Prospective Analysis of Long Term Control of Mild Hypertension on Cerebral Blood Flow

John Stirling Meyer, M.D., Robert L. Rogers, M.S., and Karl F. Mortel, Ph.D.

SUMMARY A group of 12 otherwise normal elderly volunteers (mean age = 69.8 years), were detected to have mild hypertension. Cerebral blood flow (CBF) values were measured using $^{133}$Xe inhalation method prior to initiating medical treatment and repeated at 6, 12, 24 and 36 months after BP was adequately controlled and restored to normal (below 150/90). Results indicate that CBF values increased markedly during follow-up intervals at 6, 12 and 24 months but not at 36 months. Hypertension is known to be a risk factor for stroke and 4 of the 12 subjects subsequently developed symptoms of cerebrovascular disease (stroke, multi-infarct dementia or transient ischemic attacks) despite control of hypertension. Analyses separating asymptomatic and symptomatic groups indicated that the eight asymptomatic patients continued to maintain increased CBF levels throughout the entire three year interval, whereas the 4 symptomatic patients developed declines in CBF which began, and progressively decreased below the initial pretreatment values, during the second and third years.

RECENT EPIDEMIOLOGICAL SURVEYS report decreasing mortality rates and clinical studies confirm the decreased prevalence of stroke which has been most striking in the past three decades. Factors that may have contributed to the declining incidence of stroke are control of identifiable risk factors for atherothrombotic cerebrovascular disease. Control of hypertension appears to be the most important, although some controversy still persists as to whether or not control of hypertension is the main factor responsible for these remarkable declines in stroke morbidity and mortality. There is still limited understanding of the pathogenetic mechanisms by which chronic hypertension predisposes to stroke and whether or not it is possible to reverse some of these mechanisms if mild to moderate hypertension is controlled and sustained within normal limits.

Long-term observations in hypertensive animal models have provided evidence that as blood pressure increases the lumen diameter of cerebral arterioles becomes reduced due to the "Bayliss effect" resulting in cerebral vasoconstriction. Hypertension that is sustained for weeks or months produces hypertrophy of the muscularis media which causes diffuse stenosis and enhances atherogenesis of cerebral vessels. Increased cerebrovascular resistance due to reversible cerebral vasoconstriction which has been shown to occur in animal models as well as in hypertensive patients produces reductions of mean bihemispheric cerebral gray matter blood flow levels. These decreases of cerebral blood flow and increases in cerebral vascular resistance have been shown to be reversible even after short term control of hypertension.

In normal subjects, vasoconstriction of cerebral vessels also occurs when blood pressure increases, maintaining constant CBF despite changes in perfusion pressure a physiologic process termed autoregulation. If manipulation of the blood pressure is excessive, either by raising or lowering it beyond the limits of autoregulatory compensation, autoregulation fails. In patients with chronic hypertension the lower limits of cerebral autoregulation become shifted upward so that if mean blood pressure is acutely decreased below a threshold that is known to be well tolerated in normal subjects, autoregulation fails and cerebral blood flow decreases so that symptoms of cerebral ischemia will follow unless blood pressure is promptly elevated. It has been shown in such patients with chronic hypertension that if hypertension is gradually and effectively controlled then cerebral autoregulation gradually becomes restored toward normal. It has also been shown during treatment of severe chronic hypertension among a series of patients with mild stroke that within 2–5 weeks of reducing blood pressure by means of treatment with alpha-methyl-dopa cerebral blood flow becomes increased and cerebrovascular resistance becomes decreased. Other investigators have reported no changes or mild reductions in cerebral blood flow during abrupt administration of beta-blocking agents among mild hypertensive subjects without stroke.

In addition to these cerebral hemodynamic changes in hypertensive patients which result from chronic hypertension, morphological changes have been shown to occur in the cerebral vessels at necropsy both in patients dying of the disease, as well as in animal models. Cerebral arteries and arterioles show in-terstitial changes in hypertensive and decreased cerebrovascular resistance and the decreased elasticity of cerebral vessels. Increases in cerebrovascular resistance and the decreased cerebral blood flow resulting from chronic hypertension in both human subjects and animal models are enhanced later by the superimposition of atherosclerosis, hyperplastic arteriosclerosis and thromboembolism.
The hypothesis to be tested and the questions to be considered were as follows: Assuming that chronic hypertension reduces cerebral blood flow due to increased cerebral vascular resistance, does long-term control of hypertension result in increases of cerebral perfusion? If so is there evidence of reduced risk from stroke by reversing these cerebrovascular alterations?

