Abnormal Pressure Passive Dilatation of Cerebral Arterioles in the Elderly With Isolated Systolic Hypertension

Sergio Castellani, Marzia Bacci, Andrea Ungar, Patrizio Prati, Claudia Di Serio, Pierangelo Geppetti, Giulio Masotti, Gian Gastone Neri Serneri, Gian Franco Gensini

Abstract—The aim of this study was to investigate the cerebrovascular adaptability to 2 sequential pressor stimuli in elderly patients with isolated systolic hypertension. Ten healthy elderly normotensive subjects (68 to 82 years), 10 elderly subjects with isolated systolic hypertension (63 to 82 years), and 10 young normotensive subjects (24 to 40 years) took part in the study. A pressor reaction, using sequential cold pressor and handgrip stimulation, was induced. The cerebrovascular response to the pressor stimulation was measured by transcranial Doppler determination of the mean flow velocity in the middle cerebral arteries. In all of the subjects, blood pressure increased during handgrip (+12 mm Hg, \( P<0.001 \) in the young; +18 mm Hg, \( P<0.01 \) in the elderly normotensive subjects; +19 mm Hg, \( P<0.001 \) in the hypertensive patients versus baseline). In the hypertensive subjects, the pressure increase persisted well into the recovery period. The pressure increase caused a significant increase in mean flow velocity in the middle cerebral arteries only in the elderly subjects. Cold pressor test increased blood pressure in all of the subjects during stimulation and the first 2 minutes of the recovery period (at whole-curve ANOVA: \( F=22.03, P<0.001 \) in the young participants; \( F=18.3, P<0.001 \) in the normotensive elderly; and \( F=13.04, P<0.001 \) in the hypertensive elderly). Mean flow velocity in the middle cerebral arteries significantly increased only in the hypertensive subjects. In the elderly hypertensive patients, the cerebrovascular reaction to adrenergic stimuli was more impaired than in the elderly normotensive subjects. This event can amplify the pressure insult on cerebral hemodynamics and increase the predisposition to cerebral damage, such as vascular cognitive impairment or stroke. (Hypertension. 2006;48:1143-1150.)

Key Words: cerebrovascular adaptability ■ adrenergic stimulation ■ isolated systolic hypertension

In the elderly, and especially in elderly hypertensive subjects, the risk of vascular cognitive impairment and stroke increases.\(^1\)-\(^5\) In patients with isolated systolic hypertension (ISH), the incidence of cognitive impairment\(^6\)-\(^7\) and acute cerebrovascular events\(^8\),\(^9\) rises. The lowering of systolic blood pressure (SBP) leads to a significant reduction in the incidence of vascular cognitive impairment\(^10\) and in both ischemic and hemorrhagic strokes.\(^11\),\(^12\) In normotensive elderly subjects, cerebrovascular autoregulatory adaptation to pressor stimuli is delayed,\(^13\) thus defining the limits of the vascular adaptation of the brain to pressure oscillations. In hypertensive patients and chronically hypertensive baboons,\(^14\),\(^15\) both the lower and upper thresholds of cerebral blood flow autoregulation curve are shifted to the right, thus maintaining a constant cerebral blood flow in the presence of further increases in blood pressure. However, the shift to the right of the lower limit of cerebral autoregulation may impair the cerebral adaptation to blood pressure lowering\(^15\) as it occurs in hypertensive humans.\(^16\),\(^17\) To the best of our knowledge, the adaptation of cerebral vessels to arterial blood pressure (ABP) oscillations in patients with ISH has not yet been investigated, in spite of the fact that an abnormal autoregulation of renal blood flow has already been reported in ISH patients.\(^18\) Therefore, we studied the adaptations of cerebral circulation to blood pressure increases in patients with ISH by investigating the cerebrovascular reactions to acute adrenergic pressor stimulation using transcranial Doppler (TCD) evaluation of cerebral hemodynamics. TCD testing is considered a reliable method for the study of cerebral autoregulation.\(^19\),\(^20\)

