

Physiological Fluctuation of the Human Left Ventricle Sympathetic Nervous System Assessed by Iodine-123-MIBG

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It has been proposed that sympathetic nervous system pathophysiology is involved in the development of cardiovascular disorders. Since cardiac adrenergic activity has been difficult to assess in humans, physiological changes in the sympathetic nervous system in the human left ventricle remain unclear. **Methods:** To determine if age and gender influence the sympathetic nervous function of the left ventricle, 300 angiographically normal subjects (170 men, 130 women; age range 40–79 yr) had ¹²³I-metaiodobenzylguanidine (MIBG) cardiac imaging. Regional quantitative analysis of MIBG uptake and washout rate was performed. **Results:** Men and women had prominent age-related decreases in MIBG uptake in the inferior and lateral walls ($r^2 = 0.34$, $p < 0.0001$ for both). Both genders had a significant positive correlation between regional washout rate and age in each region. In contrast to men, women had strong positive correlations in all regions ($r^2 = 0.54$, $p < 0.0001$ in the anterior wall, $r^2 = 0.56$, $p < 0.0001$ in the lateral wall and $r^2 = 0.44$, $p < 0.0001$ in the inferior wall). According to the decade-by-decade analysis of washout rate, women had a significantly lower washout than men under 50 yr in every region and a significantly higher washout in the lateral wall than men over 70 yr. **Conclusion:** The sympathetic nervous system in the human left ventricle showed age- and gender-related regional changes. The findings suggested that men have high sympathetic nerve activity from a younger age, and women have a progressive increase in sympathetic nerve activity with aging. These changes may contribute to the age and gender differences in the incidence and development of cardiac disorders.

Key Words: iodine-123-MIBG images; cardiac disorders; left ventricle; sympathetic nervous system; age; gender

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Sympathetic nervous system pathophysiology has been proposed as a causal component for the development of cardiovascular disorders, including ischemic heart disease, essential hypertension and ventricular arrhythmias resulting in sudden cardiac death (1–5). The prevalence of cardiovascular disease and sudden death increases with advancing age, and the incidences are generally higher in men than in women (6,7). The precise mechanisms responsible for this are unknown, but an age-related rise and gender difference in efferent sympathetic nervous system activity have been postulated as factors (1). Since cardiac adrenergic activity has been difficult to assess in vivo, this hypothesis is based largely on experimental observations of age- and gender-associated changes in plasma norepinephrine concentration and its appearance rate, directly recorded sympathetic nerve activity in skeletal muscle and heart rate variability (8–12). However, it is well recognized that neural activity measured by these methods does not necessarily reflect what happens at the ventricle, where life-threatening cardiac disorders often manifest themselves.

Recently, radioiodinated metaiodobenzylguanidine (MIBG), an analog of guanidine that shares many neuronal transport and storage mechanisms with norepinephrine, has been used for probing the sympathetic activity and innervation of the heart (13). Using ¹²³I-MIBG imaging, it is easy to assess regional efferent adrenergic neuronal function in the human left ventricle of a patient suffering from various heart diseases (14–18). The aim of this study was to determine if age and gender influence sympathetic nervous function of the left ventricle in normal subjects by using ¹²³I-MIBG imaging.

MATERIALS AND METHODS

Patients

Three hundred fifteen patients, age range 40–79 yr, were referred for cardiac catheterization because of chest pain or ECG abnormality, which revealed a normal coronary artery without spasm and normal cardiac function. After cardiac catheterization, they had MIBG imaging. Subjects consisted of 170 men and 130 women who did not have obvious heart disease, hypertension (160 mmHg or greater systolic blood pressure or 95 mmHg or greater diastolic blood pressure), diabetes mellitus or any other disease affecting the autonomic nervous system. The remaining 15 subjects were excluded because of no obvious accumulation of MIBG on either the initial or delayed image. Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Coronary Angiography

Coronary angiography was performed by the standard Judkins technique in all patients. Before coronary angiography was performed, a temporary pacing catheter was inserted into the right ventricle, and the pacing rate was set to 40 bpm. Standard 12-lead electrocardiograms (ECGs) were recorded continuously with a six-channel recorder. After control coronary arteriograms were obtained, acetylcholine, which had been dissolved in saline solution, was injected in incremental doses of 20 and 100 μ g directly into the right coronary artery and, subsequently, the left coronary artery through the Judkins catheter. Coronary angiography was performed 1 min after the acetylcholine was injected over 1 min. After the acetylcholine provocation test, coronary angiography was performed after intracoronary injection of 0.3 mg nitroglycerin. The results of coronary angiography, after the injection of nitroglycerin, were classified according to the reporting system of the American Heart Association.