**Materials and Methods**

Among a large number of healthy, neurologically normal elderly people who agreed to participate in a longitudinal study of the effects of aging on cerebral blood flow,\(^2\) a group of twelve recruits was selected who during initial screening had previously undetected hypertension. The diagnosis was confirmed by repeated measurements documenting elevated blood pressure after suitable rest periods. These volunteers had never been treated for hypertension with medications and/or salt restricted diet. All agreed to undergo longitudinal measurements of their cerebral blood flow before and following medical control of their hypertension. Protocols for these studies plus the informed consent forms used prior to measuring cerebral blood flow have been approved for the past seven years by the Institutional Review Board of the Veterans Administration Medical Center.

All 12 volunteers were found to be otherwise normal after complete medical and neurologic and neurovascular examination (including auscultation and palpation of the carotid arteries, auscultation over the vertebral arteries and a complete cardiovascular examination including EKG). In all cases mentation was intact as determined by the Cognitive Capacity Screening Examination (CCSE).\(^2\) Nine patients showed mild hypertensive retinopathy. This did not exceed Grade 1 changes, (arteriolar narrowing and arteriovenous nicking) and none had clinical evidence of severe hypertensive end-organ disease. All subjects were free of a history of drug abuse or alcoholism. Of the group of 12 volunteers with undetected hypertension who met the criteria for admission to the study 7 were women and 5 men. Two showed mild electrocardiographic changes compatible with left ventricular hypertrophy and one had mild elevations of blood cholesterol and triglycerides. Their average age was 69.8 years and the mean blood pressure for the twelve volunteers prior to treatment was 165/96. Table 1 summarizes the demographic variables and the risk factors present for each member of the experimental group and indicates the average systolic and diastolic blood pressure of each subject before and after treatment. Medications prescribed and/or dietary restrictions used to control blood pressure are also listed in table 1.

In brief, antihypertensive treatment was instituted according to recommendations of the Veterans Administration Cooperative Group on Anti-hypertensive Agents\(^3\), \(^4\) and the Hypertension Detection and Follow-up Program Cooperative Group.\(^5\) A salt free diet was prescribed first and if hypertension persisted different antihypertensive medications were employed until blood pressure was maintained within normal limits. The first step was prescription of a diuretic (chlorothalidine, 25–100 mg/day). This was followed by addition or substitution of an anti-adrenergic drug such as methyldopa, (500–2000 mg/day) or propranolol (30–120 mg/day). If necessary, later steps included addition or substitution of other anti-adrenergic drugs such as reserpine. In one subject, Case 1, mild hyper-

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**Table 1  Description of Case Series**

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>BP before treatment</th>
<th>Mean BP after treatment</th>
<th>Medications</th>
<th>Risk factors for stroke§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1§</td>
<td>86</td>
<td>F</td>
<td>155/90</td>
<td>130/82</td>
<td>Low salt diet</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>168/108</td>
<td>128/78</td>
<td>Methyldopa, Propanolol</td>
<td>-</td>
</tr>
<tr>
<td>3§</td>
<td>76</td>
<td>F</td>
<td>180/100</td>
<td>116/60</td>
<td>Methyldopa, Chlorothiazide</td>
<td>-</td>
</tr>
<tr>
<td>4§</td>
<td>62</td>
<td>F</td>
<td>158/100</td>
<td>135/90</td>
<td>Methyldopa</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>148/100</td>
<td>120/80</td>
<td>Chlorothiazide</td>
<td>-</td>
</tr>
<tr>
<td>6§</td>
<td>82</td>
<td>M</td>
<td>164/90</td>
<td>132/80</td>
<td>Chlorothiazide, Propanolol</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td>M</td>
<td>180/100</td>
<td>148/80</td>
<td>Methyldopa</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>160/85</td>
<td>122/75</td>
<td>Metoprolol, Chlorthaldone</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>81</td>
<td>F</td>
<td>165/90</td>
<td>116/60</td>
<td>Methyldopa</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>67</td>
<td>F</td>
<td>178/85</td>
<td>100/60</td>
<td>Methyldopa</td>
<td>+</td>
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<tr>
<td>11</td>
<td>77</td>
<td>F</td>
<td>155/95</td>
<td>128/85</td>
<td>Reserpine</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>M</td>
<td>180/120</td>
<td>148/88</td>
<td>Methyldopa</td>
<td>-</td>
</tr>
<tr>
<td>X</td>
<td>69.8</td>
<td>SM/F</td>
<td>165/96</td>
<td>127/78</td>
<td>Total # of subjects</td>
<td>2</td>
</tr>
</tbody>
</table>

