Physiological Changes in Human Cardiac Sympathetic Innervation and Activity Assessed by $^{123}$I-Metaiodobenzylguanidine (MIBG) Imaging

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Background  Physiologic changes in the human sympathetic nervous system (SNS) may be associated with cardiovascular diseases, so the present study assessed the age and gender differences in global cardiac SNS in normal subjects.

Methods and Results  The 163 subjects (74 men, 89 women; age range 40–89 years) whose coronary arteriogram was normal, and who had no other cardiac or neurohormonal diseases, and no medication affecting the autonomic nervous system were included. All study subjects underwent metaiodobenzylguanidine imaging. Both initial and delayed heart-to-mediastinum (H/M) ratios had a significant gender difference and showed a progressive decrease with aging. In addition, the initial H/M ratio had a significant positive correlation with the delayed H/M ratio ($r=0.89, P<0.0001$). Females (50–59 years) demonstrated significantly higher delayed H/M ratio than males of the same age. After the age of 60, the delayed H/M ratio in females progressively decreased with aging, similar to males. As for the washout rate, both genders had a significantly progressive increase with aging. In addition, there was a significant decrease in the delayed H/M ratio in 10 females with surgical menopause compared with 15 age-matched females without surgical menopause.

Conclusion  Cardiac SNS appears to be regulated by various physiological factors. (Circ J 2009; 73: 310–315)

Key Words: Aging; Nuclear medicine; Sex; Sympathetic nervous system

The sympathetic nervous system (SNS) is an important control mechanism of the body, dysfunction of which is well known to be associated with the development of various common cardiovascular diseases, such as ischemic heart disease¹, congestive heart failure², arrhythmias³, and sudden death⁴. It is also well known that the frequency and the onset of these diseases have age- and gender-related differences⁵,⁶. Likewise, the SNS shows physiologic fluctuations with age and sex⁷–¹⁵ which are considered to be related to gender differences in the frequency of cardiovascular diseases and the markedly increased risk of cardiovascular diseases with aging. Therefore, it is very important to assess physiological changes in sympathetic cardiovascular control in humans, especially in the cardiac SNS, because many cardiovascular diseases originate from the heart. However, as there are no appropriate methods of measuring the cardiac SNS in vivo, the precise physiological changes remain unclear.

$^{123}$I-metaiodobenzylguanidine (MIBG) imaging has become widely used to evaluate human cardiac sympathetic nervous function¹⁴–²⁰ because it gives information about cardiac sympathetic nerve endings. Using MIBG imaging, the aim of this study was to assess the age- and gender-related differences in the global cardiac SNS in normal subjects.

Methods

Patients  We investigated 153 patients whose ages ranged from 40 to 89 years were referred for cardiac catheterization because of chest pain or electrocardiogram (ECG) abnormality, and which revealed a nearly normal coronary artery without coronary spasm induced by acetylcholine and with normal cardiac function and hemodynamics. After cardiac catheterization, they underwent MIBG imaging. The subjects were 74 men and 79 women who did not have obvious heart disease, hypertension ($≥140$ mmHg systolic blood pressure, or $≥90$ mmHg diastolic blood pressure), obesity (body mass index (BMI) $>25$ kg/m²), diabetes mellitus or any other diseases affecting the autonomic nervous system. In addition, they did not take any drugs known to affect MIBG kinetics. We included 10 women who fulfilled the inclusion criteria and had undergone surgical menopause due to logical menopause because we wanted to investigate the effect of menopause on the cardiac SNS. Written informed consent was given by the each patient and the study was approved by the hospital’s ethics committee.

Cardiac Catheterization  After right-heart catheterization with a Swan-Ganz catheter, all patients underwent coronary angiography (CAG) performed by the Judkins technique. Prior to CAG, a tem-
Changes in Cardiac SNS on MIBG

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After overnight fasting, each subject was administered a 111MBq IV dose of commercially available MIBG Imaging.