MIBG Scintigraphy

A dose of 111 MBq of commercially available MIBG (Daiichi Radioisotopes Labs, Ltd., Tokyo, Japan) was administered intravenously from 9 a.m. to 10 a.m. after lying in bed undisturbed for 15 min. Cardiac SPECT images were acquired 15 min (initial image) and 3–4 hr (delayed image) after the injection of MIBG, using a three-head gamma camera (Toshiba GCA 9300A/HG, Tokyo, Japan),

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with 120° rotation per head, 3° increments, 30 sec per step, and a 128 × 128 matrix. The data were reconstructed by filtered backprojection (Shepp-Logan) on a Toshiba GMS 5500A system. Neither scatter correction nor attenuation correction was performed.

Quantitative analysis of MIBG uptake in the left ventricle was performed using a computerized two-dimensional polar map of the three-dimensional myocardial radionuclide activity. For semiquantitative analysis, relative MIBG uptake of the left ventricle was calculated in all short-axis slices using a modified three-dimensional region-of-interest algorithm and setting the maximal MIBG uptake at 100%. If the maximal MIBG uptake was present in the inferior wall, we examined whether or not the point was in the liver. If so, the case was excluded or a two-dimensional polar map was made again. In this study, regional MIBG uptake was assessed only in the delayed image.

Regional quantitative analysis of the washout rate of MIBG also was performed. Regional washout rates from the heart were calculated using initial and delayed images. The regional washout was obtained from the following formula: regional washout rate (%) = (A - B)/A × 100, where A = average counts in a region on the initial image and B = average decay-corrected counts in the same region on the delayed image. Decay correction was performed assuming that the half-life of the radionuclide (¹²³I) was 13 hr. On a polar map representation, the territory in each of the three major coronary arteries was defined as the anterior wall, the lateral wall and the inferior wall (15).

Statistical Analysis

Data were expressed as mean ± s.d. A linear regression analysis was performed between regional MIBG uptake, regional washout rate and age. Chi-square test or Fisher's exact test was used to determine the significance of differences in the observed occurrence rates. ANOVA with multicomparison test was used for between-group or between-region comparisons. Probability values of less than 0.05 were considered significant.

RESULTS

Regional MIBG Uptake and Age

Figure 1 shows the correlations between age and regional MIBG uptake. In the anterior wall, both men and women had no significant correlations between age and MIBG uptake. However, women had a prominent age-related decrease in MIBG uptake in the lateral wall ($r^2 = 0.34$, $p < 0.0001$), although only a weak correlation was observed in men ($r^2 = 0.11$, $p < 0.0001$). In contrast, men had a negative correlation between age and MIBG uptake in the inferior wall ($r^2 = 0.34$, $p < 0.0001$), although only a weak correlation was observed in women ($r^2 = 0.078$, $p < 0.0012$). In both genders, no significant correlations were observed between age and maximum pixel counts in the left ventricle ($r^2 = 0.009$, $p = 0.22$ in men and $r^2 = 0.003$, $p = 0.52$ in women).

Regional MIBG Washout and Age

Figure 2 shows the correlations between regional washout rate and age. In both genders, significant positive correlations between regional washout rate and age were observed in all regions. In men, all correlations between regional washout rate and age were weak ($r^2 = 0.12$, $p < 0.0001$ in the anterior wall, $r^2 = 0.11$, $p < 0.0001$ in the inferior wall and $r^2 = 0.17$, $p < 0.0001$ in the lateral wall). In women, strong positive correlations were observed in all regions ($r^2 = 0.54$, $p < 0.0001$ in the anterior wall, $r^2 = 0.56$, $p < 0.0001$ in the lateral wall and $r^2 = 0.44$, $p < 0.0001$ in the inferior wall).

