Ambulatory Blood Pressure in Patients With Lacunar Stroke
Association With Total MRI Burden of Cerebral Small Vessel Disease

Pim Klarenbeek, MD; Robert J. van Oostenbrugge, MD, PhD; Rob P.W. Rouhl, MD, PhD; Iris L.H. Knottnerus, MD, PhD; Julie Staals, MD, PhD

Background and Purpose—Asymptomatic lacunar infarcts, white matter lesions, cerebral microbleeds, and enlarged perivascular spaces are MRI markers of cerebral small vessel disease (cSVD). Higher blood pressure (BP) levels are associated with the presence of these markers separately, but the association with the total burden of cSVD on brain MRI, expressed by the simultaneous presence of multiple markers of cSVD (a compound score), has not been investigated.

Methods—We performed 24-hour ambulatory BP monitoring in 122 patients with first-ever lacunar stroke. On brain MRI, we scored the presence of each marker of cSVD. One point was awarded for the presence of each marker, producing a score between 0 and 4. Associations with BP levels were tested with ordinal regression analyses.

Results—Eighteen (15%) patients had no markers of cSVD, and 6 (5%) patients had 4 markers. Most patients (45; 37%) had 2 different markers. After correction for age and sex, higher 24-hour, day, and night systolic (24-hour odds ratio, 1.25; 95% confidence interval, 1.02–1.52 per 10 mm Hg) and diastolic (24-hour odds ratio, 1.32; 95% confidence interval, 1.12–1.56 per 5 mm Hg) BP were all significantly associated with an increasing total burden of cSVD.

Conclusions—We found a positive association of ambulatory BP levels with total burden of cSVD on brain MRI. With increasing BP levels, there is a piling up of damage in the brain. We suggest that further cSVD studies also consider viewing the total burden in addition to each of the MRI markers separately.

Key Words: blood pressure monitoring, ambulatory ▶ cerebral microbleeds ▶ cerebral small vessel diseases ▶ enlarged perivascular spaces ▶ lacunar infarcts ▶ white matter lesions

Ambulatory Blood Pressure in Patients With Lacunar Stroke
Association With Total MRI Burden of Cerebral Small Vessel Disease

A

symptomatic lacunar infarcts, white matter lesions, cerebral microbleeds, and enlarged perivascular spaces have all been identified as silent MRI markers of arteriolar sclerotic cerebral small vessel disease (cSVD). A pathological process involving the small arteries and arterioles of the brain. However, because these markers are associated with increased stroke and mortality risk and worse functioning on domains as gait and cognition, they should not be disregarded.

Elevated blood pressure (BP) is considered to be an important and modifiable risk factor for cSVD. Previous studies showed that elevated BP levels are associated with each of the MRI markers of cSVD separately. However, these studies did not provide an overall measure for the total burden of cSVD. Because these markers may occur simultaneously in a patient and are all considered to be caused by cSVD, it seems rather artificial to investigate the presence of only 1 MRI marker while disregarding the others.

Therefore, we devised a simple, pragmatic ordinal scale to express the total MRI burden of cSVD based on the presence of the 4 previously mentioned MRI markers of cSVD. We investigated the association between BP levels and this scale in a cohort of patients with first-ever lacunar stroke. We hypothesized that the finding of an association would not only firmly substantiate the well-known association between BP and cSVD, but would also support the validity of this scale because BP is considered as an important risk factor for cSVD.

We used ambulatory BP monitoring because it is proven to be a stronger predictor of BP-related end-organ damage than single office BP measurements.

Methods

Patient Recruitment
Patient recruitment has been described in detail elsewhere. Briefly, we prospectively recruited patients with a first-ever lacunar stroke at Maastricht University Medical Center from May 2003 to January 2008 and at Orbis Medical Center Sittard, The Netherlands from September 2004 to April 2007. Lacunar stroke was defined as an acute lacunar stroke syndrome with a small, deep infarct on MRI compatible with the clinical findings, or, if MRI did not show a compatible lacunar lesion, one of the established clinical lacunar stroke syndromes. With informed consent, the patients participated in a lacunar stroke research project that was approved by the local ethics committee. We recorded the following vascular risk factors: age, sex, diabetes mellitus, current smoking, and hypercholesterolemia (total cholesterol level >5 mmol/L). We excluded patients with a clinical

Received June 18, 2013; accepted July 18, 2013.
From the Department of Neurology (P.K., R.J.v.O., R.P.W.R., I.L.H.K., J.S.), and Cardiovascular Research Institute Maastricht (CARIM) (R.J.v.O., J.S.), Maastricht University Medical Centre, Maastricht, The Netherlands.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002545/-/DC1.

