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Brachial-ankle pulse wave velocity is associated with both acute and chronic cerebral small vessel disease

Yong Bum Kim [a], Kwang-Yeol Park [b, *], Pil-Wook Chung [a], Jeong-Min Kim [b], Heui-Soo Moon [a], Young Chul Youn [b]

[a] Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, South Korea
[b] Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul 06973, South Korea

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ABSTRACT

Objective: The aim of this study was to determine the association of brachial-ankle pulse wave velocity (baPWV) with both acute and chronic cerebral small vessel disease (SVD).
Methods: We identified 1282 consecutive patients with acute ischemic stroke or transient ischemic attack. Neuroimaging correlates of chronic lacunes, white matter hyperintensity (WMH), and cerebral microbleed (CMB) were assessed using MR images. Combined SVD score was defined as the number of presence of SVD markers including chronic lacunes, WMH, deep CMB, and acute lacunar infarction. The association between baPWV and SVD was tested using linear and logistic regression analyses.
Results: Mean age of patients was 68 (±12) years. Chronic lacunes were found in 675 patients (53%), WMH in 970 patients (77%), and deep CMB in 349 patients (30%). Among the 1145 patients with ischemic stroke, 292 patients (26%) were classified as having acute SVD. On multivariate analysis, a 1-SD increase in baPWV was associated with chronic lacunes [odds ratio, 1.24; 95% CI, 1.07–1.44; $p < 0.01$], WMH (1.38; 1.13–1.71; $p < 0.01$), deep CMB (1.29; 1.11–1.51; $p < 0.01$), acute SVD (1.19; 1.01–1.40; $p = 0.04$), combined SVD score >1 (1.27; 1.06–1.53; $p = 0.01$), and combined SVD score >2 (1.40; 1.19–1.65; $p < 0.01$).
Conclusions: baPWV is associated with both acute and chronic SVD. Our findings suggest that arterial stiffness is linked to the pathogenesis of SVD. Also, baPWV could be used as a biomarker of SVD. In future trials, it should be tested whether arterial stiffness can be a therapeutic target for SVD.

1. Introduction

Arterial stiffness is one of the determinants of increasing blood pressure in the elderly and has been reported to be associated with hypertension, vascular calcification, and cardiovascular events [1–6].

Cerebral small vessel disease (SVD) is one of the major subtypes of stroke and is known to be associated with hypertension, which suggests that arterial stiffness may play a role in the pathogenesis of SVD [7]. Acute lacunar infarction, white matter hyperintensities (WMH), chronic lacunes, and cerebral microbleed (CMB) are clinical and neuroimaging correlates of SVD, but their association with arterial stiffness has been reported to be inconsistent in previous studies [8–19].

One big difference between acute and chronic small vessel disease is the presence or absence of acute neurologic symptoms and signs. However, their pathogeneses and neuroimaging findings are considered to overlap to some extents and they are frequently found together [19]. Previous studies investigated either only chronic small vessel disease or only acute small vessel disease. Therefore, it is not clear whether arterial stiffness is a common systemic factor associated with SVD in general or a factor associated with some specific presentations of SVD.

The aim of this study was to determine the association of arterial stiffness with clinical and neuroimaging correlates of SVD in patients with acute ischemic stroke or transient ischemic attack.

* Corresponding author. Department of Neurology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, 102, Heukseok-Ro, Dongjak-gu, Seoul 06973, South Korea.
E-mail address: kwangyeol.park@gmail.com (K.-Y. Park).

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2. Methods

2.1. Study population

Between February 2008 and June 2014, 1802 consecutive patients with acute ischemic stroke or transient ischemic attack who visited a tertiary university hospital within seven days of symptom onset were initially considered for inclusion. Among these 1802 patients, 520 patients (29%) were excluded from the analysis because both PWV measurement and diffusion-weighted imaging were not available. Therefore, 1282 patients were ultimately enrolled. The baseline characteristics of the original population and the study population before and after exclusion, respectively, were not significantly different except for the presence of atrial fibrillation, previous stroke history, total cholesterol, and low-density lipoprotein (LDL)-cholesterol. These variables were included in the multivariable models. This study was approved by the local institutional review boards.

2.2. Brachial-ankle pulse wave velocity (baPWV)

baPWV was measured using a volume-plethysmography device (VP-1000; Collin, Komaki, Japan). This device records the phonocardiogram, electrocardiogram, volume pulse form, and arterial blood pressure at the brachia and ankles on both sides. baPWV was calculated by time-phase analysis between the right brachial and volume waveforms at both ankles. The distance between the right brachium and ankle was estimated on the basis of body height. The average of the baPWV values obtained on both sides was used for further analysis.

