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Assessment of Autonomic Nerve Activity —Approach to Gender Differences in Cardiovascular Events in Patients With Diabetes—

(自律神経活動の評価―糖尿病患者における心血管事故の性差への取組み―)

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EDITORIAL

Assessment of Autonomic Nerve Activity
– Approach to Gender Differences in Cardiovascular Events in Patients With Diabetes –

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It has been widely accepted that there is a deep relationship between an inappropriate autonomic balance and cardiovascular diseases such as coronary artery disease (CAD) and cardiomyopathy. Among the autonomic elements, vagal activity acts as a significant cardioprotective factor, the depression of which may cause cardiovascular events, including ventricular tachyarrhythmias, and result in cardiac sudden death.[1]

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Type 2 diabetes mellitus (T2DM) is undoubtedly an important background disorder that can bring about not only CAD, but cardiac autonomic neuropathy as well. In several studies, a gender difference in the morbidity and mortality of diabetic patients has been proposed. Diabetic females have the possibility of significantly greater rates of mortality due to ischemic heart disease than do diabetic males. Although the mechanism is still unclear, there is a strong likelihood that a gender difference in the autonomic neural damage in diabetic patients is an important factor that can explain this phenomenon. Accordingly, the study designed by Yufu et al in which they investigated the relationship between impaired vagal tone and cardiovascular morbidity and the gender difference in patients with T2DM,[2] greatly deserves its evaluation as an excellent clinical study.

Different methods have been used experimentally and clinically to assess vagal tone in living animals and humans. Our colleagues and other investigators have assessed the changes in autonomic tone after radiofrequency catheter ablation procedures in an animal model and clinical patients using 3 different methods: (1) measurement of the prolongation of the sinus cycle length and occurrence of atrioventricular block after electrical stimulation of the cervical vagi or ganglionated plexi,[3] (2) spectral analysis of heart rate variability (HRV) by calculating the time series of the R-R intervals from Holter ECG monitoring, in which the high-frequency component (HF) of the frequency domain analysis was regarded as a significant parameter of vagal tone,[4,5] and (3) measurement of baroreflex sensitivity (BRS) by phenylephrine methods.[5] The first strategy is invasive and therefore can only be undertaken in an experimental investigation or intraoperative procedure. The 2nd and 3rd strategies are noninvasive tests and have been frequently used in many clinical studies. Spectral analysis of HRV is the most casual and noninvasive method of repeatedly assessing human autonomic tone, involving only the attaching of body surface electrodes and carrying of a very light recorder. However, the calculated values more or less indicate the mixture or balance of sympathetic and parasympathetic tone, although the HF power would be produced mainly by a respiratory sinus arrhythmia, the chief driving force of which is vagal tone, and therefore the results of the test must be translated carefully. Instead of a spectral analysis, Yufu et al used BRS as the parameter of vagal tone in their study presented in this issue of the Journal.[2] To obtain the BRS, venous cannulation for phenylephrine injection, stabilization for an interval of 30 min with subsequent respiration control, beat-to-beat measurement of arterial blood pressure (using tonometry, another noninvasive technique[2]) and simultaneous ECG monitoring are needed. Although this procedure is troublesome to complete clinically, the resultant parameter is considered to be highly valuable as representing the precise vagal tone of the patient. The authors carefully set each of these parameters, and also limited the time of the test period (9:00 to 11:00 AM), considering the diurnal change in autonomic tone.[2] Thus, the evaluation of BRS in this study was sufficiently reliable.

As the authors have postulated, the most important finding in their current study was that a depressed BRS had a predictive value of cardiovascular events in subjects with T2DM and without any structural heart disease, especially in female patients. Essentially, in this study population the BRS was lower in females than in males, consistent with the results of previous studies.[6] Postural stress[7] or a lower body negative pressure[8] also revealed that the BRS was attenuated more in young women than in men. However, another study using a spectral analysis found that women had a preponderance of vagal over sympathetic tone, which was opposite to that observed in men.[9] The reasons for these discrepancies are unclear, but they may represent differences in the types of test used or the age of the subjects. In the present study, the test was BRS measurement, and the subjects were middle-aged (mean age, 58 years).[2] In comparison to the group of preserved BRS females, depressed BRS females had a significantly longer duration of T2DM, higher blood pressure and older age, which may have interacted causing the decline in the subject's vagal activity.[2] It is still unclear whether a depressed BRS in diabetic women has a predictive value of

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cardiovascular events, even if the diabetes history, blood pressure and age are similar to those in preserved BRS subjects.

When discussing the effect of gender and generational differences on clinical phenomena, a change in the hormonal circumstances can not be ignored. The cardiovascular autonomic function is regulated through multiple central nuclei, many of which express estrogen receptors. Several studies have suggested that estrogen augments the BRS and acts cardioprotectively.[10,11] On the other hand, monitoring the peripheral muscle sympathetic nerve activity clarified that sympathetic nerve activity is lower in young women than in age-matched men, and increases with age in both men and women, although the magnitude of increase is greater in women than in men.[12] From these data, it is hypothesized that an age-dependent decline in estrogen status may shift the sympathovagal balance toward the sympathotonic direction in connection with the occurrence of cardiovascular events. It is natural that the effect of the decline in the estrogen is greater in women than in men, and the causal occurrence of cardiovascular events may be especially higher in women with a background disorder such as diabetes, hypertension and/or dyslipidemia. This hypothesis can partly explain the gender and age differences in autonomic tone in humans, although other complex factors can also be related to these differences.

Yufu et al[2] clearly describe the significance of a depressed BRS in female patients with T2DM, and propose an important subject for the fields of gender and geriatric medicine. Although the importance of gender differences in the morbidity and mortality associated with CVD has gradually become recognized over the decades, only scarce information is available because of a lack of studies. Further investigation will be needed to resolve several of the questions in this field.

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