Correspondence to Pim Klarenbeek, MD, Department of Neurology, Maastricht University Medical Center, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail p.klarenbeek@mmuc.nl

© 2013 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.113.002545
lacr
stroke syndrome but with a possible cardioembolic source (most commonly atrial fibrillation or a valvular prosthesis) or ≥50% ipsilateral carotid stenosis to ensure as much as possible that all patients have their stroke from cSVD.

MRI Scoring
MR images were obtained with a 1.5 T or 3.0 T MR scanner (Philips, The Netherlands) as soon as possible and within 6 months after stroke (mean, 43±44 days). We obtained standard axial T2-weighted fast spin echo-images, axial fluid–attenuated inversion recovery images, and T2-weighted gradient echo-images. MRI sequence parameters can be found in the online–only Data Supplement. All images were independently rated by 2 vascular neurologists for the presence of asymptomatic lacunar infarcts, white matter lesions, cerebral microbleeds, and enlarged perivascular spaces. In case of disagreement, a consensus meeting was held. The interobserver agreement for the presence of the different markers of cSVD, determined before this study, was substantial to excellent.1,17

We composed a scale incorporating all 4 abovementioned MRI markers of cSVD. The presence of each of these markers was awarded with 1 point, producing a minimum score of 0 and a maximum of 4, creating an ordinal scale with increasing manifestations of cSVD on brain MRI, representing an increasing burden of cSVD.

Asymptomatic Lacunar Infarcts
We defined asymptomatic lacunar infarcts as hypointense lesions on T2-weighted images with corresponding hypointense lesions with a hyperintense rim on fluid–attenuated inversion recovery, located in the basal ganglia, thalamus, internal or external capsule, or brain stem with a diameter <20 mm and not compatible with clinical findings. One point was awarded if ≥1 asymptomatic lesions were present.

White Matter Lesions
White matter lesions were graded using the Fazekas score.18,19 One point was awarded if (early) confluent deep white matter hyperintensities (Fazekas score 2 and 3) or irregular periventricular hyperintensities extending into the deep white matter (Fazekas score 3) were present. We used these Fazekas scores because they are histopathologically related to cSVD.19

Cerebral Microbleeds
Cerebral microbleeds were defined as rounded hypointense lesions on T2-weighted gradient echo-images with a diameter <10 mm. Symmetrical hypointensities in the globi pallidi, likely to represent calcification, sulcal flow voids from cortical vessels, and hypointensities possibly due to partial volume artifacts from bone were disregarded. One point was awarded if ≥1 deep cerebral microbleeds were present (ie, in the basal ganglia, thalamus, and internal or external capsule).12 We only considered deep cerebral microbleeds because the available evidence suggests that these are more specifically related to (BP-related) arteriосlerotic cSVD, while lobar cerebral microbleeds are related to amyloid angiopathy.12,20

Enlarged Perivascular Spaces
Enlarged 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 images, and (if visible) hypointense on fluid–attenuated inversion recovery images without a hyperintense rim to distinguish them from old lacunar infarcts.21 For the present study, we only counted enlarged perivascular spaces at the level of the basal ganglia because at this level they seem specifically associated with cSVD.4,12 We counted enlarged perivascular spaces on the slide with the highest number in 1 hemisphere and graded them in a formerly used 3-category ordinal scale (0–10; 10–25; >25).14 One point was awarded if moderate to extensive (10–25 or >25) enlarged perivascular spaces were present.

BP Measurements
Ambulatory BP monitoring (using Mobil O Graph equipment, IEM GmbH) during a 24-hour period was performed after the acute stroke phase, between 1 and 6 months after stroke (mean, 101±41 days). Details were described elsewhere.13 We calculated mean 24-hour, day, and night systolic and diastolic BP. Patients continued their prescribed medication, and we registered the use of antihypertensive drugs.

Statistical Analysis
Statistical analysis was performed using SPSS version 20.0 (Chicago, IL). Data are presented as n (%) for categorical variables or as mean±SD for parametric data. Differences between groups were determined using χ2, independent samples t test, ANOVA or Kruskal–Wallis where appropriate. We assessed the relationship between BP levels and the number of MRI markers of cSVD by ordinal regression analyses adjusting for age and sex. To test age as an effect modifier, we added the relevant interaction terms to our regression model. We also performed additional exploratory analyses by additionally adjusting for the recorded vascular risk factors and the number of antihypertensive drugs used by each patient. To explore independency of BP characteristics, we performed ordinal regression analyses with the corresponding systolic and diastolic BP simultaneously (respectively, 24-hour, day, and night), and with the corresponding day and night BP simultaneously (respectively, systolic and diastolic), all with correction for age and sex. Finally, we analyzed association between BP and presence of each MRI marker separately by performing logistic regression analyses, adjusting for age and sex. Statistical significance was considered at P<0.05.

