Arterial Stiffness Is Associated With Basal Ganglia Enlarged Perivascular Spaces and Cerebral Small Vessel Disease Load

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Background and Purpose—We assessed whether the load of cerebral small vessel disease (cSVD) and its individual markers, including lacunes, white matter hyperintensities, microbleeds, and enlarged perivascular spaces (EPVS), are associated with arterial stiffness.

Methods—We evaluated cSVD markers in a cohort of 782 hypertensive individuals without history of stroke or dementia. The load of the disease was calculated using an ordinal scale ranging from 0 to 4 (1 point was given for each of the 4 markers examined). The arterial stiffness was tested by measuring the carotid–femoral pulse wave velocity with an oscillometric automatic device.

Results—The mean age of the participants (49.6% women) was 62.7±5.4 years, and the mean systolic/diastolic blood pressure was 142.9/77.3 mm Hg (55.5% of the participants had poor blood pressure control). We found 7.2% cases with lacunes, 6.4% with microbleeds, 6.7% with extensive white matter hyperintensities, 24.5% with extensive basal ganglia EPVS, and 40.1% with extensive EPVS in the centrum semiovale. Regarding the cSVD load, 19.7% of the participants scored 1, 6.5% scored 2, and 1.4% scored ≥3. The median carotid–femoral pulse wave velocity was 10.5 m/s (interquartile range, 9.2–11.9) and was associated with lacunes (odds ratio per carotid–femoral pulse wave velocity SD increase, 1.51; 95% confidence interval, 1.13–2.03), extensive basal ganglia EPVS (odds ratio, 1.39; 95% confidence interval, 1.16–1.67), and cSVD load (common odds ratio, 1.42; 95% confidence interval, 1.19–1.68).

Conclusions—We found that, in a cohort of hypertensive individuals, the arterial stiffness is associated with the total load of the cSVD, especially with lacunes and basal ganglia EPVS. **(*Stroke*. 2018;49:1279-1281. DOI: 10.1161/STROKEAHA.118.020163.)**

Key Words: cerebral small vessel disease ■ hypertension

The study of cerebral small vessel disease (cSVD) is of crucial importance because its clinical consequences are associated with stroke risk, cognitive impairment, gait disturbances, and other poor outcomes.[1] The spectrum of markers delineating this disease consists of well-documented lesions, including lacunes, white matter hyperintensities (WMH), and microbleeds. Nowadays, more attention is given to other markers, such as enlarged perivascular spaces (EPVS).

However, the pathological development of cSVD or of each individual lesion is still not completely understood. For instance, increasing arterial stiffness has been consistently associated with lacunes, WMH, and microbleeds,[2] but its relation with EPVS remains unknown. Arterial stiffening is the result of aging and of various vascular risk factors, which may cause arteriosclerosis of the medial vessel layers.[3] It depends mainly on blood pressure levels, while the gold standard for its assessment is the measurement of the carotid–femoral pulse wave velocity (cf-PWV).

Our aims were to study the relationship between cf-PWV and the occurrence of different lesions of cSVD (lacunes, WMH, microbleeds, and EPVS) and that between cf-PWV and the cSVD load. Moreover, we investigated the relation between the cf-PWV and cSVD in individuals with normal and poor blood pressure.

Methods

The data that support the finding of this study are available from the corresponding author on request. Detailed Methods section is available in the online-only Data Supplement.

Received September 28, 2017; final revision received March 7, 2018; accepted March 12, 2018.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.118.020163/-/DC1.

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Study Population

This study was embedded in the ISSYS (Investigating Silent Strokes in Hypertensives, a Magnetic Resonance Imaging Study) project. This was an ongoing community-based study in randomly selected hypertensive individuals aged 50 to 71 years, without history of stroke or dementia.[4] We included 782 participants with valid brain magnetic resonance imaging (MRI) scans and cf-PWV measurements. The study was conducted according to the Helsinki Declaration, approved by the local ethics committee, with the written informed consent of all participants.

Brain MRI

A brain MRI was performed in all participants using the same 1.5T MR (Signa HDx 1.5; General Electrics, Waukesha, WI). We evaluated 4 cSVD markers and load according to previous STRIVE (Standards for Reporting Vascular Changes on Neuroimaging) criteria[5] and scale.[6]

cf-PWV Measurements

The cf-PWV was assessed using the Vicorder oscillometric device (SMT Medical, Würzburg, Germany). The definition and assessment of other covariates are included in the online-only Data Supplement.

Statistical Analysis

Logistic and ordinal regression analyses were performed to study the effect of cf-PWV increase by 1 SD on the cSVD markers and load. The analyses were adjusted by covariables related to cf-PWV, cSVD, or both, as previously described. Moreover, we performed a sensitivity analysis to exclude individuals who had an atrial fibrillation in the ECG. Finally, we performed a stratified analysis for participants with normal (<140/90) and poor (≥140/90) blood pressure.

Results

Demographic and Clinical Characteristics

The mean age of the participants was 62.7 (±5.4) years, and the cf-PWV was 10.5 m/s (interquartile range, 9.2–11.9; Table 1).

