middle finger. Automated calibration (Physiocal) was performed until the recording was stable but turned off during each test. Estimated brachial waveforms (Finometer) were calibrated offline by linear regression to 2 to 3 supine, oscillometric brachial readings, performed immediately before the monitoring period on the contralateral arm, with manual exclusion of artifacts. In patients

with a significant deterioration in recording quality during the first 5 minutes, the test was stopped and the calibration procedure repeated. If necessary, the finger cuff was moved to an adjacent finger or the proximal phalanx of the same finger, or the hand was warmed with a hand warmer. Before physiological assessment, 2 sitting clinic BPs, 5 minutes apart, were measured at ascertainment and 1 month in the nondominant arm, by trained personnel.

Analysis

BPV on beat-to-beat monitoring was calculated over 5 minutes. Ectopic beats and artifacts were automatically detected from the R-R interval of the ECG, visually reviewed and removed by linear interpolation of the R-R interval. BP artifacts were automatically detected, manually reviewed, and removed by linear interpolation to adjacent normal beats with in-house software. Patients in atrial fibrillation during the recording were excluded. SBPV and diastolic BPV (DBPV) were calculated as the SD and the coefficient of variation (CV; $CV=SD/mean$), before and after detrending of the recording about a linear regression across 5 minutes. All recordings were reviewed blinded to clinical data, after automated and manual data cleaning, to assess for the quality of recording (3, excellent quality; 2, adequate quality for analysis; 1, unusable, poor quality recording), based upon the presence of artifacts or drift in the baseline measurement.

Associations with demographic indices were determined by general linear models and by logistic regression for the top decile of BPV on each index. Models were performed for univariate associations; adjusted for age and sex and for age, sex, and cardiovascular risk factors at study entry (current smoking, history of hypertension, and diabetes).

Analyses were performed in R, Matlab r2015, or Windows Excel.

RESULTS

One thousand thirty-one assessments were performed in 1013 eligible, consecutive, consenting patients between September 2010 and October 2019, with 18 patients assessed twice after separate clinical presentations. Fifty-four of 1013 (5.3%) patients were in atrial fibrillation during the recording, while 51 (5%) patients had inadequate recordings. Patients with atrial fibrillation or poor recording quality were older, had higher BP, and were more likely to have a history of hypertension (Table 1).

Mean systolic BP (SBP) was strongly correlated with SD of SBP (Figure I in the [Data Supplement](#)) but with no correlation with CV-SBP or CV-diastolic blood pressure (DBP), before or after detrending of the recording (residual CV). However, there was an inverse correlation between CV-DBP and mean DBP before and after detrending (Figure I in the [Data Supplement](#)).

Beat-to-beat BPV increased with age (Tables 1 and 2, and Table III in the [Data Supplement](#)) with a slightly greater SBPV in women, which was not significant after adjustment for age. The other key univariate and adjusted associations of increased beat-to-beat SBPV were increased body mass index (BMI) and increased arterial stiffness (Table 2). After adjustment for age, sex, and other cardiovascular risk factors, current smoking was also associated with increased SBPV. A history of hypertension, diabetes, or dyslipidemia was not associated. Only age was associated with DBPV in univariate analysis, although BMI was associated with DBPV after adjustment for age, sex, and cardiovascular risk factors (Table II in the [Data Supplement](#)).

Table 1. Characteristics of Patients Included and Excluded From the Analysis

	All	Included	In AF	Poor data	P value
	1013	908 (90)	54 (5)	51 (5)	
Age, y	67 (13.3)	66.1 (13.3)	77.8 (8.9)	72.2 (11.1)	<0.001
Sex	427 (42)	387 (43)	18 (33)	22 (44.9)	0.35
Hypertension	453 (44)	390 (43)	36 (67)	27 (55.1)	<0.001
Diabetes	116 (11)	104 (11.5)	7 (13)	5 (10.2)	0.88
Smoking					
Current	160 (15)	148 (16)	6 (11)	6 (12.2)	0.39
Ever	535 (53)	478 (53)	32 (59)	24 (49)	0.62
FHx of stroke	303 (30)	274 (30)	12 (22)	17 (34.7)	0.12
AF					
During test	54 (5.3)	...	54 (100)
Ever	74 (7)	37 (4.1)	35 (65)	2 (4.1)	<0.001
Dyslipidemia	314 (31)	277 (31)	20 (37)	16 (32.7)	0.67
Heart failure	16 (1.6)	10 (1.1)	6 (11)	...	<0.001
Systolic BP	133 (19)	132 (18)	137 (24)	145 (27)	<0.001
Diastolic BP	78 (12)	78 (11)	83 (15)	77 (8.9)	0.01

Participants were excluded if they were in AF during the assessment or if their recording was of poor quality with a high probability of artifactual recordings. P values are given for ANOVA for continuous variables and χ^2 tests for categorical variables. AF indicates atrial fibrillation; BP, blood pressure; and FHx, family history.

