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Low carotid artery wall shear stress is independently associated with brain white-matter hyperintensities and cognitive impairment in older patients

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A B S T R A C T

Background & aims: Brain white-matter lesions and cognitive impairment are increasing because of the increasing number of patients aged ≥80 y. Wall shear stress (WSS) plays a pivotal role as a fluid mechanical mediator in vascular reactivity and atherosclerosis. In this study, we investigated the associations among common carotid artery (CCA) WSS, white-matter lesions, and cognitive impairment in patients aged ≥80 y

Methods: We enrolled 384 patients aged ≥80 y. All subjects had CCA-WSS, brain white-matter hyperintensities (WMH), and Mini-Mental State Examination (MMSE) assessments and were divided into three groups using tertiles of mean and peak CCA-WSS.

Results: For groups classified by the tertile of mean CCA-WSS, WMH, and WMH fraction were decreased; the MMSE score increased from low to high in the respective groups. Differences in WMH, WMH fraction, and the MMSE score were significant between any two groups (all adjusted $p < 0.001$). Groups classified by the tertile of peak CCA-WSS had the same pattern. Mean and peak CCA-WSS were significantly and inversely correlated with WMH ($r = -0.575$ and -0.570, respectively; $p < 0.001$) and WMH fraction ($r = -0.574$ and -0.569, respectively; $p < 0.001$) but positively correlated with the MMSE score ($r = 0.390$ and 0.278, respectively; $p < 0.001$). Multiple linear backward stepwise regression indicated the mean and peak CCA-WSS were significantly and independently associated with WMH, WMH fraction, and the MMSE score (all adjusted $p < 0.001$).

Conclusion: Carotid artery WSS was independently associated with brain white-matter lesions and cognitive impairment in patients aged ≥80 y

1. Introduction

Patients aged ≥80 y represent a rapidly growing segment of the population as human life expectancy is steadily increasing [1–3]. The risk of age-associated diseases such as cognitive impairment is increasing and represents an important factor affecting quality of life for older patients, especially for those aged ≥80 y [4–6]. Epidemiological studies have demonstrated that cognitive impairment is highly prevalent in an older population with more than one-half showing signs of dementia [7–11]. The prevalence of dementia has rapidly increased: about 2–3% of those aged 70–75 y, 24% of those aged 80–89 y, and 37% of those aged ≥90 y [7–9].

Brain white-matter hyperintensities (WMH) is a pivotal indicator and one of the pathologic changes in white-matter lesions (WMLs); they are commonly observed on structural brain scans using magnetic resonance imaging (MRI) in older populations [12–15]. An accumulated volume of WMH over time is strongly associated with cognitive decline and an increased risk of dementia

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[16].

From a hemodynamic point of view, wall shear stress (WSS) is considered to play a pivotal role as a fluid mechanical mediator in vascular reactivity and atherosclerosis [17–19]. WSS represents the tangential force per unit area exerted by circulating blood on the endothelial surface of the arterial wall in the direction of flow. Different WSS levels have different effects on vascular activities [20].

The carotid artery is a well established "observation window" for systemic structure and arterial function in humans; in the carotid arteries, the WSS may also represent the overall hemodynamic condition of the cerebral vessels [17,21,22]. A few studies have been performed to investigate potential correlations between the carotid WSS and cerebrovascular pathological changes [17,23,24]. A cross-sectional study showed that the carotid WSS is significantly correlated with the presence of periventricular WHM and cerebral infarcts after adjusting for cardiovascular risk factors [17]. van Es and coworkers [24] reported that the WSS in the carotid arteries of patients with Alzheimer's disease and mild cognitive impairment was markedly lower, as compared with normal patients.

However, to the best of our knowledge, the possible effect of the carotid artery WSS on WMLs and cognitive impairment in older patients has not been fully explored. The main goal of the present study was to explore and elucidate these effects.

2. Methods

2.1. Study population

Three hundred eighty-four older patients aged 84.65 ± 2.30 y (range, 80–91 y) were eligible and recruited from community-dwelling and geriatric practices in Shandong Province from May 2009 to September 2012. Among them, 126 were men, and 258 were women. The exclusion criteria were as follows: transient ischemic attack or stroke in the last 2 years or with cognitive decline within 3 months after having a stroke; end-stage heart disease; Parkinson's disease; seizures; major depressive disorder; bipolar disorder; schizophrenia; claustrophobia; brain tumor; contraindication to MRI; and unwilling to provide informed consent. For all subjects, brain MRI and cognitive function were evaluated, including the Mini-Mental State Examination (MMSE). This study was conducted in compliance with the ethical standards set forth in the "Declaration of Helsinki" and approved by the institutional ethics committee at Shandong Academy of Medical Sciences. Written informed consent was obtained from all subjects or their close relatives if the subject was unable to write.

