Myocardial ^{123}I -metaiodobenzylguanidine Washout and Heart Rate Variability in Asymptomatic Subjects

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Background: Myocardial ^{123}I -metaiodobenzylguanidine (MIBG) kinetics reflect the integrity and function of cardiac presynaptic sympathetic nerve terminals. Heart rate variability (HRV) is an indicator of cardiac sympatho-vagal balance. However, the function of cardiac sympathetic nerve terminals as a modulator of HRV in asymptomatic subjects has remained elusive. In addition, the physiological background for different components of HRV is not fully established.

Methods: We evaluated the relationship between myocardial MIBG washout and HRV in 30 asymptomatic subjects with familial risk of coronary artery disease (CAD). Early and delayed myocardial MIBG uptakes as well as MIBG washout between these two scans were assessed. Myocardial perfusion at rest and during bicycle exercise was evaluated with $^{99\text{m}}\text{Tc}$ -sestamibi (MIBI). HRV was measured from 24-hour ambulatory ECG recordings.

Results: Myocardial MIBG washout averaged $40 \pm 8\%$. The mean heart rate at rest was 76 ± 14 beats/min. Standard deviation of all normal RR intervals (SDNN) was 94 ± 22 ms and very low frequency (VLF) was 1625 ± 958 ms² on average. Myocardial MIBG washout correlated inversely with SDNN ($r = -0.390$; $P < 0.05$) and with VLF ($r = -0.459$; $P < 0.01$) component of HRV but not with heart rate at rest ($r = 0.207$, $P = \text{ns}$). All subjects had normal myocardial perfusion at rest and during exercise.

Conclusions: Increased cardiac presynaptic sympathetic nervous activity was related to reduced HRV in subjects with the risk of CAD but without evidence of myocardial ischemia or previous myocardial infarction. In addition, we found that VLF component of HRV includes information about sympathetic neural modulation of the heart rate.

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Severe coronary artery disease (CAD) and myocardial infarction result in cardiac sympathetic denervation, changes in myocardial ^{123}I -metaiodobenzylguanidine (MIBG) kinetics and reduction in heart rate variability (HRV).^{1–4}

The function of presynaptic sympathetic nerve terminals can be studied in vivo with MIBG scintigraphy.⁵ MIBG uptake represents the integrity of presynaptic nerve terminal whereas MIBG washout indicates the activity of presynaptic nerve terminals. Recently, myocardial MIBG

scintigraphy has been suggested to be promising in identifying heart failure patients with increased risk for ventricular tachyarrhythmias.⁶

HRV provides information about cardiac sympatho-vagal regulation. Depressed HRV is considered to reflect increased sympathetic predominance of cardiac autonomic regulation. In addition, depressed HRV has been shown to predict increased mortality and sudden cardiac death in patients with CAD, particularly in postinfarction patients.^{7,8}

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Myocardial MIBG kinetics and HRV have been reported to correlate with each other in patients with recent myocardial infarction.⁴ However, whether the function of cardiac presynaptic sympathetic nerve terminals is related to HRV in patients without prevailing myocardial infarction has remained elusive.

HRV can be divided into high frequency (HF), low frequency (LF) and very low frequency (VLF) components. HF component is considered to represent vagal regulation whereas the LF component indicates predominantly sympathetic modulation of heart rate. The physiological background of VLF component is not known.

In this study, we assessed myocardial MIBG kinetics and HRV in asymptomatic subjects who had no signs or symptoms of myocardial ischemia. In addition, we aimed to assess the relationship between myocardial MIBG kinetics and frequency domain components of HRV.

METHODS

This trial was focused to study cardiac autonomic function in subjects without any signs or symptoms of myocardial ischemia, but who are at risk for CAD in the future according to family history.

Subjects

Study subjects consisted of 30 asymptomatic subjects (16 male, 14 female) with a high family history for early CAD. High family history was considered if the subject had at least two siblings affected by severe CAD under 55 years of age—i.e., previous myocardial infarction or three-vessel disease with 50% cut off for angiographical severity of stenosis.