Comparison of MIBG Uptake and Washout by Decade

Table 1 shows the clinical characteristics of each 10-yr age

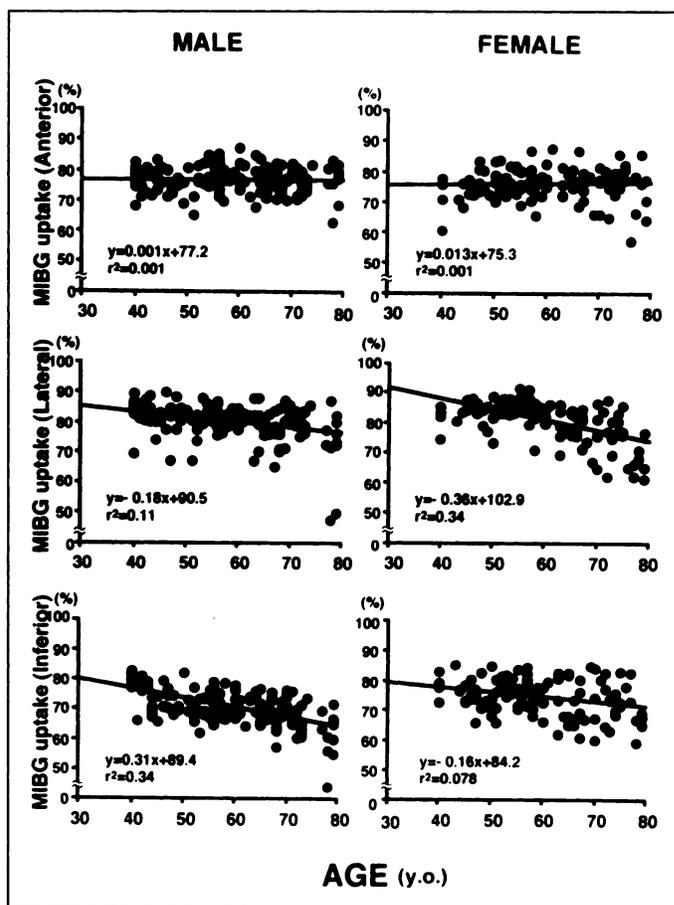


FIGURE 1. Scatterplots show relationship between age and ¹²³I-MIBG uptake.

group. There were no significant differences in the distribution of obesity. Figure 3 shows the decade-by-decade regional differences of MIBG uptake and washout in each gender. Under 50 yr, both genders had similar MIBG uptake and washout distribution, although men had a significantly higher washout in every region than women ($p < 0.01$ in the anterior wall, and $p < 0.05$ for both the inferior and lateral walls). Men in their fifth decade had the most heterogeneous MIBG uptake and washout distribution, but this heterogeneity slightly improved with aging. In contrast, women had a similar MIBG uptake distribution until 70 yr. MIBG uptake in the inferior wall was significantly lower in men than that in women ≥ 50 yr of age ($p < 0.0001$ in fifth decade; $p < 0.05$ in sixth decade; and $p < 0.0001$ in seventh decade). Although significant differences in regional washout between women and men disappeared after ≥ 50 yr of age, women had significantly higher washout rates in the lateral wall than men ≥ 70 yr of age ($p < 0.05$).

DISCUSSION

These results provide evidence that regional sympathetic nerve distribution and activity in the human left ventricle fluctuate with advancing age and vary with gender. Many investigators (13,14,16,17) have reported that MIBG uptake in the left ventricle is regionally different. Recently, Tsuchimochi et al. (17) demonstrated that there were gender- and age-differences in regional MIBG uptake in a small number of normal subjects. The present study investigated the regional changes in MIBG uptake and washout present in normal subjects in whom the absence of organic heart diseases had been confirmed by cardiac catheterization.

