Blood Pressure Variability, Arterial Stiffness, and Arterial Remodeling

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The Maastricht Study

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Abstract—Greater very short- to midterm blood pressure variability (BPV) has been associated with an increased cardiovascular disease risk, especially stroke. However, this link remains incompletely understood. We hypothesized that increased arterial stiffness and maladaptive carotid arterial remodeling may underlie this association. We, therefore, investigated the association between very short- to midterm systolic BPV, aortic and carotid stiffness and carotid arterial remodeling using cross-sectional data from The Maastricht Study (aged 60±8 years; 53% men). Aortic (carotid-femoral pulse wave velocity, n=1671) and carotid stiffness (ultrasonography, n=1690) were assessed. A composite index of systolic BPV was derived by standardizing and averaging systolic within-visit, 24-hour, and 7-day BPV. We performed linear regression analyses with adjustment for age, sex, glucose metabolism status, mean arterial pressure, and cardiovascular risk factors. A 1-SD greater systolic BPV was statistically significantly associated with 0.10 m/s (95% CI, 0.01–0.20) greater carotid-femoral pulse wave velocity, but not with carotid distensibility (−0.033×10^{-3}/kPa [−0.255 to 0.190]). In addition, a 1-SD greater systolic BPV was statistically significantly associated with greater carotid circumferential wall tension (0.84 dyne/cm [0.51–1.17]), circumferential wall stress (0.79 kPa [0.031–1.27]), and intima-media thickness (8.6 µm [1.0–16.3]). These results are indicative of maladaptive carotid remodeling, as circumferential wall tension and stress were not normalized despite greater intima-media thickness. In conclusion, greater very short- to midterm BPV is associated with greater aortic stiffness and maladaptive carotid arterial remodeling, but not with carotid stiffness. These findings may explain, at least partially, the increased BPV-associated cardiovascular disease risk, in particular stroke. **(*Hypertension*. 2018;72:1002-1010. DOI: 10.1161/HYPERTENSIONAHA.118.11325.)** • **Online Data Supplement**

Key Words: blood pressure ■ cardiovascular diseases ■ cell proliferation ■ elastin ■ glucose

Greater very short-to midterm blood pressure variability (BPV) has been associated with an increased cardiovascular disease (CVD) risk.[1,2] How BPV and CVD are linked, remains, however, incompletely understood. To provide more focused prevention and intervention strategies of future CVD, it is important to elucidate how BPV may lead to CVD.

It can be hypothesized that greater BPV and CVD are linked via increased arterial stiffness and arterial remodeling. Greater BPV causes greater mechanical stress on the arterial wall, which triggers unfavorable structural changes within the arterial wall (eg, increased extracellular matrix deposition,[3] enhanced vascular smooth muscle cell proliferation,[3] and a reduced elastin-to-collagen ratio[4]). Such changes have been shown to play an important role in the development of greater arterial stiffness.[5]

Indeed, previous studies[6–9] have shown that greater BPV is associated with greater arterial stiffness. However, these studies targeted selected populations[6,7,9] did not (fully) adjust for the use of antihypertensive medication or excluded individuals on antihypertensive medication.[6–9] In addition, most of these studies focused on aortic stiffness,[6,7,9] whereas data on carotid stiffness are scarce,[8] despite the fact that arterial stiffness is not uniformly distributed along the arterial tree and associates differentially with CVD.[10] In addition, none of the above studies examined the association between BPV and arterial remodeling, despite the fact that carotid arterial remodeling may play an important role in the development[11] and rupture of atherosclerotic plaques,[12] and in the pathophysiology of stroke.[13,14] The latter is especially important, as greater BPV has been more strongly associated with stroke than other types of CVD.[2,15,16]

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Therefore, we investigated in a large population-based cohort, the association between, on the one hand, very short- to midterm (ie, within-visit, 24-hour, and 7-day) BPV and, on the other, aortic and carotid stiffness. In addition, we examined the association between very short- to midterm BPV and carotid arterial wall properties indicative of arterial remodeling (ie, interadventitial diameter [IAD], lumen diameter [LD], intima-media thickness [IMT], and circumferential wall tension [CWT] and circumferential wall stress [CWS]).

Methods

Study Design

We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described elsewhere.[17] In brief, the study focuses on the cause, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus (T2D) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2D status, with an oversampling of individuals with T2D, for reasons of statistical efficiency. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent. Data are available from The Maastricht Study for any researcher who meets the criteria for access to confidential data, and the corresponding author may be contacted to request data.

Data Collection

BP Measurements and Determination of BPV

A detailed description of the office, 24-hour ambulatory and 7-day home BP measurements and variability have been reported previously.[18] Briefly, within-visit BPV was calculated as the SD of 3 consecutive office BP measurements, with a 1-minute interval, after 10 minutes of rest. Twenty-four–hour BPV was calculated as the average real variability of BP readings taken every 15 minutes between 08:00 AM and 23:00 PM, and every 30 minutes between 23:00 PM and 08.00 AM. Seven-day BPV was calculated as the SD of home BP measurements taken twice, with a 1-minute interval, each morning and evening, for 7 consecutive days. We calculated a composite index of systolic BPV of within-visit, 24-hour and 7-day BPV, for reasons of statistical efficiency: first, it reduces the biological variability of each individual measure,[19] as we hypothesize that the (patho)physiological mechanisms underlying the positive association between BPV and arterial stiffness overlap. Second, it reduces the chance of a type I error. This approach is justified when the individual measures within a composite index all associate in the same direction with the outcome.[20] The individual measures were standardized into *z* scores, which were calculated according to the formula: (individual value / population mean) / population SD. The individual measures were then summed and averaged to form the composite index of systolic BPV.

