White matter hyperintensities (WMHs) and lacunes of presumed vascular origin are neuroimaging correlates of cerebral small-vessel disease and are associated with cognitive decline and functional loss, particularly in high-risk populations. Although their cause is not completely understood, they are thought to result from chronic hypoperfusion of white matter because of vessel lumen restriction, wall thickening, and loss of smooth muscle cells. Evidence supporting this mechanism comes from animal studies and cross-sectional studies in humans. These studies showed that lower cerebral blood flow (CBF) is related to more WMHs and lacunes in the general population and in patients with cardiovascular disease. Also, patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) have significantly lower baseline CBF than controls. However, because these studies are cross-sectional, it could also be hypothesized that WMHs and lacunes lead to downregulation of CBF because of reduced metabolic demand, which is a normal function of blood vessels.

We aimed to investigate the bidirectional longitudinal relationship between WMHs and lacunes and CBF during 4 years of follow-up in patients with manifest arterial disease. We hypothesize that low CBF at baseline is associated with progression of WMHs and lacunes and that severity of WMHs and presence of lacunes is associated with decline of CBF.

**Background and Purpose**—Cerebral small-vessel disease and cerebral blood flow (CBF) are interrelated. However, the direction of the relationship is unknown, and longitudinal studies are scarce. We investigated the longitudinal relationship between CBF and white matter hyperintensities (WMHs) and lacunes, as representatives of cerebral small-vessel disease, in patients with manifest arterial disease.

**Methods**—Within the Second Manifestations of Arterial Disease-Magnetic Resonance (SMART-MR) study, 1.5T brain magnetic resonance imaging, including an MR angiography, was obtained at baseline and after on average 3.9 years of follow-up in 575 patients with manifest arterial disease (mean age, 57±10 years). Longitudinal associations of WMHs and lacunes with parenchymal CBF (pCBF; per 100-mL brain volume) were estimated using regression analyses, adjusted for age, sex, follow-up time, and baseline brain measures.

**Results**—Baseline pCBF was not associated with progression of WMHs and lacunes over time. However, periventricular and deep WMHs at baseline were associated with decline in pCBF; mean (95% confidence interval) decline in pCBF per % intracranial volume increase in periventricular and deep WMH volume was –0.70 (–1.40 to –0.00) and –1.01 (–1.64 to –0.38) mL/min per 100-mL brain volume, respectively. These associations were partly explained by cardiovascular risk factors but remained significant for deep WMHs (mean decline [95% confidence interval] in pCBF per % intracranial volume increase in deep WMH volume was –0.92 [–1.56 to –0.28] mL/min per 100-mL brain volume). Lacunes were not associated with change in pCBF.

**Conclusions**—In patients with manifest arterial disease, baseline periventricular and deep WMH volumes were associated with decline in pCBF over time, but baseline pCBF was not associated with progression of WMHs and lacunes over time. (Stroke. 2015;46:1233-1238. DOI: 10.1161/STROKEAHA.114.008030.)

**Key Words:** atherosclerosis • cerebral small vessel disease • magnetic resonance imaging
Methods

Second Manifestations of Arterial Disease-Magnetic Resonance Study

Data were used from the Second Manifestations of Arterial Disease-Magnetic Resonance (SMART-MR) study, a prospective cohort study aimed at investigating brain changes on magnetic resonance imaging (MRI) in patients with manifest arterial disease.11 From 2001 to 2005, all patients newly referred to the University Medical Center Utrecht with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease, or an abdominal aortic aneurysm and without MR contraindications were invited to participate. During a 1-day visit to our institution, all patients underwent an MRI of the brain, physical examination, and ultrasonography of the carotid arteries. Blood and urine samples were collected after an overnight fast. Risk factors, medical history, and medication use were assessed using questionnaires. Between 2006 and 2009, follow-up measurements took place, including MRI of the brain.

Of the 1309 patients included, 1152 patients had adequate brain segmentation and 2-dimensional (2D) MR angiography measurements. Of these 1152 patients, 1076 were still alive at follow-up and 674 participated. Of these, 575 patients had an MRI at baseline and follow-up, and adequate brain segmentation and 2D MR angiography measurements. The SMART-MR study was approved by the ethics committee of our institution and written informed consent was obtained from all patients.