Subjects and Methods

Subjects and Inclusion Criteria

Experiments were performed in 3 groups of 10 subjects, each of which was made up of 5 men and 5 women. Ten were healthy elderly normotensive participants, aged 68 to 82 years (mean: 75±5 years), 10 were young healthy normotensive volunteers, aged 24 to 40 years (mean: 31±6 years), and 10 were elderly patients aged 63 to 82 years (mean: 73±6 years) who were affected by essential ISH. The ISH group had no other known diseases that had been excluded through medical history, clinical examination, blood chemistry, urinalysis, ECG, echocardiography, and renal and carotid ultrasound evaluation.
In particular, patients with significant hemodynamic stenosis of the carotid arteries were not included in the study. Blood pressure was detected by 3 clinical measurements on 2 different days. All of the ISH patients were enrolled in the study if SBP had been ≥160 mm Hg and diastolic blood pressure (DBP) had been <90 mm Hg at the 2 screening examinations. Patients with ISH are unlikely to have pseudohypertension. Only 2 of the 10 hypertensive patients had already been treated with antihypertensive therapy. All of the subjects were nonsmokers and had a body mass index of <27. All provided their informed consent, and the protocol was approved by the local institutional review board and was adherent to the principles of the Declaration of Helsinki. All of the patients had given their informed consent to participate in the study. The normotensive subjects were considered healthy on the basis of their medical history and by using all of the same examinations as those used in the hypertensive participants. Normotensive offspring of diabetic parents and those of hypertensive parents were not included in the study. No aspirin or other cyclooxygenase-inhibiting drug had been taken for 2 weeks before the start of the study. The 2 patients under antihypertensive therapy discontinued their treatment for 2 weeks before the start of the study.

Methods
Cerebral hemodynamics were studied using a TCD (Multidop X 4, DWL, Sipplingen Bodensee) by continuous monitoring of the mean velocity in the middle cerebral artery (MCA Vm) through the temporal windows by two 2-MHz probes. This method assumes that MCA flow velocity changes completely reflect variations in small artery resistance, because the diameters of the large basal brain arteries are known to remain relatively constant during small changes in mean blood pressure, within the reference range. ABP was continuously monitored by TCD for 43 minutes and 30 seconds; the conditions were the same as in the experimental study, except repeated measures were taken at different intervals, with the same handgrip (HG) of a hand-held probe and cold pressor stimulation (CPT) by immersion of the right hand in a pan containing equal parts of water and ice (temperature: 2 to 3°C) with simultaneous applications of ice to the right hand in a pan containing equal parts of water and ice (temperature: 2 to 3°C) with simultaneous applications of ice to the lateral cervical regions. The adrenergic stimulation was applied starting at random either with HG in 15 subjects (5 young, 5 elderly normotensive, and 5 elderly with ISH subjects) or with CPT in the other 15 subjects. According to our protocol (Figure 1), data were collected at baseline, during stimulation, and during the 10-minute recovery periods. Based on our previous investigation, a 10-minute pause was observed between each experimental period, because this is the minimum lag time needed for all of the hemodynamic variables to revert to baseline after cold pressor test (CPT) stimulation. To define the possible differences between the early and subsequent phases of the whole recovery period, the 10-minute period after stimulation was divided into 2 parts: recovery 1, the first 2 minutes (rec. 1), and recovery 2, the subsequent 8 minutes (rec. 2; Figure 1).

Preliminary Experiments
In a preliminary 90-minute experiment in 5 young normotensive subjects, 5 normotensive elderly subjects, and 5 elderly patients with ISH, we investigated the stability and the reproducibility of the mean velocity measurements in the middle cerebral artery while PCO2 and mean blood pressure were constant. In this preliminary study, all of the conditions were the same as in the experimental study, except that adrenergic stimulation was not applied. After a 45-minute stabilization period the mean flow velocity in the cerebral arteries was continuously monitored by TCD for 43 minutes and 30 seconds; repeated measures were taken at different intervals, with the same sequence and duration as during HG and the CPT: 5, 1.5, 2, 8, 10, 5,

![Figure 1. Experimental sequence. Stimulus indicates 2-min CPT or 90-s HG.](image)

