Subjective Cognitive Failures in Patients With Hypertension Are Related to Cognitive Performance and Cerebral Microbleeds

Renske Uiterwijk, Marjolein Huijts, Julie Staals, Annelien Duits, Ed Gronenschild, Abraham A. Kroon, Peter W. de Leeuw, Robert J. van Oostenbrugge

Abstract—Previous studies on the relationship between subjective cognitive failures (SCF) and objective cognitive function have shown inconsistent results. In addition, research on the association between SCF and imaging markers of cerebral small vessel disease is limited. We investigated whether SCF in patients with essential hypertension, who are at high risk of cerebral small vessel disease, are associated with objective cognitive function and magnetic resonance imaging manifestations of cerebral small vessel disease. We included 109 patients with hypertension who underwent extensive neuropsychological assessment, including questionnaires measuring SCF and symptoms of anxiety and depression. Brain magnetic resonance imaging was performed to rate the presence of lacunes, cerebral microbleeds, and perivascular spaces, as well as white matter hyperintensities volume. Results showed significant associations between SCF and objectively measured overall cognition (B=−0.02; 95% confidence interval=−0.03 to −0.005), memory (B=0.02; 95% confidence interval=−0.03 to 0.004), and information processing speed (B=−0.02; 95% confidence interval=−0.03 to −0.001) after adjustment for patient characteristics and vascular risk factors. In addition, SCF were associated with the presence of cerebral microbleeds (odds ratio=1.12; 95% confidence interval=1.02–1.23) after adjustment for patient characteristics and vascular risk factors but not with other imaging markers of cerebral small vessel disease. Our study demonstrates that attention for SCF in patients with hypertension is needed because these may point to lower objective cognitive function, which might be as a result of the presence of cerebral microbleeds. Accordingly, this study emphasizes that neuropsychological assessment and brain imaging need to be considered when patients with hypertension report SCF. (Hypertension. 2014;64:653-657.)

Key Words: cerebral microbleeds ■ cerebral small vessel disease ■ cognition ■ hypertension ■ subjective cognitive failures

Subjective cognitive failures (SCF) are a common feature in elderly people with cardiovascular disease.1 SCF are personal experiences of cognitive problems in everyday life, such as difficulties in memory (eg, forgetfulness), information processing speed (eg, slowness in performing simple tasks), and executive function (eg, problems in planning or reasoning). Although these subjective problems are common, it is not completely clear what they represent. The relationship with objective cognitive performance on neuropsychological assessment is unclear. Although most studies showed no relationship with objective cognitive impairment when corrected for mood and health,1–4 some studies reported positive associations.5,6 However, studies have shown a strong association with poor physical health8 and depression.9

Research on SCF in patients with hypertension is scarce, despite the increasing support for an association between hypertension and objective cognitive impairment,9–11 which might be because of brain damage. Hypertension is a major risk factor for white matter hyperintensities (WMH)12 and other magnetic resonance imaging (MRI) manifestations of cerebral small vessel disease (cSVD),13 which include lacunes, cerebral microbleeds, and perivascular spaces.14 A possible association between SCF and cSVD-related brain damage, as proposed by previous research,1,15,16 and objective cognitive impairment has not been examined before in patients with hypertension.

Patients with hypertension expressing SCF may be a recognizable situation for clinicians. To gain more knowledge about the implications of SCF in patients with hypertension, this study investigated whether SCF are associated with objective cognitive impairment, independent of confounding factors, such as age, sex, symptoms of anxiety and depression, and vascular risk factors. In addition, we examined whether SCF are predictive for the presence of MRI markers of cSVD.
Methods

Study Population
Originally, 218 patients were recruited from the hypertension outpatient clinic of the Department of Internal Medicine of Maastricht University Medical Center, The Netherlands, for a study on brain damage in patients with essential hypertension.15 Hypertension was defined as an off-medication, clinically measured conventional blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or both. Details have been described before.17 Patients who agreed to be contacted for follow-up were offered a brain MRI and cognitive assessment 5 years later, which constitutes the present (cross-sectional) study sample. Exclusion criteria were a history of symptomatic cardiovascular or cerebrovascular disease or contraindications for MRI. Age, sex, body mass index, smoking, occupational status (currently working or not working [retired, unemployed, or on sick leave]), level of education (low, average, or high), and the presence of diabetes mellitus or hypercholesterolemia were recorded. At baseline, two 24-hour ambulatory blood pressure monitorings were performed; details about the ambulatory blood pressure monitorings have been described before.14 Hypertension load was defined as known duration of hypertension (months) × the mean of the 2 baseline 24-hour mean arterial pressure values. This study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, and all participants gave written informed consent.

