Changes of Cerebrovascular CO\textsubscript{2} Reactivity During Normal Aging

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Background and Purpose—During the past decade, transcranial Doppler sonography has widely been used to assess blood flow velocities in the basal intracranial arteries and cerebrovascular reactivity (CR) to various stimuli. Although numerous studies have shown a decline of cerebral blood flow velocity with age, the age dependency of CR, including cerebrovascular CO\textsubscript{2} reactivity, however, is controversial. Recently, we have reported a significant sex-related difference in CR, stressing the need to study the relation between normal aging and CR in both sexes separately.

Methods—By means of transcranial Doppler sonography, CR was determined in 100 healthy, nonsmoking volunteers (age 20 to 70 years, 10 men and 10 women per decade).

Results—In men, no change of CR with increasing age could be observed ($P=0.98$). In contrast, CR in women declined significantly, with a step decrease from the 4th to the 5th decades ($F=4.413; P<0.01$) and was significantly higher in the 3rd and 4th compared with the 5th, 6th, and 7th decades ($P<0.05$). Information on hormone replacement therapy (HRT) in women of the 6th and 7th decades was obtained retrospectively. HRT was associated with enhanced CR (HRT, $n=7$ versus non-HRT, $n=13; P<0.001$), with values similar to those found in premenopausal women.

Conclusions—There are no changes of CR during normal aging in men, whereas CR declines significantly from the 4th to the 5th decades in women. HRT in postmenopausal women appears to enhance CR.

Key Words: carbon dioxide — cerebral blood flow velocity — ultrasonography, Doppler, transcranial

During the past decade, transcranial Doppler sonography (TCD) has widely been used to assess blood flow velocities in the basal intracranial arteries and cerebrovascular reactivity (CR) to various stimuli. The characterization of pathophysiological conditions in the cerebral circulation, however, requires the knowledge of possible physiological age- and sex-dependent differences in CR. Numerous authors have examined the age-associated changes in cerebral blood flow (CBF) (for review, see Davis et al\textsuperscript{1} and Reich and Rusinek\textsuperscript{2}) or cerebral blood flow velocity (FV) (for review, see Adams et al\textsuperscript{3}). Most of these studies have shown a decline of CBF or FV with age.\textsuperscript{1-3} The age dependency of CR, including cerebrovascular CO\textsubscript{2} reactivity, however, is controversial. Reich and Rusinek,\textsuperscript{2} Tsuda and Hartmann,\textsuperscript{4} Yamaguchi et al,\textsuperscript{5} and Yamamoto et al\textsuperscript{6} observed a diminished CO\textsubscript{2} response in the elderly, whereas Davis et al\textsuperscript{1} could not find a change in vascular reactivity to 5% CO\textsubscript{2} corresponding to the age-related decline in gray matter blood flow. Gotoh et al\textsuperscript{2} reported that CR to hyperventilation, as estimated by the reduction in jugular venous PO\textsubscript{2}, was reduced in older compared with younger individuals. Using the N\textsubscript{2}O technique, Schieve and Wilson\textsuperscript{7} only found an insignificant trend toward reduction of CO\textsubscript{2} reactivity after the age of 35 years. Other investigators reported that CO\textsubscript{2} responsiveness was unchanged in elderly patients with “vascular dementia.”\textsuperscript{8,9}

A major criticism of all these studies is the small number of subjects and their uneven distribution over the different age categories.

We have recently reported a significant sex-related difference in CO\textsubscript{2} reactivity in subjects aged 20 to 50 years,\textsuperscript{10} stressing the need to study the relation between normal aging and CR in both sexes separately. This has not been done systematically before.

Therefore, the main objective of this study was to assess possible age- and sex-related differences of cerebrovascular CO\textsubscript{2} reactivity by means of simultaneous bilateral TCD.

Subjects and Methods

Study Population

One hundred healthy, nonsmoking volunteers (50 women, 50 men) 20 to 70 years of age were studied after they gave their informed consent. In each decade, 10 men and 10 women were represented. The younger volunteers consisted of neurology department staff members, medical students, and friends, of which 15 subjects have been previously studied.\textsuperscript{11} The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were the most carefully selected members, medical students, and friends, of which 15 subjects have been previously studied.\textsuperscript{11} The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions. The older volunteers were patients admitted to the hospital for minor illnesses, especially traumatic peripheral nerve disorders, and intervertebral disk degenerations, prolapses, and protrusions.
ism, polycythemia, diabetes mellitus, epilepsy, or obstructive cerebrovascular disease as shown by extracranial and intracranial ultrasound recordings were ruled out in each subject. The hematocrit was in the normal range. None of the subjects had used any medication with known vasoconstrictor or vasodilating properties for 36 hours before the examination.

