Age and Sex Differences in Cerebral Hemodynamics
A Transcranial Doppler Study

Maria Matteis, MD; Elio Troisi, MD; Bruno C. Monaldo, MD; Carlo Caltagirone, MD; Mauro Silvestrini, MD

Background and Purpose—Hemodynamic factors seem to play an important role in the pathogenesis of cerebral ischemic events. The aim of this study was to evaluate whether changes in cerebrovascular reactivity occur in women after menopause.

Methods—Using transcranial Doppler ultrasonography, we studied the changes of flow velocity after hypercapnia in the middle cerebral arteries of 45 healthy premenopausal women (mean age, 32.3 years; range, 20 to 47 years) and 40 postmenopausal women (mean age, 54.4 years; range, 48 to 64 years). The same measurements were recorded in two groups of healthy male subjects age matched with premenopausal (45 subjects) and postmenopausal women (40 subjects). Moreover, a subgroup of postmenopausal women aged 48 to 53 years (15 subjects) were compared with a group of 15 premenopausal women of the same age. We obtained hypercapnia with breath holding and evaluated cerebrovascular reactivity with the breath-holding index (BHI).

Results—BHI was significantly lower in postmenopausal women (0.89 ± 0.3) than in premenopausal women (1.59 ± 0.3; P < 0.0001) and in young (1.34 ± 0.5; P < 0.0001) and old men (1.20 ± 0.4; P < 0.04). In the latter group, BHI was significantly lower than in premenopausal women (P < .0001). BHI values were also significantly lower in postmenopausal women of the same age (0.81 ± 0.1 versus 1.34 ± 0.1; P < 0.0001).

Conclusions—These findings suggest that the large reduction of cerebrovascular reactivity in postmenopausal women cannot be considered a simple factor related to aging but is probably influenced by hormonal changes. The alteration in cerebrovascular regulation could be involved in the increase of cerebrovascular disease in postmenopausal women.

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Key Words: gender □ ultrasonography, Doppler, transcranial □ vasomotor reactivity

Transcranial Doppler ultrasonography permits the noninvasive measurement of blood flow velocities in the basal brain arteries that have been found to reliably correlate with changes in cerebral blood flow.1,2 Cerebral vasomotor reactivity can easily be studied by measuring changes in flow velocity in response to vasodilatory stimuli such as CO₂ inhalation, breath holding, or acetazolamide administration.3–5 The assessment of cerebral vasoreactivity can provide information regarding the reserve capacity of cerebral circulation, that is, the possibility of vessels to adapt in response to systemic modification or brain metabolic activity requiring an increase or decrease of cerebral blood flow.6,7 Reduction of this property has been found in association with situations predisposing toward cerebrovascular diseases.8–11

Epidemiological data show that there are distinctive features of cerebrovascular disease in men and women probably connected to their different patterns of sex hormones. In particular, the incidence of atherosclerotic vascular disease in premenopausal women is less than in men, but this difference disappears after menopause.12–15

Experimental studies have shown that female gerbils sustain less neuronal damage after focal ischemia than their male counterparts16 and that chronic estradiol treatment can improve regional cerebral blood flow in female rabbits during incomplete global ischemia and early reperfusion.17

Because sex hormones, in particular estrogens, have well-known vasoactive properties18,19 and their level decreases after menopause, we aimed to assess whether changes in cerebral vasomotor reactivity occur after menopause and to verify the possible existence of sexual hemodynamic differences.

Subjects and Methods
After giving informed consent, 170 right-handed healthy subjects selected from the hospital personnel (85 women and 85 men) were admitted to the study. Each female subject was matched with a male of the same age. The population was divided into four groups: 45 premenopausal women (mean age, 32.3 years; range, 20 to 47 years), 40 postmenopausal women (mean age, 54.4 years; range, 48 to 64 years), 45 men aged 47 years or younger (mean age, 36.5 years; range, 20 to 47 years), and 40 men older than 47 years (mean age, 56.5 years; range, 48 to 64). Postmenopausal status was defined as

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amenorrhea for at least 6 months, with gonadotropin and estradiol values within the postmenopausal range. The menopausal period ranged from 43 to 46 years. The interval from menopause to Doppler assessment ranged from 4 to 18 years (mean, 10.5 years).