Table 1. Clinical Characteristics of the Participants

Variables	Values
Age, y, mean±SD	62.7±5.4
Sex, female, n (%)	388 (49.6)
Carotid–femoral pulse wave velocity, m/s, median (IQR)	10.5 (9.2–11.9)
Systolic blood pressure, mm Hg, mean±SD	142.9±16.3
Diastolic blood pressure, mm Hg, mean±SD	77.3±9.0
Mean blood pressure, mm Hg, mean±SD	98.7±10.4
Normal blood pressure (<140/90 mm Hg), n (%)	347 (44.5)
Hypertension duration, y, median (IQR)	8.4 (5.4–12.4)
Heart rate, bpm, median (IQR)	64.0 (57.0–74.0)
Diabetes mellitus, n (%)	184 (23.6)
Dyslipidemia, n (%)	567 (72.9)
Active smokers, n (%)	122 (15.6)
Previous vascular disease (heart or peripheral artery), n (%)	93 (11.9)
Hypertension treatment, n (%)	745 (95.3)

IQR indicates interquartile range.

On the basis of the MRI data, we identified 40.1% cases with extensive centrum semiovale EPVS, 24.5% with extensive basal ganglia EPVS, 7.2% with lacunes, 6.4% with microbleeds (3.5% in deep areas), 4.9% with extensive deep WMH, and 1.8% with extensive periventricular WMH.

Regarding the cSVD load, 72.4% of the participants scored 0, 19.7% scored 1, 6.5% scored 2, 0.9% scored 3, and 0.5% scored 4 points. The most frequent occurrence of cSVD markers was the combination of extensive basal ganglia EPVS with extensive WMH or lacunes (Figure I in the online-only Data Supplement).

Relationship of cf-PWV With Vascular Risk Factors and cSVD Load

We found significant correlations ($P<0.001$; Table I in the online-only Data Supplement) between the cf-PWV and age (correlation coefficient, $r=0.26$), mean blood pressure ($r=0.30$), and heart rate ($r=0.11$). The cf-PWV also correlated with increasing cSVD load score (Figure II in the online-only Data Supplement).

The multivariable analysis showed that increase in cf-PWV by 1 SD was associated with lacunes and the cSVD load (Table 2). Moreover, cf-PWV was associated with extensive basal ganglia EPVS (Table 2) and also with the score of basal ganglia EPVS (common odds ratio, 1.40; 95% confidence interval, 1.17–1.67).

In the stratified analysis for participants with normal and poor blood pressure, we found that the cf-PWV was associated with extensive basal ganglia EPVS and the cSVD load in both groups. In individuals with poor blood pressure, the cf-PWV was also associated with the presence of lacunes and extensive deep WMH (Table II in the online-only Data Supplement).

We obtained similar results even after excluding the individuals with atrial fibrillation (data not shown).

Discussion

After adjusting for possible confounding factors, our analysis showed that, in hypertensive individuals, the cf-PWV is associated with the cSVD load and the presence of lacunes and basal ganglia EPVS.

Table 2. Multivariable Analysis on the Relationship Between cf-PWV and cSVD Markers

Brain MRI Marker	*P* Value	OR Common OR (95% CI)
Lacune	0.005	1.51 (1.13–2.03)
Deep microbleed	0.930	0.74 (0.61–1.43)
Extensive deep WMH (Fazekas ≥2)	0.070	1.37 (0.97–1.94)
Extensive periventricular WMH (Fazekas=3)	0.050	1.69 (0.99–2.86)
Extensive (>10) basal ganglia EPVS	<0.001	1.39 (1.16–1.67)
Extensive (>10) centrum semiovale EPVS	0.780	0.98 (0.83–1.15)
cSVD load score increase by category	<0.001	1.42 (1.19–1.68)

The analysis is corrected for age, sex, heart rate, mean blood pressure, dyslipidemia, diabetes mellitus, smoking habit, use of blood pressure–lowering drugs, and history of cardiovascular disease. cf-PWV indicates carotid–femoral pulse wave velocity; cSVD, cerebral small vessel disease; EPVS, enlarged perivascular spaces; MRI, magnetic resonance imaging; OR, odds ratio; and WMH, white matter hyperintensities.

Most cross-sectional studies, reviewed in a recent meta-analysis, have shown a relation between arterial stiffness and lacunes, WMH, or cerebral microbleeds.[2] We also found that the cf-PWV is independently associated both with individual cSVD markers and the cSVD load itself, in agreement with a previous study.[7] The association between basal ganglia EPVS and arterial stiffness is a relatively recent observation. Also, a previous study has suggested the relationship between brachial–ankle PWV and basal ganglia EPVS.[8] The relationship between arterial stiffness and certain cSVD markers or the load of the disease might be stronger in individuals with poor than those with normal blood pressure, suggesting that the arterial stiffness could be useful for risk stratification beyond blood pressure levels.

The relation between the stiffness of large vessels and cSVD is not completely understood.[9] One of the described functions of perivascular spaces is to drain interstitial fluid back to circulation. However, when the aorta is stiff, a high pulsatility wave is transmitted to end-organ vascular beds forcing small arteries to adapt to higher flows, which might facilitate the interstitial fluid leakage. Therefore, if the system is compromised and the perivascular spaces fail to drain interstitial fluid, they might enlarge.[10]

The strengths of our study include the relatively large, randomly selected sample of hypertensive individuals, the use of a simple and reproducible measurement of the cf-PWV, and the use of the state-of-the-art 1.5T MRI system. Its limitations are that the cf-PWV could not be obtained for almost 20% of the cohort, which might restrict the generalization of the results. Further, we used a semiquantitative tool to assess the cSVD load, which might be inaccurate when measuring the entire cSVD spectrum.

Sources of Funding

This research was funded by the Instituto de Salud Carlos III (PI14/01535, ICI14/307, CP15/00010, 2017_FI_B 00064, and JR15/00032) and the Spanish Research Stroke Network (RD/16/0019/0021) and cofunded by the European Regional Development Fund and also by the Education and Research in Family Practice Chair (UAB-Novartis).

Disclosures

None.

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