Blood Pressure Lowering and Cerebral Blood Flow

Intensive Blood Pressure Lowering Increases Cerebral Blood Flow in Older Subjects With Hypertension

Dinesh Tryambake, Jiabao He, Michael J. Firbank, John T. O’Brien, Andrew M. Blamire, Gary A. Ford

Abstract—Hypertension is associated with reduced cerebral blood flow (CBF). Intensive (<130/80 mm Hg) blood pressure (BP) lowering in older people might give greater reduction in cardiovascular risk, but there are concerns that this might produce hypoperfusion which may precipitate falls and possibly stroke. We determined the effect of intensive compared with usual BP lowering on CBF in hypertensive older subjects. Individuals aged >70 years with a history of systolic hypertension on 1 or no BP lowering drugs were recruited from primary care (n=37; age, 75±4 years; systolic BP, >150 mm Hg) and randomized to receive intensive (target BP, <130/80 mm Hg) or usual (target BP, <140/85 mm Hg) BP lowering for 12 weeks, with reviews every 2 weeks. CBF, determined using 3T arterial spin labeling MRI, and 24-hour ambulatory BP were performed at baseline and after 12 weeks of treatment. Baseline BP (ambulatory or in clinic) and baseline gray matter CBF were not significantly different between the groups. After treatment, BP was reduced significantly in both groups but fell more in the intensive group (26/17 versus 15/5 mm Hg; P<0.01). Over the same period, gray matter CBF increased significantly in the intensive group (7±11 mL/min per 100 g; P=0.013) but was unchanged in the usual BP target group (−3±9 mL/min per 100 g; P=0.23); P<0.01 for comparison. Intensive BP lowering in older people with hypertension increases CBF, compared with BP lowering to usual target. These findings suggest hypertension in older people shifts the autoregulatory CBF curve rightward and downward and is reversible with BP lowering. (Hypertension. 2013;61:1309-1315.)

Key Words: aging ■ blood flow ■ blood pressure ■ cardiovascular disease ■ MRI

Hypertension is associated with increased cardiovascular burden, leading to small vessel structural change, brain atrophy, and altered blood–brain barrier function. Such adverse effects on vascular integrity may be related to reduced cerebral blood flow (CBF). Hypertension has a profound impact in older people leading to a large increase in the risk of stroke and myocardial infarction and is associated with cognitive decline and dementia. Effective treatment of hypertension is therefore of key importance in older people.

Blood pressure (BP) lowering in older people to a target of 150/90 mm Hg has been shown to reduce the risk of stroke and myocardial infarction, improve cognitive function, and slow down or reverse the decline in CBF. Although some studies, such as SYSTEUR (Systolic Hypertension in Europe), have shown that antihypertensive treatment reduces the risk of dementia, others such as SHEP (Systolic Hypertension in the Elderly) and HYVET (Hypertension in the Very Elderly Trial) have not, and definitive conclusions about antihypertensive treatment and the risk of dementia cannot be drawn yet. It has also been suggested that hypotension resulting from BP-lowering drugs may be more harmful than hypertension in older people with hypoperfusion producing syncope, falls, and possibly accelerating atrophy and leukoaraiosis. Cognitive decline is associated with reduced CBF in the elderly, and we have shown reductions in CBF are associated with poststroke dementia and late life depression. Preventing reductions in CBF associated with hypertension in older people might reduce the risk of cognitive impairment and mood disorders. The effects of BP-lowering treatment on CBF are unclear. A study of cerebral perfusion using 133Xe inhalation reported reductions in CBF in hypertensive compared with normotensive subjects. A study using SPECT in healthy older men found reduced CBF with increasing BP. One study reported increases in middle cerebral artery blood flow velocity after treatment of hypertension in older men; however, a study using SPECT imaging reported no increase in CBF in 10 stroke patients treated with a calcium channel blocker, although the study had limited statistical power.

We hypothesized that intensive BP lowering in older subjects would increase CBF compared with usual BP lowering. We undertook a randomized controlled trial to compare the effects of intensive and usual BP lowering in older hypertensives on CBF using arterial spin labeling (ASL) MRI.