In a preliminary 90-minute experiment in 5 young normotensive subjects, 5 normotensive elderly subjects, and 5 elderly patients with ISH, we investigated the stability and the reproducibility of the mean velocity measurements in the middle cerebral artery while PCO2 and mean blood pressure were constant. In this preliminary study, all of the conditions were the same as in the experimental study, except that adrenergic stimulation was not applied. After a 45-minute stabilization period the mean flow velocity in the cerebral arteries was continuously monitored by TCD for 43 minutes and 30 seconds; repeated measures were taken at different intervals, with the same sequence and duration as during HG and the CPT: 5, 1.5, 2, 8, 10, 5,

### TABLE 1. Transcranial Doppler Velocity Measurements: Reproducibility Data

<table>
<thead>
<tr>
<th>Artery</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>ANOVA</th>
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<tr>
<td>MCAL Vm, young normotensive</td>
<td>51.8±9</td>
<td>51.7±7</td>
<td>49.6±8</td>
<td>50.8±8</td>
<td>51.4±10</td>
<td>51.8±10.5</td>
<td>50.6±12</td>
<td>51.2±11</td>
<td>51.6±12</td>
<td>ns</td>
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<tr>
<td>subjects, cm/s</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>MCA R Vm, young normotensive</td>
<td>60.6±9</td>
<td>59.6±9</td>
<td>59±9</td>
<td>59.8±8</td>
<td>58.8±8.5</td>
<td>58.8±9</td>
<td>58.6±9</td>
<td>59.4±10</td>
<td>59.6±10</td>
<td>ns</td>
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<tr>
<td>subjects, cm/s</td>
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<tr>
<td>MCA L Vm, elderly normotensive</td>
<td>68.2±9</td>
<td>66.6±7</td>
<td>66±29</td>
<td>67±26</td>
<td>65.2±28</td>
<td>64.6±30</td>
<td>63.8±29</td>
<td>65.6±29</td>
<td>65.8±29</td>
<td>ns</td>
</tr>
<tr>
<td>subjects, cm/s</td>
<td></td>
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<tr>
<td>MCA R Vm, elderly normotensive</td>
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<td>60.6±7</td>
<td>60.6±28</td>
<td>61.2±26</td>
<td>59.6±29</td>
<td>59±30</td>
<td>58.2±29</td>
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<tr>
<td>MCAL Vm, elderly patients</td>
<td>38.8±13</td>
<td>37.2±14</td>
<td>40.4±12</td>
<td>39.4±17</td>
<td>36.8±13</td>
<td>40.2±16</td>
<td>39.8±14</td>
<td>40±13</td>
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<tr>
<td>with ISH, cm/s</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MCA R Vm, elderly patients</td>
<td>34.2±13</td>
<td>32.6±13</td>
<td>33±15</td>
<td>33.4±14</td>
<td>34.8±13</td>
<td>36.6±17</td>
<td>35.4±15</td>
<td>33±15</td>
<td>35.6±15</td>
<td>ns</td>
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<td>with ISH, cm/s</td>
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</tbody>
</table>

MCAL Vm indicates mean velocity in the left middle cerebral artery; MCA R Vm, mean velocity in the right middle cerebral artery; ns, not significant. Values are mean±SD.
Table 1 shows that the maximum SD was slightly greater than 5 mean velocity values. Because the differences were negligible, the velocity measurements were steady and repeatable. Indeed, the intraclass coefficient of correlation was 0.98; therefore, only 2% of the total variance was situated at measurement level.

Statistical Analysis

Values reported in the tables and figure include all of the mean values, whereas, for the sake of simplicity, the text describes the mean percentage differences during and after stimulation as compared with the baseline values. Student t test for independent samples was used to compare the mean baseline values of the 3 groups. Two-step statistical analysis was used to evaluate the effect of stimuli: first, an ANOVA for repeated measures was used to evaluate the variations among periods; second, a posthoc test (least significant differences) was used to detect differences of values at different times versus the baseline. Statistical significance was set at \( P<0.05 \).

