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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. A1.5-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. Adjusted 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.

Table 1
Participant characteristics.

	CAD $N = 102$	Control $N = 48$	*P*-value
Participant characteristics			
Age, years, mean (SD)	65 (8.2)	64 (5.7)	0.50[b]
Male sex, (%)	76 (75)	19 (40)	<0.01[c]
Education, median (IQR)[a]	4 (4–5)	4 (3–5)	0.08[d]
Cardiovascular risk factors			
History of cerebrovascular events, (%)	7 (7)	0	0.15[c]
History of myocardial infarction, (%)	21 (21)	0	<0.01[c]
History of coronary surgery	56 (55)	0	<0.01[c]
Diabetes mellitus, (%)	9 (9)	2 (4)	0.49[c]
Hypertension, (%)	42 (41)	12 (25)	0.05[c]
Hypercholesterolemia, (%)	68 (67)	8 (17)	<0.01[c]
Smoking (ever), (%)	64 (63)	22 (46)	0.05[c]

CAD: coronary artery disease. LVF: left ventricular function. TIA: transient ischemic event. IQR: interquartile range.
[a] Level of education is classified according to the Verhage System and ranges from 1 (no education) to 7 (university).
[b] Student's *t* test.
[c] Chi-square test.
[d] Mann–Whitney *U* test.

After adjusting for age, sex, level of education, history of diabetes, hypertension or myocardial infarction, the effect of CAD on total brain volume was still statistically significant (adjusted β −0.008, $P = 0.03$). The model also showed an association between total brain volume and age (adjusted β −0.002 (per year), $P < 0.001$) and sex (adjusted β 0.014, $P < 0.001$).

3.3. Cognitive function

The unadjusted and adjusted results of the neuropsychological assessment are presented in Table 4. Seven patients in the CAD group had not completed at least one of the cognitive tests.

In CAD patients, the test performance was lower than in the control subjects across the four individual tests and the overall *Z*-score. The differences were statistically significant.

3.4. Post-hoc analysis

We further explored the effect of CAD and brain volumes on global cognitive function, using a multivariable linear regression model. Table 5 shows the results of the analysis. To select which brain volume parameters were to be included in the model, we first determined which brain volume parameters were independently associated with cognitive function using a separate regression model. In this model, cerebrospinal fluid volume was an independent predictor of cognitive function (cerebrospinal fluid $\beta = -0.009$, $P < 0.001$, larger cerebral spinal fluid volume is associated with poorer cognitive performance). The patient-related confounders included in the model were age, sex, level of education, smoking, hypercholesterolemia, hypertension and diabetes mellitus. In this model, CAD, higher age, lower level of education and greater cerebrospinal fluid volume were all independent predictors of poorer cognitive function.

The post-hoc power calculation showed that, based on the adjusted total brain volumes in the CAD and control groups, at a type I error (α) level of 0.05, the power ($1 - \beta$) was 0.89.

4. Discussion

We hypothesized that CAD is associated with cognitive dysfunction and a smaller total brain volume. In this cross-sectional study, we found that the total brain volume of CAD patients was 2% (expressed as fraction of intracranial volume) smaller than that of controls, and, consequently, CAD patients had more non-ventricular cerebrospinal fluid. The differences between the groups, although statistically significant, were small from a clinical perspective. CAD, increasing age, lower level of education, and greater non-ventricular cerebrospinal fluid volume were all independent predictors of poorer cognitive test performance in a regression analysis.

Table 2
Unadjusted segmental brain volumes in patients with coronary artery disease and controls, by sex.

	Men		Women	
Segment	CAD $N = 76$	Control $n = 19$	CAD $N = 26$	Control $N = 29$
Total brain volume (ml)	1139 (91)	1104 (76)	1019 (68)	1021 (75)
White matter lesions[a] (ml)	1.33 (0.94–4.54)	1.59 (0.40–2.79)	1.88 (0.99–4.29)	1.00 (0.49–2.92)
Non-ventricular CSF volume[a]	284 (263–316)	278 (245–294)	242 (225–269)	226 (210–238)
Intraventricular CSF volume[a]	28.0 (21.4–40.4)	26.9 (21.9–36.5)	24.8 (20.0–36.7)	19.9 (16.3–28.5)
Intracranial volume	1461 (106)	1409 (87)	1296 (81)	1267 (82)

Automated probabilistic segmentation on 1.5 T magnetic resonance images.
CAD: coronary artery disease. CSF: cerebrospinal fluid.
[a] Non-normally distributed volume, presented as ml, median (IQR), all other volumes presented as ml, mean (SD).

Table 3
Adjusted segmental brain volumes in patients with coronary artery disease and controls.

		CAD $N = 102$	Control $N = 48$	*P*-value
Total brain volume	Mean (SD)	0.78 (0.03)	0.80 (0.02)	**0.001**[a]
White matter lesions	Median (IQR)	1×10^3 (1×10^3 to 3×10^3)	1×10^3 (0 to 2×10^3)	0.175[b]
Non-ventricular CSF	Median (IQR)	0.19 (0.18 to 0.21)	0.18 (0.17 to 0.20)	**0.001**[b]
Intraventricular CSF	Median (IQR)	0.02 (0.02 to 0.03)	0.02 (0.01 to 0.02)	0.119[b]

Automated probabilistic segmentation on 1.5 T MR images. All volumes presented as a fraction of intracranial volume, to adjust for skull size. Non-normally distributed variables presented as median with interquartile range. CAD: coronary artery disease. CSF: cerebrospinal fluid. IQR: interquartile range.
[a] Students' *t* test.
[b] Mann–Whitney *U* test.