Table 2. Linear Models for Baseline Demographic Measures and SBP Level and Variability

	Mean SBP						SBP-rCV					
	Unadjusted		Adj age+sex		Adj CV-RFs		Unadjusted		Adj age+sex		Adj CV-RFs	
	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
Age, y	0.34	<0.001*	0.34	<0.001*	0.35	<0.001*	0.02	0.001*	0.02	0.001*	0.02	<0.001*
Women	0.47	0.692	−0.13	0.909	−0.15	0.898	0.27	0.039*	0.24	0.064	0.26	0.057
HTN reported	7.83	<0.001*	5.51	<0.001*	6.33	<0.001*	0.03	0.804	−0.11	0.415	−0.06	0.728
HTN treated	5.04	<0.001*	1.93	0.171	2.26	0.124	−0.07	0.636	−0.26	0.111	−0.25	0.139
Diabetes	1.62	0.377	1.21	0.499	1.09	0.547	0.31	0.123	0.33	0.109	0.39	0.056
Dyslipidemia												
Reported	1.4	0.274	−0.53	0.675	−0.87	0.526	−0.15	0.278	−0.23	0.119	−0.24	0.115
Treated	1.52	0.313	−0.69	0.645	−1.85	0.239	−0.15	0.383	−0.24	0.162	−0.27	0.123
Smoking												
Ever	−0.13	0.91	0.39	0.738	−0.75	0.561	0.04	0.793	0.11	0.418	0.01	0.958
Current	−0.6	0.708	3.09	0.055	3.61	0.041*	0.18	0.311	0.41	0.026*	0.42	0.036*
Height	−3.89	0.877	2.83	0.908	3.52	0.885	−1.12	0.689	−0.24	0.932	−0.06	0.982
Weight	−0.01	0.732	0.02	0.443	0.01	0.571	0	0.21	0.01	0.024*	0.01	0.032*
BMI	−0.1	0.411	0.02	0.842	0.01	0.938	0.03	0.046*	0.03	0.01*	0.04	0.005*
Creatinine	0	0.958	−0.06	0.085	−0.06	0.077	0	0.503	0	0.294	0	0.243
Cholesterol	−0.16	0.68	0.1	0.789	0.17	0.654	0.01	0.759	0.01	0.805	0.03	0.506
LDL	−0.01	0.555	−0.01	0.564	−0.01	0.593	0	0.282	0	0.229	0	0.285
HDL	1.16	0.323	0.32	0.793	0.71	0.563	−0.05	0.704	−0.2	0.127	−0.2	0.15
TSH	0.23	0.487	0.13	0.684	0.19	0.558	−0.05	0.139	−0.06	0.105	−0.05	0.13
On antihypertensive	4.18	0.002*	1.11	0.42	−5.96	0.168	−0.04	0.805	−0.21	0.175	0.16	0.736
On statin	1.11	0.439	−0.79	0.578	−1.19	0.736	−0.2	0.215	−0.28	0.078	−0.58	0.143
PWV	2.43	<0.001	2.29	<0.001	2.35	<0.001	0.14	<0.001	0.11	0.002	0.11	0.002

SBP variability is analyzed as the rCV, unadjusted or adjusted for age and sex or for age, sex, and CV-RFs. Independent variables include HTN reported by patients at baseline or defined by patient report and current treatment at baseline. Current treatment and PWV measures are given at the time of the physiological assessment. Adj indicates adjusted; BMI, body mass index; CV-RF, cardiovascular risk factor; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; PWV, pulse wave velocity; rCV, residual coefficient of variation; SBP, systolic blood pressure; and TSH, thyroid-stimulating hormone.

* $P<0.05$.