This study was approved by the Ethics Committee of the University of Tübingen.

**Determination of Cerebrovascular CO₂ Reactivity**

Cerebrovascular CO₂ reactivity was determined as described in detail previously. In brief, bilateral simultaneous flow velocity recordings of the middle cerebral arteries were obtained with the use of Hemo Dop equipment (Medizinische Elektroniksysteme, D-Sipplingen). The envelope of the spectra was used to determine the flow velocity in the middle cerebral artery. Care was taken to obtain signals with no interference from other vessels. Mean flow velocities (Vmean) were calculated from one cardiac cycle to the next and expressed in centimeters per second with a computer-assisted integration procedure. The subjects used an anesthetic mask with a 2-way valve to inhale normal air or carbogene gas (95% O₂, 5% CO₂) for induction and maintenance. The subjects were adapted to the anesthetic mask and to the environment, Vmean and Pet CO₂ were continuously recorded over a period of 5 minutes. Thereafter the anesthetic mask was connected to a 25-L reservoir bag that was constantly filled with carbogene gas, and hypercapnia readings were made over a period of 5 minutes.

To determine the CO₂ reactivity index (CRI) we averaged the mean flow velocities of the first 20 cardiac cycles of the third minute under basal conditions and of the third minute during hypercapnia. CRI was calculated according to the following equation:

\[
CRI = \frac{100}{V_{mean}(baseline)} \times \frac{V_{mean}(baseline) - V_{mean}(CO₂)}{ΔPetCO₂}
\]

Blood pressure was determined in all subjects three times, that is, at baseline, during the hypercapnic stage at the highest PetCO₂ level, and in the first minute of posthypercapnia.

**Statistical Analysis**

The statistical software used was SPSS (Statistical Package for Social Sciences, release 4.0). Values for PetCO₂ and reactivity to CO₂ were compared for paired subgroups of the study population (eg, men, women, subjects by decade) with two-sample t tests and tests and Bonferroni correction to evaluate the possible differences between the means. In each case, the t test was preceded by a F test to ensure homogeneity of variance. The data were expressed as mean±SD. We assumed statistical significance at P<0.05.

**Results**

The mean age of men and women was comparable within all 5 decades, and there was no age-associated change in PetCO₂ during baseline and during hypercapnia or any significant difference between the mean value for men and women (Table). For the entire study population, baseline systolic arterial blood pressure was 128±23 mm Hg and diastolic blood pressure was 77±12 mm Hg. During the period of hypercapnia, systolic blood pressure increased by 12.8±10.2 mm Hg (NS) and diastolic blood pressure increased by 6.9±7.1 mm Hg (NS). For the total population, there were no statistically significant side differences between the left and right middle cerebral arteries in mean blood flow velocities and reactivity indexes. Therefore, to investigate the influence of age and sex on the reactivity indexes of the middle cerebral arteries, the results of the right and left side were combined by averaging them.

The cerebrovascular reactivity indexes for each decade are shown in Figure 1. With Student’s t test evaluation, CR was significantly higher in women 20 to 40 years of age compared with men (3rd decade: t=2.83; P=0.011; 4th decade: t=2.62; P=0.017). However, this difference did not reach statistical significance for older age groups.
significance after Bonferroni correction, possibly because of the relatively small sample numbers. In the 5th, 6th, and 7th decades, this difference was no longer present (5th decade: t=0.39; P=0.7; 6th decade: t=0.20; P=0.85; 7th decade: t=0.35; P=0.73). In men, no change of CR with increasing age could be observed (F=0.089; P=0.98). In contrast, CR in women declined significantly from the 3rd to the 7th decades (F=4.413; P<0.01). However, CR did not decline steadily with increasing age. Duncan’s multiple range test at P<0.05 revealed a step decrease from the 4th to the 5th decades, with CR being significantly higher in the 3rd and 4th decades (3rd and 4th decades versus 5th, 6th, and 7th decades; P<0.05).

