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Blood pressure and neuropsychological test performance in healthy postmenopausal women

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ABSTRACT

Purpose: To study the association between blood pressure and neuropsychological test performance in healthy postmenopausal women.
Methods: Data from 88 healthy postmenopausal women aged 46–73 years, who were not experiencing hot flashes, and who had participated in a prior drug trial, were analyzed to find whether baseline blood pressure was associated with impaired performance on neuropsychological testing done at 3 follow-up visits separated by 4 weeks. Factor analysis was used to reduce the dimensions of neuropsychological test performance. Mixed linear modeling was used to evaluate the association between baseline blood pressure and repeatedly measured neuropsychological test performance at follow-up in a complete case analysis (n = 53). In a sensitivity analysis (n = 88), multiple-imputation using the Markov Chain Monte Carlo method was used to account for missing data (blood pressure results) for some visits.
Results: The variables recording neuropsychological test performance were reduced to two main factors (Factor 1 = selective attention; Factor 2 = complex processing). In the complete case analysis, the association between a 20-mmHg increase in diastolic blood pressure and Factor 1 remained statistically significant after adjusting for potential confounders, before adjusting for systolic blood pressure (slope = 0.60; 95%CI = 0.04,1.16), and after adjusting for systolic blood pressure (slope = 0.76; 95%CI = 0.06, 1.47). The positive slopes indicated an increase in the time spent performing a given task (i.e., a decrease in neuropsychological test performance). No other significant associations were found between systolic blood pressure and either factor. The results did not materially change after applying the multiple-imputation method.
Conclusions: An increase in diastolic blood pressure was associated with a decrease in neuropsychological test performance among older healthy postmenopausal women experiencing hot flashes.

1. Introduction

High blood pressure has been ranked as the tenth leading cause of the world's morbidity [1], which further motivates studies of high blood pressure effects. Many studies found that hypertension increased the risk of vascular diseases [2,3], which may lead to cognitive impairment, including dementia [4,5]. Such impairment has generally been measured as performance on a wide range of relevant psychological tests, such as verbal learning, verbal and non-verbal memory, attention, perceptuomotor speed, visual motor scanning, mental flexibility, letter and category fluency, executive impairment, and word finding [6]. The noticeably increased life expectancy over the past few decades and the increased prevalence of dementia after the age of 80 [7] have lead researchers to clarify the complex association between blood pressure and cognitive impairment. While one longitudinal study found that no strong linear association between blood pressure and cognition [8], another longitudinal study found that low blood pressure was associated with performance impairment on the Mini-Mental State Examination [9], and yet another case-control study found no association [10]. Another longitudinal study sug-

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gested a nonlinear relation between blood pressure and verbal memory.[6] Additionally, there has been some discussion about whether diastolic, systolic, or pulse pressure correlates most with cognitive decline [11,12]. Recent cross-sectional evidence suggests that systolic blood pressure (SBP) is highly inversely correlated with performance of psychological tests of attention, memory, verbal and spatial skills [12]. Moreover, participants in most of the above-mentioned studies were participants with a history of hypertension and on anti-hypertensive medications [6,8,10–12] or had cardiovascular diseases [9].

To our knowledge, no study has assessed the increase in blood pressure among healthy post-menopausal women experiencing hot flashes. The current study arose when we noticed an effect of blood pressure on several neuropsychological performance measures while producing a previous report [13]. In fact, it has been suggested that even among otherwise healthy people, hypertension can alter the brain's structure and function, including its ability to efficiently process information [14]. Another report had stated that normotensive SBP diminishes global cognitive performance [12], but we found no report that DBP in the normotensive range among healthy participants correlated with neuropsychological tests performance measures. Therefore, we examined how fluctuations in baseline blood pressure within the normal blood pressure range related to changes in neuropsychological tests performance among healthy postmenopausal women.

2. Materials and methods

2.1. Study population

Information used in this study had originally been collected while participants enrolled in a randomized controlled trial of an over-the-counter nutritional supplement for hot flashes. Participants included healthy postmenopausal women volunteers aged 46–73 years, experiencing hot flashes, and not under estrogen therapy. We extended this age into the 70s because almost 20% of women 70–74 years old reported very frequent or somewhat frequent hot flashes [15]. Participants were recruited through primary care practices, newspaper advertisements and hospital bulletin boards. They signed consent forms approved by the Brigham and Women's Hospital Institutional Review Board. Throughout the trial, one parallel participant group used the nutritional supplement while the other used a placebo supplement. A longitudinal study was conducted on the pooled data from active and placebo groups to examine the relationship between baseline blood pressure and subsequent neuropsychological tests performance measured at 3 different follow-up visits separated by 4 weeks. The follow-up between baseline blood pressure measurement and first follow-up neuropsychological performance assessment was one week.