2.2. Carotid ultrasonography

The measurements were performed for at least 24 h and started on the morning after administration of the last calcium antagonist tablet. In a quiet room with a temperature of 22–24 °C, subjects were examined after a 15-min acclimatization period in a supine position by one certified ultrasonographer who was unaware of the subjects' clinical details. Duplex ultrasonography of the left and right common carotid arteries (CCA) was performed using high-resolution ultrasound (Vivid *i*, GE Medical Systems Ultrasound Israel Ltd) with a 7.5-MHz linear array transducer (7.5-SPC mechanic sector transducer, GE Medical Systems Ultrasound Israel Ltd) and ECG triggering.

CCA intima-media thickness (CCA-IMT) was measured by recording B-mode ultrasonographic images of the left and right carotid arteries as previously described [21,22,25]. Distance from the leading edge of the lumen-intima interface to the media-adventitia interface of the distal CCA was measured offline. Three B-mode images were obtained using anterior, lateral, and medial angles. Maximum IMT in the right or left CCA was used for further analysis.

The internal diameters (IDs) of the CCAs were measured between the intima-lumen interfaces of the near and far walls of the carotid arterial segments using two-dimensionally guided continuous M-mode tracings at the R (ID_R) and peak T (ID_T) waves of the ECG, representing the minimum and maximum carotid diameter, respectively. Images of the interfaces between the lumen and intima were captured over five cardiac cycles and stored, and the diameters were measured offline using dedicated software as previously reported [26–28].

Blood flow velocity in the common carotid artery, 1–2 cm below the bifurcation, was detected at peak systole and end diastole with the sample volume reduced to the smallest possible size (1 mm) and placed in the center of flow. The insonation angle was generally kept between 44° and 56° [27,28]. Peak systolic velocity (V_{PS}), end diastolic velocity (V_{ED}), and mean velocity (V_M) were automatically recorded as the mean of three cardiac cycles. Because the flow V_M could be better estimated by time-averaged peak (TAP) over an integral number of cardiac cycles, we evaluated TAP during three cardiac cycles in the present study [27,29].

2.3. WSS calculations

MWSS and PWSS were calculated according to the following equation derived from Poiseuille's formulas [27,29]:

$$\text{MWSS (Pa)} = 8 \times \eta \times V_M/ID_R$$

$$\text{PWSS (Pa)} = 8 \times \eta \times V_{PS}/ID_T$$

where η is blood viscosity (Pa·s); V is the velocity in a cross-section of the vessel (m/s); and ID is the lumen diameter (m). The vessel wall is assumed to be rigid, with blood as a Newtonian fluid and viscosity equal to 0.0035 Pa s [18]. Minimum MWSS and PWSS in the right or left CCA were used for further analysis.

2.4. Assessment of global cognitive function

Global cognitive function was evaluated using the MMSE by neuropsychologists who were experts in cognitive function measurements. The MMSE is a 30-point test that consists of five areas of possible cognitive impairment: orientation, registration, attention, calculation, and language. It is a validated and powerful tool for diagnosis during the advanced stages of global cognitive impairment [3]. A lower MMSE score indicates impaired global cognitive functioning. Tests were interpreted taking into account both occupational and educational levels.

2.5. MRI scanning protocol and processing

WMH was assessed with MRI using a 3-T GE Signa Horizon scanner (General Electric Medical Systems, Milwaukee, WI, USA) for each subject. The following sequences were used: T1-weighted magnetization prepared rapid gradient echo sequence (isotropic 1-mm voxel; repetition time [TR] = 1900 ms; echo time [TE] = 3 ms; inversion time [TI] = 900 ms; readout flip angle = 9°; matrix 256 × 256 with 160 slices yielding 1 mm^3 isotropic voxels; sagittal acquisition with field of view [FOV] = 256 × 240 mm^2; 1-mm thick slices; and no slice gap), T2-weighted 3D fast spin-echo (TR = 3000 ms; TE = 98 ms; FOV = 24 cm; matrix = 256 × 256; number of excitations = 0.5; 3-mm slice thickness; and no slice gap), and FLAIR (TR = 5000 ms; TE = 355 ms; TI = 1800 ms; readout