Cognitive Assessment
SCF were assessed with the Cognitive Failure Questionnaire (CFQ).18 This questionnaire contains 25 questions about the frequency of failures in perception, memory, and motor function. Total scores range between 0 and 100, with higher scores indicating more CF. The scale has a high internal consistency in our sample (Cronbach’s α=0.88).

Objective cognitive performance was measured with an extensive neuropsychological assessment that covered 3 main cognitive domains. The memory domain was measured with the Rey Auditory Verbal Learning Test20 (immediate recall, delayed recall, and delayed recognition) and the Digit Span Forward (subtest of Wechsler Adult Intelligence Scale-III).20 The executive function domain was measured with the Stroop Colour-Word Test21 interference score (time of part 3 minus mean time of parts 1 and 2), Trail Making Test22 interference score (time of part 2 minus time of part 1), Category (animals and professions)23 and Letter Fluency,24 Letter-Number Sequencing (subtest of Wechsler Adult Intelligence Scale-Ill).20 The function domain was measured with the Stroop Colour-Word Test21 interference score (time of part 3 minus mean time of parts 1 and 2), Trail Making Test22 interference score (time of part 2 minus time of part 1), Category (animals and professions)23 and Letter Fluency.24 Letter-Number Sequencing (subtest of Wechsler Adult Intelligence Scale-III), and Digit Span Backward (subtest of Wechsler Adult Intelligence Scale-III). Information processing speed was measured with the Symbol Substitution—Coding (subtest of Wechsler Adult Intelligence Scale-III), Trail Making Test part A, and Stroop Colour-Word Test parts 1 and 2. For each patient, compound scores of each domain were calculated by averaging the z-scores of all tests within that domain. In addition, an overall cognition compound score was calculated by averaging the 3 domain compound scores. The Rotterdam—Cambridge Cognitive Examination was used to determine the presence of possible dementia, defined as a score <34.25

Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale. This questionnaire consists of 7 items on depression (total score 0–21) and 7 items on anxiety (total score 0–21). Because symptoms possibly caused by physical problems (eg, insomnia or weight loss) are not included in the Hospital Anxiety and Depression Scale, the scale is considered to be suitable to use in somatic populations.26

MRI Data
On brain MRI scans (standard axial T2-weighted, FLAIR, and T2* gradient echo sequences, Intera 1.5-T, Philips Medical Systems, Best, The Netherlands), 2 experienced vascular neurologists (J.S. and R.v.O.) individually rated the presence of lacunes, cerebral microbleeds, and perivascular spaces. In cases of disagreement, lesions were ascertained by consensus. Lacunes were identified as sharply demarcated hypertensive lesions (<20 mm) on T2-weighted images with corresponding hypointense lesions with a hyperintense rim on FLAIR. Cerebral microbleeds were defined as punctate (<10 mm) homogenous foci of low signal intensity on T2*-weighted images. Symmetrical hypointensities in the globi pallidi were disregarded because these most likely represent calcification. Presence of lacunes or cerebral microbleeds was indicated if ≥1 lacune(s) or cerebral microbleed(s) was present. Perivascular spaces were defined as round, oval, or linear shaped lesions with a smooth margin, absence of mass effect, and with signal intensity equal to cerebrospinal fluid on T2-weighted imaging and (if visible) hypointense on FLAIR images without hyperintense rim to distinguish them from lacunes. Perivascular spaces were distinguished in 2 different areas: the basal ganglia and the white matter of the centrum semiovale. In both areas, only the most affected hemisphere was rated on 1 slice only, using a semiquantitative scale (mild–moderate–extensive).27 Presence of perivascular spaces was indicated if moderate or extensive perivascular spaces were present in that area. WMH were defined as hyperintense areas in the periventricular and deep white matter on both T2-weighted and FLAIR images. WMH volumes were semiautomatically assessed using the image-processing software package GIANT (E.G.), version 2.V1.26 (General Imaging and Analysis Tools; Department of Psychiatry and Neuropsychology, Maastricht University, Maastricht, The Netherlands).28 A trained observer (M.H.) performed the quantitative assessments after reaching excellent interobserver agreement with an experienced neuroradiologist (intraclass correlation of 0.99 for total WMH).

