Original Article

Evaluation of Vasomotor Reactivity by Transcranial Doppler Sonography: Age and Sex Related Differences in Breath Holding Index in Iranian Population

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ABSTRACT

Background: The assessment of cerebral vasoreactivity can provide information regarding the reserve capacity of cerebral circulation. Reduction of this property has been found in association with situations predisposing one toward cerebrovascular disease. In this study, we defined the vasoreactivity of brain vesseles according to age and sex of the patients.

Methods: In this descriptive study, 289 healthy subjects (without hypertension, diabetes mellitus, obesity, smoking, CHF, CHD,) were admitted from January 2004 to June 2004. The population was divided to four groups, according to age and sex (women and men more and less than 30). After determination of each patient's flow velocity of middle cerebral artery (MCA) by mean of a transcranial doppler instrument (TCD), before and after 30s apnea, breath holding index (BHI) was calculated. Data was analyzed, using SPSS software.

Results: BHI was significantly higher in women than men (0.918±0.40 versus 0.637±0.22; P<0.001). BHI was significantly lower in older (age > 30) women (0.812±0.31) than in younger (≤ 30 years) women (0.995±0.44; P<0.001) but there was no significant difference between older (age > 30) men (0.62±0.23) and younger (≤ 30 years) men (0.65±0.20; P > 0.05).

Conclusion: The average of BHI was lower in men than in women in total and in all age subgroups. BHI was relatively constant in all age subgroups in men but there was significant decline in BHI by increasing age in women. So despite of many physiologic changes related to aging, vasomotor reactivity remains relatively constant in men but decreases in women. Findings of our study suggest that changes of cerebrovascular vasomotor reactivity in healthy subjects may be related to aging, but they are probably mainly influenced by sex.

Keywords: vasomotor reactivity, BHI, TCD

TCD is an ideal functional test for detecting rapid changes in cerebral perfusion. Functional tests are predominantly aimed at evaluating the reserve mechanism of the cerbral vasculature using various stimuli such as hypocapnia or hypercapnia, increased or reduced systemic arterial pressure, and hypoxia.

During changes of CO_2 concentration, the relationship between flow velocity and volume flow within a large cerebral artery is linear, provided that the CO_2 level does not directly affect the diameter of the large proximal arterial segments [1,2,3]. Cerebral vasomotor reactivity can easily be studied by measuring the changes of flow velocity in response to vasodilatory stimuli such as CO_2 inhalation, breath-holding, or acetazolamide administration [4,5,6]. 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 in cerebral blood flow [7,8]. Reduction of this property has been found in association with situations predisposing one toward cerebrovascular disease [9,10,11,12].

The vasomotor reserve may become exhausted if the resistance vessels of brain areas with low perfusion pressure are already maximally dilated. In this state, the resistance vessels are refractory to any further vasodilatory stimuli [13,14].

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Epidemiological data show that there are distinctive features of cerebrovascular disease in men and women probably connected to their different patterns of sex hormones [15,16].

In this study, we define vasomotor reactivity of brain vessels in different age and sex groups of normal healthy persons and some of these data are statistically tested between different subgroups.

Subjects and Methods

By the end of study, 289 healthy subjects selected from the hospital personnel (148 women and 141 men) were included in the study from January 2004 to June 2004. Each female subject was matched with a male of the same age. The population was divided into four groups: 62 women >30 years old (39.45±7.25), 86 women ≤ 30 years old (25.17±2.71), 78 men > 30 years old (38.60±7.21), and 63 men ≤30 years old (25.74±2.71).

Rigid exclusion criteria were established to avoid any bias by an unbalanced distribution of concomitant diseases or drug therapy: subjects with hypertension, diabetes mellitus, obesity, smoking (> 1 pack year), congestive heart failure (greater than New York Heart Association grade I), chronic obstructive lung disease, cerebrovascular disease (transient ischemic attack, stroke, carotid artery stenoses more than 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, ß-blocking agents, calcium channel blockers, anticoagulants, and vasodilatory drugs.

The subjects were studied in the morning in a supine resting state with their eyes closed. All subjects were drug free and had abstained from smoking, 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.

Mean flow velocity (MFV) of the MCA was continuously monitored by means of a Multi-Dop X/TCD transcranial Doppler instrument (DWL-X4-RC). One dual 2-MHz transducer, fitted on a headband and placed on the temporal bone window, was used to obtain continuous measurements. The gain of instrument was set as 20-30% for all cases and the room temperature was 20-25° of centigrades throughout the study. The highest signal was sought at a depth ranging from 40 to 55 mm. By activating the record function, it was possible to save the Doppler spectra during the entire period of each study. Reactivity was examined by calculating the breath holding index (BHI) as fallows:

$$BHI(\%) = \frac{MFV_{Apnea} - MFV_{Rest}}{MFV_{Rest} \times 30} \times 100$$

BHI was calculated for each MCA separately and the average of BHI in two sides was considered as the patients BHI. The MFV at rest was obtained by the continuous recording of a 5-minutes period of normal room air breathing. After a breath-holding period, the MFV was recorded over a 4-seconds interval. A fixed period of 30 seconds was arbitrarily chosen for breath holding. In particular, it's a fact that subjects held their breaths after a normal inspiration, which avoided a Valsalva phenomenon and the possible interference of blood pressure changes with cerebral hemodynamics.

The great limitation of our study was inability to perform apnea for 30 seconds in old patients; And so, finding of old age healthy persons without any exclusive criteria was other limiting factor. We had to perform the test more than 5 times in some persons to reach accurate and reliable data. We believe that although BHI is a fast, useful, and accurate method in checking vasomotor reactivity, but there are practical problems, limit using BHI in older patients. It may be easier for both physician and patient that the vasomotor reactivity be evaluated by using acetazolamide in old age patients.