BMI was the strongest clinical risk factor associated with increased BPV. It was not associated with mean or maximum SBP but only with SBPV (Figure II in the [Data Supplement](#)) and was negatively correlated with age ($P<0.0001$). There was a significant difference in BPV between standardly defined BMI groups in women (ANOVA $P=0.012$), with a U-shaped relationship (Figure 1), such that SBPV in women with a BMI between 25 and 30 was significantly lower than women with a BMI below 20 (post hoc Tukey honestly significant difference, $P=0.04$) or >30 ($P=0.0499$). The elevated SBPV in women with a low BMI did not reflect a specific excess of high BPV in this group, with a similarly shaped distribution of SBPV across different levels of BMI. In contrast, there was no difference between absolute BMI categories in men (Figure 2), with a linear increase in BPV when BMI was defined by quintiles (Figure I in the [Data Supplement](#)). This pattern predominantly reflected differences in weight, with a more linear increase in BPV across quintiles of weight in men, with no change across quintiles of height (Figure III in the [Data Supplement](#)).

The difference in the pattern of change with BMI between sexes was evident in a multivariate model, with a significant association between BMI and SBPV or DBPV when including all indices significantly associated with BPV after adjustment for age, sex, and CV risk factors (Table 2). Furthermore, there was a significant interaction between BMI with sex for SBPV, but not for DBPV, reflecting the linear increase in SBPV in men but not women. This was confirmed on stratifying the population by sex, with a significant association between BMI and BPV in men, exceeding even the association between age and BPV (Figure IV in the [Data Supplement](#)), while in women, there was no overall linear association with the only strong determinant being the relationships between age and low DBP with SBPV (Table 3), reflecting the nonlinear pattern in women.

In addition to BMI, arterial stiffness was the factor most strongly associated with BPV, even compared with age. A linear increase in SBPV with arterial stiffness was seen in both men and women (Figure 2), with a steeper relationship in women than in men but with no significant interaction with sex ($P=0.38$). This association was