MRI Protocol and Brain Segmentation

At baseline and follow-up, MR investigations were performed on a 1.5T whole-body system (Gyroscan ACS-NT; Philips Medical Systems, Best, the Netherlands). The protocol consisted of transversal T1-weighted (repetition time [TR]/echo time [TE], 235/2 ms), T2-weighted (TR/TE, 2200/11 and 2200/100 ms), fluid-attenuated inversion recovery (TR/TE/inversion time, 6000/100/2000 ms), and inversion recovery (TR/TE/inversion time, 2900/22/410 ms) sequences. Field of view was 230×230 mm (matrix size, 180×256; slice thickness, 4.0 mm; no gap; 38 slices).11

On the basis of a localizer MR angiographic slab in the sagittal plane, we positioned a 2D phase-contrast section at the level of the skull base to measure volume flow in the internal carotid arteries and the basilar artery (TR/TE, 169 ms; flip angle, 7.5°; field of view, 250×250 mm; matrix size, 256×256; slice thickness, 5.0 mm; number of averaged signals, 8; velocity sensitivity, 100 cm/s).12

The T1-weighted, inversion recovery, and fluid-attenuated inversion recovery sequences were used for the probabilistic segmentation technique.13 The segmentation program distinguishes cortical gray matter, white matter, cerebrospinal fluid, and lesions. Total brain volume was calculated by summing the volumes of gray and white matter and, if present, the volumes of WMHs and infarcts. All volumes cranial to the foramen magnum were included. Total intracranial volume (ICV) was calculated by summing total brain volume and the volume of cerebrospinal fluid.

Cerebral Blood Flow

Image processing of the phase-contrast MR flow measurements was performed by 2 investigators.13 Flow through the left and right internal carotid arteries and basilar artery were summed to calculate total CBF (mL/min). Because total CBF strongly depends on the amount of brain tissue, we expressed total CBF per 100-mL brain volume to obtain parenchymal CBF (pCBF).

Cerebral Small-Vessel Disease

At baseline and follow-up, the whole brain was visually searched for infarcts by a trained investigator and a neuroradiologist, blinded to all information of the patient. Discrepancies in rating were reevaluated in a consensus meeting. Infarcts were defined as focal hyperintensities on T2-weighted images of ≥3 mm in diameter. Infarcts located in the white matter also had to be hypointense on T1-weighted and fluid-attenuated inversion recovery images to distinguish them from WMHs. Dilated perivascular spaces were distinguished from infarcts on the basis of their location, form, and absence of gliosis. Brain infarcts were categorized as lacunes (sized 3–15 mm in diameter and located in the subcortical white matter, thalamus, or basal ganglia), cortical infarcts, large subcortical infarcts, and infarcts located in the cerebellum or brain stem. Progression of lacunes was defined as ≥1 new lacunes at follow-up versus no new lacunes. Periventricular WMHs were defined as adjacent to or <1 cm of the lateral ventricles and deep WMHs were located in deep white matter tracts and may or may not have adjoining periventricular lesions.11 WMH volumes were normalized for ICV to correct for differences in head size and natural log transformed because of non-normal distribution.

Covariates

At baseline, height and weight were measured and body mass index was calculated (kg/m²). Mean systolic and diastolic blood pressure (mmHg) were measured twice with a sphygmomanometer and averaged. Diabetes mellitus (DM) was defined as a referral diagnosis of DM, self-reported DM, use of glucose-lowering agents, glucose ≥11.1 mmol/L, or a known history of DM. Subjects without a history of DM, but with a fasting plasma glucose of ≥7.0 mmol/L at baseline and receiving treatment with glucose-lowering agents within 1 year after baseline, were considered as having DM. Hyperlipidemia was defined as total cholesterol >5.0 mmol/L, low-density lipoprotein cholesterol >3.2 mmol/L, or self-reported use of lipid-lowering drugs. Smoking habits and alcohol intake were assessed using questionnaires. Packyears of smoking were calculated, and alcohol intake was categorized as never, former, or current. Ultrasonography was performed to measure intima-media thickness (mm) and carotid artery stenosis.

Data Analyses

Missing data rarely occur completely at random and a complete case analyses leads to loss of statistical power and biased results.13 Therefore, we used multiple imputation (10 data sets) using the statistical program R (aregImpute; version 2.10.0) to address missing values in the study sample of 575 patients. Data were analyzed using SPSS version 20.0 (Chicago, IL) by pooling the 10 imputed datasets.