Table 1 Clinical Characteristics of Each 10-Year Age Group and MIBG Parameters

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80–89</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male No.</td>
<td>16</td>
<td>15</td>
<td>18</td>
<td>10</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Female No.</td>
<td>16</td>
<td>15</td>
<td>18</td>
<td>10</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±4</td>
<td>45±4</td>
<td>54±3</td>
<td>64±2</td>
<td>65±6</td>
<td>75±4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.72±0.06</td>
<td>1.6±0.06*</td>
<td>1.71±0.06</td>
<td>1.6±0.04*</td>
<td>1.6±0.04</td>
<td>1.59±0.04</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.9±50.6</td>
<td>53.7±4.5*</td>
<td>63.6±8.6</td>
<td>51.9±3.8*</td>
<td>51.8±3.1</td>
<td>57.8±8.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.9±2.1</td>
<td>21.0±2.1*</td>
<td>21.7±2.3</td>
<td>20.1±1.1</td>
<td>20.1±0.2</td>
<td>21.2±2.4</td>
</tr>
<tr>
<td>Washout rate (%)</td>
<td>7.5±5.1</td>
<td>4.6±7.26</td>
<td>11.5±3.4</td>
<td>5.9±8.52</td>
<td>5.6±4.02</td>
<td>22.1±17.19</td>
</tr>
<tr>
<td>Initial H/M ratio</td>
<td>1.98±0.15</td>
<td>2.1±0.23</td>
<td>1.91±0.13</td>
<td>2.11±0.21</td>
<td>2.1±0.11</td>
<td>1.93±0.22</td>
</tr>
<tr>
<td>Delayed H/M ratio</td>
<td>2.1±0.24</td>
<td>2.1±0.19</td>
<td>2.0±0.16</td>
<td>2.5±0.25</td>
<td>2.5±0.25</td>
<td>2.5±0.25</td>
</tr>
</tbody>
</table>

*P<0.0001, #P<0.001, $P<0.02 as compared with males of the same age.
MIBG, 123I-metaiodobenzylguanidine; BMI, body mass index; H/M, heart-to-mediastinum.
Statistical Analysis

Data are expressed as mean±SD. Comparisons of the 10-year age groups and between males and females were performed by 1- or 2-way ANOVA followed by Bonferroni multiple comparison test. A simple linear regression analysis used the values of the initial and delayed H/M ratios. Probability values <0.05 were considered significant.

Results

H/M Ratios and Washout Rate

Subject characteristics are presented in Table 1. The females were not as tall as the males, and their body weights were less than those of the males. However, there was no significant difference in BMI between males and females.

Fig 1 and Table 1 show the decade-by-decade changes in the initial and delayed H/M ratios in both genders. Both men and women had a significantly decrease in the initial and delayed H/M ratios with advancing age (P<0.0001, for both). In addition, the initial H/M ratio had a significant positive correlation with the delayed H/M ratio (n=153, r=0.89, P<0.0001). Men in the 4th decade had a significantly higher initial H/M ratio than those in the 7th and 8th decades (P<0.001 and P<0.005, respectively). In addition, men in the 5th decade had a significantly higher initial H/M ratio than those in the 7th and 8th decades (P<0.005, for both). Likewise, men in the 4th decade had a significantly higher delayed H/M ratio than those in the 6th, 7th and 8th decades (P<0.005, P<0.0001, and P<0.0001, respectively). In addition, men in the 5th decade had a significantly higher delayed H/M ratio than those in the 7th and 8th decades (P<0.0001, for both). In females, women in the 4th decade had a significantly higher initial H/M ratio than those in the 7th and 8th decades (P<0.0001 and P<0.001, respectively). In addition, women in the 5th decade had a significantly higher initial H/M ratio than those in the 7th and 8th decades (P<0.001 and P<0.01, respectively). Likewise, women in the 4th decade had a significantly higher delayed H/M ratio than those in the 6th, 7th and 8th decades (P<0.01, P<0.001, and P<0.0001, respectively). Moreover, women in the 5th decade had a significantly higher delayed H/M ratio than those in the 6th, 7th and 8th decades (P<0.01, P<0.01, and P<0.0001, respectively). However, the changes in the initial and the delayed H/M ratio in females were significantly different from those in males (P<0.01 and P<0.03, respectively). The delayed H/M ratio of females (50–59 years) was significantly higher than that of males of the same age (P<0.001). After the age of 60 years, however, the delayed H/M ratio in females progressively decreased with aging.

Fig 2 and Table 1 show the decade-by-decade changes in the MIBG washout rate in both genders. Both genders had a significantly progressive increase in the washout rate with advancing age (P<0.0001, for both). In males, the washout rate was calculated to quantifying cardiac MIBG uptake as a fraction of the mean counts per pixel in the heart divided by that in the upper mediastinum. The heart-to-mediastinum (H/M) ratio in both the initial and delayed images were calculated as follows: washout rate (%)={[A–B]/A]×100, where A is the average count per pixel in the left ventricle on the initial image and B is the average decay-corrected count per pixel in the same region on the delayed image. Decay correction was performed with the assumption that the half-life of the radionuclide (123I) was 13 h. This technique has been confirmed as having a high reproducibility (n=12, r=0.91, P<0.001) for quantifying cardiac MIBG uptake.

