Small Vessel Disease of the Brain and Stroke: Association with Clinic and Ambulatory Blood Pressure

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ABSTRACT

Several potential vascular risk factors exist for the development and accumulation of small vessel disease of the brain and stroke in older people. In older people followed up for several years, we and others have reported that white matter hyperintensity lesions on magnetic resonance imaging nearly doubled in volume and were associated with alterations in neurologic function. In this article, we review blood pressure (BP) as a risk factor for the development and pathogenesis of small vessel disease and stroke in older persons. The research efforts have focused on ambulatory BP measurements, which have proven to be a stronger indicator than clinic pressures for the progression of small vessel disease in older people as well as the development of stroke. Based on relations among 24 hour systolic BP levels, the accrual of small vessel disease, and relations with cognitive function and mobility, we have designed the INFINITY trial, a novel interventional study that uses ambulatory BP to guide antihypertensive therapy addressed at improving functional decline.

Keywords: Ambulatory blood pressure, Cerebral small vessel disease, Stroke, Systolic hypertension.

INTRODUCTION

Cerebrovascular Disease, Hypertension, and Functional Decline

Small vessel brain disease that is represented by white matter hyperintensity (WMH) lesions on magnetic resonance imaging (MRI) is associated with vascular risk factors, including hypertension, in older people. Postmortem histopathology of WMH shows nonspecific brain changes with gliosis, loss of myelin and axons from arteriosclerosis, tissue rarefaction, and lipohyalinosis. Although the pathophysiology of WMH remains unclear, there are several proposed mechanisms, including hypoxia, hypoperfusion due to altered cerebrovascular auto-regulation, blood–brain barrier leakage, inflammation, degeneration, and amyloid angiopathy. Marstrand and colleagues demonstrated that cerebral blood flow and cerebrovascular reactivity were reduced in areas of WMH, making tissue damage more likely during hypoperfusion states.

In most instances, WMH lesions are bilateral and symmetrical on T2-weighted MRI. They are distributed in the periventricular and deep white matter regions and less frequently in the infratentorial areas of the brain. On computed tomography (CT) scan, WMH lesions appear as hypodensities. They are commonly assessed using visual rating scales, such as Fazekas scale and Scheltens scale. Another approach uses semi-automated, computerized analyses of the MRIs providing a quantitative distribution of cerebral SVD lesions suitable for longitudinal numerical comparisons and regional localizations.

Cognitive Function

Higher degrees of small vessel disease burden are associated with impaired cognitive function, mobility impairment, depression, and impaired urinary function. The frequency of falls even in the absence of obvious neurologic deficits is more common in people with WMH lesions. Cognitive dysfunction has been studied extensively in persons with WMH lesions on MRI. Perceived cognitive dysfunction as measured by Cognitive Difficulties Scale was found to be worse with higher WMH burden and the annual rate of decline on the mini-mental status examination (MMSE) was 0.035 points per standard deviation increase in periventricular WMH. In addition, steeper declines in performance have been found on measures of speed of processing and executive functioning, such as the Stroop Color Word test (p = 0.04) and the Symbol-Digit Substitution Test (p < 0.01) are seen with WMH lesions, whereas performances on memory tests, such as the 15-word verbal learning test are not as affected. Over a decade, the European Leukoaraisis...
and DiSability Study (LADIS) showed steeper declines in the Stroop test, Trail Making A test, verbal fluency, and MMSE among patients with cerebral small vessel disease and the group found that these abnormalities predicted a doubling of risk for dementia and transition from an autonomous to dependent state.\textsuperscript{17}

Importantly, among patients with a history of stroke and/or transient ischemic attack in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the dementia risk during a median follow-up period of 3.9 years was found to be 7.7 times higher in patients with white matter disease than those without it at the time of study enrollment.\textsuperscript{16} A meta-analysis performed by Debette and Markus\textsuperscript{20} also showed a significant association between white matter disease and risk of dementia (OR 1.9, 95% confidence intervals (CIs), 1.3 to 2.8, \(p = 0.002\)) as well as faster declines in global cognitive performance, executive function, and processing speeds.

