

COMMENTARY

Listening to the sound of silence between men and women

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Stroke is a major public health problem that not only is the third leading cause of death in Japan but also induces functional disabilities and cognitive decline. A preventive approach to ischemic brain damage and neuronal loss leads to an improved quality of life in individuals. Possible gender differences have been reported in stroke. For example, most epidemiological studies have shown that men have a higher stroke incidence than women.¹ Such a gender difference in stroke incidence might be caused by the beneficial effects of estrogen on the brain in premenopausal women. In basic experiments using animal models, estrogen appeared to protect against ischemic brain damage by protection of the endothelial function and neurons.^{2,3} However, the stroke incidence was increased in postmenopausal women whose serum estradiol level was the same as or less than the level in men. Conversely, the Women's Health Initiative clinical trials on hormone therapy raised an alert that estrogen treatment after menopause increases the risk of stroke and venous thromboembolic disease.⁴ Therefore, the effect of estrogen is not a simple answer for explaining the gender difference in stroke incidence.

Silent brain infarction (SBI) is identified by brain imaging in healthy patients without clinical symptoms and has been investigated since the 1990s.⁵ The incidence of SBI in the general population is relatively high; overall, its prevalence is around 11%.⁶ The presence of SBI may allow us to clinically predict overt

stroke in the future.^{6,7} In Japanese patients, the risk of clinical stroke was significantly higher in subjects with SBI (around a three-fold increase) than in those without SBI;⁸ therefore, the presence of SBI could tell us of the need for an interventional approach to prevent the onset of severe cerebral ischemia. The risk factors for SBI, such as metabolic syndrome,⁹ hypertension¹⁰ and smoking,⁶ have been reported previously. Interestingly, among older Japanese subjects, white-coat hypertensives do not show an increase in the prevalence of SBI compared with normotensives.¹¹ However, the predicted risk factors differ from the observed results depending on the study population. Moreover, there are few population-based studies of the gender difference in SBI incidence among Japanese people.

In this issue of *Hypertension Research*, Takashima *et al.*¹² focus on the gender difference in SBI incidence among Japanese people with a population-based, cross-sectional analysis. The study comprised 266 men and 414 women with a mean age of 64.5 years. Their findings are similar to previous studies; for example, the prevalence of SBI found in this study was 11.3%. However, daily habits such as smoking and alcohol intake are quite different between men and women. Interestingly, the authors reported that a higher prevalence of such lifestyle risk factors rather than gender explains the male predominance in the incidence of SBI. Although men have a higher incidence of SBI, the gender differences disappeared after adjusting for the risk factors. Moreover, for women, the authors analyzed the age of natural menopause or early menopause, the duration of menopause, the number of children and the age at the last parturition. Interestingly, these factors had no significance for the SBI prevalence, although

menopause and parity appear to be the risk factors for stroke.

There is another interesting report from the Hisayama study that investigated secular trends in the incidence of and risk factors for ischemic stroke.¹³ The trends in the incidence of ischemic stroke subtypes were investigated from 1961 to 2002 in the town of Hisayama in Japan. The rates of ischemic stroke were reduced in both men (8.73 to 3.85) and women (4.28 to 2.57) owing to better management of hypertension for 40 years; however, there was a dramatic change in stroke subtypes. Atherothrombotic infarction increased in men, but lacunar infarction decreased; therefore, the ratio of lacunar infarction is much higher in women than in men (43% for men and 52% for women). The incidence of lacunar infarction per 1000 persons per year was 5.68 for men and 2.41 for women in 1974, but this rate changed to 1.59 for men and 1.50 for women in 2002. Therefore, SBI is thought to be mainly induced by lacunar infarction, and this chronological change in stroke subtypes may be related to a gender difference in SBI incidence. The Hisayama study also found that SBI tended to be more frequent (but not significantly so in a multivariate analysis) in women; among the 713 subjects without clinical stroke, SBI was identified in 16.2% of the 390 men and 19.2% of the 323 women, with a mean age at death of 78.3 years.

The more detailed analysis found in this study has been expected to clarify the risk profile for SBI. However, there is currently no information available about triglyceride and high-density lipoprotein cholesterol levels in this population. It would be interesting to have data on comorbid heart diseases, including arrhythmia, as well as information from an atherosclerotic analysis such as a

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pulse wave velocity or cervical echo analysis. Diurnal blood pressure variations measured with ambulatory blood pressure monitoring for assessing the role of heart diseases, endothelial dysfunction, and extreme dipper and non-dipper types could also be useful for studying the gender differences of SBI. Furthermore, the relation between vascular cognitive impairment and SBI in the elderly population is a current topic of study. Further investigations will help us understand more about the gender differences of SBI. We can learn more about gender-specific medicine for stroke by listening to the sound of silence between men and women.

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