Cerebral Hemodynamics and Incident Depression: The Rotterdam Study

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Background: According to the vascular depression hypothesis, subclinical cerebrovascular disease can cause depression in older adults. To test this hypothesis, several cross-sectional studies have assessed structural brain parameters, but few have examined hemodynamic alterations in the brain.

Methods: From the Rotterdam Study, we studied a cohort of 1494 participants (65+ years of age) free of depression, dementia, and stroke at baseline. In the middle cerebral artery blood flow velocities and vasomotor reactivity were measured with transcranial Doppler ultrasonography. All participants were repeatedly assessed for depressive symptoms with Centre for Epidemiological Studies-Depression scale (CES-D). Participants with depressive symptoms (CES-D $\geq$16) had a semi-structured interview, to classify the depression according to DSM-IV criteria. All analyses were adjusted for sociodemographic data, vascular risk factors, and incident stroke.

Results: Lower peak-systolic, end-diastolic, and mean blood flow velocities at baseline were associated with higher CES-D scale scores at follow-up. Mean blood flow velocity predicted incident depressive symptoms (odds ratio [OR]: .74, 95% confidence interval [CI]: .60–.91, $p = .004$) and depressive disorders (OR: .83, 95% CI: .69–.98, $p = .032$), whereas decreased baseline vasomotor reactivity predicted incident depressive disorders only (OR: .66, 95% CI: .53–.83, $p < .001$).

Conclusions: Lower blood flow velocity, indicating reduced cerebral metabolism, predicted depressive symptoms and depressive disorders. Reduced vasomotor reactivity, which might indicate cerebral microangiopathy, predicted depressive disorders only, in healthy older adults. These findings provide prospective evidence for vascular depression hypothesis.

Key Words: Blood flow velocity, geriatric depression, incident depression, subthreshold depression, vascular depression, vasomotor reactivity

The vascular depression hypothesis suggests that subclinical cerebrovascular changes might "predispose, precipitate, or perpetuate" depressive disorders in older adults (1). This hypothesis is supported by several observations. First, depression is associated with established stroke and more mild manifestations of cerebrovascular diseases such as transient ischemic attacks as well as cerebral infarcts, which reflect small-vessel diseases (2–9). Second, late-life depression has been associated with white-matter and deep grey-matter lesions and cerebral atrophy without overt evidence of clinical cerebrovascular disease (5,10,11). Third, an association between peripheral atherosclerosis and depression has been reported repeatedly (12,13), although we could not replicate this association in a longitudinal study of the present population with several peripheral atherosclerosis indicators (14). Finally, studies exploring pathophysiological alterations of the brain showed regional cerebral hemodynamic alterations in individuals with depressive disorders (15–17). Cerebral blood flow velocity, which increases during mental activity, and vasomotor reactivity, a compensatory mechanism for maintaining constant cerebral blood flow in cerebral arterioles, are the important cerebral hemodynamic indices. It is known that cerebral hemodynamics are associated with ischemic changes in the brain that might cause stroke or white-matter lesions (18). Therefore, measuring cerebral hemodynamics allows testing cerebrovascular functions and autoregulation directly before cerebrovascular changes occur, if studies are performed longitudinally. Depressive disorders have been associated with lower global blood flow velocity and vasomotor reactivity in previous cross-sectional clinical studies (19–21). However, only depressive symptoms were cross-sectionally associated with reduced blood flow velocity and reduced vasomotor reactivity in a population-based study (22).

Despite the growing evidence, the debate about the causality of such altered cerebrovascular hemodynamics is unresolved. Because studies exploring the association between cerebrovascular hemodynamics and depression were all cross-sectional, it remains unclear whether blood flow velocity and vasomotor reactivity decrease as a result of current depression. Moreover, previous studies were mostly carried out in clinical settings and in small samples, which are more likely to suffer from selection bias. In this study, which was designed to overcome these shortcomings, we postulated that reduced cerebral blood flow velocity and vasomotor reactivity are underlying risk factors for incident depression in healthy older adults.

Methods and Materials

Study Setting and Design

This study was part of the Rotterdam Study, a prospective population-based cohort on chronic and disabling diseases in the elderly. Detailed information on the design of the Rotterdam Study has been published elsewhere (23). The Rotterdam Study has been approved by the institutional review board of the Erasmus University Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. All participants provided written informed consent after complete description of the Rotterdam Study.

Baseline measurements for the current study were done at the third examination (1997–1999). This included a home interview and a research-center visit in which cerebral transcranial Doppler ultra-

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sonography was performed and depression screening was introduced. At the fourth examination (2002–2004), depression was assessed during home interviews. Mean duration of follow-up was 4.1 years (SD = .5).

Study Population

In total, 4797 participants were involved at the third examination. We attempted to perform transcranial Doppler ultrasonography in 3104 participants. In 998 of these participants (32.2%), no results were obtained due to window failure on both sides (n = 776), restlessness/discomfort of participants during the procedure (n = 59), participant lack of time (n = 5), and other reasons (n = 158). Excluded participants were more likely to be older ($p < .001$) and female ($p < .001$). Within 2106 participants with a valid transcranial Doppler ultrasonography measurement, 32 were excluded due to lack of a complete Center for Epidemiological Studies-Depression scale (CES-D) screening and 2 were excluded due to lack of dementia screening at baseline. Furthermore, we excluded screen-positive participants (CES-D score <16) (n = 116), screen-negative participants (CES-D score <16) who were taking antidepressant treatment (n = 48), participants with dementia (n = 8), and participants with prevalent stroke (n = 43).