**Mobility and Balance**

In addition to the aforementioned relationships between WMH burden and cognitive function, small vessel disease of the brain is also associated with impaired gait and balance in the older population.\textsuperscript{8} Furthermore, severe WMH burden has been linked to increased risk of falls (relative risk (RR) = 1.63, 95% CI, 1.11–2.40).\textsuperscript{10} In the LADIS, walking speed correlated with the white matter disease burden (1.24 ± 0.28 m/second for mild, 1.18 ± 0.32 m/second for moderate, 1.09 ± 0.31 m/second for severe categorizations respectively; \(p < 0.001\)).\textsuperscript{21} Patients with mild white matter disease burden performed better with single leg stance when compared with those with moderate and severe diseases (\(p < 0.001\)). These findings have also been found in other studies correlating cerebral small vessel disease and mobility in the elderly and will be the subject of discussion later in this paper.\textsuperscript{22}

**Ambulatory Blood Pressure in Risk Assessment for Stroke**

There has been mounting evidence for four decades on the importance of ambulatory blood pressure monitoring parameters for predicting cardiovascular events including stroke. In a meta-analysis of 17,312 persons with hypertension recently reported by the ABC-H
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In a meta-analysis of 13,844 patients with hypertension,28 blood pressure parameters were studied for prediction of cardiovascular events. In a recent report from the IDACO investigators,26 involving 8,341 people randomly recruited from 12 populations, 24 hours ambulatory systolic and diastolic BPs were analyzed on a continuous scale, was related to a modest increased risk of stroke. Progressive decrease in sleep BP mean was found to be the most significant predictor of subclinical cerebral small vessel disease.34,35

Ambulatory Blood Pressure Monitoring in Evaluating Outcomes for Recurrent Stroke

Hypertension is well known to be associated with increased risk of recurrent stroke in patients with a history of ischemic stroke.36 A recent review from Portugal found that a blunted pre-awakening BP surge due to high nocturnal BP was an important risk factor for an increased risk of stroke.37

With growing evidence of increased CV risk with elevated nocturnal BP, a randomized prospective study comparing bedtime administration of antihypertensive therapy with conventional dosing time of therapy administered in the morning—the MAPEC study—was undertaken. With a median follow-up of 5.6 years in 2,156 participants with hypertension, the study demonstrated a 67% reduction in major CV events (CV death, nonfatal MI, and nonfatal ischemic and hemorrhagic stroke) in subjects in the bedtime antihypertensive medication treatment group. Progressive decrease in sleep BP mean has been found to be the most significant predictor of event-free survival, a novel therapeutic target for primary prevention.37

Ambulatory BP Monitoring in Evaluating Outcomes for Recurrent Stroke

Hypertension is well known to be associated with increased risk of recurrent stroke in patients with a history...
of a prior ischemic or hemorrhagic event. A recent meta-analysis of 16 randomized controlled trials and 40,292 patients with history of stroke (ischemic, transient ischemic attack [TIA], or hemorrhagic), with and without hypertension, demonstrated that antihypertensive therapy reduced the risk of recurrent stroke (relative risk reduction, 18%; 95% confidence interval [CI], 9–26%). The meta-regression analysis also revealed that each 10 mm Hg reduction in systolic BP is associated with a 33% (95% CI, 9–51%) reduction in the risks of recurrent stroke. In an observational study of 426 patients with acute cerebral infarction followed up for an average 7.6 years, daytime systolic BP on ambulatory monitoring was a significant predictor of recurrence of cerebral infarction.

Ambulatory BP has demonstrated a higher sensitivity compared to office BP for evaluation of the effectiveness of antihypertensive treatment among stroke survivors. In a study of 51 patients with a recent TIA syndrome and 225 clinically healthy control subjects, ambulatory BP monitoring revealed a highly significant proportion of these patients (90%) whose hypertension was not well controlled. In another study of 187 consecutive first-ever hypertensive stroke survivors who underwent office and ambulatory BP measurements at 120 ± 30 days, effective BP control was documented in significantly (p < 0.001) fewer patients using ambulatory BP monitoring (32.1%) than those using office recordings (43.3%), whereas in 16% of the study population, there was a masked pattern (elevated ambulatory blood pressure in the presence of normal office blood pressure levels) identified.