Results
Patient Characteristics
We included 122 patients in this study. Details of patient selection can be found in the online–only Data Supplement. Table 1 presents the characteristics of all included subjects. Mean age was 64.6±11.7 years. Mean 24-hour BP was 139/82 (±17/11) mm Hg, and 80 (65.6%) patients were on antihypertensive medication. We did not record data on previous BP levels or previous treatment. Ninety-three of 122 (76.2%) patients were scanned at 1.5 T; the remaining 29 (23.8%) patients were scanned at 3.0 T. Asymptomatic lacunar infarcts were present in 68 (56%) patients.
in 77 (63.1%) patients. White matter lesions, ≥1 deep cerebral microbleeds, and enlarged perivascular spaces were present in 46 (37.7%), 17 (13.9%), and 85 (69.7%) patients, respectively.

**Total Burden of cSVD on MRI**

Eighteen (14.6%) patients had no markers of cSVD, whereas 6 (4.9%) patients had all of them. Most patients (n=45; 36.9%) had 2 different markers. Between the 5 categories with an increasing burden of cSVD, age differed significantly with higher age in higher categories (55.4±8.5, 62.7±12.0, 65.5±11.9, 69.0±10.2, 71.4±7.0 years, respectively; *P*<0.001, ANOVA). Sex, the presence of vascular risk factors, and the use of antihypertensive drugs did not differ significantly between categories. The Figure shows which combinations of markers of cSVD are present in patients with 1, 2, or 3 markers on MRI. Within each category, BP values did not differ between patients with different combinations of markers (data not shown).

**Associations With Ambulatory BP**

Table 2 shows the associations between the total burden of cSVD and various ambulatory BP levels. Higher 24-hour, day, and night systolic and diastolic BP were all significantly associated with an increasing number of different markers of cSVD, with adjustment for age and sex. Age was no effect modifier for the association between BP levels and the severity of cSVD. Exploratory analysis with additional adjustment for either one of the other vascular risk factors or the number of antihypertensive drugs did not change the results significantly.

When entering multiple BP variables simultaneously in the regression model, we found that diastolic BP was associated with total burden of cSVD independently of systolic BP, for 24-hour, day, and night values, respectively. The associations of day and night BP levels (systolic or diastolic, respectively) with SVD burden were not independent from each other (results not shown).

We also investigated the association of 24-hour ambulatory BP levels and the different MRI markers of cSVD separately (Table 3). There was a significant positive association between 24-hour systolic and diastolic BP and the presence of asymptomatic lacunar infarcts and cerebral microbleeds after correction for age and sex. Enlarged perivascular spaces were only associated with 24-hour diastolic BP, and we found no association between 24-hour BP and white matter lesions.

**Discussion**

In this study in 122 patients with first-ever lacunar stroke, we expressed the total MRI burden of cSVD by the number of different markers of cSVD simultaneously present on brain MRI. We demonstrated that higher ambulatory 24-hour, day, and night systolic and diastolic BP levels are associated with an increasing total burden of cSVD after adjustment for age and sex.

The association between higher (ambulatory) BP levels and the presence and extent of white matter lesions or asymptomatic lacunar infarcts is well known and has been extensively investigated.15,23,24 In our cohort, we found no association between BP and white matter lesions. Probably, measuring white matter lesions volumetrically would yield different results. In past years, cerebral microbleeds have become generally accepted as a third subclinical marker of cSVD.3,12,25 Enlarged perivascular spaces are only recently recognized as a marker of cSVD.18 These 2 markers were also found to have a positive association with increasing BP levels, which we confirmed in our cohort.12 However, all former research has focused on individual MRI features of cSVD without recognizing the combined components as one disorder.6 Proceeding from this point, we investigated the combined presence of the 4 MRI markers as a measure for total burden of cSVD. Our findings underline the importance of a high 24-hour BP load as a risk factor for severity of cSVD.