Abbreviation see in Table 1.

Table 2 Characteristics of Women With and Without Surgical Menopause

<table>
<thead>
<tr>
<th></th>
<th>Surgical menopause</th>
<th>Menstruation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46±2</td>
<td>45±3</td>
<td>0.49</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60±0.07</td>
<td>1.60±0.06</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.6±5.4</td>
<td>50.0±6.1</td>
<td>0.51</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.1±1.8</td>
<td>19.5±2.3</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Abbreviation see in Table 1.
Changes in Cardiac SNS on MIBG

Effect of Surgical Menopause

Table 2 shows the group characteristics of females with and without surgical menopause. The females without surgical menopause were the same group as the females in their 4th decade. No significant differences were observed in age, height, body weight or BMI. Fig 3 shows the initial and delayed H/M ratios and the washout rates of the 2 groups. There was a significant decrease in the initial H/M ratio (2.24±0.12 in females with surgical menopause vs 2.42±0.25 in menstruating females; P=0.05) and the delayed H/M ratio (2.28±0.17 in females with surgical menopause vs 2.43±0.22 in menstruating females; P=0.03) and there was a tendency toward an increase in the MIBG washout rate in females with surgical menopause than those without surgical menopause (9.7±6.1% in females with surgical menopause vs 4.7±7.5% in menstruating females; P<0.06).

Discussion

The present study showed that the initial and delayed H/M ratios of MIBG imaging had significant age- and gender-related decreases and that the MIBG washout rate had a significant age-related increase in normal subjects. In addition, menstruation could influence these MIBG parameters.

Comparison With Previous Studies

This study examined the physiological changes in MIBG uptake and washout rate of the whole human heart. In comparison with other studies, this study had several different points. First, we paid special attention to the study population, so we could examine the age- and gender-related changes in MIBG parameters in very carefully selected subjects with a wide range of ages (40–89 years). Second, we analyzed both the initial and the delayed H/M ratio. Although the clinical value of the initial H/M ratio is controversial, it is closely associated with the MIBG washout rate, which is a well-known important factor. The clinical value of the initial H/M ratio was very similar to that of the delayed H/M ratio in the present study, so this relationship is preserved in healthy normal subjects. Third, we are the first to examine the physiological effect of menstruation on MIBG parameters in the human heart. Finally, this study showed that there are gender differences in the physiological changes in the MIBG uptake and washout rate.

Implications of MIBG Imaging

Several studies have shown that the delayed H/M ratio and washout rate were key factors in the assessment of cardiac SNS function. The delayed H/M ratio reflects global cardiac sympathetic innervation, although MIBG imaging is able to disclose the regional changes in left ventricular innervation. The MIBG washout rate, which indicates MIBG spillover from the presynaptic site, is enhanced in parallel with enhanced SNS activity in various cardiovascular diseases, particularly heart failure and hypertension. In addition, Gao et al showed that a dexmedetomidine-induced decrease in SNS activity significantly lowered the MIBG washout, suggesting that MIBG imaging is a non-invasive method of studying myocardial SNS activity. Thus, it appears that the MIBG washout rate is related to cardiac SNS activity.

In the present study, changes in the delayed H/M ratio indicated that aging induces a gradual decrease in cardiac SNS innervation (norepinephrine content) in both genders, although there was a significant gender difference in cardiac...
sympathetic innervation in the 5th decade. In contrast, changes in the MIBG washout rate suggested an age-related progressive increase in cardiac SNS activity in both genders, although in females it was less than in males at all ages. Thus, age-related changes in the cardiac SNS continued for more than 80 years in both genders. In contrast to males, there was a marked change in the cardiac SNS in females between the 5th and 6th decades, a sympathetic surge that seemed to be associated with menopause.

Comparison With Other Techniques

Various new techniques, such as muscle sympathetic nerve activity (MSNA)\textsuperscript{11–13} heart rate variability (HRV)\textsuperscript{8,9} and norepinephrine spillover rate measurement\textsuperscript{10} have been used to measure the SNS. However, each method has both merits and demerits, although MSNA studies appear to be generally accepted. Ng et al first described the age- and gender-specific influences on MSNA.\textsuperscript{11} After that, more precise studies within the decades of life have been shown. Matsukawa et al showed age-related increase in MSNA that were significantly higher in males than in females under the age of 50;\textsuperscript{13} and recently Narkiewicz et al did a similar investigation and reported that the age-related increase in MSNA was more prominent in females than in males and that there was gender difference in the younger generations.\textsuperscript{13} Those MSNA studies showed that the sympathetic outflow can increase with aging in both genders, whereas females under the age of 40 had significant low activity and the increase in outflow in females overcame that of males after the age of 50–60 years. The results are quite similar to ours, although there are several differences such as the age range, race, and subject characteristics. A most distinctly different result between the MSNA studies and the present study is that in studies of MSNA the cardiac SNS activity in females is always higher than that in the males during their lifetime. The reason why the present study did not find that phenomenon in any decade remains uncertain. It may result from MIBG imaging, or study selection, study condition, and so on.