2.3. Brain MR imaging

Brain MR imaging was performed with a 3.0-T MR unit (Avanto, Philips, Eindhoven, The Netherlands). MR imaging was not available for the assessment of chronic lacunes in 17 patients (1%), WMH in 21 patients (2%) and CMB in 107 patients (8%). The assessment of neuroimages was done by two experienced neurologists (Chung, PW and Park, KY). MR imaging protocol; methods of assessing lacunes, WMH, and CMB; and interrater reliability were described in detail in online supplementation.

2.4. Covariates

Our prospectively collected stroke database was reviewed retrospectively in order to assess the vascular risk factors and demographics of patients with acute ischemic stroke or transient ischemic attack. Subtypes of ischemic stroke were classified by at least two board-certified neurologists according to categorization system of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [20]. The definitions of vascular risk factors were described in online supplementation.

2.5. Combined SVD score

We calculated combined SVD scores by adding up the number of presence of SVD markers including chronic lacunes, WMH, deep CMB, and acute lacunar infarction (presence = 1, absence = 0; range 0–4).

2.6. Statistical analyses

Bivariate analysis was performed using linear regression, in which the dependent variable was baPWV. Age, sex, atrial fibrillation, previous stroke history, total cholesterol, LDL-cholesterol, and variables whose p value was <0.05 on bivariate analysis were entered into the multivariate analysis. To investigate the association between baPWV and SVD, multivariate analyses were performed using logistic regression. Receiver operating characteristic (ROC) curve analysis was performed to investigate the usefulness of baPWV as a biomarker of combined SVD entity (combined SVD score $\geq$1). The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed with R (Version 3.1.1, The R Foundation for Statistical Computing, Platform: 64-bit).

3. Results

3.1. Baseline characteristics

The total 1282 patients comprised 740 men (58%) and 542 women (42%), and mean age was 68 (±12) years (Table 1). Mean baPWV level was 2045 (±521) cm/s.

Bivariate analysis showed that baPWV was associated with age, sex, hypertension, diabetes mellitus, current smoking, previous stroke history, HDL-cholesterol, HbA1c, systolic blood pressure, and diastolic blood pressure (Table 1).

3.2. Association between baPWV and chronic SVD

Chronic lacunes were found in 675 patients (53%; median 1; interquartile range, 0–2). WMH was assessed as grade 0 in 291 patients (23%), grade 1 in 490 patients (39%), grade 2 in 342 patients (27%), and grade 3 in 138 patients (11%). CMB was present in 484 patients (41%; median 0; interquartile range, 0–2). Deep CMB was found in 349 patients (30%) and strictly lobar CMB was found in 102 patients (9%). As the number of lacunes and deep CMB or the grading of WMH increased, the baPWV level increased (Fig. 1).

On bivariate analysis, a 1-SD increase in baPWV was associated with chronic lacunes (OR, 1.58; 95% CI, 1.40–1.79), WMH (OR, 2.35; 95% CI, 1.98–2.80), and deep CMB (OR, 1.45; 95% CI, 1.29–1.65) (Table 2). However, there was no association between baPWV and strictly lobar CMB (OR, 1.04; 95% CI, 0.85–1.26). The results were the same on multivariate analyses.

3.3. Association between baPWV and acute SVD

Among the 1282 patients, 1145 patients (89%) had acute ischemic stroke. Stroke was classified as large artery atherosclerosis in 371 patients (32%), cardioembolism in 246 patients (21%), small vessel occlusion in 292 patients (26%), other determined etiology in 25 patients (2%), and undetermined etiology in 211 patients (18%). Mean baPWV levels were 2071 (±509) cm/s in patients with large artery atherosclerosis, 2069 (±494) cm/s in patients with cardioembolism, 2129 (±518) cm/s in patients with small vessel occlusion, 1784 (±633) cm/s in patients with other determined etiology, and 2016 (±510) cm/s in patients with undetermined etiology.

On bivariate analysis, a 1-SD increase in baPWV was associated with acute small vessel occlusion (OR, 1.16; 95% CI, 1.02–1.32) (Table 3). The association remained significant even after adjustment for confounders. Large artery atherosclerosis was not associated with baPWV. Cardiac embolism was inversely associated with baPWV on multivariate analyses (OR, 0.74; 95% CI, 0.61–0.88).

3.4. Association between baPWV and combined SVD marker

Combined SVD score was 0 in 134 patients, 1 in 251 patients, 2 in 335 patients, 3 in 254 patients, and 4 in 76 patients. On bivariate analysis, a 1-SD increase in baPWV was associated with combined SVD score >1 (OR, 1.81; 95% CI, 1.56–2.11; $p < 0.01$) and combined