(SD = 11.3/10.1) (SD = 13.6/9.4)

*Average blood pressure taken at 6, 12, 24 and 36 months after blood pressure was controlled.
†Cigarette smoking: 0) no history; 1) less than 1 pack/day; 2) more than 1 pack/day; 3) history of smoking but quit for at least 1 year.
‡Alcohol consumption: 0) nondrinkers and less than 2 drinks/year; 1) up to 2 drinks/week; 2) up to 2 drinks/day; 3) greater than 2 drinks/day; 4) quit drinking.
§HD = heart disease; HL = hyperlipidemia; DM = diabetes mellitus.
¶Developed cerebrovascular symptoms.
tension was controlled after a salt free diet, without any medications, was prescribed. All other patients required single or combination drug therapy. Once blood pressure was maintained within normal limits the same treatment and medications were continued without change throughout the study.

Regional cerebral blood flow (CBF) was measured utilizing the $^{133}$Xe inhalation method. Complete medical, neurologic and CCSE examinations were recorded together with a review of all available medical records prior to institution of antihypertensive intervention. The entire series of examinations were repeated subsequently at 6, 12, 24 and 36 months after treatment was instituted and hypertension was satisfactorily controlled.

Normative data from this laboratory among 250 neurologically normal and healthy volunteers (mean age = 62.39; range = 24–98 years; standard deviation = 12.70) have demonstrated a mean gray matter CBF of 71.14 ± 0.68 standard error of measurement (standard deviation = 10.66). Earlier reports from this laboratory of test-retest reliability for gray matter CBF scores have indicated a reproducibility coefficient of $r = 0.89$.

**Statistical Methods of Analysis**

Changes in mean bihemispheric gray matter cerebral blood flow were analyzed using an analysis of variance repeated measures design. Each follow-up measurement (6, 12, 24 and 36 months) was compared statistically to pretreatment levels utilizing pairwise comparisons. Statistical significance for pairwise comparisons were adjusted for overall significance using the Dunnett test. Since four of the 12 subjects developed symptoms of cerebrovascular disease (stroke, multi-infarct dementia and/or transient ischemic attacks) during the course of the study, additional analyses were performed comparing cerebral regional blood flow values of symptomatic subjects with remaining asymptomatic volunteers at each follow-up interval. Comparisons between symptomatic and asymptomatic subjects were accomplished using the nonparametric Mann-Whitney U test.

**Results**

During the first three year interval of this hypertension treatment trial, eight subjects remained asymptomatic but four of the initially normal subjects developed symptoms and signs of cerebrovascular disease despite effective control of hypertension. One patient (Patient 4) developed vertebrobasilar arterial insufficiency with transient ischemic attacks referable to the brainstem and cerebellum (indicated as VBI on figure 1; and as patient #3 in table 1). Patient 3 developed a left hemiparetic stroke (indicated as STROKE in figure 1; and as patient #1 in table 1). Her diagnosis was based on the criteria described by Hachinski et al. She developed sudden onset of mental deterioration with step-wise progression. On examination there were focal neurologic signs and she complained of focal neurological symptoms. The cognitive deficits were confirmed by Cognitive Capacity Screening Examination. She scored only 15 questions correctly (normal age = 62.39; range = 24–98 years; standard deviation = 10.66). Earlier reports from this laboratory of test-retest reliability for gray matter CBF scores have indicated a reproducibility coefficient of $r = 0.89$.

Another patient an elderly woman who developed multi-infarct dementia (indicated as MID in figure 1; and as patient #1 in table 1). Her diagnosis was based on the criteria described by Hachinski et al. She developed sudden onset of mental deterioration with step-wise progression. On examination there were focal neurologic signs and she complained of focal neurological symptoms. The cognitive deficits were confirmed by Cognitive Capacity Screening Examination. She scored only 15 questions correctly (normal age = 62.39; range = 24–98 years; standard deviation = 10.66). Earlier reports from this laboratory of test-retest reliability for gray matter CBF scores have indicated a reproducibility coefficient of $r = 0.89$.