Castilla-Guerra et al. reported a chronic disruption of circadian rhythm of BP after the acute phase of stroke in a prospective study of 101 patients admitted within 24 hours after stroke onset and followed up for 1 year. The normal diurnal variation in BP was abolished in 87.1% of patients during the acute phase of stroke, in 76.9% after 6 months, and in 74.6% after 1 year. Another study found that the nocturnal BP reduction was blunted in most (−90%) of 48 elderly bedridden hypertensive patients assessed within 1 to 3 months after stroke. In an interesting observational study, a reverse dipper pattern and high nighttime heart rate in patients with acute cerebral infarction were independently associated with total mortality.

A meta-analysis of studies of acute ischemic stroke patients admitted within 24 hours of onset and undergoing ABPM within 24 hours of admission showed that both high systolic and diastolic BP levels derived from ambulatory BP monitoring were associated with poor short-, intermediate-, and long-term outcomes, but the same was not found for casual (clinic) BP measurements. Additionally, in a study of 128 initial acute stroke patients who underwent ABPM within 24 hours of stroke onset and computerized tomography scans of the brain on both admission to the hospital and 5 days later, multivariate logistic regression analysis showed that each 0.1 mm Hg/minutes increase in the time rate of 24 hours SBP variation was associated with a 13.9% increased probability of presence of brain edema. A longer-term study of 109 patients with stroke whose 24 hours BP variability was assessed within 24 hours of onset showed that higher systolic BP variation at baseline promoted negative outcomes at 1 year.

Higher 24 hours, daytime, and nighttime systolic and diastolic BPs at baseline in patients with new lacunar infarctions have also been associated with the development of new cerebral microbleeds at 2 years follow-up. A 3 months follow-up study of acute ischemic stroke patients found that mean values of systolic BP, diastolic BP, pulse pressure, and HR on day 1 of admission on ambulatory BP monitoring were inversely associated with their independence.

The data mentioned before highlight the importance of ambulatory BP monitoring for potentially improving the secondary prevention of stroke using several parameters in the acute phase. Ambulatory BP monitoring not only helps in identifying patients with inadequate blood pressure control despite “apparently” well-controlled office BP, but can also help decide the appropriate timing of medications individualized to circadian rhythm. Furthermore, inadvertent excessive lowering of BP—which has been associated with recurrence of stroke—may be avoided with assessment of 24 hours BP levels and patterns. Further research might best focus on using ambulatory BP parameters to guide antihypertensive therapy in patients with a history of stroke to facilitate further fine-tuning of secondary prevention strategies prevalent at this point.

The Importance of Blood Pressure as a Risk Factor for Cerebral Small Vessel Disease and Functional Decline in Older Persons

White matter hyperintensities and its progression, present in the MRIs of older people, have been associated with hypertension, and evidence suggests that WMHs occur as a result of arteriosclerosis within the wall of the arteriole. Large arterial and small vessel disease of the cerebral circulation share risk factors (e.g., hypertension and diabetes) and may coexist in individuals as noted earlier. Although given the differences noted in Table 1, it is unclear if they both produce white matter tissue damage through similar mechanisms.

White matter lesions have also been associated with deterioration of mobility, urinary control, and cognition. Evidence of WMHs within brain pathways known to
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support mobility, cognition, or voiding confirms this association. Details seen on MRI of the brain have allowed localization and quantification of the disseminated WMHs. Cross-sectional and prospective cohort studies have documented the relationships among WMHs and neurologic function in older people and the distinctive nature of the distribution and volume of brain WMHs that are responsible for deterioration of these functions, particularly in older groups. Approximately two-thirds of individuals over 75 years of age have detectable WMHs using MRI of the brain. The lower limit of detection of WMH by experts in neuroradiology is approximately 0.2 to 0.3% of intracranial contents, and 0.5% is easily visible to the naked eye based on our experience. Our cohort studies have demonstrated an increase of WMH volume from 0.99 to 1.47 to 1.7% of the intracranial contents volume from baseline to 2 and 4 years respectively. This increase was even present in participants with normal mobility throughout the study period.