Arterial Stiffness Measurements

All measurements were done by trained vascular technicians unaware of the participants' clinical or diabetes mellitus status, in a dark, quiet temperature-controlled room (21°C–23°C), as described previously.[21,22] Participants were asked to refrain from smoking and drinking coffee or tea or alcoholic beverages 3 hours before the study. Participants were allowed to have a light meal (breakfast or lunch). All measurements were performed in supine position after 10 minutes of rest. Talking or sleeping was not allowed during the examination. During the vascular measurements (≈45 minutes), brachial systolic, diastolic, and mean arterial pressure (MAP) were determined every 5 minutes with an oscillometric device (Accutorr Plus, Datascope Inc, Montvale, NJ). The mean MAP and heart rate during these measurements were used in the statistical analysis. A 3-lead ECG was recorded continuously during the measurements to facilitate automatic signal processing.

Carotid-Femoral Pulse Wave Velocity

Carotid-femoral pulse wave velocity (cfPWV) was determined according to international guidelines[23] with the use of applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). Pressure waveforms were determined at the right common carotid arteries and right common femoral arteries. Difference in the time of pulse arrival from the R-wave of the ECG between the 2 sites (transit time) was determined with the intersecting tangents algorithm. The pulse wave travel distance was calculated as 80% of the direct straight distance (measured with an infantometer) between the 2 arterial sites. The median of 3 consecutive cfPWV (defined as traveled distance/transit time) recordings was used in the analyses.

Local Carotid Arterial Properties

Measurements were done at the left common carotid artery (10-mm proximal to the carotid bulb), with the use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, The Netherlands). This setup enables the measurement of diameter, distension, and IMT as described previously.[21,22] Briefly, during the ultrasound measurements a B-mode image on the basis of 19 M-lines was depicted on screen, and an online echo-tracking algorithm showed real-time anterior and posterior arterial wall displacements. The M-mode recordings were composed of 19 simultaneous recordings at a frame rate of 498 Hz. The distance between the M-line recording positions was 0.96 mm; thus, a total segment of 18.24 mm of each artery was covered by the scan plane. For offline processing, the radiofrequency signal was fed into a dedicated PC-based acquisition system (ART.LAB, Esaote Europe B.V. Maastricht, The Netherlands) with a sampling frequency of 50 MHz. Data processing was performed in MatLab (version 7.5, Mathworks, Natick, MA). The distension waveforms were obtained from the radio frequency data with the use of a wall track algorithm.[21] Carotid IMT was defined as the distance of the posterior wall from the leading edge interface between lumen and intima to the leading edge interface between media and adventitia.[22] The median diameter, distension, and IMT of 3 measurements were used in the analyses.

Local arterial elastic properties were quantified by calculating the following indices[24]:

- Distensibility coefficient (DC)

$$DC = (2\Delta D * IAD + \Delta D^2) / \left(PP * IAD^2\right) \quad \left(10^{3}\ kPa^{-1}\right)$$

- Compliance coefficient (CC)

$$CC = \pi * (2IAD * \Delta D + \Delta D^2) / 4PP \quad \left(mm^2\ kPa^{-1}\right)$$

- Young's elastic modulus (YEM)

$$YEM = IAD / \left(IMT * DC\right) \quad \left(10^{3}\ kPa\right)$$

where IAD is interadventitial arterial diameter; ΔD, distension; IMT, intima-media thickness; and PP, brachial pulse pressure (calculated as systolic BP minus diastolic BP).

DC represents arterial distensibility; CC. arterial buffering capacity; and YEM, the stiffness of the arterial wall material at operating pressure. As carotid arterial remodeling indices, IAD, LD, IMT, CWT, and CWS were used. Carotid LD was calculated as LD (μm)=IAD−(2×IMT). CWT and CWS were derived according to Laplace ($T=P_t \times r$, where T is tension, P_t is transmural pressure, and r is the carotid lumen radius) and the Lamé equation ($\sigma=P_t \times r/h$, where σ denotes stress and h is carotid wall thickness [in this study approximated by the carotid IMT]), respectively. We determined the pulsatile

CWT and CWS as follows: CWT (dyne/cm)=PP_{car}×(LD/2), and CWS (kPa)=CWT/IMT, where PP_{car} is local carotid pulse pressure, which was estimated by calibrating the systolic-diastolic amplitude of the carotid artery tonometry waveform $(sys\text{-}dias)_{tono}$ to pressure, assuming a constant difference between MAP and diastolic BP along the large arteries: $PP_{car}=(sys\text{-}dias)_{tono}*(MAP\text{-}diastolic\ BP)_{brachial}/(mean\text{-}dias)_{tono}$.[25,26] We considered carotid arterial remodeling maladaptive when, despite appropriate changes in IAD, LD and IMT, CWT, and CWS remained elevated.[27]

Reproducibility

Reproducibility was assessed in 12 individuals (6 men; 60.8±6.8 years; 6 T2D) who were examined by 2 observers at 2 occasions spaced 1 week apart. The intra- and interobserver intraclass correlation coefficients were for cfPWV, 0.87 and 0.69; for carotid DC, 0.85 and 0.73; for carotid CC, 0.95 and 0.72; for carotid YEM, 0.72 and 0.71.