Mechanisms Contributing to Physiological Changes

Possible mechanisms that contribute to the unique features of the physiologic changes in the cardiac SNS have been proposed. There are significant differences in the MIBG uptake and washout rate in the females under the age of 50 compared with males of the same age, which may result from higher parasympathetic nerve activity in younger females than in males, because HRV studies\textsuperscript{8,9} have shown that younger females have a higher HF than males and older females. With regard to the reduced MIBG uptake and increased MIBG washout rate with aging, several mechanisms have been postulated. Animal studies report a diminished number of neurons in the heart with aging\textsuperscript{3,24} and increased central sympathetic nervous activity with aging has been reported by the MSNA studies\textsuperscript{12–14} as well as attenuation of parasympathetic nerve activity with advanced aging\textsuperscript{9,25,26} all of which may contribute to the age-related changes in MIBG parameters. Furthermore, over the age of 50 years, Esler et al found that extraction of tritiated norepinephrine across the heart is reduced in healthy human subjects, suggesting an age-related reduced neuronal uptake of norepinephrine at presynaptic sites\textsuperscript{10} A similar result was also shown by Li et al\textsuperscript{2} using 18F-fluorodopamine positron emission tomography. Thus, the decrease in MIBG uptake over the age of 50 appears in part to result from reduced neuronal reuptake of norepinephrine with aging. Finally, there was the cardiac sympathetic surge observed in females around the 5th decade, a time of life that is usually consistent with the onset of menopause. Menopause enhances sympathetic nervous activity\textsuperscript{12} and estrogen influences the autonomic nervous system\textsuperscript{8,28}. In addition, surgical menopause could be a cardiovascular risk.\textsuperscript{21} It is likely that the duration of menopause after surgery can affect the SNS, but it remains unclear and further studies are needed to resolve the problem.

Although it seems that menstruation has a protective effect on SNS, Narkiewicz et al reported that menopause per se did not explain the age-related increase in central SNS activity\textsuperscript{13} and hormone replacement therapy did not confer a clinical benefit on postmenopausal women.\textsuperscript{21} The present study showed a significant difference in the delayed H/M ratio, but not in the washout rate, between females with and without surgical menopause, suggesting that menopause caused cardiac sympathetic denervation but did not increase cardiac sympathetic activity. Considering the controversy surrounding this issue, our results suggest that menopause, together with aging, dramatically changes the cardiac SNS in climacteric women, although menopause alone has more or less a deleterious effect on the cardiac SNS.

Clinical Implications

Advancing age brings about various physiological changes in the human body. The present study demonstrated the age- and gender-related changes in the global cardiac SNS, similar to the age- and gender-related changes in coronary heart disease mortality and morbidity in comprehensive epidemiologic studies,\textsuperscript{3,6} suggesting that gender differences may explain the higher event rate in cardiovascular diseases in males. The concept that aging is the most powerful risk factor for cardiovascular diseases may stem from age differences in the event rate in cardiovascular disease in both genders.\textsuperscript{32} However, it is unlikely that these changes directly lead to the development of cardiovascular diseases, because the present study showed normal physiological changes of the cardiac SNS. Therefore, the present study suggests that the healthy older person has protective mechanisms against enhanced cardiac sympathetic activity. Moreover, it is quite natural to pose the following questions: What factors influencing the cardiac SNS can lead to the cardiovascular diseases? Will modification of the cardiac SNS delay or prevent the onset of cardiovascular diseases? Where in the course of aging should we start the modification? and so on. Based on the present results, various interventional studies are needed to answer to these questions.

Conclusion

Cardiac sympathetic innervation (norepinephrine content) has gender- and age-related changes, whereas cardiac sympathetic activity probably had age-related changes alone. Such information might help us unravel the contribution of cardiac SNS to age- and gender-related disease interactions and, furthermore, its modification may be useful in preventing cardiovascular diseases.

References