Analysis of variance revealed statistically significant ($p < 0.001$) increases in mean gray matter bihemispheric cerebral blood flow values following the control of hypertension and restoration of blood pressure values within normal limits. Individual comparisons between pretreatment and each follow-up measurement indicated significant increases in CBF values at 6 months ($p < 0.01$), 12 months ($p < 0.01$) and 24 months ($p < 0.05$) after control of hypertension. After the third year (36 months), mean CBF values for the entire group failed to show significant differences from pre-
treatment levels. The mean CBF level prior to treatment was 59.8 ml/100g/min, which is reduced compared to age-matched normals without hypertension consonant with earlier reports. For the 6, 12, 24 and 36 month visits mean CBF values were increased to 70.56, 72.54, 69.37 and 66.81. The average percent increase for mean CBF values at the 6-month interval was 18% and 11 of the 12 subjects had higher CBF levels compared to pretreatment measures. For the 12-month follow-up, the average CBF increase was 21.3% and all 12 subjects had increased CBF levels compared to pretreatment values. At 24 months the average increase was 16%.

Comparisons of sequential mean bihemispheric gray matter flow values among asymptomatic versus symptomatic subjects at 12, 24 and 36 month intervals are illustrated in figures 1 and 2. Figure 1 shows individual changes in CBF while figure 2 contrasts mean CBF levels among asymptomatic and symptomatic groups. At year 1, both subgroups had increased CBF levels compared to pretreatment values and there were no differences between the two subgroups. Starting at the 24-month follow-up interval the group of four patients who later developed cerebrovascular symptoms had significantly lower CBF values compared to the asymptomatic subjects (p < .001). As can be seen in figure 2, these differences were even more remarkable during the third year (p < .005). At the third year interval the four subjects were now suffering from clear cut cerebrovascular symptoms and all had cerebral blood flow levels well below pretreatment levels. To the contrary, all eight subjects who remained free of neurological symptoms and signs sustained marked increases in cerebral perfusion. Mean bihemispheric gray matter CBF levels and standard errors for the asymptomatic subjects were 58.9 ± 2.9, 69.6 ± 1.8, 71.9 ± 1.9 and 70.2 ± 0.9 ml/100g/min for the initial visit and three yearly follow-up visits; and for symptomatic patients means and standard errors were 61.4 ± 3.9, 75.3 ± 4.8, 63.3 ± 5.1, and 58.6 ± 5.4 ml/100g/min.

There were no statistically significant differences for expired tensions of carbon dioxide or oxygen between measurements. The mean expired carbon dioxide levels were 32.35, 34.97, 30.62, and 33.18 mm Hg for the initial and follow-up visits. After treatment blood pressures remained within normal limits and respiratory rates and EKG rhythms did not significantly alter during the three year follow-up period. It is considered highly unlikely that the measured CBF changes after treatment and control of hypertension reflected fluctuations in any of these variables.

### Discussion

Serial measurements of CBF during long-term treatment of chronic hypertension appear to indicate clearly that control of blood pressure is accompanied by sustained increases in cerebral perfusion. Although untreated control subjects were not used for ethical reasons (this would have required the withholding of antihypertensive medication for three years), it has been documented that similar groups of normal volunteers, both hypertensive and normotensive subjects, show declining trends in CBF during follow-up measurements over similar intervals of time. If CBF declines thereafter, despite control of hypertension, impending stroke may be anticipated. These decreases in CBF presumably indicate irreversible atherogenesis related to long-standing and undetected hypertension. Previous data have demonstrated that hypertensive patients have significant and diffuse reductions of CBF values estimated by the 133Xe inhalation or nitrous oxide methods. Present results are offered as evidence that early and effective control of hypertension reverses cerebral hemodynamic mechanisms that decrease cerebral blood flow and, if hypertension is detected early enough, then prevention of stroke may be anticipated.