Covariates

Alcohol consumption, smoking status, history of CVD, and moderate-to-vigorous physical activity were assessed by questionnaire. Alcohol consumption was defined as nonconsumer, low-consumer (≤7 alcoholic drinks/week for women; ≤14 alcoholic drinks/week for men) or high-consumer (>7 alcoholic drinks/week for women; >14 alcohol drinks/week for men). Smoking status was categorized into never, former, and current smoker. Body mass index (BMI), waist circumference, total cholesterol, HDL (high-density lipoprotein) cholesterol, LDL (low-density lipoprotein) cholesterol, triglycerides, fasting plasma glucose, postload glucose, and glycated hemoglobin (HbA1c) were determined as described elsewhere.[17] Glucose metabolism status was categorized into normal glucose metabolism, prediabetes mellitus (impaired fasting glucose and impaired glucose tolerance) and T2D, according to the World Health Organization 2006 criteria.[28] Estimated glomerular filtration rate was computed with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula, using serum creatinine and cystatin C.[29] Information on the use of lipid-modifying and antihypertensive medication, that is, generic names, doses, and frequencies, were collected during an interview. The presence of hypertension was defined as an office systolic BP of 140 mm Hg or higher, an office diastolic BP of 90 mm Hg or higher, or the use of antihypertensive medication.

Statistical Analysis

All data were analyzed using IBM SPSS software version 23.0 for Windows (IBM Corp, Somers, NY). Data are presented as n (%), mean±SD, or median [interquartile range]. Associations between composite systolic BPV, and cfPWV, carotid stiffness (DC), and carotid arterial remodeling indices were examined with the use of multiple linear regression models. Model 1 was adjusted for age, sex, and glucose metabolism status (entered as an ordinal variable, ie, as normal glucose metabolism status, prediabetes mellitus, and T2D); model 2 was additionally adjusted for 24-hour ambulatory MAP; and model 3 was additionally adjusted for smoking behavior, alcohol use, body mass index, estimated glomerular filtration rate, total cholesterol-to-HDL cholesterol ratio, lipid-modifying medication, and antihypertensive medication classes (β-blockers, calcium channel blockers, ACE inhibitors, angiotensin II receptor blockers, and nonloop diuretics separately). Although MAP and BPV may be correlated, we found no evidence of multicollinearity (ie, the CIs did not diverge, the effect sizes did not change unexpectedly, and all variance inflation factors were <2.0). Several additional analyses were performed. First, we investigated the associations between composite systolic BPV and other carotid stiffness indices (CC and YEM). Second, we included interaction terms in the fully adjusted models to examine whether any significant associations were modified by age, sex, glucose metabolism status, or the presence of hypertension. Regardless of significant interaction, we (1) stratified according to the presence of hypertension for the purpose of comparing our results to previous studies,[7–9] (2) excluded individuals with (pre)diabetes mellitus because of our oversampling strategy, and (3) excluded individuals who used antihypertensive medication. Second, we additionally adjusted for potential confounders prior CVD, moderate-to-vigorous physical activity, and other glycemic indices (ie, fasting plasma glucose, 2-hour postload glucose, and HbA1c). Fourth, we performed a multiple logistic regression analysis, using the same models as stated earlier, with 10 m/s cfPWV as the cutoff value for high/low cfPWV, according to international consensus.[23] Fifth, we investigated the associations between the individual indices of BPV (ie, within-visit, 24-hour [additionally separated into day and night], and 7-day BPV) with cfPWV, the indices of carotid arterial stiffness and carotid arterial remodeling. Finally, we examined the associations between the composite of diastolic BPV, cfPWV, and the indices of carotid stiffness and carotid arterial remodeling. A 2-sided P-value of <0.05 was considered statistically significant, except for the interaction analyses, where we used P<0.10.

Results

Characteristics of the Study Population

From the initial 3451 participants, 41 participants with other types of diabetes mellitus than T2D were excluded. Of the remaining 3410 participants, data were missing or inadequate on within-visit, 24-hour, and 7-day BPV for 8, 548, and 1015 participants, respectively. Subsequently, we divided the population in those with complete cfPWV data and those with complete data on carotid arterial properties. With regard to cfPWV, of the remaining 2015 participants, cfPWV was available in 1735 participants. Data on key covariates were missing in 64 participants. Hence, the final cfPWV study population consisted of 1671 participants (Figure). With regard to carotid arterial properties, of the remaining 2015 participants, carotid arterial stiffness was available in 1758 participants. Key covariates were missing in 68 participants. Hence, the final carotid stiffness study population consisted of 1690 participants (Figure). The characteristics of the included versus excluded participants because of missing data were similar (Tables S1 and S2 in the online-only Data Supplement).