2.2. Inclusion and exclusion criteria

Inclusion criteria were no menstrual cycles for the last 12 months and a minimum of five hot flashes throughout a 24-hour period. Menopausal status had been verified by Follicle Stimulating Hormone (FSH) assays in a previous study of hot flashes [16] from which data were retrospectively analyzed for the present study. The mean FSH was 64 mIU/ml (SD = 24). Hot flashes were measured by self-reported diary and questionnaires [16]. All estrogen therapy was discontinued at least 60 days prior to participants' admittance and for the remainder of the study. Participants consented not to consume new medications, nutritional supplements, or hormones except for multivitamins for the remainder of the study.

Letters from all participants' primary health care providers were received that approved participation in the study. A copy of their medical charts was also used to screen for exclusion criteria. These included SBP greater than 160 mmHg or (DBP) greater than 95 mmHg; unstable hypertension, BMI $\geq$ 35 kg/m2; major medical conditions, such as bleeding-related problems (vaginal bleeding, endometrial hyperplasia, thromboembolism, thrombophlebitis), breast cancer in the last 5 years, known or suspected neoplasia, coronary or cerebral vascular disease; lung, neurological, endocrine-metabolic, gastrointestinal, liver, or urogenital disease or allergy, sleep, bladder or disorders; addiction, current clinically treated depression; systemic infection within 7 days prior to start of study; current use of exogenous estrogen, hypnotics, sedatives or experimental medications or instruments, expected shiftwork throughout the study; and history of shiftwork in the past 6 months, or simultaneous participation in other clinical trials within 30 days prior to start of the study.

The current analysis included data from the baseline and the 3 follow-up visits from the 88 women recruited for the original study, resulting in a total of 264 observations ($n = 88 \times 3 = 264$). Participants with missing information on baseline blood pressure ($n = 1$) or neuropsychological test performance on any of the 3 visits ($n = 34$) were excluded from our main complete case analysis, resulting in a total exclusion of 106 observations. Hence, 53 participants with158 observations (1 participant had a missing observation) remained for the complete case analysis.

2.3. Outcome definition

Neuropsychological test performance was measured during 3 follow-up visits by computerized tests from Neurobehavioral Evaluation Systems (Atlanta, GA) [18], chosen for their sensitivity to subtle hormonal changes in menopausal women, as validated in several populations [17–19]. These included the following tests: (1) The 30-second finger-tapping test of motor speed, scored as the sum of one trial for the dominant hand and non-dominant hand each. Participants were instructed to press a button rapidly and repeatedly to produce their maximum number of button presses [20]; (2) The 6-minute continuous performance test of selective attention. Alphabet letters were displayed at 1 per second. Participants were instructed to rapidly push a button only when the letter 'X' appeared, which accounted for 20% of stimuli [21,22]; (3) The 7-minute switching attention test: participants were seated before a monitor screen and a small platform containing two buttons. The participants first went through learning and practice intervals for each of two different 2-choice discrimination tasks, and then performed the discrimination tasks repeatedly presented one at a time in random order. Each task started with a monitor screen that displayed one of two possible words that cued whether the next task would be the "side" or the "direction" task. The next screen displayed a large white rectangle appearing to the right or to the left on the screen, inside of which is a left- or a right- pointing arrow. As soon as the display appeared for the "side" task, the participant was to immediately push the button ipsilateral to the rectangle without delay. When the display appeared in the "direction" task, the participant was to push the button on the side towards which the arrow pointed without delay. Performance measures included reaction time, numbers of long reaction times (> 432 msec) and errors (> 2500 msec). The test engaged executive functions, such as working memory, directional sense, suppression of primed responses and planned shifting of mental set, as described elsewhere;[17] and 4) The 6-minute color-word test: A word that denoted a color was displayed approximately every 3 s. Participants were to push a button only when the displayed word was shown in the color it denoted, e.g., the word "red" displayed in the color red, rather than yellow, green or blue. The test measured inhibition of over-learned, default responses [23].