Premenopausal women had significantly higher CR than their male counterparts or than postmenopausal women, which indicates that this effect appears to be related to differences in hormone status. Information on hormone replacement therapy (HRT) in women of the 6th and 7th decades was obtained retrospectively. Seven women were taking estrogens and 13 women refused HRT at the time the CR was determined. Interestingly, HRT was associated with CR values comparable to premenopausal values (t=4.89; P<0.001).

Discussion
Cerebral vasomotor reactivity can easily and reliably be assessed by measuring the vasodilatory response to altered carbon dioxide tensions. Blood flow velocity measurements can provide information regarding volume flow in a supply artery and its perfusion territory if the diameter of the artery remains constant. As demonstrated angiographically by Huber and Handa,13 the diameter of the large cerebral arteries remains constant during changes in arterial carbon dioxide tensions. Further studies have shown convincingly that the effect of altered carbon dioxide tensions is restricted mainly to the peripheral vascular bed.14,15 TCD is able to record blood flow velocity in the basal cerebral arteries and their main branches. Bishop et al16 showed that changes in middle cerebral artery blood flow velocity correlated reliably (r=0.849, P<0.001) with changes in CBF measured with intravenous Xe 133 when hypercapnia was induced. Hence the CO2 reactivity of blood flow in the cerebral arteries can be determined from changes in flow velocity.

It is well agreed that under pathological circumstances, such as cerebral atherosclerosis or cerebral infarction, cerebrovascular CO2 reactivity is impaired.6 Yet the influence of normal aging on CO2 reactivity is controversial.

Although some investigators have reported little or no difference in CR associated with aging,18 others observed a diminished CO2 response in the elderly.24-6 Because of our previous results of sex-related differences in CR,11 we studied the relations between normal aging and cerebral vasomotor reactivity in both sexes separately. Although we found no change of CR with increasing age in men (maximum age studied, 70 years), CR in women declined significantly with a step decrease from the 4th to the 5th decades. Discrepancies to previous reports may result from the fact that none of these studies considered sex-related differences on CR. Moreover, methodological differences must be taken into account; the results of this study need confirmation with the use of other techniques such as single photon emission CT or positron emission tomography.

We have recently reported a significant sex-related difference in CO2 reactivity,11 determined during dynamic changes in PetCO2 and FV. Our current study has looked at the CO2 reactivity under essentially steady-state conditions, and we
have shown increased CR in women 20 to 40 years of age compared with their male counterparts. These results add a further demeanor of knowledge to our previous findings and in addition demonstrate a step decrease of CR from the 4th to the 5th decades in women, indicating a possible influence of estrogens on CO2 reactivity. The mechanisms and the biological significance of an increased vasomotor reactivity in premenopausal women is unclear, but it is tempting to argue that hormonal influences play a role. During the past few years, evidence has accumulated that prostanoids are important both in the regulation of resting CBF and in the vasodilatory response to hypercapnia.15–20 Prostacyclin is formed by the vascular endothelium and can be produced in vitro by cerebral vessels.21 It is a potent endogenous vasodilator and inhibitor of platelet aggregation in human beings.22 Estrogens have been shown to stimulate prostaglandin cyclooxygenase and prostacyclin synthetase activities of rat aortic smooth muscle cell,23–25 suggesting that estrogen might enhance basal levels of prostacyclin secretion from endothelial cells. Although the in vivo cerebral production of prostaglandins in women has not yet been reported, one may speculate that enhanced cerebrovascular reactivity to hypercapnia in premenopausal women is mediated by increased basal levels in prostanoids. In agreement with this, one group of investigators26 found higher prostacyclin levels in young women than young men. Moreover, Mikkola et al27 demonstrated that HRT in postmenopausal women was associated with an increased production of prostacyclin in cultured endothelial cells.

In our study we have evaluated HRT retrospectively only, and we did not obtain information on dosage in all questioned subjects. Nevertheless, HRT was clearly associated with enhanced CR compared with non-HRT. Although the body of literature suggests that postmenopausal hormone use does not affect the risk of ischemic stroke,28 2 studies have reported a reduced stroke incidence in postmenopausal women with HRT.29,30 Therefore, enhanced CR associated with HRT is of special clinical interest. Moreover, increased CBF velocity and cerebrovascular CO2 reactivity in younger women might be reasons for their relative protection from strokes.

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