We have also observed that progression of WMH over time was strongly linked to the initial presence of WMH. The accumulation of WMH often occurred by expansion of preexisting periventricular lesions in a stereotyped manner. Regional analysis of the distribution of WMH lesions demonstrated a robust link to expansion of lesions in the splenium of the corpus callosum, a posterior periventricular structure important for the integration of cortical sensorimotor function.

Blood pressure and other cardiovascular risk factors have been related to brain WMH, although predictors of quantitative WMH progression and their effect on the function of older persons have not been well understood. In our past work in this area, we have evaluated the progression of WMH over 2 and 4 years in a cohort of 95 patients 75 to 90 years (mean baseline age, 82 years) who had office and ambulatory BP and volumetric MRI. Neither clinic BP nor changes in clinic BP predicted progression of WMH, while the 24 hours ambulatory BP and changes in ambulatory BP significantly correlated with both WMH volume (p < 0.04) and changes in WMH (p < 0.003). Further analyses demonstrated associations for WMH and mobility indexes with level of systolic BP based on tertiles of the cohort – i.e., those in the higher (24 hours systolic BP = 144 mm Hg) ambulatory BP group showed increases in WMH and slower mobility compared with the middle tertile (ambulatory systolic BP = 130 mm Hg) (Table 2). Furthermore, gait speed in the

### Table 1: Comparison of some characteristics of stroke and white matter hyperintensity lesions*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stroke (large artery)</th>
<th>White matter hyperintensities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset/progression</td>
<td>Sudden/brief if any</td>
<td>Ill-defined/gradual over years</td>
</tr>
<tr>
<td>Manifestations</td>
<td>Focal neurologic deficit</td>
<td>Functional limitations</td>
</tr>
<tr>
<td>Location</td>
<td>Vascular distribution</td>
<td>Grow from head/tail-lateral ventricles</td>
</tr>
<tr>
<td>Size</td>
<td>Stroke (cm) → lacunae (mm)</td>
<td>&lt;1 mm</td>
</tr>
<tr>
<td>Vessel</td>
<td>Large to small artery</td>
<td>Arteriolar</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Ischemic</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Note: There may be infarction due to small vessel disease that has onset/progression and manifestations that are similar to large artery stroke; *Modified from White et al with permission of Elsevier, Ltd

### Table 2: Functional parameters at 24 months of observation according to clinic and ambulatory blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinic blood pressure tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n = 25)</td>
</tr>
<tr>
<td>Total WMH (%)</td>
<td>120.7 ± 1.2</td>
</tr>
<tr>
<td>Mobility assessments</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>Tinetti Gait</td>
<td>11.2 ± 0.2</td>
</tr>
<tr>
<td>Stair descent time (second)</td>
<td>6.7 ± 0.6</td>
</tr>
<tr>
<td>Maximal gait velocity (m/s)</td>
<td>0.69 ± 0.04</td>
</tr>
<tr>
<td>Walk time (second)</td>
<td>3.4 ± 0.2</td>
</tr>
</tbody>
</table>

24 hours ambulatory blood pressure tertile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinic blood pressure tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n = 26)</td>
</tr>
<tr>
<td>Total WMH (%)</td>
<td>116.7 ± 1.4</td>
</tr>
<tr>
<td>Mobility assessments</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Tinetti Gait</td>
<td>11.2 ± 0.3</td>
</tr>
<tr>
<td>Stair descent time (second)</td>
<td>6.4 ± 0.8</td>
</tr>
<tr>
<td>Maximal gait velocity (m/s)</td>
<td>0.71 ± 0.04</td>
</tr>
<tr>
<td>Walk time (second)</td>
<td>3.1 ± 0.1</td>
</tr>
</tbody>
</table>

Unpublished data from our cohort study; WMH: White matter hyperintensity lesions; m/s: meters/second; Significant values are bold typeface
higher ambulatory BP group decreased 0.15 m/second more than that in the low BP group and while this difference appears small, it represents a between-group change after only 2 years of observation. Mobility limitation linked to WMH occurs gradually so that this decrement may be part of a long-term process that compromises gait velocity over 10 or more years. These data have suggested that an intervention using mean 24 hours systolic BP as the target could reduce progression of microvascular disease in the elderly and thus favorably impact function.