Statistical Analysis
The associations between CFQ score and patient characteristics and vascular risk factors were tested with independent samples t tests (for categorical variables with 2 categories), 1-way ANOVA (for categorical variables with 3 categories), Pearson correlations (for normally distributed continuous variables), or Spearman correlations (for non-normally distributed continuous variables). The relationships between total CFQ score and the overall cognition score and the scores of the 3 separate cognitive domains were investigated using simple linear regression analyses. The relationships were then adjusted for patient characteristics (age, sex, occupational status, high or low educational level, anxiety score, and depression score) with multiple linear regression analyses (entry method). Next, vascular risk factors (hypertension load, hypercholesterolemia, smoking, diabetes mellitus, and Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (SD)</td>
<td>56.1 (12.1)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>64 (58.7)</td>
</tr>
<tr>
<td>Educational level (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>27 (24.8)</td>
</tr>
<tr>
<td>Average</td>
<td>41 (37.6)</td>
</tr>
<tr>
<td>High</td>
<td>41 (37.6)</td>
</tr>
<tr>
<td>Currently working (%)</td>
<td>62 (56.9)</td>
</tr>
<tr>
<td>Median of HADS anxiety score (IQR)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>Median of HADS depression score (IQR)</td>
<td>2 (1–5)</td>
</tr>
<tr>
<td>Smokers (%)*</td>
<td>16 (14.8)</td>
</tr>
<tr>
<td>Mean MAP (SD)</td>
<td>111.2 (12.6)</td>
</tr>
<tr>
<td>Median duration of hypertension, mo</td>
<td>43.2 (13.8–129.8)</td>
</tr>
<tr>
<td>Median hypertension load (IQR)</td>
<td>4299.3 (1537.8–15182.8)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>40 (38.1)</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>27.3 (4.2)</td>
</tr>
<tr>
<td>Mean CFQ score (SD)</td>
<td>33.7 (10.3)</td>
</tr>
</tbody>
</table>

CFQ indicates Cognitive Failure Questionnaire; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; and MAP, mean arterial pressure.

*One missing value for smoking; 4 missing values for hypercholesterolemia.
body mass index) were added to these analyses (entry method). To investigate the relationship between total CFQ score and the presence of cSVD manifestations on MRI, simple logistic regression analyses were performed with CFQ score as an independent variable and the presence of each cSVD manifestation as a dependent variable. These relationships were then adjusted for patient characteristics and for both patient characteristics and vascular risk factors. The association between CFQ score and WMH volume was examined with a Spearman correlation because of the non-normal distribution of WMH volume. To adjust this correlation for patient characteristics, a linear regression analysis with the patient characteristics as independent variables and CFQ as dependent variable was performed, and standardized residuals were saved, and these residuals were then used in Spearman correlation analysis. The same procedure was used to adjust for both patient characteristics and vascular risk factors.

IBM SPSS Statistics 20 software was used for all analyses. Results were considered significant at \( P<0.05 \).

### Results

From the original 218 patients, 198 agreed to be contacted for this study, and 112 patients completed brain MRI and neuropsychological assessment. Reasons for exclusion were not interested (n=69), ischemic stroke (n=7), death (n=4), preexisting cognitive problems (n=3), or other reasons (n=3). Two patients were additionally excluded from analyses because of a Rotterdam—Cambridge Cognitive Examination score <34, and 1 patient was excluded based on a deviant score on the CFQ.