Subjects with diseases known to influence autonomic nervous system, such as diabetes and Parkinson's disease, or atrial fibrillation were excluded. All medication known to influence cardiac adrenergic innervation or MIBG uptake was temporarily withdrawn four half lives before data acquisitions.⁹ At least 12 hours before MIBG imaging, the subjects were not allowed to drink coffee, tea, or cola drinks or to smoke.

Study Protocol

The study protocol consisted of MIBG imaging to analyze the initial and delayed tracer uptake

and washout. Myocardial perfusion was assessed with ^{99m}Tc-sestamibi (MIBI) at rest and during bicycle ergometer exercise to exclude exercise-induced myocardial ischemia. HRV in time domain and frequency domain were calculated from 24-hour ambulatory ECG recordings.

Patients gave written informed consent before participation of the study. The study was carried out in accordance with the Declaration of Helsinki (2000) and the local ethics committee approved the study protocol.

Radionuclide Studies

MIBG and MIBI dual isotope study at rest was performed during the first day. Myocardial perfusion imaging during exercise was conducted on the following day. The specific activity of MIBG was 26,000 MBq/mmol. A dose of 400 MBq of MIBI tracer was followed by 200 MBq of MIBG tracer 15 min later. Both tracers were injected into the left antecubital vein.

The first SPECT imaging was started 15 minutes after MIBG injection (30 minutes after MIBI injection) to assess initial MIBG uptake and myocardial perfusion at rest and the second SPECT imaging was performed 4 hours after MIBG injection using the same imaging settings to study delayed MIBG uptake. In addition, planar imaging was performed to study initial (imaging started 10 minutes after MIBG injection) and delayed (imaging started 4 hours after MIBG injection) myocardial MIBG and MIBI tracer uptakes.

To study myocardial perfusion during exercise on the next day, a 400 MBq dose of MIBI was injected during the last minute of maximal bicycle ergometer stress and imaging was started 30 minutes after the injection.

A Siemens Multispect 3 gamma camera (Siemens Gammasonics, Hoffman Estates, IL, USA) equipped with high-resolution collimators was used to assess myocardial distribution of MIBG and MIBI tracers. The imaging resolution was 13 to 14 mm. The three detectors (3 × 120°) acquired 30 views with 4° steps of 45 seconds each. The matrix size used was 128 × 128 without zooming and the voxel size was 3 × 3 × 3 mm. The energy window of ^{99m}Tc was 133–147 keV and that of ¹²³I was shifted to 154–170 keV. Overlapping of the energies was corrected using a matrix inversion technique with the standard doses of ¹²³I and ^{99m}Tc. Overlapping of

^{123}I activity onto the $^{99\text{m}}\text{Tc}$ window was, on average, 18% and vice versa 4%.

Heart Rate Variability Analysis

Twenty-four-hour ambulatory ECG recording was performed using digital ambulatory ECG-recorders (Oxford Medilog FD-3, Oxford Instruments Medical System, Abingdon, UK). Normal daily-living activities were allowed during the ECG recordings.

Artefactual beat labels were manually eliminated from the ECG recordings with an Excel Medilog II system (Oxford Instruments Medical System, Abingdon, UK). HRV analysis was performed with HEARTS5 analysis program (Heart Signal, Kempele, Finland).¹⁰ Recordings at least 18 hours in duration, including whole night-time (00–06) and with high quality (accepted beats >90%) were used for further analysis.

For the assessment of HRV in time domain, standard deviation of all normal RR intervals (SDNN), root mean square of successive difference in RR intervals (rMSSD), and percentage of difference between adjacent RR intervals that are over 50 msec (pNN50) were measured. Frequency domain analysis of HRV was performed with fast Fourier transform algorithm. The power spectrum of RR interval variability was divided into VLF (0.005–0.04 Hz), LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) bands. The integrals under the power spectral density functions were measured and expressed in absolute units. All recordings were edited and analyzed by the same investigator (SS).

