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Brain volume and cognitive function in patients with revascularized coronary artery disease

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ABSTRACT

Background: The pathogenesis of cognitive dysfunction in patients with CAD remains unclear. CAD is associated with brain atrophy and specific lesions. Detailed knowledge about the association of brain volume measured with MRI, and cognitive function in patients with CAD is lacking. We therefore investigated brain volume and cognitive function in patients with revascularized coronary artery disease (CAD), and controls without CAD.
Methods: Brain MRI scans and cognitive tests from patients with CAD were compared with data from control subjects without CAD. Cognitive performance was assessed with the Rey Auditory Verbal Learning (short term memory) and Trailmaking (divided attention) tests. Multivariable regression analysis was used to study associations between CAD, brain volume and cognitive function.
Results: A total of 102 patients with CAD and 48 control subjects were included. Level of education and age were comparable between the groups. Compared with controls, patients with CAD had smaller total brain volume (expressed as fraction of intracranial volume) [%ICV, mean (SD), 0.78 (0.03) vs 0.80 (0.02), $P = 0.001$] and larger volume of non-ventricular cerebrospinal fluid [%ICV, median (IQR) 0.19 (0.18 to 0.21) vs 0.18 (0.17 to 0.20), $P = 0.001$]. Patients in the CAD group had poorer cognitive function [mean (SD) *Z*-score −0.16 (0.72) vs 0.41 (0.69), $P < 0.01$]. Multivariable regression showed that CAD, higher age, lower level of education and greater cerebrospinal fluid volume were independent predictors of poorer cognitive function.
Conclusions: CAD patients had a smaller total brain volume and poorer cognitive function than controls. Greater volume of cerebrospinal fluid was an independent predictor of poorer cognitive function.

1. Introduction

Patients with coronary artery disease (CAD) who undergo revascularization are at risk of cognitive dysfunction [1,2]. The etiology of cognitive dysfunction after coronary revascularization is not completely understood. Cerebral micro-emboli, consisting of air, atheromatous material or fat that are introduced into the circulation during such procedures have been proposed as an etiological factor [3,4]. Although it seems feasible that revascularization procedures that cause less cerebral micro-embolization would reduce cognitive dysfunction, studies have not been able to demonstrate such advantages. The avoidance of cardiopulmonary bypass during coronary artery bypass grafting (CABG) (off-pump), or avoiding surgery altogether in favor of percutaneous coronary intervention (PCI) does not improve cognitive outcome [5–7].

CAD should be regarded as the cardiac manifestation of atherosclerotic vascular disease, a systemic disease that affects vascular beds throughout the body. In a study of 582 patients scheduled for cardiac surgery with cardiopulmonary bypass, the prevalence of significant carotid artery stenosis was 22%, which illustrates that often, multiple vascular beds are significantly affected by atherosclerosis [8].

It has been shown that patients with CAD, even without a history of revascularization, have an increased risk of cognitive dysfunction [9]. Many large cohort studies, such as the Second Manifestations of ARTerial disease (SMART-MR) study [10], the Rotterdam Scan Study [11] and the AGES-Reykjavik study [12] have demonstrated that patients with CAD have more brain atrophy, more infarcts and more white matter lesions on magnetic resonance imaging (MRI), and that those changes are

Abbreviations: CABG, Coronary Artery Bypass Grafting; CAD, Coronary Artery Disease; MRI, Magnetic Resonance Imaging; PCI, Percutaneous Coronary Intervention; UDES, Utrecht Diabetic Encephalopathy Study.

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associated with cognitive dysfunction, such as reduced attention and executive function [10,13]. Detailed knowledge about brain volume and the association with cognitive function in CAD patients is lacking. This knowledge could be helpful to further clarify how cognitive dysfunction in patients with CAD is related to structural changes in the brain.

This study aims to investigate segmental brain volume and cognitive function in patients with revascularized CAD. We hypothesized that patients with CAD would have smaller brain volume and poorer cognitive function compared to controls without CAD. Brain volume measurements, acquired with MRI, and results of neuropsychological tests were compared between patients with CAD and a history of coronary revascularization, and a control group without CAD or revascularization.

2. Methods

2.1. Design

For this cross-sectional study, we used volumetric MRI-data and cognitive test results from a cohort of 102 patients with significant CAD from the OCTOSTENT trial, and compared these with data from 48 subjects without CAD, available from the control group of the Utrecht Diabetic Encephalopathy Study (UDES). The study size was based on the maximum number of available subjects from the original studies.

The OCTOSTENT trial was carried out at the University Medical Centre Utrecht (UMC Utrecht) and two non-university teaching hospitals in the Netherlands. Participants in the OCTOSTENT trial (NCT00975858) have been randomized towards percutaneous coronary intervention with stenting versus off-pump coronary artery bypass grafting between 1998 and 2001. All of the inclusion and exclusion criteria, study design and results are described elsewhere [7,14,15]. All patients who were included in this study had documented stable or unstable angina pectoris (Braunwald class I–II, b) and/or documented ischemia due to single vessel or multivessel disease. All included patients were considered candidates for PCI with stenting or off-pump CABG according to the patient's referring cardiologist. A set of pre-procedural confirmation tests was carried out, which included a review of the history, medication intake, electrocardiography and angina assessment. During a long-term follow-up study at 7.5 years after the index revascularization treatment, 102 patients underwent an MRI-scan of the brain and cognitive testing.