Table 1 shows the clinical characteristics of the carotid arterial properties study population according to tertiles of composite systolic BPV (tertile 1: lowest BPV). In general, participants with the highest as compared with the lowest BPV were older, had a higher body mass index, had more often T2D. In addition, they had lower estimated glomerular filtration rate, and higher office, 24-hour, and 7-day BPs, and more often used antihypertensive medication. Participants with highest as compared with lowest BPV had higher levels of cfPWV, and with regard to carotid stiffness measurements, had lower levels of CC and DC, and a higher level of YEM. The characteristics of the cfPWV study population were similar (Table S3).

BPV, Aortic and Carotid Stiffness

After adjustment for age, sex, and glucose metabolism status (model 1), and 24-hour mean ambulatory BP (model 2), a 1 SD greater composite index of systolic BPV was associated with statistically significantly higher cfPWV (regression coefficient [β] and 95% CI: 0.12 m/s [0.01–0.20]; Table 2). After additional adjustment for smoking behavior, alcohol use, body mass index, total cholesterol-to-HDL cholesterol ratio, lipid-modifying medication, estimated glomerular filtration rate, and antihypertensive medication (model 3),

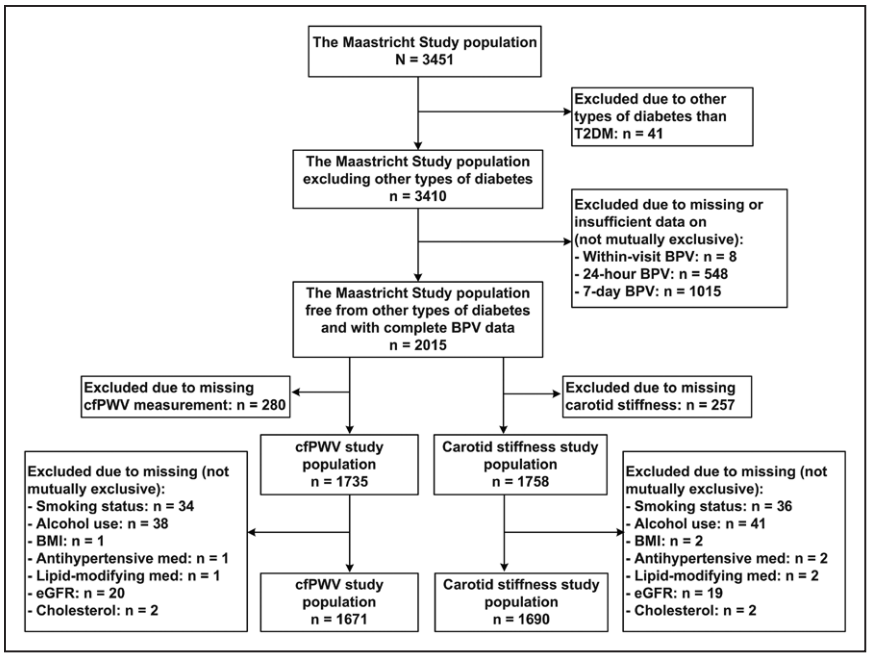

Figure. Flow diagram delineating the derivation of the study populations with available data on carotid-femoral pulse wave velocity (cfPWV) and carotid arterial properties. BMI indicates body mass index; BPV, blood pressure variability; eGFR, estimated glomerular filtration rate; and T2DM, type 2 diabetes mellitus.

the association remained statistically significant (0.10 m/s [0.01–0.20]).

After adjustment for the covariates of model 1, a 1 SD greater composite index of systolic BPV was associated with statistically significantly greater carotid stiffness, that is, a lower DC (-0.470×10^{-3}/kPa [−0.690 to −0.251]; Table 2). After additional adjustment for the covariates of the model 3, the association did not remain statistically significant (-0.033×10^{-3}/kPa [−0.255 to −0.190]), where the most important confounders were age (explained 46% of the effect between BPV and carotid stiffness) and 24-hour mean ambulatory BP (explained 19% of the effect).

BPV and Carotid Artery Remodeling Indices

A 1 SD greater composite index of systolic BPV was associated with statistically significantly greater IAD (101.7 µm [60.9–142.5]), LD (58.1 µm [21.3–94.9]), IMT (21.6 µm [14.3–28.8]), CWT (1.99 dyne/cm [1.65–2.32]), and CWS (1.38 kPa [1.02–1.74]; Table 3 [crude model]). After additional adjustment for the covariates of model 3, the association with IAD (−0.2 µm [−37.3 to 37.0]) and LD (−17.8 µm [−52.2 to 16.5]) did not remain, whereas the associations with IMT (8.6 µm [1.0–16.3]), CWT (0.84 dyne/cm [0.51–1.17]), and CWS (0.79 kPa [0.031–1.27]) did. In terms of effect sizes, the effect size of systolic BPV on CWT and CWS was ≈3.5 to 4× greater than that of mean BP (for CWT 0.22 dyne/cm [0.17–0.26], for CWS 0.22 kPa [0.16–0.29]).