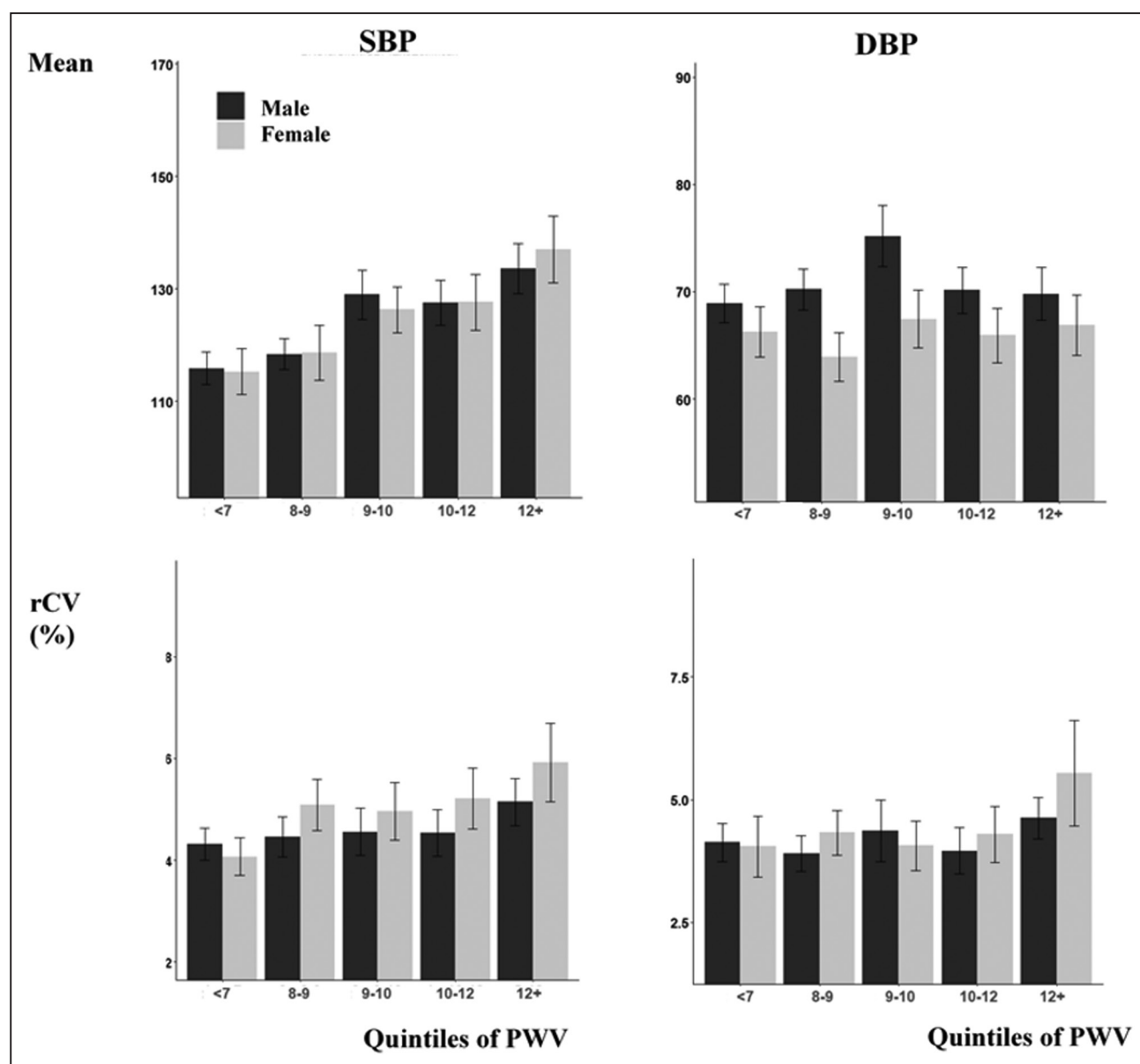


Figure 1. Relationship between increased carotid-femoral pulse wave velocity beat-to-beat blood pressure variability, stratified by sex.

Results are presented as the mean and CI for each group. Residual coefficient of variation (rCV) is calculated as the coefficient of variation of detrended recordings. y axes are set to the 95% range of each measure across the whole population. DBP indicates diastolic blood pressure; PWV, pulse wave velocity; and SBP, systolic blood pressure.

sufficiently strong that there was no association between age and SBPV after adjustment for pulse wave velocity (PWV; adjusted for age and sex: age, $P=0.19$; sex, $P=0.007$; PWV, $P=0.002$).

There was no univariate association between BMI and PWV ($\beta=0.03$, $P=0.17$), but after adjustment for age and sex, there was a strong association ($\beta=0.06$, $P<0.001$), which persisted after adjustment for other cardiovascular risk factors ($\beta=0.05$, $P=0.008$). In a combined model allowing for the sex×BMI interaction, BMI and PWV independently predicted SBPV, with no residual significant association between either age or DBP with SBPV, although associations remained for

sex and smoking (Table 3). There was no interaction between smoking and BMI for BPV and no association between thyroid-stimulating hormone level and either BMI or BPV. In a causal mediation analysis allowing for adjustment for age and sex, there was also a significant indirect mediation effect of the relationship between BMI and SBPV by PWV (average causal mediation effect: 0.008, $P<0.001$; average direct effect: 0.016, $P=0.3$; total effect: 0.024), explaining 32% of the relationship between BMI and SBPV. There was no significant indirect mediation by BMI of the relationship between PWV and SBPV (average causal mediation effect, $P=0.12$; 10% variance explained).