The results of our cohort studies have been supported by a larger longitudinal population-based study of 665 persons from the Rotterdam study. Over a 5 years period, clinic BP and WMH lesion progression were measured 3.5 years apart, and after adjusting for baseline WMH, only systolic BP was significantly associated with progression (0.05 mL/year of standard deviation (SD) increase). Of interest, people with uncontrolled and untreated hypertension had significantly greater white matter lesion progression than people with uncontrolled but treated hypertension (Fig. 2). These studies suggest that antihypertensive treatment could reduce white matter lesion progression in uncontrolled hypertension. However, guiding therapy through the use of ambulatory BP monitoring could make this process more precise since ambulatory BP is more reproducible than clinic BP in older people and ambulatory BP recordings would provide a means to target BP elevations during sleep, a period that is strongly related to WMH and cerebrovascular disease.

The INFINITY Study

The Intensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline in The Elderly (INFINITY) study has been designed to evaluate the functional impact of a clinically relevant separation in 24 hours mean ambulatory systolic BP in an older population (i.e., <130 mm Hg vs <145 mm Hg). The study has been designed to evaluate these two levels of ambulatory BP control in hypertensive individuals 75 years or older with normal or mildly impaired mobility and cognition who already have detectable cerebrovascular disease (≥0.5% WMH fraction of intracranial volume). The key outcomes monitored over the 3 years of the trial are white matter lesion progression and measures of mobility and cognition. INFINITY is a prospective, randomized, open-label trial with blinded end points that will evaluate the changes from baseline in mobility and cognitive function and accumulation of WMH volume and changes in diffusion tensor imaging.

Our objective is to achieve a 24 hours systolic BP of ≤130 mm Hg in an intensively treated group or standard goal of 24 hours systolic BP of ≤145 mm Hg for a total of 36 months using similar classes of antihypertensive

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**Fig. 2:** Mean WML progression in mL (95% confidence interval [CI]; black bars) on top of the baseline WML volume (gray bars) for four blood pressure categories. Categories were defined as follows based on their mean blood pressure and medication use in the 5 years before the first scan: (1) Normotensives: Normal mean blood pressure and receiving no antihypertensive medication (n = 255); (2) controlled treated hypertensives: Normal mean blood pressure and receiving antihypertensive medication (n = 83); (3) uncontrolled treated hypertensives: Hypertensive mean blood pressure and receiving antihypertensive medication (n = 155); and (4) uncontrolled untreated hypertensives: Hypertensive mean blood pressure and receiving no antihypertensive medication (n = 172). Hypertensive mean blood pressure was defined as diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg. A statistically significant difference in WML progression was observed between the uncontrolled untreated hypertensive group and the uncontrolled treated hypertensive group, after adjusting for age, sex, intracranial volume, time between scans, and the baseline WML load (p < 0.05) (From Verhaaren et al (2013) with permission from the American Heart Association)
therapies. Data from the Hypertension in the Very Elderly Trial (HYVET) demonstrated that antihypertensive therapy decreases stroke mortality in patients in their mid-80s. In HYVET, the goal of therapy was to reduce systolic BP to <150 mm Hg, and this intervention did result in a 39% reduction in stroke mortality that was related to a 15 mm Hg difference in systolic BP between the active treatment and placebo groups. The goal of the standard of care 24 hours mean ambulatory systolic BP in this age group is 140 to 145 mm Hg. No clinical trial in older patients with systolic hypertension has used ambulatory BP to guide therapy and to specifically assess cerebrovascular outcomes. The INFINITY trial will be the first study to guide antihypertensive therapy using ambulatory BP monitoring rather than clinic BP to reduce small vessel disease of the brain. Initiated in 2012, we project that the study will be completed in 2018.69

DISCLOSURES

Neither of the authors has any disclosures related to the content and topic of this manuscript.

REFERENCES