Additional Analyses

After adjustment for the covariates of model 3, a 1 SD greater BPV was not significantly associated with carotid CC −0.002 mm^2/kPa (−0.015 to 0.011) and YEM -0.004×10^3 kPa (−0.021 to 0.013; Table S4).

Age, sex, glucose metabolism status, and hypertension did not significantly modify the associations between BPV, and aortic stiffness and carotid arterial remodeling indices (all *P* values >0.22). Nonetheless, when we stratified according to the presence of hypertension, or when we restricted the analyses to individuals without (pre)diabetes mellitus or those who did not use antihypertensive medication, the results did not materially change (Tables S5 and S6).

When we additionally adjusted for moderate-to-vigorous physical activity, prior CVD, or other glycemic indices (ie, fasting plasma glucose, 2-hour postload glucose, and HbA1c), the associations were not materially changed (Tables S7 through S10).

If we used 10 m/s as a cutoff value for high/low cfPWV, we found that, after adjustment for the covariates of model 3, for every 1 SD greater composite index of systolic BPV, the odds of having a high cfPWV, as opposed to low cfPWV, was 1.20 (95% CI, 1.06–1.37; Table S11).

When we analyzed the associations between the individual indices of systolic BPV, that is, within-visit, 24-hour, and 7-day BPV, with cfPWV, we observed that, after adjustment for the covariates of model 3, a 1 SD (1.82 mm Hg) greater 7-day systolic BPV was statistically significantly associated with cfPWV (0.101 m/s [0.011–0.192]), whereas within-visit (0.081 m/s [−0.010 to 0.172]) and 24-hour BPV (−0.008 m/s [−0.109 to 0.093]) were not. In addition, we observed that, after adjustment for the covariates of model 3, none of the associations between the individual indices of systolic BPV and carotid stiffness indices were statistically significant. After adjustment for the covariates of model 3, similar results were seen in the individual indices of systolic BPV as compared with the associations with composite systolic BPV, except that the associations between within-visit, 7-day BPV, and carotid IMT, and 24-hour BPV and CWS were not statistically significant. When we separated 24-hour BPV into day and night, we found that the results with aortic and carotid stiffness did not materially differ. However, day BPV was associated with maladaptive carotid arterial remodeling, whereas nocturnal BPV was not (Tables S12 through S14)

Table 1. Clinical Characteristics of the Study Population With Data on Carotid Arterial Properties According to Tertiles of BPV

Characteristic	Entire Population n=1690	Tertiles of Composite Systolic BPV		
		Tertile 1 (Low) n=563	Tertile 2 (Middle) n=564	Tertile 3 (High) n=563
Demographics				
Age, y	60.1±8.1	57.8±8.7	60.5±7.4	61.9±7.6
Men	896 (53%)	313 (55.6%)	290 (51.4%)	293 (52.0%)
History of cardiovascular disease*	288 (17.0%)	81 (14.6%)	102 (18.2%)	105 (19.2%)
Cardiovascular risk factors				
BMI, kg/m^2	26.9±4.2	26.1±4.1	27.0±4.2	27.7±4.3
Waist circumference, cm*	95.7±13.2	93.2±13.1	95.7±13.0	98.2±13.2
Glucose metabolism status				
Normal glucose metabolism	952 (56.3%)	374 (66.4%)	323 (57.3%)	255 (45.3%)
Prediabetes mellitus	250 (14.8%)	74 (13.1%)	87 (15.4%)	89 (15.8%)
Type 2 diabetes mellitus	488 (28.9%)	115 (20.4%)	154 (27.3%)	219 (38.9%)
Fasting plasma glucose, mmol/L				
Normal glucose metabolism	5.2±0.4	5.1±0.4	5.2±0.4	5.2±0.4
Prediabetes mellitus	5.9±0.6	6.0±0.6	5.8±0.6	5.9±0.6
Type 2 diabetes mellitus	7.9±2.0	7.9±2.2	7.7±1.6	7.9±2.1
HbA1c (mmol/mol)*				
Normal glucose metabolism	36.5±3.6	36.1±3.6	36.8±3.8	36.7±3.4
Prediabetes mellitus	38.8±4.4	38.5±5.0	38.9±4.4	38.8±4.0
Type 2 diabetes mellitus	51.5±11.2	50.1±10.1	50.9±9.6	52.7±12.7
Total cholesterol, mmol/L	5.2±1.2	5.2±1.1	5.2±1.2	5.3±1.2
HDL cholesterol, mmol/L	1.5±0.5	1.5±0.5	1.5±0.4	1.5±0.4
LDL cholesterol, mmol/L	3.1±1.0	3.1±1.0	3.1±1.0	3.1±1.1
Triglycerides, mmol/L	1.20 (0.88–1.69)	1.12 (0.83–1.49)	1.21 (0.86–1.72)	1.30 (0.96–1.82)
Total-to-HDL cholesterol ratio	3.7±1.2	3.6±1.2	3.7±1.1	3.8±1.2
eGFR, mL/min per 1.73 m2	87.9±14.9	89.1±14.7	87.5±14.3	85.9±15.5
Lifestyle variables				
Smoking behavior				
Never	581 (34.4%)	224 (39.8%)	161 (28.5%)	196 (34.8%)
Former	898 (53.1%)	272 (48.3%)	324 (57.4%)	302 (57.4%)
Current	211 (12.5%)	67 (11.9%)	79 (14.0%)	65 (11.5%)
Alcohol consumption				
None	319 (18.9%)	89 (15.8%)	114 (20.2%)	116 (20.6%)
Low	931 (55.1%)	347 (61.6%)	300 (53.2%)	284 (50.4%)
High	440 (26.0%)	127 (22.6%)	150 (26.6%)	163 (29.0%)
Medication				
Use of antihypertensive medication	664 (39.3%)	164 (29.7%)	211 (37.4%)	286 (50.8%)
β-Blockers	289 (17.1%)	68 (12.1%)	92 (16.3%)	129 (22.9%)
Calcium channel blockers	162 (9.6%)	50 (8.9%)	54 (9.6%)	58 (10.3%)
ACE inhibitors	213 (12.6%)	39 (6.9%)	70 (12.4%)	104 (18.5%)
Angiotensin II receptor blockers	290 (17.2%)	74 (13.1%)	99 (17.6%)	117 (20.8%)
Diuretics	269 (15.9%)	58 (10.3%)	91 (16.1%)	120 (21.3%)
Lipid-modifying medication	619 (36.6%)	177 (31.4%)	201 (35.6%)	241 (42.8%)