Exclusion criteria were established to avoid any bias by an unbalanced distribution of concomitant diseases or drug therapy; subjects with hypertension, diabetes mellitus, obesity, congestive heart failure (greater than New York Heart Association grade I), chronic obstructive lung disease, cerebrovascular disease (transient ischemic attack, stroke, carotid artery stenoses >30%, and intracranial stenosis evaluated by cervical Doppler sonography and TCD), hematologic disease, and cancer were excluded from the study, as well as patients being treated with hormonal substances, nitrates, \( \beta \)-block ing agents, calcium channel blockers, anticoagulants, and vasodilatory drugs. The female group included 6 premenopausal and 4 postmenopausal smokers. Hyperlipemia (cholesterol >200 mg/dL) was present in 2 postmenopausal women. The male group comprised 12 smokers: 7 in the younger group and 5 in the older group. In a second study, to compare premenopausal and postmenopausal women of similar age, a subgroup of postmenopausal subjects aged 48 to 53 years (15 subjects) was matched with 15 premenopausal women, each coupled with a postmenopausal woman of the closest age with similar weight and height.

Informed consent was obtained according to the declaration of Helsinki. The study was approved by the local ethics committee.

The subjects were studied in the morning in a supine resting state with their eyes closed. Twenty-two premenopausal women were recorded during the follicular phase (days 3 to 8 of the menstrual cycle), that is, estrogen dominant with high concentrations of estrogen and low progesterone levels, and 23 during the luteal phase (days 18 to 23 of the menstrual cycle), that is, estrogen dominant with high concentrations of estrogen and low progesterone levels, and 23 during the luteal phase.

The menstrual cycle was established by considering the interval between two consecutive menses. The time of this interval ranged from 25 to 31 days, with a mean of 28 days. All subjects were drug free and had abstained from smoking, alcohol, and caffeine-containing beverages for at least 12 hours before the study. A routine hemogram performed at the time of TCD evaluation showed normal hematocrit values in all the study subjects without significant differences among groups (premenopausal women, 41 \( \pm \) 3; postmenopausal women, 40 \( \pm \) 2; young men, 43 \( \pm \) 3; old men, 42 \( \pm \) 4; young postmenopausal women, 41 \( \pm \) 4; premenopausal women of similar age, 41 \( \pm \) 2).

The MFV of the MCA was continuously monitored by means of a Multi-Dop X/TCD transcranial Doppler instrument (DWL Elektronische Systeme GmbH). One dual 2-MHz transducer fitted on a headband and placed on the temporal bone window was used to obtain continuous measurements. The highest signal was sought at a depth ranging from 46 to 54 mm. This unit allows for continuous-wave Doppler recording of the intracranial artery with on-line calculation of MFV in centimeters per second. By activating the record function, it is possible to save the Doppler spectra during the entire period of each study. Reactivity was examined by calculating the BHI. This index is obtained by dividing the percent increase in MFV occurring during breath holding by the length of time (seconds) that subjects hold their breath after a normal inspiration (%MFV increase per second). The MFV at rest was obtained by the continuous recording of a 1-minute period of normal room air breathing. After a breath-holding period, the MFV over a 4-second interval was recorded. A fixed period of 30 seconds for breath holding was arbitrarily chosen. The efficacy of breath holding was checked by means of a respiratory activity monitor (Normocap-Oxy, Datex). With this kind of procedure, this method of induction of hypercapnia proved to be effective and reproducible in the study of cerebral hemodynamics. In particular, the fact that subjects hold their breath after a normal inspiration avoids a Valsalva phenomenon and the possible interference of blood pressure changes with cerebral hemodynamics. MBP and HR were continuously monitored by means of a blood pressure monitor (2300 Finapress, Ohmeda).

A preliminary analysis was performed on premenopausal women to detect whether there were differences in BHI in the follicular and luteal phases. A one-way ANOVA was used with BHI as dependent factor and phase of the menstrual cycle (follicular and luteal) as between factors. Since no significant difference was detected, all values were considered together as premenopausal values. To investigate possible differences related to sex and age, a two-way ANOVA (BHI as dependent factor) was performed with sex (men and women) and age (premenopausal and postmenopausal women, men aged 47 years or younger, or men older than 47 years) as between factors. Moreover, post hoc comparisons (Scheffé’s test) were performed when necessary. The same analysis was used for MFV, HR, and MBP values at rest. The comparison between BHI of the subgroup of younger postmenopausal women and premenopausal woman of similar age was performed by means of a one-way ANOVA with the group (postmenopausal and premenopausal women) as between factor and BHI as dependent factor.