Baseline characteristics were calculated according to tertiles of total WMH volume for the total study population (n=575). Between-group differences were analyzed with 1-way ANOVA for continuous variables and χ² test for proportions. Prospective associations of baseline pCBF with progression of periventricular and deep WMH volume over time were estimated with linear regression and with logistic regression analysis if risk of new lacunes was the outcome. Analyses were adjusted for age, sex, follow-up time, and baseline periventricular or deep WMH volume or baseline presence of lacunes, respectively (model 1). We additionally adjusted for systolic and diastolic blood pressure, DM, body mass index, alcohol use, pack-years of smoking, hyperlipidemia, intima-media thickness, and carotid stenosis >50% (model 2). To examine whether the associations were independent of large brain infarcts, we additionally adjusted for nonlacunes (model 3).

Prospective associations of baseline periventricular and deep WMH volume, and presence of lacunes with decline in pCBF over time were estimated using linear regression analyses. In model 1, we adjusted for age, sex, baseline pCBF, and follow-up time. Further adjustments were made according to models 2 and 3 as mentioned above. Finally, linear regression analysis was used to study whether change in WMH volume and incidence of new lacunes was associated with change in pCBF during follow-up.

Results

At baseline, the mean age of the study population was 57 (SD, 10) years and 81% were male. Median (10th–90th percentile) periventricular and deep WMH volume were 0.05 (0.01–0.22) % ICV and 0.04 (0.01–0.19) % ICV, respectively. Ninety-five...
patients had one or more lacunes. Mean (SD) pCBF was 52.3 (9.8) mL/min per 100-mL brain volume. Patients with larger WMH volume were older, had higher systolic blood pressure, more often had cerebrovascular disease, abdominal aortic aneurysm, DM, and severe carotid stenosis than patients with smaller WMH volume. They also had smaller brain volumes and more infarcts on MRI. There were no differences in pCBF for the different WMH groups (Table 1).

Baseline pCBF and Progression of WMH and Lacunes

After a mean (range) follow-up of 3.9 (3.0–5.8) years, mean (SD) increases in periventricular and deep WMH volume were 0.04 (0.11) % ICV and 0.02 (0.15) % ICV and 48 patients (8%) developed ≥1 new lacunes. Baseline pCBF was not associated with progression of WMHs and lacunes and adjusting for cardiovascular risk factors and carotid atherosclerosis did not change the effect estimates (Table 2).

Baseline WMHs and Lacunes and Change in pCBF

During follow-up, mean (SD) decline in pCBF was −1.6 (11.0) mL/min per 100-mL brain volume. Baseline periventricular and deep WMH volume were significantly associated with decline in pCBF; per % ICV increase in periventricular and deep WMH volume, mean (95% confidence interval) decline in pCBF was −0.70 (−1.40 to −0.00) and −1.01 (−1.64 to −0.38) mL/min per 100-mL brain volume (Table 3, model 1). Further adjusting for cardiovascular risk factors, carotid atherosclerosis, and nonlacunes slightly attenuated the effect estimates (Table 3, models 2 and 3). The presence of lacunes at baseline was not associated with change in pCBF (Table 3). Finally, change in WMH volume and incidence of lacunes