(*Continued*)

Table 1. Continued

Characteristic	Entire Population n=1690	Tertiles of Composite Systolic BPV		
		Tertile 1 (Low) n=563	Tertile 2 (Middle) n=564	Tertile 3 (High) n=563
BP measurements				
Office SBP, mm Hg	134.9±18.3	127.4±15.0	134.1±17.8	143.3±18.3
Office DBP, mm Hg	76.1±9.9	73.8±9.2	75.8±9.9	78.8±10.1
Twenty-four–hour SBP, mm Hg	120.0±11.6	116.4±9.2	119.6±11.0	124.5±12.8
Twenty-four–hour DBP, mm Hg	74.3±7.1	72.9±6.2	74.1±6.9	75.9±7.7
Seven-day home SBP, mm Hg	127.7±13.7	120.8±10.5	127.0±12.4	135.2±13.9
Seven-day home DBP, mm Hg	77.4±8.3	75.3±7.3	77.3±7.9	79.7±9.1
BPV parameters				
Within-visit systolic BPV, mm Hg	4.6±2.8	2.8±1.5	4.4±2.0	6.7±3.2
Twenty-four–hour systolic BPV, mm Hg	10.0±2.5	8.2±1.4	9.9±1.6	12.0±2.6
Seven-day systolic BPV, mm Hg	9.3±3.9	6.9±1.7	8.9±2.3	12.2±4.9
Arterial parameters				
Aortic stiffness				
cfPWV, m/s†	9.0±2.2	8.5±2.0	9.0±2.2	9.6±2.1
Carotid ultrasound measurements				
Compliance coefficient, mm^2/kPa	0.69±0.27	0.73±0.28	0.68±0.27	0.65±0.26
Distensibility coefficient, 10^{-3}/kPa	14.3±5.1	15.6±5.2	13.9±5.0	13.2±4.7
Young's elastic modulus, 10^3 kPa	0.75±0.4	0.68±0.31	0.78±0.36	0.80±0.39
Lumen diameter, μm	6125.0±781.8	6043.3±739.7	6170.9±814.9	6160.9±783.9
Intima-media thickness, μm	855.4±155.3	829.6±142.2	855.8±161.5	880.8±157.5
Wall-to-lumen ratio, %	14.2±3.1	13.9±2.6	14.1±3.2	14.5±3.4
Circumferential wall tension, dyne/cm	20.4±7.3	18.4±6.4	20.3±6.7	22.7±7.6
Circumferential wall stress, kPa	24.4±9.5	22.6±7.9	24.4±10.4	26.5±9.6

Data are presented as n (%), mean±SD, or median [interquartile range]. ACE indicates angiotensin-converting enzyme; BMI, body mass index; BPV, blood pressure variability; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c (glycated hemoglobin); HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SBP, systolic BP.

*Data were available in n=1660 (history of cardiovascular disease), n=1689 (waist circumference), n=1684 (HbA1c).

†Data shown for cfPWV study population, n=1671.

When we analyzed the associations between the composite index of diastolic BPV, and aortic and carotid stiffness, none of the associations were significant. In addition, after adjustment of the covariates of model 3, the composite index of diastolic BPV was statistically significantly associated with CWT, but not with IAD, LD, IMT, and CWS (Tables S15 and S16).