Finally, 109 patients were included in the present analyses. The included patients did not differ from the excluded patients (n=89) about age (56.1±12.1 versus 58.7±13.4 years; \( P=0.17 \)) and sex (male 58.7% versus 44.9%; \( P=0.054 \)). Compound scores for memory, information processing speed, executive function, and overall cognition were missing for 2, 1, 1, and 3 patients, respectively; therefore, analyses that included these scores were performed with different numbers of subjects. The characteristics of the patients are shown in Table 1.

### Subjective Cognitive Failures

Mean CFQ score was 33.7 (SD=10.3; range, 12–63). The CFQ score was positively correlated with age (\( r=0.22; P=0.02 \)), anxiety score (\( r=0.49; P<0.001 \)), and depression score (\( r=0.32; P=0.001 \)). Currently working patients had significant lower CFQ scores compared with patients who were retired, unemployed, or on sick leave (\( t_{107}=2.24; P=0.03 \)). There was no difference in CFQ score between sexes (\( t_{107}=1.72; P=0.09 \)), smokers and nonsmokers (\( t_{107}=1.03; P=0.31 \)), patients with and without hypercholesterolemia (\( t_{103}=-0.96; P=0.34 \)), with and without diabetes mellitus (\( t_{103}=-0.25; P=0.80 \)), or with different educational levels (\( F_{2,106}=1.44; P=0.24 \)). There was no correlation between CFQ score and body mass index (\( r=0.02; P=0.82 \)) and hypertension load (\( r=0.06; P=0.54 \)).

### SCF and Objective Cognitive Performance

In simple linear regression analyses, the CFQ score was significantly associated with overall cognition, memory, executive function, and information processing speed (Table 2). After adjusting for age, sex, high and low educational level, occupational status, anxiety score, and depression score, these associations remained significant. After additional adjustment for vascular risk factors, the associations with overall cognition, memory, and information processing speed were still significant (Table 2).

### SCF and cSVD Manifestations on MRI

The prevalence of cSVD manifestations and the median WMH volume are shown in Table 3. In unadjusted analyses, CFQ was not associated with any of the MRI manifestations of cSVD (Table 4). However, after adjustment for patient characteristics (age, sex, high and low educational level, occupational status, anxiety score, and depression score), the association between CFQ and cerebral microbleeds became significant, and this remained after further adjustment for vascular risk factors (Table 4).

### Discussion

In the present study, we investigated the association between SCF and objective cognitive function and cSVD manifestations on MRI in 109 patients with hypertension. We demonstrated that SCF were significantly related to objective

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#### Table 2. Association Between CFQ and Cognition

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
<th>Overall Cognition, ( B ) (95% CI)</th>
<th>Memory, ( B ) (95% CI)</th>
<th>Executive Function, ( B ) (95% CI)</th>
<th>Information Processing Speed, ( B ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>-0.02 (−0.04 to −0.01)*</td>
<td>-0.02 (−0.03 to −0.007)\†</td>
<td>-0.02 (−0.03 to −0.008)\†</td>
<td>-0.02 (−0.04 to −0.01)\†</td>
</tr>
<tr>
<td>Adjusted for patient characteristics \‡</td>
<td>-0.02 (−0.03 to −0.007)\†</td>
<td>-0.02 (−0.03 to −0.004)§</td>
<td>-0.01 (−0.03 to −0.002)§</td>
<td>-0.02 (−0.03 to −0.001)§</td>
</tr>
<tr>
<td>Adjusted for patient characteristics and vascular risk factors \¶</td>
<td>-0.02 (−0.03 to −0.005)\†</td>
<td>-0.02 (−0.03 to −0.004)§</td>
<td>-0.01 (−0.02 to 0.003)</td>
<td>-0.02 (−0.03 to −0.001)§</td>
</tr>
</tbody>
</table>

\( B \) indicates unstandardized regression coefficient; CFQ, Cognitive Failure Questionnaire; and CI, confidence interval.

\*\( P<0.001 \).
\†\( P<0.01 \).
\‡Age, educational level, occupational status, sex, anxiety score, and depression score.
\§\( P<0.05 \).
\¶Hypertension load, smoking, hypercholesterolemia, diabetes mellitus, and body mass index.