Results

Mean baseline ABP was higher in ISH patients than in the other 2 groups. The MCA Vm was higher in the young versus the elderly subjects. Mean velocities were similar in both of the elderly groups (Table 2). The PCO2 in the expired air of all 30 subjects did not vary throughout the experiment or during the use of either of the stimuli.

Effects of HG

HG pressor stimulation increased APB in all of the subjects (Table I, available online at http://hyper.ahajournals.org), with the largest increases found in patients with ISH. More precisely, the relative increase in peak ABP compared with baseline in each group was +13.9% in the young volunteers, +18.9% in the elderly normotensive subjects, and +19.6% in the ISH patients. Only in the ISH patients did the APB remain significantly higher than baseline during the 2 recovery periods (rec.1 and rec.2). In all of the groups, SBP and DBP varied in the same way as mean arterial pressure did. The changes in SBP and DBP were similar and showed the same time course of variation (Figure 3). In the young subjects, MCA Vm did not significantly increase during any period of the study. On the contrary, it significantly rose in the 2 elderly groups during stimulation. In the elderly normotensive subjects, it was +18% and +20% versus baseline in the right and left middle cerebral artery, respectively; and in the ISH group it was +20% and +21.4% versus baseline in the right and left MCA, respectively. In the ISH patients, MCA Vm remained significantly higher than baseline during the whole 10-minute recovery period (Table I and Figure 3). Three examples of the different individual patterns observed in each group are given in Figure 4.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hemodynamic Parameters</th>
<th>Young Normotensive Subjects (n=10)</th>
<th>Elderly Normotensive Subjects (n=10)</th>
<th>Patients With ISH (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP, mm Hg</td>
<td>90±7</td>
<td>96±7</td>
<td>105±8</td>
<td></td>
</tr>
<tr>
<td>MCAR Vm, cm/s</td>
<td>58±9</td>
<td>40±5</td>
<td>45±6</td>
<td></td>
</tr>
<tr>
<td>MCAL Vm, cm/s</td>
<td>58±13</td>
<td>41±3</td>
<td>51±5</td>
<td></td>
</tr>
<tr>
<td>ABP, mm Hg</td>
<td>94±8</td>
<td>87±7</td>
<td>100±6</td>
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<tr>
<td>MCAR, cm/s</td>
<td>58±7</td>
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<td>46±10</td>
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<tr>
<td>MCAL, cm/s</td>
<td>56±5</td>
<td>45±7</td>
<td>48±6</td>
<td></td>
</tr>
</tbody>
</table>

AbP indicates baseline mean arterial blood pressure; MCAR Vm, mean velocity in the right middle cerebral artery; MCAL Vm, mean velocity in the left middle cerebral artery.

\*\( P<0.05 \).

\#\( P<0.01 \).
Figure 3. Effects of isometric HG on blood pressure and cerebral hemodynamics. Left, SBP (dotted line), DBP (dashed line), and mean ABP (unbroken line) values. Right, individual (thin lines) and mean (thick line) MCAL Vm in the 3 groups. (A) Young normotensive subjects; (B) elderly normotensive subjects; (C) patients with isolated systolic hypertension. *P<0.05; **P<0.01; ***P<0.001.
CPT stimulation led to an increase in systemic blood pressure in all of the subjects (Table II and Figure 5). Compared with baseline, ABP rose +23.6% in the young subjects, +16.3% in the elderly normotensive group, and +15.6% in the ISH patients. In all 30 of the subjects, blood pressure reverted to baseline values during the first 2-minute recovery period (rec. 1). In all of the groups, SBP and DBP varied in the same way as the mean arterial pressure. The changes in SBP and DBP were similar and showed the same time course of variation (Figure 5). The MCA velocity remained constant during the whole experiment despite the increase in ABP in both the young and elderly normotensive subjects. CPT induced a significant increase in mean velocity in the cerebral arteries only in the ISH patients (+13.8% versus baseline in the right middle cerebral artery and +15.7% versus baseline in the left middle cerebral artery). At the end of stimulation, the velocity quickly reverted to baseline (Table II and Figure 5). Three examples of the different individual patterns observed in each group are given in Figure 6.