To assess the total burden of cSVD is certainly more complex than the method we used. Not only should all different MRI markers of cSVD be taken into account, but the extent, location, and progression of each individual marker are also important aspects. We did take into account the location of brain microbleeds (we only considered deep cerebral
Enlarged perivascular spaces and cerebral microbleeds are known to occur in the setting of cerebral small vessel disease (cSVD). Although, for example, the absolute number of asymptomatic lacunar infarcts and cerebral microbleeds were not incorporated into our scale, we did not distinguish between deep and periventricular white matter lesions, and we dichotomized all markers. With the limitations of our study in mind, we made a first attempt to provide an overall score for burden of cSVD. We found an accumulation of different markers of cSVD with increasing BP levels. There was however no clear trend in the order in which the MRI markers appeared and almost any combination occurred. The pathogens of the brain damage that results from cSVD might be heterogeneous and is not completely known. Undoubtedly, besides BP there are other factors involved that will determine the eventual combination of brain damage visible on MRI in the individual patient.

Enlarged perivascular spaces were most prevalent in our cohort. Elevated BP may cause endothelial and blood–brain barrier dysfunction, which has been suggested as a main initial pathogenic feature in cSVD. Because blood–brain barrier dysfunction first leads to leakage of fluid and blood products into the vessel wall and perivascular space, it may be suggested that enlarged perivascular spaces are an early marker of blood–brain barrier dysfunction. This is supported by a recent pathological study in the brains of patients with dementia that observed that enlarged perivascular spaces are seen more frequently than lacunar infarcts and white matter lesions, suggesting that these appear early in the course of cSVD.

Remarkably, we found that cerebral microbleeds were never a single marker but always occurred in combination with other silent markers, which could indicate that cerebral microbleeds occur preferentially in more advanced cSVD. However, a longitudinal study is needed to confirm this observation.

Our study has limitations. First, it is cross-sectional. Results of ambulatory BP monitoring represent the actual BP level without accounting for BP level and treatment in the past. We cannot exclude that BP levels changed as a consequence of increasing brain damage attributable to cSVD. Longitudinal studies are needed to confirm a causal relation of BP levels and the total burden of cSVD. Second, our patient selection favors less disabled patients, able to undergo MRI. However, this selection bias would probably lead to an underestimation of the association between the total burden of cSVD and BP levels. Third, not all patients were scanned at the same field strength, which potentially introduced bias into our results, especially regarding the yield of cerebral microbleeds. However, most patients with microbleeds in our cohort happened to be scanned at 1.5 T (14/17), so we think that possible higher lesion detection of microbleeds at 3T will not have introduced much bias. To further exclude the possibility of bias, we repeated our main analysis with only those patients scanned at 1.5 T, the results remained largely unchanged. Fourth, diffusion-weighted imaging to confirm the acute symptomatic lacunar infarct was not part of the standard imaging protocol when we started this study. However, because all patients had a distinct clinical lacunar stroke syndrome, we think that this did not lead to unrightfully included patients. Fifth, we did not correct for multiple testing on the associations of the burden of cSVD on brain MRI. Further studies are now needed to validate and refine this scale.

### Table 2. Ambulatory Blood Pressure Levels in Relation to the Total Burden of Cerebral Small Vessel Disease

<table>
<thead>
<tr>
<th>Mean BP, mm Hg</th>
<th>cSVD 0 (n=18)</th>
<th>cSVD 1 (n=24)</th>
<th>cSVD 2 (n=45)</th>
<th>cSVD 3 (n=29)</th>
<th>cSVD 4 (n=6)</th>
<th>OR Adjusted for Age and Sex (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>132±14</td>
<td>138±15</td>
<td>140±18</td>
<td>142±18</td>
<td>141±12</td>
<td>1.25 (1.02–1.52)*</td>
</tr>
<tr>
<td></td>
<td>79±9</td>
<td>81±10</td>
<td>83±13</td>
<td>85±12</td>
<td>81±4</td>
<td>1.32 (1.12–1.56)†</td>
</tr>
<tr>
<td>Day</td>
<td>136±13</td>
<td>141±15</td>
<td>145±19</td>
<td>147±19</td>
<td>146±12</td>
<td>1.25 (1.03–1.51)*</td>
</tr>
<tr>
<td></td>
<td>82±9</td>
<td>83±10</td>
<td>86±14</td>
<td>88±13</td>
<td>83±4</td>
<td>1.30 (1.12–1.52)†</td>
</tr>
<tr>
<td>Night</td>
<td>115±19</td>
<td>126±17</td>
<td>125±20</td>
<td>129±16</td>
<td>130±17</td>
<td>1.21 (1.01–1.45)*</td>
</tr>
<tr>
<td></td>
<td>68±12</td>
<td>72±11</td>
<td>73±12</td>
<td>75±10</td>
<td>73±9</td>
<td>1.32 (1.13–1.55)†</td>
</tr>
</tbody>
</table>

Results of ordinal regression analysis presented as odds ratio (OR) per 10 mm Hg increase in systolic blood pressure (SBP) or 5 mm Hg in diastolic blood pressure (DBP). CI indicates confidence interval; cSVD 0–4, categories of the cerebral small vessel disease severity scale; and OR, odds ratio.