Epidemiological studies indicate that increased awareness of the deleterious effects of hypertension on the cardiovascular system together with better methods of antihypertensive intervention appear to have measurably reduced both the prevalence and the mortality from stroke throughout the United States. Epidemiological studies only show that reductions in the incidence of stroke and improved control of hypertension occurred at approximately the same time. However, there are other factors which may have contributed to the declines of stroke incidence such as dietary modifications, treatment of diabetes and heart disease, prevention of rheumatic fever, declines in smoking habits and improved fitness programs. The present investigation appears to demonstrate that detrimental effects of
hypertension on cerebral perfusion are, at least, partly reversed by control of hypertension.

Studies among animal models, as well as among human subjects, demonstrate that chronic hypertension produces both structural and functional changes in cerebral vessels which predispose to stroke and which appear to be reversible if hypertension is controlled. The lower limit at which autoregulation compensates for decreases in blood pressure is raised by chronic hypertension, but is restored to normal after treatment. The chronic vasocostriction and/or stenosis of cerebral vessels brought about by prolonged hypertension has been shown to be reversible if hypertension is treated. These hemodynamic alterations have been shown to be associated with decreased CBF and diminished cerebral collateral reserve both of which predispose to symptoms of cerebral thromboembolism.

Increases in CBF following antihypertensive treatment apparently results from the control of hypertension rather than from direct action of drugs on vessel walls. Administration of propranolol and other beta blocking agents may reduce CBF in normotensive baboons and initially reduce CBF in human subjects with hypertension but subsequently increase CBF when given to hypertensive patients over extended periods of time. Tri-methanaph which apparently has no direct effect on vessel lumen diameter, when administered to severely hypertensive patients increases CBF proportionately as the blood pressure is cautiously decreased. In the present study all patients showed increased CBF levels 12 months after control of hypertension regardless of the treatment used. Thus, control of hypertension by medications which either have no direct effect, or are known to cause vasocostriction when given acutely, have long term affect of raising CBF, supporting the hypothesis that control of hypertension reverses hemodynamic alterations associated with chronic hypertension.

In summary, patients with chronic hypertension benefit from control of hypertension which apparently improves cerebral perfusion and may decrease but not abolish the likelihood of stroke. This benefit results no matter what method is used to control hypertension. Periodic monitoring of CBF, in individuals at risk from stroke due to hypertension, appears to be a useful method for early detection of cerebral ischemia since previous studies indicate that CBF reductions occur prior to the appearance of stroke symptoms.

References
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Altered Membrane Properties of Cerebral Vascular Smooth Muscle Following Subarachnoid Hemorrhage: An Electrophysiological Study

I. Changes in Resting Membrane Potential (Em) and Effect on the Electrogenic Pump Potential Contribution to Em

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SUMMARY Subarachnoid hemorrhage was produced experimentally in cats by intracisternal injection of non-heparinized autologous arterial blood obtained by cardiac puncture under ketamine and xylazine anesthesia. Cats were sacrificed at varying time intervals between 30 min and 7 days post ictus. Measurements of resting membrane potential were recorded from smooth muscle cells of the basilar artery. These measurements were obtained by impalement from the adventitial surface of isolated but otherwise intact segments of the artery using glass microelectrodes with tip sizes less than 0.1 μm. The resting membrane potential recorded in vitro from animals previously subjected to subarachnoid hemorrhage in vivo was consistently and significantly depolarized when compared to normal controls. This depolarization was present as early as 30 min post ictus. Addition of the cardiac glycoside, ouabain, in a concentration of 10^-5 M depolarized cells from both control and experimental animals. There is a significant electrogenic pump potential contribution to the resting membrane potential of vascular smooth muscle cells. Ouabain is a potent blocker of Na⁺, K⁺-ATPase, the enzyme responsible for maintaining the cation electrochemical gradients. The depolarization recorded in these cells following subarachnoid hemorrhage is not, therefore, due to impairment of the electrogenic pump. The significance and implications of these findings are discussed.

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IT HAS BECOME INCREASINGLY EVIDENT that the pathophysiology of cerebral vasospasm following subarachnoid hemorrhage (SAH) is complex and multifactorial. Numerous investigations have been undertaken to define the role of blood and/or blood products in the pathogenesis of vascular spasm, decreased cerebral perfusion and ischemia, all of which may occur clinically following SAH. Release of serotonin from platelets, prostaglandins (specifically the labile metabolite thromboxane A₂), catecholamines, thrombin, histamine, both hemoglobin and oxygen-hemoglobin, an unidentified polypeptide and an hypothalamic extract are amongst many sub-
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