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Relationship of retinal vascular caliber variation with intracranial arterial stenosis☆

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ABSTRACT

Background & purpose: To investigate the associations of retinal vessel parameters with intracranial arterial stenosis (ICAS) assessed by Transcranial Doppler ultrasonography.

Method: Data on transcranial Doppler ultrasonography and quantitative retinal vessel parameters from 627 participants in a health screening program were included in this study. ICAS was defined as >50% intracranial arterial stenosis (ICAS) based on criteria modified from the stroke outcomes and neuroimaging of intracranial atherosclerosis (SONIA) trial assessed by transcranial Doppler (TCD) ultrasonography. A semi-automated computer-assisted program (Singapore I Vessel Assessment) was used to measure the retinal vascular parameters from the photographs. Multivariate analysis was performed to identify which retinal vessel parameters were associated with increased risk of ICAS.

Results: Among 627 participants, 24 (3.8%) had ICAS diagnosed by TCD. Subjects with ICAS had eyes with wider mean central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) in comparison to subjects without ICAS. Men (odds ratio [OR]:13.1, 95% confidence interval: 3.13–33.33) and a large standard deviation of mean arterial width (STDWa) were associated with ICAS (first vs. third tertile: OR ratio: 14.04, 95% confidence interval: 1.71–115.32; first vs. third tertile: OR ratio: 22.1, 95% confidence interval: 2.56–190.97) after adjusting for possible confounders.

Conclusion: A large variation in retinal arteriolar diameter is associated with ICAS. This study suggests the possible relationship between retina vessel and early changes within the cerebrovascular network.

Retina function as two way mirror which provides the outside visual input to visual cortex but also can provide information regarding cerebrovascular conditions to outside world. But until now, there have been inconsistent results of how or when retina vasculature reflects cerebrovascular conditions (Patton et al., 2005; Ikram et al., 2012; Cheung et al., 2007a; De Silva et al., 2009; De Silva et al., 2011; Ikram et al., 2013; Ong et al., 2013; Hilal et al., 2014; Cheung et al., 2014; Knudtson et al., 2003; Witt et al., 2006; Cheung et al., 2013). The implications of retinal microvascular changes in the pathogenesis of cerebrovascular diseases are largely unknown until recently. Previous studies suggested that narrower arteriolar caliber and wider venular caliber are associated with ischemic stroke. Some study showed, in addition to vessel caliber change, other parameters indicative of tortuous vascular network were associated with ischemic stroke. However, in other study, retinal vessel caliber was not related with intracranial stenosis (Patton et al., 2005; Ikram et al., 2012; Cheung et al., 2007a; De Silva et al., 2009; De Silva et al., 2011; Ikram et al., 2013; Ong et al., 2013; Hilal et al., 2014; Cheung et al., 2014; Knudtson et al., 2003; Witt et al., 2006; Cheung et al., 2013).

Intracranial arterial stenosis (ICAS) is a major cause of ischemic stroke, especially in Asians, with a reported prevalence of up to 50% (Guan et al., 2013). In addition to advances in treatment that improve the prognosis of ICAS-related stroke patients, detecting ICAS at an early stage can significantly improve stroke management and decrease socio-economic burden related to treatment. Transcranial Doppler (TCD) ultrasonography is a non-invasive, safe, and cost effective method to diagnose ICAS (Wong et al., 2007; Leng et al., 2014; Sacco et al., 1995; Standards of Medical Care in Diabetes, 2016).

In this study, we analyzed quantitative retinal vascular parameters of participants with ICAS diagnosed by TCD. These findings were compared to measurements of those without ICAS to investigate the possibility that retinal vessel parameters are associated with early intracranial vascular change.

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1. Method

1.1. Participants

This cross-sectional study was a part of the Kangbuk Samsung Health Study, in which subjects were participants in a medical health checkup program at the Health Promotion Center of Kangbuk Samsung Hospital of Sungkyunkwan University in Seoul, Korea. The purpose of medical health checkup programs is to promote employee health through regular examinations and to enhance early detection of existing diseases. Most examinees are employees of various industrial companies and their family members from around the country. Employers largely cover the costs of the medical examinations, and a considerable proportion of examinees undergo health examinations annually or biannually.

A total of 627 participants who underwent TCD from January 2011 to December 2011 and for whom gradable fundus photographs were available were included. The ophthalmic examinations, systemic examinations, and questionnaires for sociodemographic and behavioral characteristics were administered to each participant. The study was approved by the institutional review board of Kangbuk Samsung Hospital (KBSMC2015-01-003) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained prior to recruitment.

1.2. Anthropometric measurement and laboratory assessment

Data on medical history, medication use, and health-related behaviors were collected through a self-administered questionnaire, while trained staff obtained physical measurements and serum biochemical parameters during health examinations. Body weight was measured with the participants in light clothing without shoes to the nearest 0.1 kg by using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure with standard mercury sphygmomanometers.