Results

289 healthy persons entered the study, 140 were above 30 years old (78 male, 62 female), and 149 were ≤ 30 years old (63 male, 86 female).

Values of MFV at rest were 60.16±8.31 cm/s in younger women; 58.27±9.52 cm/s in older women; 54.65±6.94cm/s in younger men; and 52.41±9.38 cm/s in older men.

Values of MFV at end of 30 seconds apnea were 78.01±12.76cm/s in younger women; 72.48±13.42cm/s in older women; 65.31± 8.37cm/s in younger men; and 62.38± 12.23cm/s in older men.

BHI was significantly higher in women than men (0.918±0.40 versus 0.637±0.22; P<0.001).

BHI was significantly lower in older (age > 30) women (0.812±0.31) than in younger (≤ 30 years)

women (0.995±0.44; P<0. 001) but there was no significant difference between older (age > 30) men (0.62±0.23) and younger (≤ 30 years) men (0.65±0.20; P > 0. 05).

Each sex group was divided by 5-year intervals to some subgroups and the average of BHI in each subgroup was calculated separately (Table1).

Table 1. Average of BHI in different age and sex groups.

	20-25	26-30	31-35	36-40	41-45	46-50	>50
Men	0.681357	0.633374	0.61648	0.611962	0.602829	0.662177	0.686269
Women	1.001059	0.988806	0.868486	0.737208	0.78988	0.814681	0.78622

Discussion

In this study the range of BHI in normal healthy individuals was calculated by exact TCD measurements and the known risk factors for atherosclerosis and disturbances of cerebrovascular hemodynamics were omitted. The normal ranges of BHI in age subgroups also calculated in both sexes and its changes have been illustrated in Figure1.

The average of BHI was lower in men than in women in total and in all age subgroups. BHI was relatively constant in all age subgroups in men but there was significant decline in BHI by increasing age in women. So despite many physiologic changes related to aging, vasomotor reactivity remains relatively constant in men but decreases in women.

Findings of our study suggest that changes in cerebrovascular vasomotor reactivity in healthy subjects may be related to aging, but they are probably mainly influenced by sex.

In previous TCD study by Karnik and colleagues, describing sex-related differences in cerebral vasomotor reactivity, increased vasodilatory response to the acetazolamide test has been showed in female compared with male subjects [17]. In another study, Matteis and colleagues have suggested 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 [18]. These data are comparable with ours. Matteis and colleagues also found a significantly lower cerebrovascular reactivity in young postmenopausal women with respect to premenopausal women of similar age and concluded that changes of sex hormones may influence the reduction of cerebrovascular reactivity in women at the end of the fertility period.

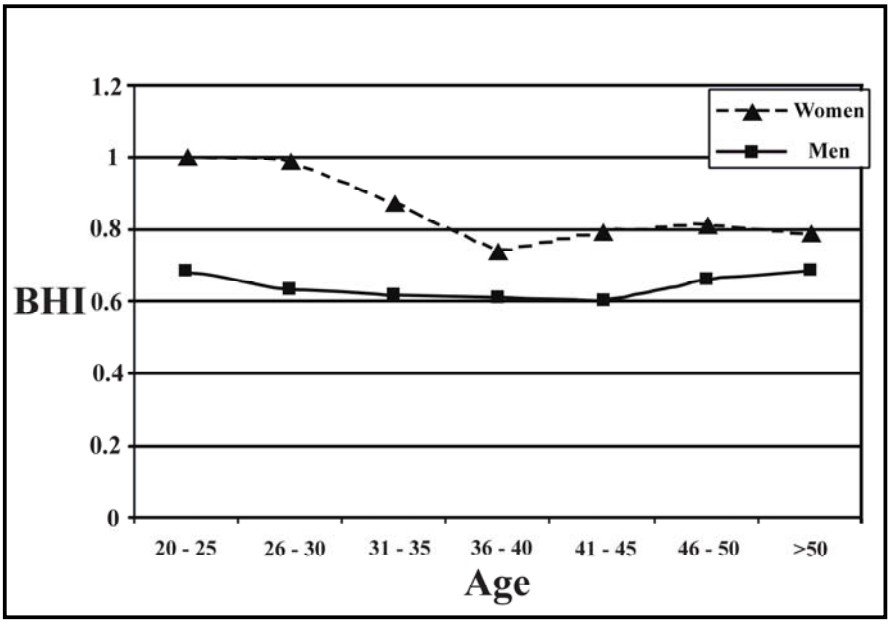

Figure 1. Age-related decline in BHI in both sexes.

Although we did not find any reasonable cause for changes in BHI of women maximally in 4th decade of life (Figure 1); when menopause has not actually any significant role, and we believe that some other factors may influence cerebrovascular reactivity particularly in women. Certainly 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.

There is evidence that in brain areas with limited capacity for further capillary vasodilatation, susceptibility to ischemic damage is increased. For this reason, altered cerebral hemodynamics can be considered as a sign of increased risk of cerebrovascular events. This seems confirmed by several investigations showing an association between risk factors for stroke and the presence of a reduced cerebrovascular reserve capacity [18]. Considering this concept, potential risk of brain hypoxic/Ischemic attacks before cardiovascular surgery, other great surgeries, and some situations which rise the risk of hypoxia or hypotension can be evaluated by test of vasomotor reactivity in a safe and fast manner.

Our finding that cerebrovascular reactivity to hypercapnia in the men was significantly lower than that of age-matched women is difficult to explain, but furthermore, it suggests the existence of differences in the susceptibilites to ischemic-hypoxic events between the two sexes.

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