Both genders had a similar MIBG uptake distribution under

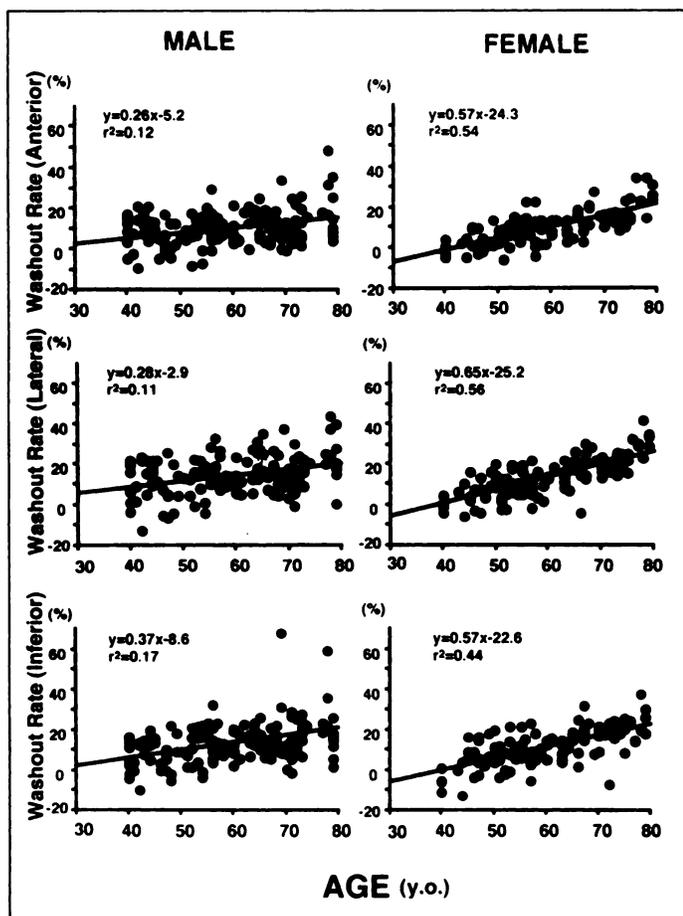


FIGURE 2. Scatterplots show relationship between age and MIBG washout rate.

50 yr. After ≥ 50 yr, MIBG distribution showed a unique pattern in each gender. The most interesting pattern of changes in MIBG uptake was observed in the inferior wall. Consistent with Tsuchimochi et al. (17), a prominent age-related decrease in MIBG uptake in the inferior wall in men was characteristic, although women had a mild age-related decrease in MIBG uptake in the inferior wall. This finding also indicated that a sympathetic dominance greater in the anterior wall than in the inferior wall was progressively prominent with aging, which agrees with the previous clinical observation of sympathetic activity greater in acute anterior than in inferior myocardial infarction (18,19). In contrast to men, we found that an age-related decrease in MIBG uptake in the lateral wall was characteristic in women. On the other hand, MIBG washout rates in the all three regions in women were significantly lower than those in men under 50 yr and had prominently increased

with advancing age, whereas MIBG washout rates in all the regions mildly increased in men. Thus, age- and gender-related regional changes in MIBG washout and uptake must be considered carefully when analyzing MIBG images, as well as assessing sympathetic nervous function by MIBG imaging.

Possible Mechanisms and Implications of Age- and Gender-Related Changes in MIBG Uptake and Washout Rate

Based on a large number of studies on ^{123}I -MIBG imaging (14-18), it is considered that myocardial MIBG uptake primarily reflects innervation of sympathetic neurons available or norepinephrine content, and myocardial MIBG washout mainly reflects sympathetic nerve activity.

Therefore, under 50 yr, a significantly higher MIBG washout in men than women, without any differences in MIBG uptake, was considered to indicate that men had more enhanced sympathetic activity in the left ventricle than women. However, assessment of sympathetic innervation and activity on MIBG imaging becomes rather complex since aging brings many morphological and functional changes in the sympathetic nervous system that could affect MIBG kinetics. Various age-related changes in the sympathetic nervous system have been reported: histologically, an enhancement of the distance between the nerve terminals and the cardiovascular adrenoceptors (20) and a reduction in the number of neurons and loss of nerve fibers (21-25); and, functionally, a reduction in the sensitivity of presynaptic α_2 -adrenoceptors with aging in animal tissues (26), impaired reuptake of norepinephrine in older men (27) and reduced human parasympathetic nerve activity with aging (28).

Recently, several investigators (25,27) have reported that there was no evidence of enhanced sympathetic nerve activity in older men. In addition, Esler et al. (27) suggested that high plasma norepinephrine concentration in older men resulted from impaired reuptake at the presynaptic site. However, these studies were based on the assumption that the sympathetic nervous system in the human left ventricle would change homogeneously with aging. As shown in this study, age-related changes in MIBG uptake and washout were not uniform in the left ventricle. More importantly, the intensity of the age-related decrease in MIBG uptake was not necessarily consistent with that of the age-related increase in MIBG washout in each region, suggesting that many mechanisms work together in the left ventricle with aging. In particular, the marked age-related decreases in MIBG uptake in the inferior wall of men are not simply explained by impaired reuptake alone. Other mechanisms, such as age-related denervation, probably play an important role in the decreases.

