Antihypertensive Therapy Increases Cerebral Blood Flow and Carotid Distensibility in Hypertensive Elderly Subjects

Lewis A. Lipsitz, Margaret Gagnon, Mitul Vyas, Ikechukwu Iloputaife, Dan K. Kiely, Farzaneh Sorond, Jorge Serrador, Debbie M. Cheng, Viken Babikian, L. Adrienne Cupples

Abstract—Many physicians are reluctant to lower blood pressure to recommended levels in elderly hypertensive patients because of concern about producing cerebral hypoperfusion. Because hypertension is associated with potentially reversible structural and functional alterations in the cerebral circulation that may improve with treatment, we investigated whether long-term pharmacological reduction of systolic blood pressure will improve, rather than worsen, cerebral blood flow and its regulation. Three groups of elderly subjects 65 years of age or older were studied prospectively: normotensive subjects (N=19), treated hypertensive subjects with systolic pressure <140 mm Hg (N=18), and uncontrolled hypertensive subjects with systolic pressure >160 mm Hg at entry into the study (N=14). We measured beat-to-beat blood flow velocity in the middle cerebral artery (transcranial Doppler ultrasonography), finger arterial pressure (photoplethysmography), and pulsatile distensibility of the carotid artery (duplex Doppler ultrasonography) at baseline and after 6 months of observation or antihypertensive therapy. After baseline hemodynamic measurements, uncontrolled hypertensive subjects underwent aggressive treatment with lisinopril with or without hydrochlorothiazide or, if not tolerated, nifedipine or an angiotensin receptor blocker to bring their systolic pressure <140 mm Hg for 6 months. The other 2 groups were observed for 6 months. After 6 months of successful treatment, uncontrolled hypertensive subjects had significant increases in cerebral blood flow velocity and carotid distensibility that was not seen in the other groups. Treatment reduced cerebrovascular resistance and did not impair cerebral autoregulation. Therefore, judicious long-term treatment of systolic hypertension in otherwise healthy elderly subjects does not cause cerebral hypoperfusion. (Hypertension. 2005;45:216-221.)

Key Words: aging ■ angiotensin-converting enzyme inhibitor ■ brain ■ hemodynamics ■ ultrasonography

Although the treatment of systolic hypertension has been shown in prospective randomized controlled trials to reduce cardiovascular morbidity and mortality in subjects up to age 80, many physicians are reluctant to lower systolic blood pressure (BP) to the recommended level of 140 mm Hg or lower in elderly patients, because of concern that aggressive treatment may cause cerebral hypoperfusion and associated syncope, falls, or cognitive dysfunction. Because hypertension is associated with potentially reversible structural and functional changes in the cerebral circulation, we hypothesized that long-term BP reduction would improve, rather than worsen, cerebral blood flow and its regulation. Therefore, we conducted the current study to determine the effects of systolic BP reduction over 6 months on cerebral perfusion in elderly hypertensive patients. We also examined structural and functional changes in the cerebral vasculature potentially affected by BP-lowering, including carotid distensibility and cerebral autoregulation.

Methods

Design

The study was a prospective 3-group comparison of the effect of pharmacological BP reduction versus observation over a 6-month period, on cerebral autoregulation, systemic BP regulation, and pulsatile distensibility of the carotid artery in subjects 65 years of age and older. More details on the design are available in an online supplement at http://www.hypertensionaha.org.

Subjects were assigned to 3 groups according to the average of 36 BP measures taken by an experienced research nurse during 3 screening visits ~1 week apart (12 measures per visit). On each visit, 2 sets of the following BP measurements were obtained with a random zero sphygmomanometer: 3 measures supine with a 2-minute rest period between each, then during 1, 3, and 5 minutes of standing. These values were averaged and subjects were grouped as: “normotensive,” BP <140/90 using no BP-lowering medications; “controlled hypertensive,” BP <140/90 using long-term BP-lowering medications; and “uncontrolled hypertensive,” systolic BP >160 with or without BP-lowering medications. Subject characteristics are summarized in the Table.
The study was approved by the Hebrew Rehabilitation Center for Aged Institutional Review Board and all subjects provided written informed consent.