In addition, subjects were divided into two groups according to SDNN: group 1, those with moderately depressed HRV (SDNN $\leq$ 100ms) (n = 19) and group 2, those with normal HRV (SDNN >100 ms) (n = 11). SDNN was chosen because it has shown to carry prognostic information in patients after acute myocardial infarction.¹¹

Data Analysis

The raw data of MIBG and MIBI studies were reconstructed using a Butterworth filtered (order 8, cutoff frequency 0.65 cm^{-1}) back projection technique. For semiquantitative analysis of regional uptakes, an interpolative background subtraction was used to reduce the effect of background activity. Transaxial slices were reconstructed.

Table 1. Clinical Characteristics of the Subjects

N	30
Female	14 (47%)
Age (years)	55 ± 7
BMI (kg/m^2)	28 ± 3
Heart rate (beats/min)	74 ± 10
Diastolic blood pressure (mmHg)	83 ± 11
Systolic blood pressure (mmHg)	141 ± 18
Medication	
ACE inhibitors	5 (17%)
Acetylsalicylic acid	4 (13%)
Beta-blocking agents	4 (13%)
Calcium channel-antagonists	3 (10%)
Statins	5 (17%)
Estrogen replacement therapy	4 (13%)

ACE = angiotensin converting enzyme, BMI = body mass index.

Mean myocardial MIBG and MIBI counts obtained from the initial and delayed planar acquisition were normalized by the mean upper-mediastinal counts of the respective imaging and expressed as heart-to-mediastinum (H/M) ratio. Quantitative analysis of the MIBG washout rate was calculated using the initial and delayed SPECT imaging. Myocardial MIBG washout was calculated as follows: $(A-B)/A \times 100$, where A represents the number of absolute counts of the region of interest on the initial image and B represents the number of absolute counts of the corresponding region of interest on the delayed image. Myocardial perfusion was visually evaluated from SPECT data.

Statistical Methods

Logarithmic (ln) transformation was made to normalize the distribution of HRV variables. To test the significance of differences between groups, *t*-test was used for continuous variables and chi-square test for categorical variables. To control the effect of gender, partial correlation was calculated to estimate linear correlation between variables. A P-value < 0.05 was considered statistically significant. Results are expressed as mean $\pm$ standard deviation (SD).

RESULTS

The mean age of the subjects was 55 ± 7 years (range 42–68 years). Five subjects (17%) were smokers at the time of the study. Hypertension was diagnosed in 11 subjects (37%) and estrogen

Figure 1. Correlation between myocardial MIBG washout and components of HRV. Abbreviations: SDNN = standard deviation of all normal RR intervals, VLF = very low frequency of HRV power spectrum, and LF = low frequency components of HRV power spectrum.

replacement-therapy was used by four subjects (13%). The demographic data of the subjects are shown in Table 1. There were no statistically significant differences in HRV measures or MIBG measures between normotensive or hypertensive subjects.

Normal myocardial perfusion at rest and the absence of bicycle ergometer exercise induced perfusion abnormalities were confirmed by visual evaluation of myocardial MIBI uptake at rest and during maximal exercise by an experienced nuclear medicine specialist (EV).

Myocardial MIBG Uptake and Washout

H/M ratio of myocardial MIBG uptake averaged 2.0 ± 0.1 in the initial imaging and 2.1 ± 0.2 in the delayed planar imaging. Myocardial MIBG washout was $40 \pm 8\%$ on average.

Heart Rate Variability

The mean heart rate at rest was 76 ± 14 beats/min. HRV assessed in time domain averaged 94 ± 22 ms for SDNN, $7.6 \pm 6.0\%$ for pNN50, and 977 ± 635 ms for rMSSD. In the frequency domain analysis, the average powers of VLF, LF and HF spectral components were 1625 ± 958 ms², 708 ± 496 ms², and 296 ± 228 ms², respectively, and LF/HF ratio averaged 3.10 ± 2.51 .

Myocardial MIBG Washout and Heart Rate Variability

Myocardial MIBG washout showed significant correlation to SDNN ($r = -0.390$, $P < 0.05$), to VLF power ($r = -0.459$, $P < 0.01$), and borderline correlation to LF power ($r = -0.339$, $P = 0.06$) but not to HF power ($r = -0.121$, $p = \text{ns}$) of HRV

when the effect of gender was taken into account (Figure 1). Myocardial MIBG washout and heart rate at rest did not correlate with each other ($r = 0.207$, $P = \text{ns}$).