Study Limitations
Because the results of the present investigation may have significant clinical implications, we would like to point out some limitations of the study. Although the cerebral and systemic hemodynamic parameters were homogeneous, only a limited number of subjects was investigated. Secondly, for both ethical reasons and to define pathophysiological mechanisms, the study was performed only in class I hypertensive subjects according to World Health Organization classification. Therefore, the results may not be applicable to patients with more severe hypertension and/or patients during or after long-term antihypertensive treatment.

Discussion
The results of this study indicate that, in patients with ISH, the adaptability of the cerebral vessels to increases in blood pressure is reduced, as suggested by the pressure-passive increase in flow velocity in the middle cerebral artery. As demonstrated by TCD studies, the mean flow velocity in the middle cerebral arteries can undergo a wide range of changes after various kinds of stimulation.20,23,24 According to angiographic studies, whereas flow velocity varies, the cross-sectional area of the middle-sized basal cerebral arteries does not change.26 It has already been recognized that the increase in mean velocity of the middle cerebral arteries mirrors the increase in cerebral flow.33–35 Because the cross-section of the middle cerebral artery does not vary, the flow velocity changes in response to blood pressure elevation most probably reflect changes in arteriolar resistance vessels.23,26 In ISH patients, the arteriolar vasoconstrictive response does not seem adequate to cope with pressure increases or to protect the brain from deleterious arterial overflow. In the 3 groups of patients, ABP increases were similar and never exceeded the established upper limit of autoregulation (ie, 150 mm Hg36). However, in the ISH patient group, the mean flow velocity did increase. This finding suggests that the autoregulation threshold of patients affected by ISH is lower than that usually reported in systolic-diastolic hypertensive patients.37 The changes in mean flow velocity after HG are different from those observed after CPT. In patients with ISH, the increase in mean flow velocity after HG lasts longer than the one observed during CPT. In patients with ISH, the increase in mean flow velocity seems to track the blood pressure increase. Hence, it is not possible to rule out that this increase in blood pressure and the following increase in flow velocity through the middle cerebral arteries may be because of an additional anxious reaction to HG application manifest only in the elderly hypertensive subjects. In contrast to the CPT, HG might detect a gradient of abnormality in autoregulation of cerebral blood flow rising from that which is normal in the
young group to that progressively impaired in the elderly normotensive subjects and elderly with ISH. According to the law of autoregulation of cerebral blood flow, any impairment of this feedback mechanism leads to an increase in blood tissue perfusion. Indeed, the high perfusion related to episodes of increased ABP has been found to be associated with leukoaraiosis, cerebral microhemorrhages, and perivascular encephalolysis. In hypertensive patients, MRI has revealed several features suggesting that blood products pass into the vessel wall and perivascular space, in addition to possible arteriolar intraluminal thrombi responsible for lacunar infarction. Wardlaw has suggested that these pathological findings may be because of some failure of the blood–brain barrier resulting in extravasation of the blood.

![Figure 5](image_url) Effects of CPT on blood pressure and cerebral hemodynamics. Left, SBP (dotted line), DBP (dashed line), and mean ABP (unbroken line) values. Right, individual (thin lines) and mean (thick line) MCAL Vm in the 3 groups. (A) Young normotensive subjects; (B) elderly normotensive subjects; (C) patients with isolated systolic hypertension. *P<0.05; **P<0.01; ***P<0.001.
components. Notably, in our ISH patients, the increases in ABP induced by the experimental adrenergic stimulation were significantly smaller than the increases in blood pressure that occur in everyday life.\textsuperscript{43} Therefore, the pressure passive increase in cerebral blood flow, especially if recurrent, may be effective in inducing cerebral damage. In conclusion, the results of this study provide evidence that in elderly patients with ISH, cerebral microvascular adaptability to sudden elevations of ABP is impaired. This failure of microcirculation in coping with pressure elevations may be the underlying mechanism that eventually results in cerebral damage independent of ischemic damages.