All subjects were examined after an overnight fast. The hexokinase method was used to measure fasting serum glucose concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). The total cholesterol and triglyceride concentrations were measured with an enzymatic calorimetric test. The selective inhibition method was used to evaluate the level of high-density lipoprotein cholesterol, and a homogeneous enzymatic calorimetric test was used to measure the level of low-density lipoprotein cholesterol.

The presence of diabetes mellitus was determined according to the self-questionnaire results, as well as from the fasting serum blood glucose and glycated hemoglobin (HbA1c) levels of participants, as suggested by the American Diabetes Association (Standards of Medical Care in Diabetes, 2016). In brief, diabetes was defined as a fasting serum glucose level of ≥126 mg/dl or HbA1c of ≥6.5%, self-reported diabetes history, or current antidiabetic medication use. The presence of hypertension was determined if the subject was taking anti-hypertensive medication or had a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg (James et al., 2014).

HbA1c was measured by immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value of 4.4–6.4%. The methodology conformed to the Diabetes Control and Complications Trial and National Glycohemoglobin Standardization Program (NGSP) standards (List of NGSP Certified Methods, 2016).

1.3. TCD ultrasonography evaluation and diagnosis of ICAS

A trained ultrasonographer performed TCD ultrasonography using single-channel TCD ultrasonography (Nicolet SONARA TCD system, Natus Medical Incorporated, San Carlos, CA). The following mean flow velocity (MFV) cut-offs on TCD ultrasonography were used for identification of ≥50% stenosis according to the SONIA (stroke outcomes and neuroimaging of intracranial atherosclerosis) trial criteria (Feldmann et al., 2007): middle cerebral artery MFV > 100 cm/s, distal internal carotid artery MFV > 90 cm/s, vertebral artery MFV > 80 cm/s, and basilar artery MFV > 80 cm/s. Because the anterior and posterior cerebral arteries were not evaluated in the SONIA trial, previously validated criteria for detection of ICAS in these vessels was adapted (Rumberger et al., 1999; Tsivgoulis et al., 2007; Tsivgoulis et al., 2008; Tsivgoulis et al., 2014): anterior cerebral artery MFV ≥ 80 cm/s and posterior cerebral artery MFV ≥ 80 cm/s. ICAS was diagnosed if at least one of the studied arteries showed evidence of stenosis. Subjects with poor temporal windows were excluded from the study.

1.4. Retinal photography & vascular parameters

Fundus photographs were acquired using a nonmydriatic fundus camera (CR6-45NM; Canon Inc., Tokyo, Japan). We used a semi-automated computer-assisted program (Singapore I Vessel Assessment [SIVA], software version 3.0) to quantitatively measure the retinal vascular parameters from the photographs. SIVA automatically identifies the optic disc, places a grid with reference to the center of the optic disc, identifies vessel type, and calculates retinal vascular parameters (Ikram et al., 2013; Ong et al., 2013; Hilal et al., 2014; Cheung et al., 2014; Thomas et al., 2014). Trained graders, unaware of participant characteristics, were responsible for the visual evaluation of SIVA automated measurement as well as manual measurement, if required, according to a standardized protocol (Ikram et al., 2013). The measured area was standardized and defined within the region between 0.5 and 2.0 disc diameters away from the disc margin, and all visible vessels coursing through the specified zone were measured. The detailed definitions and measurement methods for each retinal vascular parameter are previously explained elsewhere (Ikram et al., 2013; Ong et al., 2013; Hilal et al., 2014; Cheung et al., 2014). In brief; retinal vascular caliber measurements were based on the revised Knudtson-Parr-Hubbard formula with arteriolar caliber summarized as central retinal arteriolar

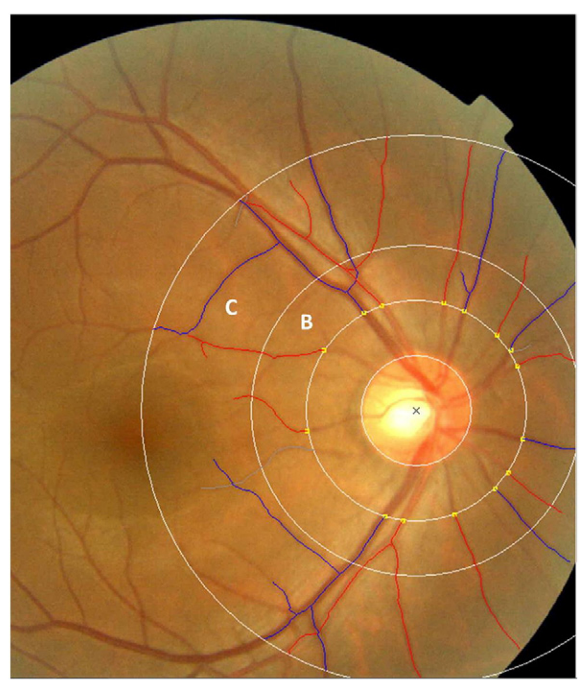

Fig. 1. Representative photography showing retina vessel caliber measurement used in this study (Singapore I Vessel Assessment). B: zone B, C: zone C, red line indicate arteriole tracking, blue line indicate venule tracking.