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1309
Methods

Subjects

Patients with a history of systolic hypertension on 1 or no BP-lowering drugs were recruited from primary care. Subjects were recruited by written invitation from their general practitioner. Patients were eligible if they were aged ≥70 years and had uncontrolled hypertension, defined as the average of the second and third of 3 sitting systolic BP measurements ≥150 mm Hg taken on the left arm with an interval of 5 minutes after 15 minutes seated rest on the screening day. Subjects were excluded if they had additional vascular risk factors to hypertension, diabetes mellitus, recurrent falls, concomitant/contradictory ≥1 antihypertensive medications, previous stroke, myocardial infarction, angina, peripheral vascular disease, cognitive impairment (mini-mental state examination, MMSE <27), or concomitant to MRI. Subjects for this MR study were recruited from 68 patients participating in a clinical study of intensive versus usual BP lowering. The larger clinical study was powered to detect a 5 mm Hg difference in 2 groups with 78% power at 5% α. The MR study was exploratory and had resources to recruit up to 40 patients. Thirty-seven patients were randomized to receive either intensive (n=20) or usual (n=17) BP-lowering treatment (Figure 1) using an independent web-based randomization system hosted by the Newcastle Clinical Trials Unit. The CBF measurement and data analysis were performed blinded to treatment allocation. Clinical BP and ambulatory BP were collected using standard equipment for all subjects. Patients and researchers were aware of treatment allocation, and blinding was not feasible. The study was approved by Newcastle and North Tyneside 1 Research Ethics Committee. Informed written consent was obtained from subjects.

BP Treatment Protocol

BP was treated according to the algorithm recommended in the BHS/NICE (British Hypertension Society/National Institute for Health and Clinical Excellence) guidance. Subjects were reviewed and had BP recorded at 2-week intervals (Figure 1). Treatment decisions were made on the average of the second and third of 3 seated BP measurements taken in the left arm at intervals of 5 minutes after 15 minutes of seated rest, using an Omron BP machine (Model no. OMRON M5-1). In the usual treatment group, BP-lowering therapy was increased at 6 weeks if BP readings averaged over the previous 6 weeks were ≥140/85 mm Hg. In the intensive treatment group, BP-lowering therapy was increased at 2 weeks if the BP reading was ≥130/80 mm Hg. The following drugs were used: amlodipine 5 to 10 mg, lisinopril 5 to 20 mg, atenolol 25 to 50 mg, and bendroflumethiazide 2.5 mg all once daily.

Ambulatory BP

For each subject, ambulatory BP was performed at baseline and 12 weeks using a Spacelabs ambulatory BP monitor (Model No: 90207) with BP recorded every 20 minutes between 0600 and 2200 hours and every 30 minutes between 2200 and 0600 hours. More than 70% of readings were obtained in all recordings and used for analysis. Mean 24 hours, day and night time BP, heart rate, and mean arterial pressure were extracted for further analysis.

Magnetic Resonance Imaging

MR imaging was obtained on a 3T whole-body MRI scanner (Philips Medical Systems, Best, Netherlands) using the integrated radio frequency body coil for transmission and signal detection through an 8-channel SENSE head coil. A T₁-weighted anatomic volume with 1 mm isotropic resolution was collected using a standard clinical protocol (3D MPRAGE sequence, 240×240×180 mm³ field of view, echo time=15 ms, repetition time=9.6 ms, accelerated by a SENSE factor of 2). CBF was measured using a flow-sensitive alternating inversion recovery (IR) ASL sequence with gradient-echo echo-planar imaging readout (inversion times=1700 ms, echo time=26 ms, repetition time=4 s, 4x4 mm² in-plane resolution, 6-mm slice thickness, and 256x256 mm² field of view) and incorporating a 10-ms bipolar gradient to suppress bulk flow. Twelve contiguous transverse slices were positioned parallel to the anterior commissure–posterior commissure line with the center of the volume passing through the most anterior part of the corpus callosum. To avoid contrast reduction resulting from a large transit zone in ASL, data were acquired in 3 separate but contiguous segments with identical flow-sensitive alternating IR protocols each containing 4 contiguous slices. The selective inversion width was set to 48 mm centered on the 24-mm imaging slab to avoid static tissue contamination. In previous studies examining reproducibility of CBF in 13 healthy volunteers over 3 months, the mean percentage difference in CBF was 4.6%. Quantitative T₁ maps were collected using a fast T₁ mapping IR sequence, covering 72 transverse slices with gradient-echo echo-planar imaging readout (echo time=23 ms, repetition time=15 s, in-plane resolution 2x2 mm², 2-mm slice thickness, and 256x256 mm² field of view). The IR curve was sampled at 12 inversion times beginning at 208 ms with successive increments of 208 ms. The anatomic ASL, and T₁ mapping protocols were performed in each subject at baseline and 12 weeks (Figure 1).