**Experimental Protocols**

Baseline and 6-month follow-up studies were conducted in the cardiovascular laboratory at the same time of day, under identical conditions. Each study consisted of: (1) supine ultrasound measures of carotid pulsatile distensibility; (2) sit-to-stand tests of cerebral blood flow regulation; and (3) cerebrovascular reactivity to carbon dioxide.

### Pulsatile Distensibility

Subjects rested supine for 5 minutes while optimal carotid images were obtained. Then, continuous recording of carotid diameters and BP was performed for 2 minutes. A Hewlett-Packard SONOS 2500 ultrasound imaging system with a high-resolution linear array transducer (7.5 MHz) and vascular enhancement software were used.
to provide longitudinal B-mode images of the carotid artery (≈1 cm distal to the bulb). The transducer was positioned parallel to the vessel to obtain clear visualization of the anterior wall media-adventitial interface and the posterior wall intima–lumen interface. Ultrasound images were digitally recorded to a computer in real time for subsequent analysis. Vessel image acquisition was gated on the R-wave of the electrocardiogram, and 15 images (of a 30-Hz video signal) were captured for each R-wave. Simultaneous with the acquisition of vascular images, continuous BP measurements were obtained from the Finapres. Moment-to-moment changes in lumen diameters were subsequently analyzed offline using a custom software package. Within each cardiac cycle, we measured the largest diameter (Ds), smallest diameter (Dd), systolic BP, and diastolic BP to calculate carotid artery distensibility according to the following formula:

\[
\text{Distensibility} = \frac{2(Ds - Dd)}{Dd} \cdot \frac{SBP - DBP}{H_11002}
\]

The average of values for each cardiac cycle over 1 minute of recording was used as the measure of carotid artery distensibility.

### Sit–Stand Protocol

Transcranial Doppler ultrasound was used to measure the changes in middle cerebral artery blood flow velocity in response to an active sit-to-stand procedure used to induce orthostatic hypotension to assess cerebral autoregulation. Detailed description of this protocol was reported previously and described in the supplemental section.

### CO₂ Reactivity Protocol

Two CO₂ vasoreactivity trials were performed, in which subjects breathed a mixture of 5% CO₂ and 95% air from a 5-L re-breathing bag at 15 breaths per minute (0.25 Hz) for 1 minute each trial. Detailed description of this protocol was reported previously and described in the supplemental section.

### Data Processing and Analysis

Postprocessing was performed using custom-written MATLAB scripts. Beat-to-beat R-R intervals were determined from the R-wave of the electrocardiogram, along with systolic, diastolic, and mean values for BP and flow velocity from the associated waveforms. To evaluate the cerebral autoregulatory response to orthostasis, we calculated the differences between the sitting and standing values of mean pressure, cerebral blood flow velocity (CBFV), or cerebrovascular resistance (CVR) (CVR = mean arterial pressure [MAP]/CBFV). The sitting values were averaged over a period of 50 seconds during rest, and the standing values were computed as the average of 5 values surrounding the nadir of MAP for each trial. The average of 2 trials for each subject was used in the analysis.

We also determined the dynamic autoregulatory index using the method described by Tiecks et al. to quantify the CBFV response to dynamic changes in MAP. The actual CBFV response was compared with a family of theoretical responses calculated for the given ABP decrease, and the closest fit was selected as that trial’s dynamic autoregulatory index. An autoregulatory index of 0 suggests no regulation and 9 suggests maximum regulation.

The effects of group and time (treatment), and their interaction, on the absolute values and changes in CBFV, CVR, heart rate, MAP, CO₂ reactivity, and carotid distensibility were assessed using 2-factor repeated-measures ANOVAs (SAS for Windows Version 8.2; SAS Institute Inc, Cary, NC). The comparison of changes in carotid distensibility over 6 months between the 3 subject groups was adjusted for baseline differences in BP by adding baseline MAP as a covariate to the model. Data are presented as mean±SD unless otherwise indicated. An α level <0.05 is considered statistically significant.

### Results

Subject characteristics are shown in the Table. The 3 groups of subjects were similar in their demographic characteristics, medication use, and disease history. The uncontrolled hypertensive subjects had significantly higher systolic and diastolic pressures than the other groups. Heart rate was lower in the normotensive subjects compared with the other 2 hypertensive groups. CO₂ vasoreactivity was also higher in the normotensive subjects compared with controlled and uncontrolled hypertensive subjects.