**Results**

HR and MBP at rest were comparable in the four groups considered (Table 1). Values of MFV at rest were also comparable: 62.3 \( \pm \) 12.1 cm/s in premenopausal women; 59.8 \( \pm \) 9.3 cm/s in postmenopausal women; 60.5 \( \pm \) 11.4 cm/s in men aged 47 years or younger; and 61.6 \( \pm \) 10.2 cm/s in men older than 47 years. Regarding cerebrovascular reactivity during apnea, the sex effect was not significant. In fact, when

**TABLE 1. BHI, HR, and MBP in the Four Groups of Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Premenopausal Women</th>
<th>Postmenopausal Women</th>
<th>Men ( \leq ) 47 y</th>
<th>Men ( &gt; ) 47 y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BHI</strong></td>
<td>1.59 (0.3)</td>
<td>0.89 (0.3)</td>
<td>1.34 (0.5)</td>
<td>1.20 (0.4)</td>
</tr>
<tr>
<td><strong>HR, bpm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>73.3 (10.3)</td>
<td>66.5 (9.2)</td>
<td>72.2 (14.6)</td>
<td>69.7 (9.8)</td>
</tr>
<tr>
<td>After BH</td>
<td>78.2 (8.8)</td>
<td>74.5 (6.9)</td>
<td>77.3 (6.6)</td>
<td>76.4 (9.9)</td>
</tr>
<tr>
<td><strong>MBP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83.2 (10.4)</td>
<td>85.7 (13.1)</td>
<td>79.6 (8.6)</td>
<td>85.9 (9.6)</td>
</tr>
<tr>
<td>After BH</td>
<td>88.7 (9.3)</td>
<td>90.2 (9.9)</td>
<td>85.2 (6.5)</td>
<td>89.3 (8.7)</td>
</tr>
</tbody>
</table>

*Values of HR and MBP are during basal conditions and after the breath-holding (BH) period. Values in parentheses are SDs.*

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**Selected Abbreviations and Acronyms**

- **BHI** = breath-holding index
- **HR** = heart rate
- **MBP** = mean blood pressure
- **MCA** = middle cerebral artery
- **MFV** = mean flow velocity
- **TCD** = transcranial Doppler ultrasonography
establishing the number of women in the fertile period and holding (BH) period. Values in parentheses are SDs.

Women of Similar Age

Postmenopausal

Premenopausal

BHI

0.81 (0.1)

1.34 (0.1)

HR, bpm

Baseline

68.1 (10.1)

68.8 (8.3)

After BH

73.4 (7.7)

73.7 (9.4)

MBP, mm Hg

Baseline

84.5 (9.5)

84.8 (10.1)

After BH

91.6 (7.9)

90.7 (13.2)

Values of HR and MBP are during basal conditions and after the breath-holding (BH) period. Values in parentheses are SDs.

all the included subjects were considered without distinction for age, BHI was comparable in women and men (1.24 versus 1.19). The age effect was significant ($F=38.9; P<0.0001, df = 1$ and 166). In fact, considering woman and men together, the BHI was significantly higher in the younger (premenopausal women and young men) than in the older (postmenopausal women and old men) subjects (1.47 versus 0.96). Finally, the sex×age interaction was significant ($F=16.8; P<0.0001, df = 1$ and 166). Post hoc comparison (Scheffé’s test) showed that BHI was significantly lower in the postmenopausal women with respect to premenopausal women ($P<0.0001$), young men ($P<0.001$), and old men ($P<0.04$) and in old men with respect to premenopausal women ($P<0.001$). These data are shown in Table 1.

HR and MBP at rest were comparable in the subgroup of young postmenopausal women and in the group of premenopausal women of similar age (Table 2). Values of MFV at rest were also comparable: 60.2±8.3 cm/s in postmenopausal women and 63.1±10 cm/s in premenopausal women. Regarding BHI, the group effect was significant ($F=65.2; P<0.0001, df = 1$ and 28). This was due to the fact that the BHI values were lower ($P<0.0001$) in postmenopausal than in premenopausal women (Table 2).

HR and MBP during breath holding showed a slight increase. These modifications, as shown in Tables 1 and 2, were comparable in all groups. For this reason, when the analysis on BHI was repeated introducing HR and MBP changes as covariant factors, the results remained unchanged. Changes of HR and MBP with respect to baseline were calculated considering the values of the 4-second interval after the breath-holding period.

**Discussion**

The results of our study suggest that changes of cerebrovascular reactivity in healthy subjects may be related to aging, but they are probably mainly influenced by hormonal changes. The only previous TCD study describing sex-related differences in cerebral vasomotor reactivity has shown increased vasodilatory response to the acetazolamide test in female compared with male subjects.20 These data are not comparable with ours. In fact, the study design did not permit establishing the number of women in the fertile period and the number in the postmenopausal period at the time of the assessment.