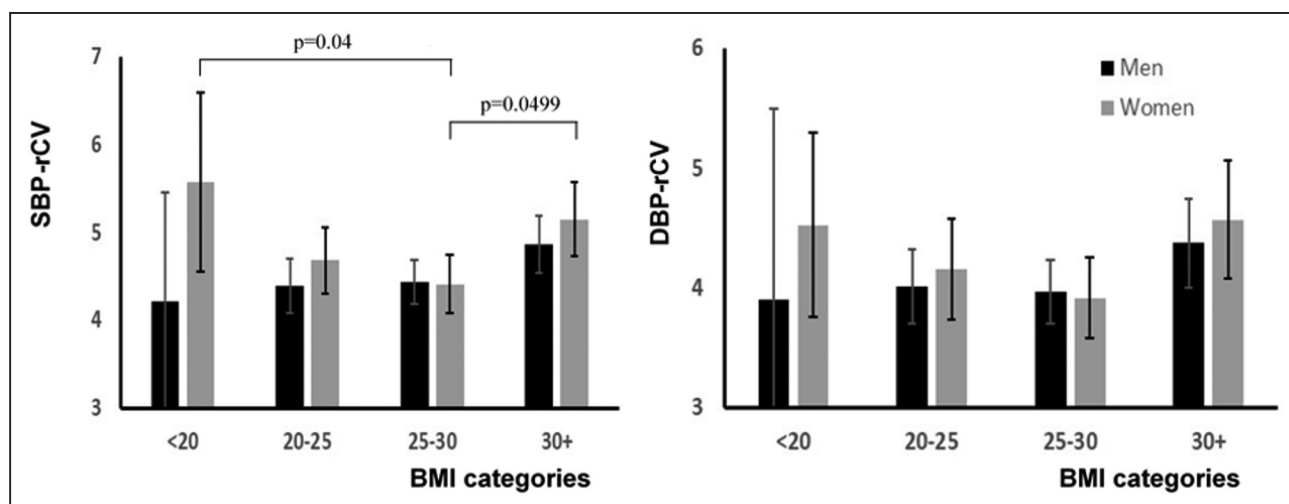


Figure 2. Mean values of residual coefficient of variation (rCV) for systolic blood pressure (SBP) and diastolic blood pressure (DBP), stratified by sex and standard thresholds for body mass index (BMI).

Results are presented as the mean and CI for each group. rCV is calculated as the coefficient of variation of detrended recordings. There is a significant difference between groups for SBP-rCV for women only (ANOVA, $P=0.014$), with significant post hoc tests adjusted for multiple comparisons shown (Tukey test).

DISCUSSION

In an at-risk population with recent transient ischemic attack or minor stroke, beat-to-beat BPV over 5 minutes was associated with increased BMI and arterial stiffness. There was a linear increase in SBPV with BMI in men, but both low and high BMI were associated with increased SBPV in women. PWV and BMI were independently associated with SBPV, but PWV also mediated a proportion of the effect of BMI on SBPV. Associations between current smoking and increased SBPV persisted despite adjustment, but associations between both age and falling DBP were not significant after adjustment for PWV, indicating a likely primary role for arterial stiffness in mediating the relationship between age, DBP, or BMI with beat-to-beat BPV.

Despite the large number of studies demonstrating that visit-to-visit and day-to-day BPV are associated with an increased risk of cardiovascular events,^{1–4,7–9,11,12,18} few studies have determined the prognostic significance of beat-to-beat blood variability,^{15,19} despite its widespread use in the assessment of autonomic function in both research and clinical practice.^{20,21} We previously demonstrated in an earlier report from this population that beat-to-beat BPV was associated with a 47% increased risk of stroke and 37% increased risk of cardiovascular events per SD of beat-to-beat BPV,¹⁵ compared with 24% and 33% for day-to-day BPV. One other study demonstrated that beat-to-beat BPV was increased in acute stroke and associated with poor outcome,^{19,22} albeit with SD as the principle index of BPV, while beat-to-beat BPV was associated with markers of end-organ injury and vascular aging, both in this population¹⁶ and in limited studies in other populations.²³ This was also consistent with limited studies using intra-arterial continuous BP measurements.^{24,25}

However, there is as yet little evidence identifying the determinants and clinical characteristics of patients with increased beat-to-beat BPV. We previously demonstrated in a much smaller sample that beat-to-beat BPV was associated with aortic stiffness and pulsatility, as well as with markers of cardiovascular reactivity,¹⁶ and that SBPV increases with age with an increased skew of the distribution of SBPV in a subset of the population. In this report, increased BMI was the strongest clinical factor associated with increased SBPV. However, the relationship between BMI and SBPV was complex, with a linear association in men. However, in women, there was a U-shaped relationship, with increased SBPV in women with both a reduced and increased BMI compared with normal BMI, consistent with an increased risk of mortality for patients when both overweight and underweight. Although this could reflect physiological variability in women with a reduced BMI that could be beneficial, the marked positive skew of the distribution of SBPV in women with a BMI below 20 suggests that this is not the case, and that the elevation in SBPV is driven by patients with an excess of pathological SBPV, even in women with a reduced BMI. This may reflect increased autonomic instability and sympathetic overactivity in obese patients but could reflect reverse causation, with frailer patients being predisposed both to being underweight and to having increased BPV. Alternatively, elevated SBPV may mediate some of the relationship between obesity or being underweight and cardiovascular risk and represent a new treatment target.