Table 4
Cognitive test results, per domain.

	CAD ($N = 95$)		Control ($N = 48$)		*P*-value
	Raw score[a]	*Z*-score[b]	Raw score[a]	*Z*-score[b]	
Verbal memory					
RAVL IR (words)	32 (23–40)	−0.26 (0.88)	42 (33–52)	0.58 (0.97)	<0.01
RAVL DR (words)	6 (4–8)	−0.28 (0.86)	9 (6–11)	0.54 (1.04)	<0.01
Divided attention					
Trailmaking A (s)	46 (35–56)	−0.07 (1.08)	43 (33–49)	0.25 (0.56)	0.03
Trailmaking B (s)	100 (73–142)	−0.05 (1.06)	93 (73–119)	0.25 (0.56)	0.03
Overall		−0.16 (0.72)		0.41 (0.69)	<0.01

Results of the timed Trailmaking task inverted for standardization, so that higher *Z*-scores reflect better performance in all tests.
RAVL: Rey Auditory Verbal Learning Test. DR: Delayed recall.
[a] Median (IQR).
[b] Mean (SD).

This association should be interpreted carefully because it was found in a post-hoc analysis. However, clear associations between CAD, brain volume and cognitive function have been described by other studies, such as the AGES-Reykjavik study [12,19,20]. It is important to realize that, in association studies of cognitive function and structural brain measurements on MRI, the effects are dependent on the choice of cognitive tests and population investigated [21]. We characterize our study population as a typical group of patients with a CAD for a tertiary center, in terms of age and comorbidity. All CAD patients had a history of at least one revascularization procedure, most often PCI or CABG without cardiopulmonary bypass. The cognitive test battery focused on short-term memory and attention.

The association between of CAD, brain atrophy and cognitive dysfunction suggest that the pathogenesis of CAD, brain atrophy and cognitive dysfunction share a common pathway, such as the presence of systemic atherosclerosis, or that risk factors for CAD also affect brain atrophy and cognitive function. However, because of the cross-sectional design of our study, we cannot draw any conclusions about causality of the associations between CAD, smaller brain volume and poorer cognitive function.

Table 5
Regression analysis of the effect of CAD and patient-related confounders on global cognitive function.

Univariable analysis			Multivariable analysis	
	β	*P*-value	β	*P*-value
Coronary artery disease	−0.57	<0.01	−0.40	<**0.01**
Age (years)	−0.04	<0.01	−0.03	<**0.01**
Sex (male = 0)	0.34	0.01	0.18	0.18
Smoking	−0.24	0.07	−0.12	0.27
Hypercholesterolemia	−0.34	0.01	−0.06	0.63
Hypertension	−0.18	0.16	−0.14	0.20
Diabetes mellitus	−0.07	0.78	0.06	0.74
Level of education* 4 (finished secondary school, lower level)	0.42	0.01	0.44	<**0.01**
Level of education* 5 (finished secondary school, medium level)	0.49	0.01	0.58	<**0.01**
Level of education* 6 or higher (finished secondary school, high level, college degree or university degree)	0.70	<0.01	0.95	<**0.01**
Non-ventricular CSF volume	−0.01	<0.01	−0.00	**0.06**

Dependent variable: global cognitive function. Multivariable model R^2 0.439.
Level of education classified according to the Verhage classification of the Dutch education system. Reference category is lowest levels of education (either did not finish primary school, finished primary school or did not finish secondary school).
CSF: cerebrospinal fluid.
* Dummy variables. Level of education classified according to the Verhage classification of the Dutch education system. Reference category is lowest levels of education (either did not finish primary school, finished primary school or did not finish secondary school).

4.1. Study limitations

The OCTOSTENT and UDES study were separate studies. The cognitive data and MRI volumes in the UDES group were not collected for the purpose of being used as control data for another study. The results of this study must be therefore be interpreted with some caution. However, the use of patient data collected in the same hospital has a clear advantage over published population norms. Also, the MRI data were collected with precisely the same protocol using the same MRI-scanner.

Because the control group of this study was recruited among spouses and partners of a study on diabetes mellitus, there were more women in this group compared than our group of patients with CAD. To reduce this potential bias, we controlled for the anatomic difference in brain volume between men and women by adjusting brain volumes by intracranial volume and used a multivariable analysis to control the effect of gender on the association between cognitive function and brain volumes. We considered the sample size of the control group adequate, as the calculated power was well above the generally accepted level of 0.80.

Although automated segmentation of brain volume on MRI is a well-established method, it is vulnerable to measurement errors. The investigators took great care to manually check and correct such segmentation errors. We avoided the use of white and grey matter volume as separate variables in statistical comparisons to ensure that the analyses were robust for both the CAD and control group.

In terms of validity, a longitudinal follow-up study design would give more insight into the relation between CAD, brain atrophy and subsequent cognitive dysfunction than the current cross-sectional design allows for. This is in particular true for assessments of cognitive function, which are subject to considerable natural variability over time [22,23].

Because we have only studied patients that have undergone coronary revascularization procedures, our results have limited eternal validity for populations with coronary disease who have not yet required intervention.

5. Conclusion

In conclusion, in this population of CAD patients who had a history of coronary revascularization procedures, we found that CAD patients had smaller total brain volume compared to controls. The presence of CAD, increasing age, lower level of education, and greater volume of cerebrospinal fluid were independent predictors of poorer cognitive function.

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Conflicts of interest

The authors report no industry relations or other conflicts of interest relevant to this work.

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