The UDES-study was a cross-sectional, population-based study on determinants of cognitive dysfunction in patients with diabetes mellitus. Its control group was recruited among the patients' spouses and acquaintances. Control subjects underwent an MRI-scan of the brain, as well as cognitive testing. The UDES-study was carried out at UMC Utrecht, and recruited its control group between 2002 and 2004. Its design and findings are described in detail elsewhere [16].

Both original studies were approved by the Institutional Review Board of the UMC Utrecht, and adhered to relevant national and international laws. Written informed consent was obtained from all participants.

2.2. Outcome

The primary outcome of this study was total brain volume, measured with MRI. The secondary outcome was cognitive function, measured by a set of neuropsychological tests that assess verbal memory and divided attention.

2.3. Data acquisition

2.3.1. MRI-scan

Patients and controls were scanned using to the same protocol. *A* 1.5-Tesla Philips whole body magnetic resonance imaging system (Philips Medical Systems, Best, The Netherlands) was used. The MRI protocol consisted of axial, T1 234/2 ms (repetition/echo time), T2 2200/100 ms, Inversion Recovery 2900/22 ms, and Fluid Attenuation Inversion Recovery 6000/2000/100 ms (repetition/inversion/echo time) scans, performed with 38 contiguous 4 mm slices, covering the entire brain, with a field of view of 230 × 230 mm and a 256 × 256 scan matrix.

Intracranial volumes were calculated and segmented into white matter, grey matter, cerebrospinal fluid, and white matter lesion volume using an automated probabilistic segmentation method [17]. Total brain volume is the sum of grey matter, white matter and white matter lesion volume. The automatic segmentation results were reviewed and corrected where necessary by trained investigators.

2.3.2. Cognitive tests

In both study groups, the participants originally underwent extensive neuropsychological assessment, but the test batteries were partly different. For this study, the results of the identical tests from the two batteries were compared. The tests covered the domains of verbal memory (Rey Auditory Verbal Learning, immediate and delayed recall subtests) and divided attention (Trailmaking test, subtests A and B). We multiplied the result of the timed Trailmaking test by −1, so that a higher Z-score indicates better performance in all tests. In both study groups, the original neuropsychological assessment took approximately 60–90 min to complete, and was administered by trained researchers. Cognitive test performance in each group was calculated as follows. For each of the neuropsychological tests, a *Z*-score was calculated by subtracting the total study populations mean test score from a subjects' individual test score, and dividing the residue by the study population's standard deviation. An overall cognitive function *Z*-score was calculating by adding up each participant's *Z*-scores and dividing them by the number of tests.

2.3.3. Disease variables

In the CAD group, information on the participant's medical history was extracted from the OCTOSTENT trial database. For control subjects, this information was obtained from the UDES prospective database.

2.4. Data analysis

Total brain volume and the other brain volume segments were expressed as fraction of intracranial volume to adjust for differences in skull size. Brain volumes were then compared between groups using Students' *t*-test or the non-parametric Mann–Whitney *U* test where appropriate [17,18]. The effect of CAD on brain volume was adjusted for confounding with use of a multivariable linear regression model. To compare cognitive function between the groups, the mean *Z*-score for the different tests was calculated. To pool the results of the different tests and get an overall impression of cognitive function, an overall cognitive *Z*-score was calculated. These variables were compared using Students' *t*-test. Baseline patient characteristics were compared using Students' *t* test, the Mann–Whitney *U* test, or *chi*-squared test, where appropriate. Normally distributed continuous data are presented as means with standard deviation, and not-normally distributed continuous data are presented as medians with interquartile range. Some patients could not complete all cognitive tasks. Patients with missing cognitive data were excluded from the between-groups comparison of cognitive function. A post-hoc power calculation was carried out to determine if the sample size of the control group was adequate.

To further explore the relation between brain volumes, CAD, and cognitive function, we performed a post-hoc multivariable regression analysis.

Following the Dutch educational system, a patient's level of education was scored according to the Verhage system as one of seven possible ordinal categories, ranging from 1 (no education) to 7(university). In the post-hoc regression model, reference cell coding (dummy variables) was used because linearity in this categorical system cannot be assumed. To avoid poor model fit, we collapsed the smallest categories before entering the dummy variables into the regression model.

We considered a two-sided *P*-value of 0.05 or greater to be significant and used SPSS version 18.0 for the statistical analyses.

3. Results

3.1. Patients

We included 102 CAD patients and 48 control participants in this analysis. In the original UDES-study control group, two subjects had a history of CAD, and one had highly abnormal brain volumetry results, and these were excluded. Table 1 summarizes the participants' characteristics and the prevalence of several disease variables in the study population.

There was no difference between CAD patients and control subjects' mean age or level of education. The control group contained significantly more women [60% vs. 25%, $P < 0.001$]. Of all CAD patients, 21% had suffered a previous myocardial infarction. At 7.5 years follow-up, 56 patients (55%) had a history of coronary bypass surgery, and the median number of angiographies was 2. Hypertension and hypercholesterolemia were more prevalent in the patient group, but only the difference in hypercholesterolemia was statistically significant. There were only few patients and controls with diabetes mellitus, as a result of the inclusion strategies of the original studies. Smoking was more prevalent in the CAD group, although the difference was not statistically significant.

3.2. Brain volume

The unadjusted brain volumetry findings are presented separately for men and women in Table 2. *A*djusted volumes (expressed as fraction of intracranial volume, (%ICV)) are presented in Table 3. The total brain volume of CAD patients was statistically significantly smaller, and the volume non-ventricular cerebrospinal fluid (CSF) statistically significantly larger compared to controls. CAD patients had a larger volume of white matter lesions, but this difference was not statistically significant.

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