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### Table 1. Baseline Characteristics of the Study Sample (n=575)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tertiles of Baseline WMH (% ICV)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–0.062 (1)</td>
<td>0.062–0.14 (2)</td>
</tr>
<tr>
<td>Age, y</td>
<td>54±9</td>
<td>56±9</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>Vascular disease location, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27±3</td>
<td>27±4</td>
</tr>
<tr>
<td>Smoking, packyears*</td>
<td>19 (0–46)</td>
<td>20 (0–46)</td>
</tr>
<tr>
<td>Alcohol intake, % current</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>Baseline systolic blood pressure, mm Hg</td>
<td>138±20</td>
<td>137±19</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure, mm Hg</td>
<td>82±11</td>
<td>81±10</td>
</tr>
<tr>
<td>Follow-up systolic blood pressure, mm Hg</td>
<td>143±19</td>
<td>140±17</td>
</tr>
<tr>
<td>Follow-up diastolic blood pressure, mm Hg</td>
<td>83±12</td>
<td>81±10</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Carotid atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intima-media thickness, mm</td>
<td>0.9±0.2</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Carotid stenosis &gt;50%, %</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Brain volumes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial volume, mL</td>
<td>1460±122</td>
<td>1475±122</td>
</tr>
<tr>
<td>Total brain volume, % ICV</td>
<td>80±2.3</td>
<td>79±2.3</td>
</tr>
<tr>
<td>Cerebrovascular pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WMH volume, mL*</td>
<td>0.55 (0.19–0.87)</td>
<td>1.33 (0.98–1.78)</td>
</tr>
<tr>
<td>Periventricular WMH volume, mL*</td>
<td>0.26 (0.08–0.52)</td>
<td>0.71 (0.34–1.12)</td>
</tr>
<tr>
<td>Deep WMH volume, mL*</td>
<td>0.23 (0.05–0.49)</td>
<td>0.61 (0.32–0.98)</td>
</tr>
<tr>
<td>Lacunes, %</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Nonlacunes, %</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Parenchymal CBF, mL/min per 100-mL brain volume</td>
<td>52.5±9.3</td>
<td>52.6±9.7</td>
</tr>
</tbody>
</table>

Characteristics presented as mean±SD, unless stated otherwise. Percentage of missing values before imputation: BMI 0.2%, smoking 0.3%, alcohol intake 0.5%, hyperlipidemia 1.9%, intima-media thickness 1.4%, carotid stenosis 3.1%, and other variables 0.0%. BMI indicates body mass index; CBF, cerebral blood flow; ICV, intracranial volume; and WMH, white matter hyperintensity volume.

*Median (10th–90th percentile).
Table 2. Association Between Baseline Parenchymal CBF and Progression of WMHs and Lacunes

<table>
<thead>
<tr>
<th>Model</th>
<th>Change in Periventricular WMH (% ICV)</th>
<th>Change in Deep WMH (% ICV)</th>
<th>New Lacunes</th>
<th>OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.00 (−0.05 to 0.05)†</td>
<td>0.03 (−0.04 to 0.11)†</td>
<td>0.97 (0.69 to 1.35)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>−0.01 (−0.06 to 0.05)</td>
<td>0.03 (−0.05 to 0.11)</td>
<td>0.95 (0.67 to 1.33)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.00 (−0.06 to 0.05)†</td>
<td>0.04 (−0.04 to 0.12)</td>
<td>0.93 (0.66 to 1.31)</td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, sex, follow-up period, baseline periventricular or deep WMHs (for analyses with WMHs), or presence of baseline lacunes (for analyses with lacunes); model 2: additionally adjusted for systolic and diastolic blood pressure, diabetes mellitus, body mass index, alcohol use, packyears, hyperlipidemia, intima-media thickness, and carotid stenosis >50%; model 3: additionally adjusted for nonlacunes. CBF indicates cerebral blood flow; CI, confidence interval; ICV, intracranial volume; OR, odds ratio; pCBF, parenchymal CBF; and WMH, white matter hyperintensity volume (natural log transformed).

Discussion

In a large cohort of patients with manifest arterial disease, lower pCBF was not associated with progression of WMHs and lacunes. However, periventricular and deep WMH volumes were associated with a decline in pCBF during 4 years of follow-up.

More WMH can lead to relatively less normal cerebral tissue, with subsequent decrease in brain activity. As a result, less CBF is necessary to supply the brain with oxygen and nutrients. Indirect support for this hypothesis comes from studies in cognitively healthy individuals showing that severity of WMH is related to reduced glucose metabolism. However, other findings contradict this hypothesis. For instance, studies in patients with WMHs that investigated the balance between perfusion and metabolic demand provided conflicting results with some showing impaired and others showing preserved oxidative metabolism in addition to reduced CBF. Also, we found no association between baseline pCBF and WMH volume although other cross-sectional studies did.