This study confirmed the previously demonstrated association between arterial stiffness and beat-to-beat BPV, with no significant association between age and SBPV after adjustment for PWV. Furthermore, the mediation analysis suggests that it is partly increased arterial

Table 3. Multivariate Associations and Interactions Between BMI and Sex for Variability in SBP and DBP

	Entire population				Stratified by sex			
	SBP		DBP		SBP		DBP	
	β	P value	β	P value	β	P value	β	P value
Model 1					Men			
Age, y	0.02	0.0003†	0.05	0.33	0.02	0.01*	0.05	0.49
Women	0.22	0.11	0.69	0.65
DBP	−0.01	0.046*	−0.07	0.21	−0.01	0.29	−0.05	0.48
Smoking	0.47	0.01*	3.6	0.09	0.39	0.07	3.0	0.23
BMI	0.04	0.003†	0.35	0.02*	0.07	0.0002†	0.49	0.02*
Model 2					Women			
Age, y	0.02	0.0002†	0.06	0.31	0.03	0.004†	0.07	0.43
Women	1.78	0.015*	9.1	0.26
DBP	−0.01	0.03*	−0.07	0.18	−0.02	0.04*	−0.12	0.22
Smoking	0.50	0.01*	3.7	0.08	0.66	0.06	4.9	0.20
BMI	0.07	0.0003†	0.51	0.02*	0.02	0.45	0.2	0.35
BMI×women	−0.06	0.03*	−0.31	0.29
Model 3								
Age, y	0.015	0.06	−0.01	0.88				
Women	2.31	0.01*	1.29	0.21				
DBP	−0.01	0.07	−0.07	0.29				
Smoking	0.60	0.008*	0.47	0.07				
PWV	0.10	0.008*	0.11	0.01*				
BMI	0.06	0.01*	0.029	0.28				
BMI×women	−0.07	0.03*	−0.042	0.27				

β -Coefficients and P values are given from general linear models, adjusted for significant covariates and for the interaction between BMI and sex or stratified by sex. BP variability is measured as the residual coefficient of variation after detrending of data (rCV). BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; PWV, pulse wave velocity; rCV, residual coefficient of variation; and SBP, systolic blood pressure.

* $P < 0.05$, † $P < 0.01$.

stiffness in patients with increased BMI that results in increased SBPV, although this does not explain the increased SBPV in patients with reduced BMI. One possible link between arterial stiffness, increased BMI, and SBPV is an enhanced inflammatory cascade in obesity leading to endothelial dysfunction, increased arterial stiffness and atherosclerosis, and potentially increased SBPV,^{26,27} either directly or indirectly, with recent trials of anti-inflammatory interventions reducing recurrent cardiovascular events,²⁸ independently of mean BP effects.²⁹ This also implies that weight loss in the obese has the potential to reduce cardiovascular morbidity, and stroke in particular, through reductions in arterial stiffness and, therefore, reductions in BPV. Furthermore, given the negative correlation between age and BMI, this supports the hypothesis that the rising incidence of stroke in younger patients, and women in particular, may partly be driven by increasing weight that may partly be mediated by increased SBPV.

There are limitations to our study. First, all patients were assessed after a cerebrovascular event, limiting generalizability to other disease groups. However, this population is at an increased risk of recurrent stroke,³⁰ and

this risk has been shown to be associated with beat-to-beat BPV in this group.¹⁵ Second, 5% of patients did not have adequate recordings, despite repeated measures to improve quality, particularly in elderly patients who may be at a particularly increased risk of stroke. As such, the prevalence of elevated BPV may be underestimated, with consequent underestimation of the risk associated with elevated BPV. Third, we measured beat-to-beat BPV in a highly controlled environment, using expensive equipment. Development of more cost-effective methods would be essential to apply beat-to-beat BPV to routine clinical practice. Fourth, we extensively cleaned and detrended the data, improving precision of measurement but also limiting its direct applicability to clinical practice. As such, further development is required to standardize methods of acquisition, data cleaning, and analysis of beat-to-beat BPV in a practical method for use in clinical practice. Finally, obesity may cause systematic bias in the assessment of PWV through artificially increasing the measured distance between the carotid and femoral applanation sites, while also affecting accuracy of BP measurement.