When the subjects were divided into tertiles according to HRV, MIBG washout of the highest SDNN tertile was lower as compared to MIBG washout of the middle SDNN tertile (36% vs. 42%, $P < 0.05$, respectively) (Figure 2). Accordingly, MIBG washout was significantly lower in the highest VLF and LF tertiles (34%, 35%, respectively) as compared to the middle (43%, $P < 0.01$; 41%, $P < 0.01$, respectively) and to the lowest VLF and LF tertiles (41%, $P < 0.01$; 42%, $P < 0.01$, respectively).

Myocardial MIBG washout tended to be higher among subjects with decreased SDNN (≤ 100 ms) as compared to subjects with normal SDNN (> 100 ms) ($41\% \pm 8\%$ vs. $36\% \pm 7\%$, $P = 0.08$, respectively) (Figure 3).

Early or delayed H/M MIBG ratio did not correlate with any HRV measures.

DISCUSSION

In this study, we found an inverse correlation between myocardial MIBG washout and HRV in subjects without symptoms or signs of myocardial ischemia.

Myocardial MIBG washout reflects the activity of presynaptic sympathetic nerve terminals.¹² On the other hand, the etiology of HRV is multifactorial as it consists of reciprocal and complementary effects of sympathetic and parasympathetic nervous system on heart rate.¹³ High MIBG washout is associated with increased sympathetic activity and reduced HRV is known to indicate sympathetic predominance of cardiac autonomic regulation.¹⁴ This

Figure 2. Myocardial MIBG washout and HRV. HRV is expressed in tertiles of HRV parameters. Abbreviations: SDNN = standard deviation of all normal RR intervals, VLF = very low frequency of HRV power spectrum, LF = low frequency of HRV power spectrum, 1 = lowest tertile, 2 = middle tertile, 3 = highest tertile (highest HRV). The values are mean + SD. Significances: * $P < 0.05$, ** $P < 0.01$.

is well in agreement with our finding that myocardial MIBG washout and HRV variables correlated inversely.

Previous studies have reported that increased myocardial MIBG washout is associated with depressed HRV in postinfarction patients, i.e., in patients with myocardial necrosis.^{4,15} However, whether this is evident also in subjects without myocardial ischemia or myocardial necrosis has remained elusive. In this study, we demonstrated that increased myocardial sympathetic activity (indicated by increased myocardial MIBG washout) was related to depressed HRV even in subjects without evidence of myocardial ischemia or necrosis.

Myocardial MIBG washout correlated with SDNN, an index of total HRV, which is in line with the concept that MIBG washout reflects sympathetic activity. In addition, myocardial MIBG washout yielded a borderline correlation with LF component ($P = 0.06$) but not with HF component of HRV. According to the current opinion about the physiological interpretation of components of HRV, sympathetic activity contributes to LF component of HRV whereas vagal activity is

Figure 3. Myocardial MIBG washout among subjects with decreased (SDNN ≤ 100 ms) and normal (SDNN > 100 ms) HRV. Abbreviations: SDNN = standard deviation of all normal RR intervals. The values are mean + SD.

considered as the major contributor to HF component of HRV.¹³ This agrees with our finding that myocardial MIBG washout did not correlate with HF component but tended to do so with LF component of HRV.

The physiological basis for VLF has remained elusive.¹³ In our study, VLF component of HRV correlated significantly with myocardial MIBG washout. This finding suggests that, in addition to LF component, also VLF component of HRV includes information about the function of presynaptic sympathetic nerve terminals.

Previously, Morozumi et al. reported an inverse correlation between MIBG uptake of the inferior myocardial region and HF power of HRV based on the short-term recordings.¹⁶ In our study, HRV assessment was based on long-term ECG recordings. HRV variables derived from recordings of different duration provide different information about cardiac autonomic control and therefore cannot be compared with each other.

CONCLUSION

We conclude that cardiac presynaptic sympathetic nervous activity contributes to reduced HRV in subjects without myocardial ischemia or myocardial infarction. In addition, VLF component of HRV includes information about sympathetic nervous modulation of heart rate. These new findings enhance the understanding of the physiological basis of HRV.

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