The finding that WMHs but not the presence of lacunes was associated with changes in pCBF over time could be because WMHs cause more widespread hypometabolism and reduction of CBF, whereas the CBF effect of lacunes is probably more local and depends on the location of the infarct. Another explanation could be that WMHs trigger endothelial dysfunction by impairing nitric oxide synthesis, which is normally responsible for relaxation of vascular smooth muscle cells in response to decrease in perfusion pressure. As a result, cerebrovascular resistance in areas with WMHs will be impaired, which might result in CBF decline. Both deep and periventricular WMHs were associated with decline in CBF. Several studies have attributed different causes and behavioral consequences to the 2 classes of WMHs. However, periventricular, deep, and total WMHs are highly correlated; within both types of WMH, there is vascular fibrosis and lipohyalinosis, supporting a common ischemic vascular pathological mechanism for WMHs.

Although it is plausible that chronic cerebral hypoperfusion leads to ischemic brain lesions, our longitudinal study does not support this hypothesis. This ischemic mechanism has been demonstrated in animals; however, human studies studying the effect of lower CBF on development of WMHs and lacunes are scarce and cross-sectional. A possible explanation for the lack of an association between baseline pCBF and progression of WMHs and lacunes could be that they represent different pathological processes. The development of WMHs and lacunes could be the result of mechanisms unrelated to hemodynamic processes, such as neurodegeneration and genetic predisposition. Circulating β-amyloid peptides have been associated with more WMHs in patients with cognitive impairment and in CADASIL patients, only cerebrovascular resistance and not CBF itself had prognostic value for WMH development. These studies suggest that other factors than cerebral hypoperfusion play a role in the pathogenesis of WMHs. Another possibility could be that our follow-up period was not long enough to show an association between pCBF and progression of WMHs and lacunes; cerebral perfusion may need to decrease below a certain threshold before...
it will result in ischemia-related injury. If this is the case, the relationship between WMHs and CBF decline might be part of a cascade, and by preventing CBF decline and WMH progression, consequent cognitive and physical decline might be prevented. Smaller nonrandomized studies have shown that CBF could be increased by increasing systemic blood pressure, the use of angiotensin receptor blockers, or exercise training. However, randomized studies should be performed to investigate the efficacy of these possible interventions.

Strengths of our study include the longitudinal design and the available data on quantitative measurements of pCBF, WMHs, and lacunes, which allowed us to examine the bidirectional relationships between pCBF, WMHs, and lacunes over time in a large cohort of patients with manifest arterial disease. The extensive information on cardiovascular risk factors and other cerebrovascular lesions allowed us to investigate the independent associations between pCBF, WMHs, and lacunes.

Limitations of this study are, first, that participants in the follow-up examination represent a relatively healthy group, which may have led to an understimation of the progression of WMHs and lacunes and decline in pCBF. Second, CBF divided by total brain volume (pCBF) is an indirect measure of cerebral perfusion, and no information was available on regional differences in cerebral perfusion. The value of regional perfusion measures has been shown in studies where WMHs were more often present in regions with lower perfusion values. Third, we had no data on flow in the cerebellar arteries although we did include the cerebellum in the total brain volume. Fourth, no information was available on other components that determine cerebral hemodynamics, such as cerebrovascular reactivity. Finally, as our study sample consisted of patients with manifest arterial disease, we do not know to what extent our results are generalizable to the general population.

Conclusions

In patients with manifest arterial disease, larger baseline periventricular and deep WMHs were associated with decline in pCBF after 4 years, but reduced baseline pCBF was not associated with progression of WMHs and lacunes. Future longitudinal studies with longer follow-up periods could further elucidate the possible bidirectional relationship between cerebral hyperperfusion, WMHs, and lacunes.

Appendix

The Second Manifestations of Arterial Disease-Magnetic Resonance (SMART-MR) Study Group of University Medical Center Utrecht; A. Algra, MD, PhD, Julius Center for Health Sciences and Primary Care and Department of Neurology; P.A. Doevendans, MD, PhD, Department of Cardiology; Y. van der Graaf, MD, PhD, D.E. Grobbbee, MD, PhD, and G.E.H.M. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care; L.J. Kappelle, MD, PhD, Department of Neurology; W.Th.M. Mali, MD, PhD, Department of Radiology; F.L. Moll, MD, PhD, Department of Vascular Surgery; F.L.J. Visseren, MD, PhD, Department of Vascular Medicine.

Disclosures

None.

References


Longitudinal Relationship Between Cerebral Small-Vessel Disease and Cerebral Blood Flow: The Second Manifestations of Arterial Disease-Magnetic Resonance Study
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