Of these 1857 participants, 174 died (9.4%) after the baseline interview and 142 refused to participate (7.6%) in the follow-up interview. At the follow-up visit, 1541 participants were screened with CES-D, and 47 did not have a valid CES-D interview. The final study sample thus consisted of 1494 participants. Within this study sample, the following indices of cerebral hemodynamics were available for participants as follows: end-diastolic blood flow velocity, n = 1488; peak-systolic blood flow velocity, n = 1488; mean blood flow velocity, n = 1488; and vasomotor reactivity, n = 1445.

Participants with transcranial Doppler ultrasonography measures but who were excluded from the study were older ($p < .001$) and more likely to be female ($p < .001$).

Assessment of Depression

Depressive disorders were diagnosed with a two-step procedure. First, all participants were screened for depressive symptoms on the basis of a CES-D scale (24) during the home interview at the baseline and at the follow-up visit. A cutoff of 16 was used to detect participants with clinically significant depressive symptoms. This score has a very high sensitivity for major depression in older adults in The Netherlands (25).

In the second step, screen-positive participants were invited for a semi-structured interview, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (26), which was performed by trained and experienced clinicians. Depression was categorized according to the DSM-IV-TR. The category of clinical depressive disorders included DSM-IV-TR–defined major depressive disorder, dysthymia, and depressive disorder not otherwise specified (including the former category of minor depression). Participants who were screen-positive according to CES-D; did not meet criteria for diagnoses of major depression, dysthymia, or minor depression; and had at least one core symptom of major depression (i.e., depressed mood or loss of interest) and associated with evidence of dysfunction were categorized as persons with subthreshold depression (27).

History of depression was evaluated with CES-D and Hospital Anxiety-Depression Scale in the second examination of the Rotterdam Study. A score of 16 or greater for CES-D and 9 or greater for Hospital Anxiety-Depression Scale were considered as depressive symptoms.

Transcranial Doppler Assessment

Details on the transcranial Doppler ultrasonography procedure used in the Rotterdam Study have been described earlier (28). Transcranial Doppler ultrasonography was performed (Multi-Dop X-4; DWL, Sipplingen, Germany) during the third visit of the Rotterdam Study. Cerebral blood flow velocity (cm/sec) was measured in the middle cerebral artery, on both sides when possible. End-diastolic, peak-systolic, and mean cerebral blood flow velocities were recorded automatically. All velocities were measured at a depth of 50 mm or as close as possible. If a flow velocity was measured on both sides, the mean value was used. Otherwise, the available measurement was used.

Cerebrovascular carbon dioxide (CO_2) reactivity was measured as follows: during the continuous cerebral blood flow velocity measurements, participants first breathed room air through an anesthetic mask that fitted tightly over the nose and mouth. When a steady expiratory end-tidal CO_2 had been obtained, participants inhaled a mixture of 5% CO_2 in 95% oxygen for 2 min. Cerebrovascular CO_2 reactivity was defined as a percentage increase in mean cerebral blood flow velocity during inspiration of 5% CO_2 divided by the absolute increase in end-tidal CO_2 during the same time period (%/kPa).

Covariate Assessment

Age, gender, education, cognitive function, incident stroke, hypertension, diabetes mellitus, and peripheral arterial disease were considered to be possible confounding variables, on the basis of previous publications (5,22). Education was rated from primary education to university level and then grouped into three categories: low, intermediate, and high education. Cognitive function was evaluated with the Mini Mental State Examination (MMSE). Smoking status was categorized as never, former, and current smoker, on the basis of the baseline interview. Participants with no smoking history were categorized as never smokers. Former smokers were categorized in two groups: those quitted smoking at least 10 years ago and <10 years ago. Finally, participants who were currently smoking were categorized as current smokers. Both prevalent stroke at baseline and incident stroke at follow-up were obtained through automated linkage of the study database with files from general practitioners, hospital records, and the municipality. Diabetes mellitus was defined as having fasting blood glucose concentrations ≥11.1 mmol/L or the use of anti-diabetic medication according to pharmacy records. Blood pressure was measured in the right upper arm with a random-zero sphygmomanometer after the participant had been seated for ≥5 min. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication according to pharmacy records. As an indicator of peripheral arterial disease, the ankle-brachial index was used by taking the ratio of the systolic blood pressure measured at the tibial artery to that measured at the right arm. Intima-media thickness (IMT) was measured as the average of the near and the far wall measurements of both the right and left common carotid artery. B-mode ultrasonography was performed with a 7.5-MHz linear-array transducer (ATL Ultra-Mark IV; Advanced Technology Laboratories, Bethel, Washington) (29).

Statistical Analyses

Cerebral hemodynamic variables were used continuously in all analyses. The covariates of age, education, MMSE score, ankle-brachial index, and IMT were also used as continuous variables. Gender, hypertension, diabetes mellitus, smoking status, and new-on-