Table 2. Associations of Composite Systolic BPV With Aortic and Carotid Stiffness

BPV Variable	Model	Aortic Stiffness (cfPWV [m/s]) β (95% CI)	Carotid Stiffness (DC [10^{-3}/kPa]) β (95% CI)
Composite of systolic BPV	Crude	0.49 (0.39 to 0.59)*	−1.043 (−1.277 to −0.809)*
	1	0.26 (0.16 to 0.35)*	−0.470 (−0.690 to −0.251)*
	2	0.11 (0.01 to 0.20)*	−0.088 (−0.310 to 0.134)
	3	0.10 (0.01 to 0.20)*	−0.033 (−0.255 to 0.190)

Regression coefficient (β) represents the increase in carotid-femoral pulse wave velocity in m/s or increase in carotid distensibility coefficient in 10^{-3}/kPa per 1 SD increase of composite systolic BPV. Model 1 adjusted for age, sex, and glucose metabolism status; model 2 additionally adjusted for 24-h mean ambulatory BP; model 3 additionally adjusted for smoking behavior, alcohol use, body mass index, total-to-high density lipoprotein cholesterol ratio, lipid-modifying medication, estimated glomerular filtration rate, and antihypertensive medication. BPV indicates blood pressure variability; cfPWV, carotid-femoral pulse wave velocity; and DC, distensibility coefficient.

*$P<0.05$.

Table 3. Associations of Composite Systolic BPV With Carotid LD, IMT, and CWS

		Carotid Artery Remodeling Indices				
		IAD, μm	LD, μm	IMT, μm	CWT, dyne/cm	CWS, kPa
BPV Variable	Model	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Composite of systolic BPV	Crude	101.7 (60.9 to 142.5)*	58.1 (21.3 to 94.9)*	21.6 (14.3 to 28.8)*	1.99 (1.65 to 2.32)*	1.82 (1.36 to 2.27)*
	1	45.9 (9.9 to 81.7)*	21.6 (–11.7 to 54.8)	12.1 (4.9 to 19.3)*	1.36 (1.04 to 1.68)*	1.52 (1.05 to 1.98)*
	2	13.1 (–24.0 to 50.3)	–5.7 (–40.3 to 28.8)	9.2 (1.7 to 16.7)*	0.87 (0.55 to 1.20)*	0.85 (0.37 to 1.33)*
	3	–0.2 (–37.3 to 37.0)	–17.8 (–52.2 to 16.5)	8.6 (1.0 to 16.3)*	0.84 (0.51 to 1.17)*	0.79 (0.31 to 1.27)*

Regression coefficient (β) represents the increase in carotid remodeling indices per 1 SD increase of composite systolic BPV. Model 1 adjusted for age, sex, and glucose metabolism status; model 2 additionally adjusted for 24-h mean ambulatory BP; model 3 additionally adjusted for smoking behavior, alcohol use, body mass index, total-to-high density lipoprotein cholesterol ratio, lipid-modifying medication, estimated glomerular filtration rate, and antihypertensive medication. BPV indicates blood pressure variability; CWS, circumferential wall stress; CWT, circumferential wall tension; IAD, interadventitial diameter; IMT, intima-media thickness; and LD, lumen diameter.

*$P<0.05$.

Discussion

Our study had 2 main findings. First, very short- to midterm systolic BPV was significantly associated with aortic stiffness, to the extent that a 1 SD greater systolic composite index of BPV was associated with 0.101 m/s higher cfPWV. In terms of vascular aging, this modest increase in cfPWV is comparable to the effect of only 1 additional year of vascular aging.[30] This suggests that other mechanisms than greater arterial stiffness play a role in linking greater BPV with CVD. Second, very short- to midterm systolic BPV was not associated with carotid stiffness. However, with regard to the indices of carotid arterial remodeling, greater very short- to midterm systolic BPV was associated with greater carotid IMT, CWT, and CWS. These findings thereby suggest that, despite the absence of any association with carotid stiffness, the process of arterial remodeling in the carotid artery in the context of greater BPV is maladaptive: despite wall thickening (greater IMT), wall tensile stress did not normalize (CWT and CWS remained elevated).[27,31] To the best of our knowledge, this is the first study that reports on the association between greater BPV and maladaptive carotid arterial remodeling. The latter is important because of its link with stroke, as an elevated CWT is more often seen in the carotid arteries of the affected side of stroke patients.[13] Taken together, our results show that greater very short- to midterm BPV is associated with greater aortic stiffness and greater carotid CWS and CWT, and may thereby, at least partially, explain the increased BPV-associated CVD risk, especially stroke.

Our findings about the association between BPV and aortic stiffness are in accordance with previous studies.[6,7,9] Similar (small) effects of BPV on arterial stiffness (measured as cfPWV) were observed in studies performed by Schillaci et al[7] and Wei et al[9] wherein untreated hypertensive patients were included, whereas our study was population-based and very well controlled with regard to hypertension. This may imply that, despite well-controlled BPs, the detrimental effects of greater BPV on aortic stiffness are still present. Three Japanese studies also investigated the association between BPV and brachial-ankle PWV and have shown comparable effects, ranging from a 0.062 m/s to a 0.23 m/s increase in brachial-ankle PWV per unit increase in systolic BPV.[32–34] Hence, the results of previous studies and the current study suggests that greater BPV is associated with greater arterial stiffness as determined by cfPWV and brachial-ankle PWV, but that the magnitude of the detrimental effects of greater BPV on aortic stiffness is relatively modest.