Overall, beat-to-beat SBPV reflected both age-associated arterial stiffness and changes in BMI. This suggests

a potential role for weight loss to reduce SBPV in the obese, with a resulting reduction in cardiovascular risk, but further research is required in underweight women to determine why SBPV may be increased and whether this is a marker of frailty or an independent treatable factor. Furthermore, it implies that measures that reduce SBPV, such as amlodipine,⁴ may be particularly effective at reducing cardiovascular risk in patients who are overweight or women who are underweight.

CONCLUSIONS

Beat-to-beat BPV reflects increased arterial stiffness and an increased BMI in both sexes and a low BMI in women alone. This may be a potentially modifiable mechanism resulting in the increased risk of cardiovascular events due to increased arterial stiffness and alterations in BMI.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Figures I–IV
Tables I–III

REFERENCES

- Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet*. 2010;375:938–948. doi: 10.1016/S0140-6736(10)60309-1
- Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Sever PS, Poulter NR. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010;375:895–905. doi: 10.1016/S0140-6736(10)60308-X
- Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlöf B, Poulter NR, Sever PS; ASCOT-BPLA and MRC Trial Investigators. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol*. 2010;9:469–480. doi: 10.1016/S1474-4422(10)70066-1
- Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375:906–915. doi: 10.1016/S0140-6736(10)60235-8
- Webb AJ, Fischer U, Rothwell PM. Effects of β -blocker selectivity on blood pressure variability and stroke: a systematic review. *Neurology*. 2011;77:731–737. doi: 10.1212/WNL.0b013e31822b007a
- Webb AJ, Wilson M, Lovett N, Paul N, Fischer U, Rothwell PM. Response of day-to-day home blood pressure variability by antihypertensive drug class after transient ischemic attack or nondisabling stroke. *Stroke*. 2014;45:2967–2973. doi: 10.1161/STROKEAHA.114.005982
- Muntner P, Whittle J, Lynch AJ, Colantonio LD, Simpson LM, Einhorn PT, Levitan EB, Whelton PK, Cushman WC, Louis GT, et al. Visit-to-visit variability of blood pressure and coronary heart disease, stroke, heart failure, and mortality: a cohort study. *Ann Intern Med*. 2015;163:329–338. doi: 10.7326/M14-2803
- Muntner P, Shimbo D, Tonelli M, Reynolds K, Arnett DK, Oparil S. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension*. 2011;57:160–166. doi: 10.1161/HYPERTENSIONAHA.110.162255
- Chiriacò M, Pateras K, Virdis A, Charakida M, Kyriakopoulou D, Nannipieri M, Emdin M, Tsioufis K, Taddei S, Masi S, et al. Association between blood pressure variability, cardiovascular disease and mortality in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2019;21:2587–2598. doi: 10.1111/dom.13828
- Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, Kovesdy CP. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. *J Am Coll Cardiol*. 2016;68:1375–1386. doi: 10.1016/j.jacc.2016.06.054
- Oishi E, Ohara T, Sakata S, Fukuhara M, Hata J, Yoshida D, Shibata M, Ohtsubo T, Kitazono T, Kiyohara Y, et al. Day-to-day blood pressure variability and risk of dementia in a General Japanese Elderly Population: the Hisayama Study. *Circulation*. 2017;136:516–525. doi: 10.1161/CIRCULATIONAHA.116.025667
- Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, McManus RJ. Blood pressure variability and cardiovascular disease: systematic review and meta-analysis. *BMJ*. 2016;354:i4098. doi: 10.1136/bmj.i4098
- Johansson JK, Puukka PJ, Virtanen R, Jula AM. Beat-to-beat, ambulatory hour-to-hour, and home day-to-day variabilities in blood pressure, pulse pressure, and heart rate in comparison with each other and with target-organ damage. *Blood Press Monit*. 2015;20:113–120. doi: 10.1097/MBP.0000000000000101
- Kikuya M, Ohkubo T, Metoki H, Asayama K, Hara A, Obara T, Inoue R, Hoshi H, Hashimoto J, Totsune K, et al. Day-by-day variability of blood pressure and heart rate at home as a novel predictor of prognosis: the Ohasama study. *Hypertension*. 2008;52:1045–1050. doi: 10.1161/HYPERTENSIONAHA.107.104620
- Webb AJ, Mazzucco S, Li L, Rothwell PM. Prognostic significance of blood pressure variability on beat-to-beat monitoring after transient ischemic attack and stroke. *Stroke*. 2018;49:62–67. doi: 10.1161/STROKEAHA.117.019107
- Webb AJ, Rothwell PM. Physiological correlates of beat-to-beat, ambulatory, and day-to-day home blood pressure variability after transient ischemic attack or minor stroke. *Stroke*. 2014;45:533–538. doi: 10.1161/STROKEAHA.113.003321
- Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, et al; Oxford Vascular Study. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet*. 2005;366:1773–1783. doi: 10.1016/S0140-6736(05)67702-1
- Shimbo D, Abdalla M, Falzon L, Townsend RR, Muntner P. Studies comparing ambulatory blood pressure and home blood pressure on cardiovascular disease and mortality outcomes: a systematic review. *J Am Soc Hypertens*. 2016;10:224–234.e17. doi: 10.1016/j.jash.2015.12.013
- Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early

