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Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study

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Abstract

Background: The relationship between blood pressure and dementia is incompletely understood in elderly individuals. Blood pressure variability may have a role in the risk of dementia.

Methods: This investigation was a cohort study of 6506 elderly individuals followed-up for 8 years (1999–2001 through 2008) with assessments at years 2, 4, and 7–8. Blood pressure was measured by electronic devices at baseline and at 2- and 4-year follow-up examinations. Cox proportional hazard models adjusted for potential confounders were used to estimate the risk of incident dementia according to blood pressure (means and coefficients of variation of the three measures).

Results: During the 40,151 person-years of follow-up 474 participants developed dementia. We observed no association between mean blood pressure and risk of dementia. In contrast, an increase of 1 standard deviation in the coefficient of variation of blood pressure was associated with a 10% increased risk of dementia. Analysis by deciles of the coefficient of variation showed that the higher the variability, the higher the risk of dementia ($P < .02$ for trend). In the fully adjusted Cox model, the risk of dementia for those in the highest decile of the coefficient of variation of systolic blood pressure was 1.77 (1.17–2.69) compared with the lowest decile.

Conclusions: In this cohort study, variability of blood pressure during follow-up was associated with an increased risk of incident dementia, whereas mean blood pressure was not. Limitation of blood pressure fluctuation may be an important target to preserve cognitive function in the elderly.

Keywords: Cohort studies; Alzheimer's disease; Hypertension; Risk factors in epidemiology; Blood pressure; Vascular brain injury; Cox model

1. Introduction

High blood pressure is a major predictor of the risk of stroke and silent vascular brain lesions (silent infarcts, leukoaraiosis, and white matter hyperintensities), which are, in turn, well-established risk factors for dementia and cognitive deterioration [1,2]. However, the relation between blood pressure and risk for dementia seems to be more complex. Although long-term studies have consistently shown that elevated midlife blood pressure is associated with an increased risk of late-life dementia, most longitudinal studies performed in elderly populations have not demonstrated a strong relation between blood pressure and dementia [3–6].

Blood pressure variability increases with age and recent studies have further focused on the possible influence of blood pressure variability on vascular brain lesions. Clinical and community-based studies using different measures reported an association between blood pressure variability and silent cerebral lesions, in particular white matter hyperintensities [7–9]. It was also recently shown that visit-to-visit

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variability of systolic blood pressure was a strong predictor of stroke [10,11].

Based on these findings, it can be hypothesized that blood pressure variability in elderly individuals may be an independent risk factor for dementia. In this study, we assessed the association between variability of blood pressure and incident dementia in a large cohort of community-dwelling elderly persons.

2. Methods

2.1. Study population

The Three-City (3C) Study is a cohort study conducted in three cities in France (Bordeaux, Dijon, and Montpellier), aiming to estimate the risk of dementia and cognitive impairment attributable to vascular factors [12]. A sample of noninstitutionalized subjects aged 65 years and older was selected randomly from the electoral rolls of each city; 37% of eligible persons agreed to participate. Between January 1999 and March 2001, 9294 subjects were enrolled (Bordeaux, $n = 2104$; Dijon, $n = 4931$; Montpellier, $n = 2259$). Over an 8-year period, three follow-up examinations were performed (at years 2, 4, and 7–8). They consisted of face-to-face interviews (sociodemographic characteristics, lifestyle, medical history) and cognitive and physical examinations conducted at the participant's home and at the study center. Blood pressure was measured at each wave of the study except for the 8-year examination. A detailed description of the study protocol has been reported previously [12]. Written informed consent was obtained from all participants, and the study protocol was approved by the ethics committee of the University Hospital of Kremlin-Bicêtre.

To be eligible for the study, participants had to be nondemented at baseline and to have their blood pressure measured at baseline and at the 2- and 4-year follow-up examinations. Among the initial sample, 1643 participants were not eligible, 551 died in the first 4 years, and 594 were excluded due to lack of follow-up information on their dementia status (217 refused to participate and 377 were lost to follow-up), leaving a working sample of 6506 participants (Figure 1).

Individuals with missing blood pressure measures were older ($P < .0001$), more often men ($P = .01$), less likely to have a high education level ($P < .0001$), more likely to have diabetes ($P < .0001$) and vascular disease ($P < .0001$), to be disabled ($P < .0001$), and to have high blood pressure and/or to take blood-pressure-lowering drugs ($P = .0005$). Individuals who refused to participate and those lost to follow-up were older ($P < .0001$), less likely to have a high education level ($P < .0001$), more likely to have diabetes ($P = .009$) and depressive symptoms ($P < .0001$), and to be disabled ($P < .0001$).

2.2. Measure of blood pressure variability

Brachial blood pressure was measured twice after at least 5-minute rest in a seated position, with an appropriately sized cuff placed on the right arm, using a validated digital electronic tensiometer (M4; OMRON Corp., Kyoto, Japan) at baseline and at each follow-up examination. Averaging of the two measures was used to estimate blood pressure at each examination.

For each subject, we computed the mean (SD) of the systolic and diastolic blood pressure (SBP and DBP, respectively) from the three measures (baseline and 2- and 4-year visits). As in recent studies that addressed the association between blood pressure variability and the risk of stroke, we used the coefficient of variation (SD/mean blood pressure) for both SBP and DBP as a measure of blood pressure variability across the three visits [10,11].

2.3. Other measurements

Education level was defined as low (no school or primary) or high (high school diploma or university degree). All drugs prescribed in the preceding month were inventoried and coded according to the of the WHO Anatomical Therapeutic Chemical (ATC) classification. All participants had a fasting blood sampling for routine biologic measurements including glycemia and lipid levels. Past and present medical history was assessed from self-reported diseases, medication use, and objective biologic and physical measures. Subjects using antihypertensive medication were differentiated according to reason for use, specifically high blood pressure or cardiac disease. Subjects with SBP >140 mm Hg or DBP >90 mm Hg or using blood-pressure-lowering drugs for a history of high blood pressure were classified as hypertensive. Diabetes mellitus was considered present when antidiabetic drugs were taken or when fasting blood glucose was ≥ 7 mmol/L. Depressive symptoms were defined by a score ≥ 17 for men or ≥ 23 for women according to the Center for Epidemiologic Studies–Depression (CESD) scale [13]. Presence of vascular disease was defined as self-reported history of myocardial infarction, bypass cardiac surgery, angioplasty, stroke, or peripheral vascular disease. Data about atrial fibrillation and heart failure were also collected. Functional incapacity was measured on the Instrumental Activities of Daily Living (IADL) scale [14].

2.4. Screening and diagnosis of dementia

Diagnosis of dementia was based on a three-step procedure at each follow-up screening, as described elsewhere [15]. First, trained psychologists administered a battery of neuropsychological tests. Second, a neurologist examined all participants in Bordeaux and Montpellier. In Dijon, due to the large number of participants, only those who were screened positive for dementia using the Mini-Mental State Examination and the Isaacs Set Test underwent further clinical examination. For subjects suspected of having dementia, further data on cognitive disorders and their consequences on daily activities were collected using a standardized protocol, and the study neurologist or geriatrician established