*P<0.05.
†P<0.001.

### Table 3. Ambulatory Blood Pressure Levels in Relation to the Different Markers of cSVD Separately

<table>
<thead>
<tr>
<th>Mean BP, mm Hg</th>
<th>Asymptomatic Lacunar Infarcts</th>
<th>Extensive White Matter Lesions</th>
<th>Enlarged Perivascular Spaces</th>
<th>Cerebral Microbleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>1.28 (1.02–1.63)*</td>
<td>0.89 (0.70–1.14)</td>
<td>1.26 (0.97–1.63)</td>
<td>1.42 (1.04–1.93)*</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>1.28 (1.05–1.56)*</td>
<td>1.07 (0.89–1.31)</td>
<td>1.32 (1.05–1.65)*</td>
<td>1.28 (1.00–1.63)*</td>
</tr>
</tbody>
</table>

Results are presented as odds ratio (OR) per 10 mm Hg increase in systolic blood pressure (SBP) or 5 mm Hg in diastolic blood pressure (DBP). All analyses are after correction for age and sex. cSVD indicates cerebral small vessel disease.

*P<0.05.
of cSVD with multiple different BP characteristics. However, because the results were consistent across all BP characteristics, the possibility that these are all false-positive findings is unlikely. Despite these limitations, the main strength of our study is that we collected a substantial homogeneous cohort of patients with lacunar (small vessel) stroke, with a substantial prevalence of MRI markers of cSVD. Investigating the total burden of cSVD in other populations with lower prevalence of cSVD is needed.

In conclusion, we found a positive association of day and night systolic and diastolic BP levels with an increasing total burden of cSVD in other populations with lower prevalence of cSVD. With increasing BP levels, there is a piling up of damage in the brain attributable to cSVD. We suggest that further research into the clinical consequences of cSVD, such as cognition, also consider the total burden of cSVD in addition to each of the MRI markers separately.

Disclosures

None.

References

Ambulatory Blood Pressure in Patients With Lacunar Stroke: Association With Total MRI Burden of Cerebral Small Vessel Disease
Pim Klarenbeek, Robert J. van Oostenbrugge, Rob P.W. Rouhl, Iris L.H. Knottnerus and Julie Staals

Stroke. published online August 27, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2013/08/27/STROKEAHA.113.002545

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/08/27/STROKEAHA.113.002545.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Ambulatory blood pressure in lacunar stroke patients: association with total burden of cerebral small vessel disease

Pim Klarenbeek, Robert J. van Oostenbrugge, Rob P.W. Rouhl, Iris L.H. Knottnerus, Julie Staals

Supplemental methods

MRI sequence parameters

1.5T: T2-weighted turbo spin echo sequence (TR/TE = shortest(5144)/100 ms), T2*-weighted gradient echo sequence (TR/TE = shortest(783)/23 ms) and FLAIR sequence (TR/TI/TE = 8000/2000/120 ms), all with slice thickness 5mm and 0.5mm interslice gap.

3.0T: T2-weighted turbo spin echo sequence (TR/TE = 3000/80 ms), T2*-weighted gradient echo sequence (TR/TE = shortest(794)/16 ms) and FLAIR sequence (TR/TI/TE = 11000/2800/125 ms), all with slice thickness 5mm and 0.5mm interslice gap.

Supplemental results

Patient recruitment data

From May 2003 to January 2008 281 patients with a first-ever lacunar stroke presented at Maastricht University Medical Centre, 35 were excluded because of potential cardioembolic source or symptomatic carotid artery stenosis, 116 patients had contra-indications for MRI or refused participation, 34 subjects were excluded because of inadequate MRI or ambulatory blood pressure data, leaving 96 patients. There were more males among the included patients (62.9% vs. 47.0%, p<0.05); age did not differ significantly between included and excluded patients. By applying the same criteria we recruited 26 patients from Orbis Medical Centre Sittard (number and characteristics of non-included patients were not listed), which totals 122 patients for the current study.