Despite higher perfusion pressures in the untreated hypertensive group, CBFV and CVR were similar to those with normal pressures (Table). MAP decreased to a similar extent in the 3 groups during posture change. The changes in CBFV and CVR, the autoregulatory index, and the time to the CBFV and MAP nadirs during orthostatic BP reduction were also similar in the 3 groups.

The MAP, CBFV, and CVR for the 3 groups of subjects in the sitting and standing positions at baseline and after 6 months of observation or treatment were recorded (please see Figure 1). All 3 groups of subjects experienced similar orthostatic declines in MAP, CBFV, and CVR during standing at both time points. Although the controlled hypertensive subjects had a small 3±5 mm Hg decline in mean arterial BP over the 6-month observation period (P<0.05), possibly because of more attention being paid to their BP control, neither they nor the normotensive subjects had any significant change in CBFV, CVR, or other hemodynamic variables over this time period. After 6 months of antihypertensive therapy, subjects with uncontrolled hypertension had a 17±5 mm Hg decline in mean arterial BP. All of these subjects achieved brachial BPs <140/90, which were similar to the other 2 groups. This lowering of BP was associated with a significant increase in CBFV (P<0.03) and decrease in CVR (P<0.001) in both the sitting and standing positions.

Figure 1 shows the individual mean finger pressures and cerebrovascular resistance values in the sitting position for the 3 groups of subjects at baseline and 6 months. In the uncontrolled hypertensive group, 6 months of antihypertensive therapy did not change the autoregulatory response to posture change or CO₂ vasoreactivity. All subjects tolerated treatment well, without symptoms of cerebral hypoperfusion such as dizziness, syncope, falls, or transient neurological events. There were no significant differences in BP, CBFV, or CVR after 6 months in subjects using angiotensin-converting enzyme inhibitors (N=21) compared with those using other medications (N=11) to control their pressure. Carotid artery distensibility also increased in uncontrolled hypertensive subjects after 6 months of antihypertensive therapy but remained unchanged in the other 2 groups (Figures 1 and 2; P=0.001, controlling for baseline MAP). The change in diameter of the carotid artery with each beat of the heart (pulsatile diameter change) also tended to increase, but this did not reach statistical significance (Figure 2). There was a weak, but statistically significant, correlation between the change in carotid distensibility and change in cerebral blood flow velocity over 6 months for all groups combined (R=0.31; P=0.03).

### Discussion

The results of this study demonstrate that judicious long-term treatment of systolic hypertension in otherwise healthy el-
derly subjects can be achieved safely, without precipitating cerebral hypoperfusion or impairing cerebral autoregulation. In addition, 6 months of antihypertensive therapy based primarily on an angiotensin-converting enzyme inhibitor regimen improved carotid distensibility. Although this study was not designed to examine the effects of any one particular BP-lowering strategy, it appears that favorable cerebral hemodynamics were achieved regardless of whether an angiotensin-converting enzyme inhibitor or other agent was used to lower pressure.

Several previous studies with a variety of medications suggest that hypertension can be successfully treated without compromising cerebral blood flow. However, the effects of these medications on cerebral blood flow during orthostatic stress have not been established, particularly in elderly patients with systolic hypertension.

Our results also demonstrated that 6 months of BP reduction improved carotid distensibility, and that changes in carotid distensibility correlated with changes in cerebral blood flow. The increase in distensibility may serve to dampen oscillations in pressure and thereby maintain continuous blood flow through the cerebral circulation. Our data are supported by a previous study of younger hypertensive subjects aged 29 to 76 years, in which 6 months of antihypertensive therapy with trandolapril, verapamil, or their combination also increased carotid distensibility, regardless of the drug’s mechanism of action.

Our subjects with hypertension, whether controlled or uncontrolled, had evidence of normal cerebral autoregulation. This finding is consistent with the results of previous studies by us and others showing that dynamic autoregulation is preserved in hypertension. Because chronic hypertension has been reported to shift the lower limit of cerebral autoregulation toward higher pressures, it is possible that greater orthostatic declines in pressure below this autoregulatory threshold would have caused a much greater decline in cerebral blood flow in hypertensive subjects.

