Visit-to-visit blood pressure variability in the elderly: Associations with cognitive impairment and carotid artery remodeling

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Michiaki Nagai, Satoshi Hoshide, Mami Nishikawa, Shimpo Masahisa, Kazuomi Kario*

Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Yakushiji 3311-1, Shimotsuke, Tochigi 329-0498, Japan

ABSTRACT

Objective: Recently, visit-to-visit blood pressure (BP) variability has been shown to be associated with vascular remodeling and cognitive dysfunction. However, there have been no studies that focused on the relationship between visit-to-visit BP variability and cognitive dysfunction in relation to vascular remodeling. In this study, we investigated the relationships among visit-to-visit BP measures, carotid artery remodeling and cognitive function in the elderly at high risk of cardiovascular disease.
Methods: The cognitive function was evaluated using a Mini-Mental State Examination (MMSE) and global deterioration scale (GDS) in 201 elderly subjects at high risk of cardiovascular disease (79.9 ± 6.4 years old; female 75%). Based on 12 visits (once a month), visit-to-visit BP variability (expressed as the coefficient of variation [CV] and as delta [maximum − minimum] BP) were measured. Carotid ultrasound was performed to measure intima-media thickness (IMT) and the stiffness parameter β.
Results: The patients having both high delta systolic BP (SBP) and high IMT had significantly higher prevalence of low MMSE score than those with both low delta SBP and low IMT ($p < 0.05$), and the patients having both high delta SBP and high stiffness parameter β also had significantly higher prevalence of low MMSE score than those with both low delta SBP and low stiffness parameter β ($p < 0.01$). In the logistic regression analysis adjusted for age, calcium channel blocker use, low density lipoprotein, average heart rate, and average SBP level, a significant interaction was found between delta SBP and stiffness parameter β for the low MMSE score ($p < 0.05$).
Conclusions: In the high risk elderly, exaggerated visit-to-visit BP variability and advanced carotid artery remodeling have a synergetic association with cognitive dysfunction.

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1. Introduction

Blood pressure (BP) levels are strong predictors of first and recurrent strokes [1,2]. Average BP over a period of time is widely considered to be important as a cause of vascular disease [2]. On the other hand, in a large cohort of patients with previous transient ischemic attack (TIA; UK-TIA Aspirin Trials), and a broad population of patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA), Rothwell et al. [3] reported that visit-to-visit systolic blood pressure (SBP) variability was a strong predictor of stroke independently of average SBP.

Although hypertension is a risk factor for vascular dementia [4,5], trials of BP-lowering drugs have not shown a consistent

reduction in the risk of dementia [6–8]. Most of the studies had been focused on the absolute BP levels in relation with cognitive dysfunction. On the other hand, Brickman et al. reported that white matter hyperintensity volume was increased in the elderly with high BP and high visit-to-visit BP variability [9]. Recently, we have shown that indices of visit-to-visit BP variability such as coefficient of variation [CV] and delta [maximum − minimum] in SBP were significant indicators for cognitive impairment in the elderly at high risk of cardiovascular disease [10].

Increased carotid artery intima-media thickness (IMT) has been shown to be a marker of cardiovascular disease [11]. The stiffness parameter β has been used mainly to examine the elastic properties of the carotid artery [12], and an increased stiffness parameter β was found to be associated with coronary artery disease [13]. In a cross-sectional study, we showed that exaggerated visit-to-visit BP fluctuations were significantly associated with carotid artery atherosclerosis and stiffness independently of average BP [14]. We hypothesized that stiffness itself, caused by vascular remodeling,

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* Corresponding author. Tel.: +81 285 58 7538; fax: +81 285 44 4311.
E-mail address: kkario@jichi.ac.jp (K. Kario).

might be associated with cognitive impairment in conjunction with increased BP variability. To our knowledge, there have been no studies that have mainly focused on the interaction of vascular remodeling with the relationship between visit-to-visit BP variability and cognitive function.

From these standpoints, not only the absolute BP level but also BP variability might be associated with cognitive impairment in relation to vascular remodeling. Although some data have been published previously [10,14], in this study, we mainly investigated whether exaggerated visit-to-visit BP variability and advanced carotid artery remodeling had a synergetic association with cognitive dysfunction.

2. Subjects and methods

2.1. Subjects

This study was conducted as a part of the Shobara City/Soryo Town Cohort Study (3SCO), on high-risk Japanese outpatients with one or more cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and current smoking). Hyperlipidemia was defined as a total cholesterol level >240 mg/dl or the use of an oral lipid-lowering agent [15]. Current smoking was defined as having smoked daily over the past month regardless of the quantity. The inclusion criteria included 1) being ≥70 years in age; 2) being a resident of Shobara City/Soryo Town; and 3) consenting to a carotid ultrasound. After all physical and laboratory examinations were performed (including blood tests, chest X-ray, and electrocardiography at rest), we excluded from this study any patients with hepatic damage (aspartate aminotransferase or alanine aminotransferase >40 IU/L), and we also excluded patients with a history of coronary artery disease, stroke (including transient ischemic attacks), atrial fibrillation, congestive heart failure, renal failure, or malignancy. Ultimately, we included 206 patients in this study. Fig. 1 summarizes the flow of potential participants. Some of the data from the 3SCO study have been published previously [10,14]. This article is a subanalysis of the 3SCO study.