outcome after acute ischemic stroke? *Stroke*. 2000;31:463–468. doi: 10.1161/01.str.31.2.463

20. van Wijnen VK, Finucane C, Harms MPM, Nolan H, Freeman RL, Westerhof BE, Kenny RA, Ter Maaten JC, Wieling W. Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages. *J Intern Med*. 2017;282:468–483. doi: 10.1111/joim.12636
21. Romano SM, Lazzeri C, Chiostrì M, Gensini GF, Franchi F. Beat-to-beat analysis of pressure wave morphology for pre-symptomatic detection of orthostatic intolerance during head-up tilt. *J Am Coll Cardiol*. 2004;44:1891–1897. doi: 10.1016/j.jacc.2004.07.046
22. Eames PJ, Blake MJ, Dawson SL, Panerai RB, Potter JF. Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2002;72:467–472. doi: 10.1136/jnnp.72.4.467
23. Wei FF, Li Y, Zhang L, Xu TY, Ding FH, Wang JG, Staessen JA. Beat-to-beat, reading-to-reading, and day-to-day blood pressure variability in relation to organ damage in untreated Chinese. *Hypertension*. 2014;63:790–796. doi: 10.1161/HYPERTENSIONAHA.113.02681
24. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens*. 1987;5:93–98. doi: 10.1097/00004872-198702000-00013
25. Veerman DP, de Blok K, van Montfrans A. Relationship of steady state and ambulatory blood pressure variability to left ventricular mass and urinary albumin excretion in essential hypertension. *Am J Hypertens*. 1996;9:455–460. doi: 10.1016/0895-7061(95)00437-8
26. Della Corte V, Tuttolomondo A, Pecoraro R, Di Raimondo D, Vassallo V, Pinto A. Inflammation, endothelial dysfunction and arterial stiffness as therapeutic targets in cardiovascular medicine. *Curr Pharm Des*. 2016;22:4658–4668. doi: 10.2174/1381612822666160510124801
27. Tuttolomondo A, Casuccio A, Della Corte V, Maida C, Pecoraro R, Di Raimondo D, Vassallo V, Simonetta I, Arnao V, Pinto A. Endothelial function and arterial stiffness indexes in subjects with acute ischemic stroke: relationship with TOAST subtype. *Atherosclerosis*. 2017;256:94–99. doi: 10.1016/j.atherosclerosis.2016.10.044
28. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). *Eur Heart J*. 2018;39:3499–3507. doi: 10.1093/eurheartj/ehy310
29. Rothman AM, MacFadyen J, Thuren T, Webb A, Harrison DG, Guzik TJ, Libby P, Glynn RJ, Ridker PM. Effects of interleukin-1 β inhibition on blood pressure, incident hypertension, and residual inflammatory risk: a secondary analysis of CANTOS. *Hypertension*. 2020;75:477–482. doi: 10.1161/HYPERTENSIONAHA.119.13642
30. Rothwell PM, Giles MF, Chandratheva A, Marquardt L, Geraghty O, Redgrave JN, Lovelock CE, Binney LE, Bull LM, Cuthbertson FC, et al; Early Use of Existing Preventive Strategies for Stroke (EXPRESS) Study. Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet*. 2007;370:1432–1442. doi: 10.1016/S0140-6736(07)61448-2