Image Processing

The ASL images were motion corrected using Automated Image Registration (AIR 5.2.5), and then split into tag and control image sets. Perfusion weighted images (dM) were generated by taking the difference between the 2 sets, and magnitude images (M) obtained by averaging the 2 sets. Results for each segment were spatially concatenated to form the full perfusion weighted and magnitude volumes for each examination. maps were generated by 3 parameter fitting (M, T₁, and effective inversion angle) of the interrogated IR curve to the Bloch equation on a pixel by pixel basis.
Image Analysis

MRI data were analyzed to determine global and regional CBF within the gray matter by applying the following protocol using SPM5.21

The MR physicist who determined CBF measurements was blind to treatment allocation. Each T1-weighted anatomic scan was segmented into cerebrospinal fluid, gray and white matter, and normalized to a standard Montreal Neurological Institute (MNI) space26 template. ASL scans were also registered to MNI space by first coregistering the magnitude flow-sensitive alternating inversion recovery images M to the anatomic scan and subsequently applying the coregistration parameters to the dM images. The normalization parameters determined when registering the anatomic image to MNI space were then applied to the registered dM and M images, which were also resampled in MNI space to a voxel size of 4×4×4 mm3. The T1 maps were similarly coregistered and resampled in MNI space.

Analysis was restricted to areas which were imaged in all individuals. The spatially normalized gray matter images were compared across all subjects and a gray matter mask generated for pixels which were sampled in every subject. The main analysis was performed using this gray matter mask, but regional variations across the brain were also explored by further dividing the gray matter into 25 standardized regions of interests (ROIs) defined using the MarsBaR29 plugin.

Statistics

The Kolmogorov–Smirnov test was used to assess normality of all the measured parameters. All variables apart from MMSE and Rankin score were normally distributed. Levine’s test was used to compare homogeneity of variance between the 2 groups. All variables had homogenous variance. Student t tests were used to compare normally distributed variables smoking history, use of aspirin, use of antihypertensive therapy, Fisher exact test to compare proportions between groups, and Mann–Whitney to compare MMSE and Rankin scores. Paired t tests were used to compare BP and CBF at baseline and 12 weeks within groups, and unpaired t tests to compare BP and CBF changes between groups. Friedman test for repeated measurements was performed on the changes in CBF measured in the 25 cortical ROIs studied to test whether these changes were spatially uniform throughout the cortex.

Results

Subject characteristics and baseline antihypertensive drug use are shown in Table 1. There were no statistically significant differences in BP between the 2 groups at baseline, although mean clinic systolic BP was 6 mm Hg higher and 24-hour ambulatory systolic BP was 3 mm Hg higher in the usual treatment group. The changes in clinic and ambulatory BP results between the baseline and 12 weeks in the 2 groups are shown in Table 2. The fall in BP was significantly greater in the intensive compared with the usual group (26/17 versus 15/5 mm Hg; P=0.018). There was a significant reduction in BP in both groups between baseline and 12 weeks with a 17/9 mm Hg difference between the intensive and usual treatment groups (123/70 versus 140/79 mm Hg at 12 weeks). Ambulatory BP was significantly reduced between baseline and 12 weeks in the intensive but not usual treatment group. At 12 weeks no participants were taking channel blockers (90% versus 76%; P=0.38).

It is well known that quantitative CBF values vary depending on the measurement technique used. Both the mean and the SD of our results (baseline gray matter CBF, 74±14 mL/100 g per minute) are in good agreement with values obtained using ASL in other studies: 71±15 mL/100 g per minute23 and 80±9 mL/100 g per minute23 with very similar values of 78±17 mL/100 g per minute reported for positron emission tomography using 15O water.31

There was no significant difference between groups in the baseline measurement of whole gray matter CBF. Over the 12 weeks, whole gray matter CBF showed no significant change compared with baseline in the usual treatment group (73 against 76 mL/100 g per minute; P=0.23; Figure 2). In contrast, CBF significantly increased in the intensive treatment group (81 against 74 mL/100 g per minute; P=0.013; Figure 2). The CBF increase in the intensive group was significantly greater than in the usual group (P=0.008). The scatter plot of CBF at 12 weeks against baseline (Figure 3) shows an overall increase in CBF. Increase in CBF in intensive group against the usual group is across the full range of baseline CBF. The change in CBF significantly correlated with change in systolic BP across all participants (Figure 4; r=0.213; P=0.004).