Epidemiological21,22 and experimental16,23 studies suggest that many different aspects must be considered in the relationship between sex and cerebrovascular disease. There is evidence that cerebral ischemic events have a more benign natural course in women than in men13 and that there are sex differences in the antithrombotic effect of aspirin.24 Moreover, the incidence of stroke in premenopausal women is lower than in age-matched men and, after menopause, there is a strong increase in the incidence of vascular diseases in women.12-15 These facts suggest that the relevance of several pathophysiological substrates involved in verifying stroke events may not be the same in the two sexes.

Strict exclusion criteria were used in the present investigation to eliminate any bias caused by concomitant drug therapy or diseases or lifestyle that might influence cerebral vasomotor reactivity. The main finding of our study was the reduction of cerebrovascular reactivity in postmenopausal with respect to premenopausal women. We also found that while BHI was significantly lower in the postmenopausal women with respect to men of the same age, the latter subjects did not differ from younger men but had a significantly lower cerebrovascular reactivity to hypercapnia in comparison to premenopausal women. These findings lead us to believe that factors other than age may influence the reduction of cerebrovascular reactivity in women at the end of the fertile period. This is also confirmed by the fact that we found a significantly lower cerebrovascular reactivity in young postmenopausal women with respect to premenopausal women of similar age. At present, the mechanisms of the decrease of vasomotor reactivity in women after menopause and the pathophysiological significance of this phenomenon cannot be completely defined. At menopause, levels of estradiol, primarily produced by the ovary, fall, and this hormone is replaced by estrone, a less active estrogen, produced mainly by conversion of androstenedione in adipose tissue. After menopause there is little further decrease in endogenous estrogens with advancing age.25 The low cerebrovascular reactivity in postmenopausal women could be connected with these changes, but further studies comparing changes in concentrations of specific sex hormones with changes in cerebral hemodynamics are needed before we can state this with certainty.

From a clinical point of view, estrogen administration in postmenopausal women has been associated with a significant reduction in the development of clinical manifestations of coronary artery disease and stroke.26,27 These observations have been interpreted as probable evidence that female reproductive hormones provide vascular protection in ischemic heart disease and stroke. However, it is unclear whether estrogens per se are critical for modulating the risk of stroke or which mechanism provides protection. Although estrogens have been shown to favorably alter the lipid profile14 and inhibit endothelial hyperplasia,24 these effects do not fully account for the degree of clinical benefit attributed to estrogen therapy in postmeno-
pausal women. Another mechanism proposed for the vascular protective effect of estrogens is favorable modulation of vasoreactivity. In fact, estrogens are well known for their systemic vasoactivity. Intravenous administration of ethinyl estradiol in postmenopausal women produces an increase in coronary flow and cross-sectional area and a decrease in resistance of coronary arteries. Several studies have demonstrated that estrogens improve vascular flow and arterial pulsatility. A recent TCD study has shown an increase of flow resistance of the internal carotid artery and MCA during postmenopausal years, suggesting that this effect may be one of the mechanisms by which menopause is associated with the increased risk of vascular disease.

The mechanism for the estrogen-related arterial vasodilation and improved pulsatility is most likely mediated through increased production of prostacyclin or enhanced release and/or activity of nitric oxide. The possibility of a direct effect of estrogens on the arterial wall must also be considered, because estrogens influence artery wall metabolism, as suggested by the presence of estrogen receptors in the arterial wall.

The possible pathophysiological significance of reduced cerebral reactivity to hypercapnia in postmenopausal women does not necessarily imply that cerebrovascular disorders after menopause should be considered predominately on a hemodynamic basis, excluding other well-known mechanisms of ischemic events. However, there is evidence that in areas of the brain where there is limited capacity for further capillary vasodilatation, susceptibility to ischemic damage is increased. For this reason, altered cerebral hemodynamics can be considered a sign of increased risk of cerebrovascular events. This seems confirmed by several investigations showing an association between risk factors for stroke such as smoking or carotid lesions and the presence of a reduced cerebrovascular reserve capacity. Our finding that cerebrovascular reactivity to hypercapnia in the postmenopausal women was significantly lower than that of age-matched men is difficult to explain, but it furthermore suggests the existence of differences in the pathogenesis of stroke in the two sexes. This is also confirmed by the fact that atherosclerotic vascular lesions are more severe in men than in women of similar age. On the basis of our data we hypothesize that impaired cerebral hemodynamics, probably related to low levels of estrogen, may be particularly important in the pathophysiology of cerebrovascular disease in postmenopausal women. Further studies, also associated with measures of sex hormonal levels, are needed to confirm our data and to determine whether estrogen replacement therapy is able to bring about an improvement in cerebrovascular reactivity.

References


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