There are a few limitations to our study. The transcranial Doppler methodology used in our study measures cerebral blood velocity rather than flow. For velocity changes to be equivalent to flow changes, arterial diameter at the point of insonation must remain constant. Recent measures of middle cerebral artery diameter by magnetic resonance imaging have demonstrated that diameter at the Doppler insonation point does not change during

Figure 1. Individual subject values for mean arterial blood pressure (top), cerebrovascular resistance (middle), and carotid distensibility (bottom) for the 3 groups of subjects at baseline and after 6 months of follow-up.
large changes in cerebral flow velocity elicited by stimuli such as lower body negative pressure and changes in end tidal CO₂. Thus, it is very likely that the changes in CBFV provided a good estimate of cerebral blood flow.

Furthermore, the finger BPs obtained by Finapres for the calculation of carotid distensibility may not accurately represent carotid pressures, because of pulse wave amplification or vasoconstriction in peripheral finger arteries. The advantage of the Finapres instrument was that it permitted us to noninvasively measure beat-to-beat BP and estimate pulsatile carotid distensibility within each beat. Although this technique may not provide accurate absolute values of pressures in larger arteries, pressure changes can be measured reliably, particularly in hypertensive patients using cardiovascular medications. Therefore, the change in distensibility we observed after 6 months of BP reduction within the hypertensive group should be valid. This conclusion is supported by the associated trend toward greater pulsatile diameter change, which is an indicator of greater distensibility that does not rely on Finapres BP measures.

Because the hypertensive subjects who met our strict selection criteria were otherwise healthy, we cannot generalize the findings to elderly people with significant comorbidity. Because of the high rate of exclusion and dropout, which is unfortunately common in clinical studies of elderly patients, our sample size was relatively small. Nevertheless, the increase in cerebral blood flow and carotid distensibility was striking, allowing us to conclude that 6 months of antihypertensive therapy in elderly people may reduce cerebral blood flow and result in syncope, falls, or dementia. The results of our prospective treatment trial will hopefully mollify this concern. Because hypertension itself may cause these syndromes by damaging the microcirculation in frontal subcortical regions of the brain, antihypertensive therapy may actually prevent cerebral microangiopathy and its clinical consequences. There is accumulating evidence that BP reduction can reduce the incidence of dementia or cognitive decline in elderly hypertensive patients, possibly by improving cerebral blood flow. Currently, the weight of evidence suggests that antihypertensive therapy can improve cerebral perfusion, improve carotid artery distensibility, and prevent some of the adverse functional consequences of both large and small vessel disease of the brain.

Perspectives
The relation between BP elevation and stroke risk is now well-established, even in patients with unilateral carotid occlusion. In only a very small minority of patients with bilateral carotid stenosis is stroke risk increased by lower BP. However, many practicing physicians remain concerned that aggressive antihypertensive therapy in elderly people may reduce cerebral blood flow and result in syncope, falls, or dementia. The results of our prospective treatment trial will hopefully mollify this concern. Because hypertension itself may cause these syndromes by damaging the microcirculation in frontal subcortical regions of the brain, antihypertensive therapy may actually prevent cerebral microangiopathy and its clinical consequences. There is accumulating evidence that BP reduction can reduce the incidence of dementia or cognitive decline in elderly hypertensive patients, possibly by improving cerebral blood flow. Currently, the weight of evidence suggests that antihypertensive therapy can improve cerebral perfusion, improve carotid artery distensibility, and prevent some of the adverse functional consequences of both large and small vessel disease of the brain.

Acknowledgments
This work was supported by grants AG04390, AG08812, and AG05134 from the National Institute on Aging, Bethesda, Md. Dr Lipsitz holds the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at the Hebrew Rehabilitation Center for Aged, Boston, Mass.

References
Antihypertensive Therapy Increases Cerebral Blood Flow and Carotid Distensibility in Hypertensive Elderly Subjects

Lewis A. Lipsitz, Margaret Gagnon, Mitul Vyas, Ikechukwu Iloputaife, Dan K. Kiely, Farzaneh Sorond, Jorge Serrador, Debbie M. Cheng, Viken Babikian and L. Adrienne Cupples

Hypertension. 2005;45:216-221; originally published online January 17, 2005; doi: 10.1161/01.HYP.0000153094.09615.11

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/45/2/216

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2005/01/24/01.HYP.0000153094.09615.11.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/