We conducted an assessment of cognition and function, clinic BP measurement, and carotid ultrasound, and obtained blood samples from all of the study subjects. Body mass index (BMI) was

calculated as weight (kg)/height (m^2). This study was approved by the local medical ethics committee and all participants gave written informed consent. All examinations including blood tests, visit-to-visit BP measurements, assessment of cognition and function, and ultrasound were performed between April 2007 and March 2008.

2.2. Measurement of blood pressure

At every visit, clinic BP was measured three times in the sitting position after a 5 min rest with an automated oscillometric device (Omron HEM-5001; OMRON Healthcare, Kyoto, Japan) [16]. The mean of the second and third readings at each visit was used. Over a series of 12 visits (one each month), average BP, visit-to-visit BP variability (expressed as the standard deviation [SD] and as the coefficient of variation [CV]; CV = SD/average value in the 12 visits × 100 [%]), and the maximum, minimum, and delta (maximum − minimum) in SBP and diastolic BP (DBP) were measured. In this study, the analysis was focused mainly on CV SBP and delta SBP. High CV SBP was defined as inclusion in the higher half of CV SBP (≥22.2%), while low CV SBP was defined as inclusion in the lower half of CV SBP (<22.2%). The high delta SBP was defined as inclusion in the higher half of delta SBP (≥44.0 mmHg), while low delta SBP was defined as inclusion in the lower half of delta SBP (<44.0 mmHg).

2.3. Assessment of cognitive function

The cognitive function was assessed using the battery of neuropsychological tests making up the Mini-Mental State Examination (MMSE) [17]. Because a standard MMSE cut-score of 24 has been widely used, we diagnosed cognitive impairment if the MMSE score was 24 or less [18]. The Global Deterioration Scale (GDS) was administered to all patients. The GDS was used to assess the severity of the clinical characteristics of the impairment for cognition and function [19]. The GDS is divided into seven identifiable stages (scores 1–7), which encompass the earliest to the most severe symptoms of cognitive and functional impairment, as well as behavior disturbances. Because a GDS cut-score of 3 has been widely used, we diagnosed cognitive impairment if the GDS score was 3 or more [19]. In almost all of the subjects, assessment of cognitive function was performed within 3 months after April 2007.

2.4. Biochemical evaluation

Blood samples were drawn after an overnight fast for the analysis of serum concentrations of glucose, HbA1c, triglyceride, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol by standard laboratory methods.

2.5. Measurement of IMT and stiffness parameter β by ultrasound

The intima-media thickness (IMT) of the common carotid artery (CCA) was measured using high-resolution ultrasound (SSA-660A Xario; Toshiba Medical Systems, Tochigi, Japan) with a 7.5-MHz linear array transducer and with automatic border detection methodology. The examination included approximately 4 cm of the CCA. This region was scanned bilaterally in longitudinal and transverse projections. The image was focused on the far wall of the artery. IMT defined as the distance between the lumen-intimal interface and the media-adventitia interface of the far wall was measured in both carotid arteries. Three determinations of IMT were conducted at the site of the greatest thickness (maximum IMT), including plaque, and at two other points, 1 cm upstream and 1 cm downstream from the site of the greatest thickness. These three values were averaged. The averaged IMT value (three from
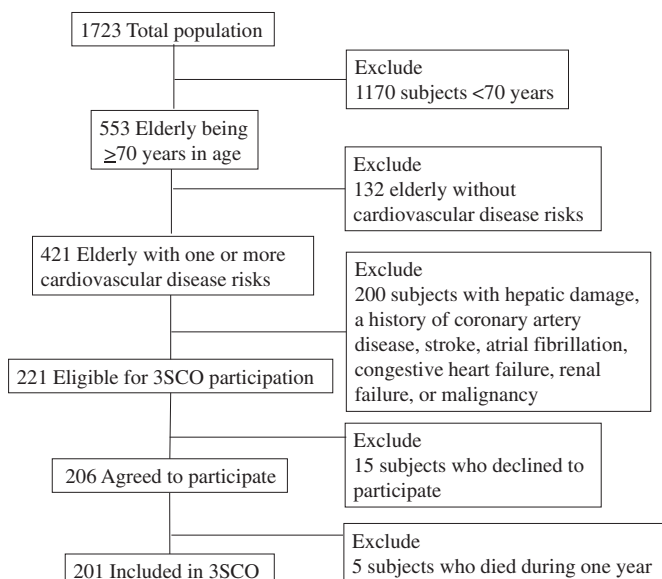

Fig. 1. Study sample inclusion and exclusion flow chart.