There was no statistically significant heterogeneity between cortical brain regions in the increases in CBF seen in the intensively treated group based on Friedman’s test (mean change across ROIs, 7.7; SD, 2.8; χ2 23=35; P=0.074) indicating no evidence of localized differences in regional increases in CBF. There was no significant correlation between baseline CBF and clinic, ambulatory or aortic baseline, systolic, or diastolic BP (P>0.15).

Discussion

This study has shown that intensive BP lowering in older people with hypertension increases whole gray matter CBF compared with usual BP lowering to a BP target recommended in most current hypertension guidelines. Our findings suggest that more intensive BP lowering might reduce the risk of cerebrovascular complications, such as development and progression of leukoaraiosis and vascular cognitive impairment, because CBF is an indicator of metabolic supply to the tissue and reduction in CBF can cause ischemic damage to the tissue. It is possible that increased CBF in ischemic tissues may facilitate tissue repair and halt disease progression. Our study supports the undertaking of clinical trials comparing more intensive to usual BP control in older people and effect on brain structure and function. We found a correlation between the reduction in systolic BP in individuals and the increase in CBF with a generalized effect across all brain regions examined. The ASL technique was not sufficiently sensitive, at the time of our studies, to determine effects on white matter blood flow. Further studies examining the effect of intensive BP lowering on white matter blood flow would be valuable because white matter changes are a major complication of hypertension.

Our results are in agreement with some but not all previous observational studies in midlife hypertensive patients, where lower BP was associated with higher CBF20,22,23 and some interventional studies which have shown BP lowering increases CBF.34–36 However, this has not been a finding in all
studies,19,20 which may reflect methodological or small sample sizes in some studies.19,20 Our study has specific features which add to understanding of the effects of BP lowering on CBF. It is the largest interventional study of the effects of BP lowering on CBF, employed more intensive BP lowering than previous studies, was conducted in a population recruited from primary care, and is in an older population than other series.

The brain receives a much larger proportion of blood flow compared with other organs and has a complex system of cerebral autoregulation to maintain CBF at a constant level across a range of BP.37 Previous work has shown hypertension shifts the autoregulatory curve rightward placing patients at risk of impaired ability to tolerate hypotension. Long-term treatment of hypertension may partially reverse this rightward shift. This study suggests in an older population that intensive BP lowering moves the autoregulatory curve upward and leftward with an increase in CBF (Figure 5).

There are some limitations of our study. Although not significant, baseline systolic BP was slightly higher in the usual care group, although if anything, this would be expected to have biased the results against the difference in CBF seen in the intensive BP group. We did not study CBF response to orthostatic challenge. However, there were no major hypotensive symptoms reported by study participants (unpublished observations). The treatment regimen algorithm used in both groups was the same but the main difference in drug treatment received was angiotensin-converting enzyme inhibition, although the large BP difference makes this unlikely. However, other

Table 1. Baseline Subject Characteristics

<table>
<thead>
<tr>
<th>Parameter Name</th>
<th>Usual Group (n=17)</th>
<th>Intensive Group (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74 (3)</td>
<td>75 (4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex, women</td>
<td>11</td>
<td>11</td>
<td>0.55</td>
</tr>
<tr>
<td>Mini-mental state examination</td>
<td>30 [28–30]</td>
<td>30 [29–30]</td>
<td>0.64</td>
</tr>
<tr>
<td>Modified Rankin score</td>
<td>0 [0–2]</td>
<td>1 [0–2]</td>
<td>0.07</td>
</tr>
<tr>
<td>BP systolic, mmHg</td>
<td>155 (13)</td>
<td>149 (13)</td>
<td>0.22</td>
</tr>
<tr>
<td>BP diastolic, mmHg</td>
<td>84 (9)</td>
<td>87 (10)</td>
<td>0.41</td>
</tr>
<tr>
<td>Aortic BP systolic</td>
<td>151 (11)</td>
<td>148 (15)</td>
<td>0.55</td>
</tr>
<tr>
<td>Aortic BP diastolic</td>
<td>86 (10)</td>
<td>91 (7)</td>
<td>0.11</td>
</tr>
<tr>
<td>24-h ambulatory BP systolic, mmHg</td>
<td>131 (12)</td>
<td>128 (10)</td>
<td>0.50</td>
</tr>
<tr>
<td>24-h ambulatory BP diastolic, mmHg</td>
<td>71 (8)</td>
<td>69 (7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Gray matter CBF, mL/min per 100 g</td>
<td>76 (15)</td>
<td>74 (14)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.4 (0.82)</td>
<td>5.2 (1.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Smoking history</td>
<td>7 (42%)</td>
<td>6 (30%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Use aspirin</td>
<td>1 (6%)</td>
<td>4 (20%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Use of any antihypertensive</td>
<td>15 (88%)</td>
<td>19 (95%)</td>
<td>0.58</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>3 (18%)</td>
<td>4 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1 (6%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>6 (35%)</td>
<td>5 (25%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diuretic</td>
<td>5 (29%)</td>
<td>9 (45%)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Baseline characteristics of the usual and the intensive treatment groups. Values are mean (SD), median [range], or number [percentage]. There is no significant difference between the 2 groups in any of these characteristics. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; BP, blood pressure; CBF, cerebral blood flow; and NS, not significant.