TABLE 1
Group Characteristics

Age	≥ 40 yr		≥ 50 yr		≥ 60 yr		≥ 70 yr	
	Men	Women	Men	Women	Men	Women	Men	Women
Patient no.	43	24	47	45	41	28	39	33
Age (yr)	44 ± 3.0	45 ± 2.8	54 ± 3.0	55 ± 2.2	65 ± 3.0	65 ± 2.6	74 ± 3.4	74 ± 2.9
Height (m)	1.67 ± 0.8	$1.58 \pm 0.6^*$	1.67 ± 0.8	$1.53 \pm 0.7^*$	1.66 ± 0.6	$1.55 \pm 0.7^*$	1.64 ± 0.2	$1.54 \pm 0.6^*$
Weight (kg)	62.6 ± 5.6	$52.7 \pm 5.0^*$	61.0 ± 4.7	$55.2 \pm 5.8^*$	60.0 ± 3.7	$54.8 \pm 6.2^*$	61.7 ± 5.8	$53.2 \pm 6.1^*$
Body mass index ($\text{kg}\cdot\text{m}^{-2}$)	22.6 ± 2.2	21.4 ± 3.2	22.0 ± 2.5	23.0 ± 3.1	21.9 ± 2.1	22.7 ± 2.5	22.9 ± 2.1	22.6 ± 3.4

* $p < 0.0001$. Values are expressed as mean \pm s.d.

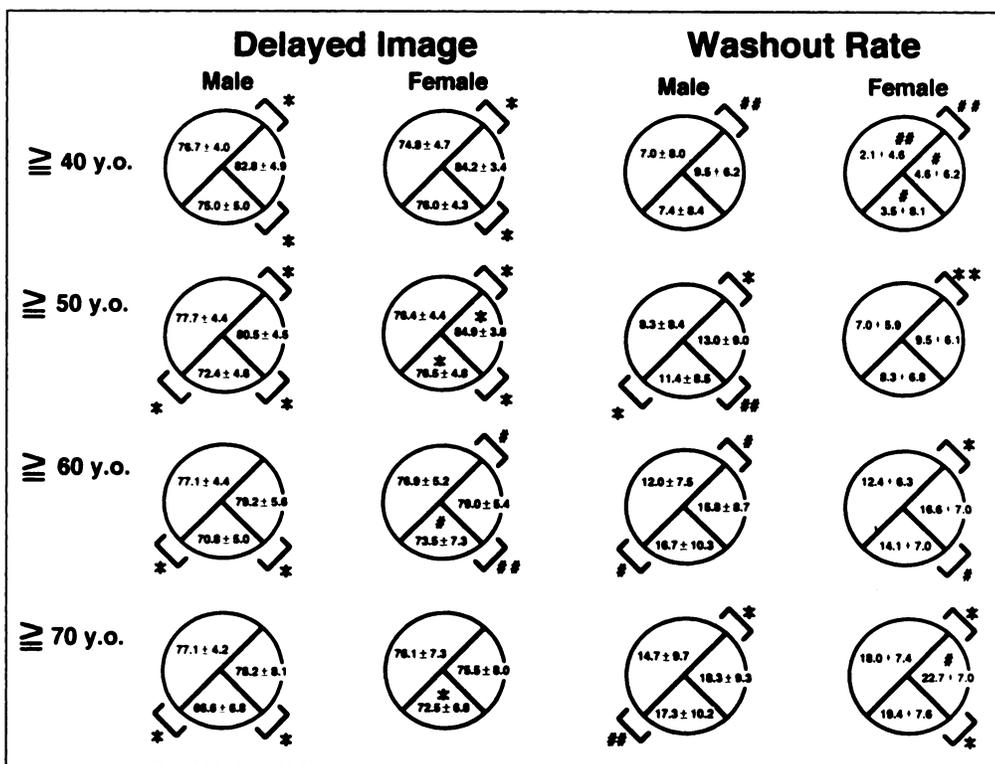


FIGURE 3. Comparisons of regional MIBG uptake and washout rate in each left ventricular wall on two-dimensional polar map between men and women by each decade. On a polar map representation, the territory in each of three major coronary arteries was defined as anterior wall, lateral wall and inferior wall (15,16). Symbols over values in regions on polar map in women show p values compared to same region in men in same decade. Values are expressed by mean \pm s.d. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

It is well known that older men have reduced parasympathetic nerve activity (28), which leads to enhanced sympathetic activity. It is possible that enhanced sympathetic nerve activity, probably secondary to reduced parasympathetic activity, may contribute to enhanced MIBG washout in some regions of the older human heart. In particular, reduced parasympathetic nerve activity appears to be important in women. Compared with the age-related changes in MIBG washout and uptake in men, age-related increases in washout in women were extremely prominent, indicating that this phenomenon did not result only from denervation and/or impaired reuptake. Recently, Huikuri et al. (12) demonstrated that age-related reduction in vagal function is more marked in women than in men. Considering the evidence that older women have high sympathetic activity secondary to reduced parasympathetic nerve activity, and that increased MIBG washout usually reflects intense sympathetic activity; the increased washout in women strongly suggested that women had a progressive sympathetic activation in the left ventricle with aging.