Only 1 previous study examined the relationship between BPV and carotid artery stiffness. In contrast to our results, Tedla et al[8] found within the MESA (Multiethnic Study of Atherosclerosis), in individuals without hypertension, a statistically significant (small) effect, that is, for every 1 mm Hg increase in systolic BPV, the DC decreased by 0.73% (ie, 0.225×10^{-3}/kPa) and YEM increased by 2.86% (ie, 0.009×10^{3} kPa), compared with baseline over a period of 10 years. When we restrict our analyses to individuals without hypertension, our results show similar effect sizes but are hampered by a loss of statistical power.

Our study may support the stress fatigue theory,[35,36] which states that a greater pulsatile stress causes greater deterioration of the elastin component of the arterial wall than steady stress. Accordingly, we observed that very short- to midterm BPV (ie, pulsatile stress) had a 3.5 to 4× greater effect on carotid CWT and CWS than mean BP (ie, steady stress). Our study, therefore, suggests that greater BPV may be a more important factor than mean BP in the process of maladaptive arterial remodeling.

The discrepancy in our findings may be explained by the difference in the arterial wall structure of the aorta (ie, mixed muscular and elastic) and carotid artery (ie, elastic). According to the stress fatigue theory, the carotid arteries are more susceptible to pulsatile damage and indeed, when we look at the age- and sex-adjusted model (ie, model 1) in Table 2, we found that greater BPV is statistically significantly associated with lower carotid DC. However, when MAP was entered in model 2, the association attenuated. This may suggest that greater MAP damaged the elastin components of the carotid arterial wall already in such a way that the effects greater BPV could not add any more. This is further demonstrated by the fact that the effect of greater BPV on carotid DC was more prominent in individuals without hypertension (where the elastin component is still intact) than in individuals with hypertension (where the elastin component has already been damaged).

Because of the cross-sectional design of our study, we cannot exclude reverse causality, that is, we hypothesized that

greater BPV damages the arterial wall, leading to arterial stiffening. However, the reverse may also be true. For instance, greater carotid arterial stiffness may reduce the arterial baroreceptor sensitivity by limiting the stretch of the baroreceptors, which plays an important role to maintain constant levels of BP, and thus lead to greater BPV.[37,38] Indeed, both hypotheses may be true at the same time, which then leads to a vicious cycle of greater very short- to midterm BPV and greater arterial stiffness. In addition, this may also explain the stronger association between day BPV with maladaptive carotid arterial remodeling than with nocturnal BPV. Indeed, external stimuli during the day, such as physical activity during the day,[39] may increase day BPV, causing greater arterial stiffness and vice versa.

Our study had some further limitations. First, our study consisted only of whites, which may limit the generalizability of our results. Second, the use of a composite BPV score assumes that all BPV indices share the same underlying (patho)physiological mechanism and contribute similarly to greater arterial stiffness, which may not necessarily be true.[39] However, when we performed the analyses for the BPV indices separately, we found that the 95% CIs of all estimates overlapped, suggesting that the different BPV indices indeed share the same underlying (patho)physiological mechanism. Third, given the design of our study, we were unable to study the effect of long-term (ie, visit-to-visit) BPV on aortic and carotid stiffness and carotid arterial remodeling. Fourth, the SD and average real variability may be dependent on the overall BP levels, which could be problematic when both are entered into the same model.[40] However, when we did so, we did not detect problems with regard to multicollinearity.

Perspectives

Greater very short- to midterm BPV is associated with moderately greater aortic stiffness, but not with carotid stiffness. In addition, greater very short- to midterm BPV associates with maladaptive carotid arterial remodeling, as shown by elevated CWT and CWS despite greater IMT. Taken together, these findings may, at least partially, explain the increased BPV-associated CVD risk, in particular, stroke. Our findings suggest that lowering BPV, next to lowering mean BP,[41] could be meaningful in preventing arterial stiffening and maladaptive carotid arterial remodeling and subsequent (incident) CVD, especially stroke. However, future studies should investigate how greater BPV and CVD are linked via other mechanisms than arterial stiffness, as greater arterial stiffness explains a small part of this link. Additionally, future research should include dedicated randomized controlled trials to lowering BPV and investigate whether any subsequent reduction in CVD risk is mediated by lower arterial stiffness and maladaptive carotid arterial remodeling.

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Disclosures

None.

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Novelty and Significance

What Is New?

- To provide more focused prevention and intervention strategies for future cardiovascular disease (CVD), it is important to elucidate how blood pressure variability (BPV) may lead to CVD, we investigated the association between very short- to midterm BPV, aortic and carotid stiffness, and carotid arterial remodeling.

What Is Relevant?

- Greater aortic stiffness and maladaptive carotid remodeling in the context of greater very short- to midterm BPV may partially explain the increased BPV-associated CVD risk, especially stroke.
- The detrimental effects of greater very short- to midterm BPV on arterial stiffness remained, despite well-controlled hypertension in our population-based cohort.

Summary

Greater very short- to midterm BPV is associated with moderately greater aortic stiffness, but not with carotid stiffness. In addition, greater BPV associates with maladaptive carotid arterial remodeling, as shown by elevated circumferential wall tension and circumferential wall stress despite greater intima-media thickness. Taken together, these findings may partially explain the increased BPV-associated CVD risk, in particular, stroke. Our findings may suggest that lowering BPV, next to lowering mean BP, could prevent arterial stiffening and subsequent CVD.