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#### Table 3. Prevalence of cSVD Manifestations on Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th>Presence of cSVD Manifestations</th>
<th>All Patients (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunes (%)</td>
<td>24 (22.0)</td>
</tr>
<tr>
<td>Cerebral microbleeds (%)</td>
<td>16 (14.7)</td>
</tr>
<tr>
<td>Perivascular spaces basal ganglia (%)</td>
<td>17 (15.8)</td>
</tr>
<tr>
<td>Perivascular spaces centrum semiovale (%)</td>
<td>60 (55.0)</td>
</tr>
<tr>
<td>Median of WMH volume, mm(^3) (IQR)</td>
<td>655 (146–2012)</td>
</tr>
</tbody>
</table>

cSVD indicates cerebral small vessel disease; IQR, interquartile range; and WMH, white matter hyperintensities.
cognitive function in 3 important domains, independent of age, sex, occupational status, educational level, and symptoms of anxiety and depression. After additional adjustment for vascular risk factors, overall cognition, memory, and information processing speed remained significantly related to SCF. In other patient populations, only a few studies have reported a relationship between SCF and cognitive performance. In contrast, the majority of studies reported no such association but found a relationship between SCF and mood. This discrepancy might be because of several drawbacks in these studies. Some of these studies based their SCF measure on a small number of questions about cognitive complaints, investigated memory complaints only, or used a short screening instrument for cognitive functioning, such as the Mini-Mental State Examination. In addition, no association between SCF and cognitive performance was found in patients with stroke. It is possible that this association is only apparent in healthy people, without a preceding symptomatic event, such as a stroke. This might reduce the occurrence of problems in adjustment, such as anxiety and depression, after an event. This study showed an association between SCF and the presence of cerebral microbleeds in patients with hypertension, after adjustment for patient characteristics and vascular risk factors. Only one other study also found a relationship between the presence of microbleeds and SCF. In our study, SCF were not significantly related to the presence of other cSVD manifestations, namely, WMH, lacunes, and perivascular spaces. Although not studied before in a group of patients with hypertension, this is consistent with most of the earlier results found in other populations. One study investigated the relationship in patients with cardiovascular disease, including patients with hypertension, and showed that SCF were related to WMH. However, that study did not adjust for possible confounders. Two studies found an association between WMH and SCF after adjustment for possible confounders in nondemented elderly from the general population. The contradicting results might be explained by the different sample or by a lack of statistical power in our study because our sample size was relatively small compared with these studies (n=109 versus n=1779 and n=1049, respectively).

Strengths of our study include the use of a standardized, 25-item questionnaire to determine SCF, analysis of the SCF score as a continuous variable, and the extensive neuropsychological assessment performed by the same psychologist for all patients. A limitation of the study is the cross-sectional design. Longitudinal studies in patients with hypertension are needed to examine the long-term predictive value of SCF on cognitive function and brain damage and to provide more evidence that SCF could be an early predictor of dementia, as has been suggested in other studies involving healthy elderly people.

Perspectives
The findings of our study indicate that it is necessary to inquire for the presence of cognitive complaints during consultation of patients with hypertension because SCF might be a symptom of objective cognitive impairment and cerebral microbleeds. In contrast to other studies, our results show that SCF point to an association between certain antihypertensive medications and better memory performance in patients with subjective memory complaints.

Sources of Funding
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Disclosures
None.

References
Novelty and Significance

What Is New?

- Subjective cognitive failures in patients with hypertension are associated with lower overall objective cognitive function, memory function, and information processing speed.
- After adjustment for patient characteristics and vascular risk factors, subjective cognitive failures are related to the presence of microbleeds but not to other imaging markers of cerebral small vessel disease.

What Is Relevant?

- Because patients with hypertension are at high risk of cerebral small vessel disease, it is important to identify patients with subjective cognitive failures as we demonstrated that this may point to cognitive problems and cerebral small vessel disease markers.

Summary

This study found that subjective cognitive failures in patients with hypertension may point to lower objective cognitive function and cerebral microbleeds. This study emphasizes that neuropsychological assessment and brain imaging need to be considered when patients with hypertension report subjective cognitive failures.
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