It is reasonable to assume that plural mechanisms affecting the sympathetic nervous system work together with aging, resulting in heterogeneous changes in the sympathetic nervous system of the human left ventricle. However, we could not differentiate any of the possible mechanisms that make MIBG uptake decrease and MIBG washout increase (16-18,29) by MIBG imaging. In addition, it is unclear why the intensity of the mechanisms contributing to a change in the sympathetic nervous system differs with region and gender.

Study Limitations

In general, a normal population consists of volunteers with the absence of cardiac symptoms and ECG abnormalities, who have a low probability for significant heart disease. However, we selected subjects with chest pain or ECG abnormality who had normal coronary angiograms without spasm (assessed by acetylcholine provocation test) and normal ventriculograms. In addition, they did not have hypertension, diabetes mellitus or

any other disease affecting the autonomic nervous system. As our study subjects with chest pain or ECG abnormality are different from the normal population, we defined our subjects as angiographically normal subjects. That may be why 15 (4.8%) of 315 angiographically normal subjects had no obvious accumulation of MIBG. However, since our study subjects did not have any other abnormalities suspicious of heart diseases, except for ECG abnormality or chest pain, and their MIBG data were similar to those of normal volunteers (17), we consider that our study subjects are within the normal range.

Clinical Implications

A link between coronary artery disease development, sudden cardiac death and sympathetic nervous system activity has been postulated (1-5). There is evidence of a significant involvement of alpha-adrenergic coronary vasoconstriction in the initiation and aggravation of experimental and clinical myocardial ischemia, and alpha-adrenoreceptor-mediated effects on myocytes and platelets may contribute to myocardial ischemia and its complications as well (30). In addition, ample findings support the possible relationship between the genesis of sudden cardiac death and enhanced sympathetic nerve activity (4,5).

As shown in this study, men under 50 yr have significantly higher sympathetic nerve activity in the whole left ventricle than women. In the Framingham Heart Study (3,4), it was reported that men have about a three times higher rate of sudden death and morbidity of coronary heart disease under 50 yr than women. These phenomena may be partially explained by the high sympathetic activity in men under 50 yr. This study also demonstrated that with a more than 10-yr delay, sympathetic nerve activity in women reached the same level as in men. Interestingly, this time lag is similar to the time demonstrated in the Framingham Heart Study, which showed that clinical manifestations of coronary artery disease occurred more than 10 yr later in women compared to those in men (6,7). Furthermore, great emphasis has been placed on the recognition of risk factors for ischemic heart disease in women, which are different

from those in men. One reason why women suffer from coronary artery disease about 10 yr later than men may be related to hormone differences. Frequent evidence of a cardio-protective effect for estrogen has been reported (31). In this study, sympathetic nerve activity in women markedly increased after age 50, which appears to be in parallel with the rapid increase in the incidence of coronary heart disease in women after age 50 (32), the average age of menopause. Although estrogens exert many actions on the sympathetic nervous system (33,34), it is questionable that estrogens produce the prominent sympathetic change observed in the study. Therefore, it appears that this sympathetic surge in women occurs at menopause. Furthermore, it has been demonstrated in women that the short-term prognosis of women who had an acute myocardial infarction is worse than that for men (35). As this study suggested that older women had a high sympathetic nerve activity, probably secondary to reduced parasympathetic nerve activity, an autonomic imbalance resulting in a relative sympathetic dominance appears to contribute to this worse prognosis of older women after myocardial infarction.

CONCLUSION

This study demonstrated that men have a high MIBG washout in the left ventricle from a younger age and have an age-related progressive decrease in MIBG uptake in the inferior wall, whereas women had an age-related progressive decrease in MIBG uptake in the lateral wall and an accelerated increase in MIBG washout in the whole left ventricle with advancing age. Thus, the regional sympathetic nervous system in the human left ventricle showed age- and gender-differences, and this might explain the age and gender differences in the incidence and development of coronary artery disease and sudden cardiac death.

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