**Perspectives**

Present findings show that ISH modifies the cerebral autoregulation response in a different way from that induced by systodiatolic hypertension. In systodiatolic hypertension, the upper limit of cerebral autoregulation has been found to be normal\textsuperscript{37} or elevated\textsuperscript{44} (which provides protection from the sudden pressure increases). In our ISH study, the autoregulation threshold shifted to lower values. This is consistent with reduced cerebral protection from sudden pressure increases. This displacement of the autoregulation threshold exposes cerebral tissue to sudden overflow in relation to blood pressure increases. Repeated ABP increases may contribute to vascular cognitive impairment, which is highly prevalent in patients with ISH.\textsuperscript{6,7} These results suggest that the choice of any antihypertensive treatment in patients with ISH should be carefully evaluated to offer the most benefit to the subject. A recent meta-analysis of controlled clinical trials\textsuperscript{44} reports a higher risk of stroke associated with the use of traditional β-blockers (ie, metoprolol and atenolol) compared with other classes of antihypertensive agents. These data suggest that traditional β-blockers should not be viewed as first line therapy for hypertension, especially in the elderly.\textsuperscript{45} Indeed, traditional β-blockers can be less efficacious to prevent stroke in elderly patients with predominantly systolic hypertension, possibly because of their negative chronotropic effect, which can be compensated by an increase in stroke volume, which, in turn, can elevate (or diminish the hypotensive effect in) systolic pressure while exacerbating the decrease of diastolic pressure, thus leading to an increase in pulse pressure values.\textsuperscript{46}

Treatment should be chosen not only in terms of arterial pressure reduction, but also for the improvement of cerebral autoregulation. The agent should be selectively targeted to reduce primarily SBP. Epidemiological findings\textsuperscript{8,47–49} and experimental studies\textsuperscript{50} have shown that the noxious component in ISH is not only the absolute blood pressure increase but also increases in the pressure gradient.

**Acknowledgments**

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**Disclosures**

None.

**References**


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Table I: Effects of handgrip on cerebral hemodynamics

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Young normotensives (n=10)</th>
<th>Elderly normotensives (n=10)</th>
<th>Patients with isolated systolic hypertension (n=10)</th>
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<tr>
<td><strong>Baseline</strong></td>
<td>90±7 ***</td>
<td>96±7 *** 114±18</td>
<td>105±8 *** 124±11 112±14 109±12</td>
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<td><strong>Handgrip</strong></td>
<td>102±7</td>
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<td><strong>Recovery 2 (8 min)</strong></td>
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<td>ANOVA for the whole curve</td>
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<td>0.01 6.07</td>
<td>0.001 29.06</td>
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ABP = baseline mean arterial blood pressure.

MCAR Vm = mean velocity in the right middle cerebral artery.

MCAL Vm = mean velocity in the left middle cerebral artery.

The values are expressed as mean ± SD.

* = p < 0.05

*** = p < 0.001
Table II: Effects of cold pressor test on cerebral hemodynamics

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Young normotensives (n = 10)</th>
<th>Elderly normotensives (n = 10)</th>
<th>Patients with isolated systolic hypertension (n = 10)</th>
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<td>Baseline</td>
<td>Cold Pressor Test</td>
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<tr>
<td>MCAL Vm (cm/sec)</td>
<td>56±5</td>
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<td>ABP (mmHg)</td>
<td>87±7</td>
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</tr>
<tr>
<td>ABP (mmHg)</td>
<td>100±6</td>
<td>115±12</td>
<td>107±11</td>
</tr>
<tr>
<td>MCAR Vm (cm/sec)</td>
<td>46±10</td>
<td>52±11</td>
<td>46±8</td>
</tr>
<tr>
<td>MCAL Vm (cm/sec)</td>
<td>48±6</td>
<td>55±11</td>
<td>49±11</td>
</tr>
</tbody>
</table>

ABP = baseline mean arterial blood pressure.

MCAR Vm = mean velocity in the right middle cerebral artery.

MCAL Vm = mean velocity in the left middle cerebral artery.

The values are expressed as mean ± SD.

* = p < 0.05

** = p < 0.01

*** = p < 0.001