Table 2. Changes in Blood Pressure and Cerebral Blood Flow After 12 Weeks of Treatment

<table>
<thead>
<tr>
<th>Parameter Name</th>
<th>Changes in Usual Group</th>
<th>Changes in Intensive Group</th>
<th>Differences Between Usual and Intensive (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>−15 (14)**</td>
<td>−26 (14)**</td>
<td>0.018</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>−5 (7)*</td>
<td>−17 (9)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic BP systolic, mmHg</td>
<td>−20 (14)**</td>
<td>−35 (12)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic BP diastolic, mmHg</td>
<td>−6 (10)*</td>
<td>−20 (7)**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h ambulatory BP systolic, mmHg</td>
<td>−2 (10)</td>
<td>−12 (7)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24-h ambulatory BP diastolic, mmHg</td>
<td>−1 (6)</td>
<td>−6 (5)**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gray matter CBF, mL/min per 100 g</td>
<td>−3 (9)</td>
<td>7 (11)*</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Change in BP, whole gray matter CBF within the 2 groups (12 weeks [baseline]). In the columns, the asterisks indicate a significant change within the group (paired t test *P<0.05, **P<0.01). The last column is the result of an unpaired t test comparing the changes in both groups. Values are mean (SD). BP indicates blood pressure; and CBF, cerebral blood flow.
drug therapies might have different effects. The study was conducted in healthy older people with hypertension and the results might not apply to frail older people or individuals with autonomic dysfunction. The lower smoking prevalence and higher aspirin use in the intensive group may have led to greater increase in CBF in the intensive group if smoking and aspirin modify the CBF response to BP-lowering therapy.

In conclusion, we have demonstrated that intensive BP treatment increases CBF in older people with hypertension, suggesting cerebral autoregulatory curve is shifted upward and leftward.

**Perspectives**

This study demonstrates that intensive BP treatment to <130/80 mmHg with a calcium channel and angiotensin-converting enzyme inhibitor–based regimen in older people with hypertension increases CBF. This finding, consistent with previous observational studies, suggests that intensive BP lowering might protect the aging brain from leukoaraiosis and brain atrophy, which may be related to hypoperfusion. This raises the possibility that intensive BP lowering might reduce the risk of vascular cognitive impairment and dementia compared with current more conservative BP targets. The findings of this...
study suggest that the cerebral autoregulatory curve is shifted upward and leftward in hypertension in older people. Further work is necessary to determine whether similar changes are seen in white matter CBF with intensive BP lowering as the increase in gray matter CBF seen in this study. Clinical trials of intensive versus standard BP lowering are required to determine whether cognitive decline and the risk of dementia are reduced with more intensive BP lowering in older people.

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Disclosures
None.

References


**Novelty and Significance**

**What Is New?**

- We used magnetic resonance arterial spin labeling imaging to look at the effect of intensive (target, <130/80 mmHg) versus standard (target, <140/85 mmHg) blood pressure (BP) lowering on cerebral blood flow in older people (>70 years) with hypertension.

**What Is Relevant?**

- Hypertension leads to brain damage in older people with increased brain atrophy, strokes, and damage to brain white matter. Increasing cerebral blood flow through more intensive BP lowering might reduce the risk of these complications and the risk of developing memory problems and dementia.

**Summary**

Intensive BP lowering to <130 mmHg systolic BP in older hypertensives increased cerebral blood flow. This indicates that hypertension is associated with reduced cerebral blood flow in older people and is reversible with intensive BP lowering.
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