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Alternating myocardial sympathetic neural function of athlete's heart in professional cycle racers examined with iodine-123-MIBG myocardial scintigraphy

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Myocardial sympathetic neural function in professional athletes who had the long-term tremendous cardiac load has not been fully investigated by myocardial iodine-123-metaiodobenzylguanidine (MIBG) uptake in comparison with power spectral analysis (PSA) in electrocardiography. Eleven male professional cycle racers and age-matched 11 male healthy volunteers were enrolled in this study. The low frequency components in the power spectral density (LF), the high frequency components in the power spectral density (HF), the LF/HF ratio and mean R-R interval were derived from PSA and time-domain analysis of heart rate variability in electrocardiography. The mean heart-to-mediastinum uptake ratio (H/M ratio) of the MIBG uptake, in professional cycle racers was significantly lower than that in healthy volunteers ($p < 0.01$) and HF power in professional cycle racers was significantly higher than that in healthy volunteers ($p < 0.05$). In the group of professional cycle racers, the H/M ratio showed a significant correlation with the R-R interval, as indices of parasympathetic nerve activity ($r = 0.80$, $p < 0.01$), but not with the LF/HF ratio as an index of sympathetic nerve activity. These results may indicate that parasympathetic nerve activity has an effect on MIBG uptake in a cyclist's heart.

Key words: iodine-123-metaiodobenzylguanidine (MIBG), myocardial sympathetic neural function, power spectral analysis (PSA) of heart rate variability, athlete's heart

INTRODUCTION

MYOCARDIAL SYMPATHETIC NEURAL FUNCTION in professional athletes who had a long-term tremendous cardiac load has not been fully investigated. In Japan, there are about one thousand professional cycle racers called "Keirin racers." Their hard training is continued daily for many years. ^{123}I-labeled metaiodobenzylguanidine (MIBG) is widely used to noninvasively assess myocardial sympathetic nerve distribution. The usefulness of MIBG scintigraphy for the assessment of sympathetic neural function and integrity has been reported in patients with myocardial infarction,[1] surgical denervation,[2] hypertrophic myopathies,[3] and congestive heart failure.[4,5] And power spectral analysis (PSA) of heart rate variability is also well established as a clinical estimate of autonomic nerve function. A correlation between myocardial uptake of ^{123}I-MIBG and indices of PSA is reported in healthy subjects and patients with heart failure,[6,7] but few studies on the relationship of myocardial uptake of MIBG and PSA indices in professional athletes have been reported. Professional cycle racers have a hypertrophied left ventricle.[8]

The aim of this study was to assess the myocardial sympathetic neural function in professional cycle racers by measuring the myocardial MIBG uptake and PSA of the heart rate variability.

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MATERIALS AND METHODS

Subjects
Eleven male professional cycle racers and age-matched 11 male healthy volunteers were enrolled in this study (Table 1). The mean age of the professional cycle racers was 39.4 ± 5.5 years and that of the healthy volunteers was 43.0 ± 6.2 years. Experience as professional cycle racers ranged from 10 to 31 yr (mean 19 ± 5 years). They took no medication known to inhibit MIBG myocardial uptake. Informed consent was obtained before the study.

Study protocol
All participants fasted for at least 4 hours before ^{123}I-MIBG scintigraphy, and they stopped their exercise before their examination on the study day.

MIBG scintigraphy was started at 15-min post-injection of MIBG. After the first scan, rest electrocardiography (ECG), echocardiography (UCG) and measurements of body weight, body height and blood pressure were conducted (Fig. 1). To evaluate the autonomic nerve activity, measurement of the plasma catecholamine level and power spectral analysis (PSA) of heart rate variability were also conducted. Delayed myocardial images of MIBG were obtained at 4-hr post-injection.

Scintigraphy
Anterior planar images were taken at 15 minutes and 240 minutes after the injection of 111–148 MBq MIBG (Daiichi Radioisotope Laboratories, Tokyo, Japan). A three-head gamma camera (Prism 3000, Picker, Ohio) with a low-energy general purpose collimator attached was used for imaging with an energy window of 159 keV ± 15%. In the planar studies, each image was recorded for 5 min and the data stored on 128 × 128 image matrices.

Heart rate variability analysis
Spectral heart rate variability indices were computed. The high frequency (0.15–0.40 Hz) components in the power spectral density (HF) as an index of parasympathetic nerve activity, the low frequency (0.05–0.15 Hz) components in the power spectral density (LF) and the LF/HF ratio as indices of sympathetic nerve activity were derived from the PSA. As an index of parasympathetic nerve activity, a mean R-R interval was also derived from the time-domain analysis of heart rate variability.

Echocardiography
Intraventricular septal thickness (IVST), posterior wall thickness (PWT), left ventricular end-systolic dimension (LVDs), left ventricular end-diastolic dimension (LVDd), left ventricular ejection fraction (LVEF), and left ventricular mass (LVM) were estimated with an echocardiogram. Measurements were taken from a parasternal long-axis view in the left decubitus position with transducer placement in the third to fifth intercostal space on echocardiography. LVM was calculated with the following formula.[9]

$$LVM\ (g) = 1.04 \times [(IVST + PWT + LVDd)^3 - LVDd^3] - 13.6.$$

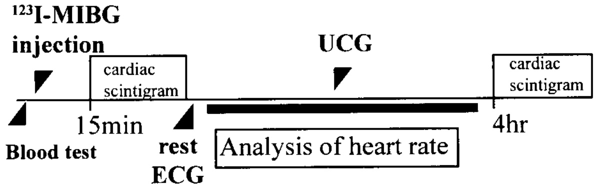

Fig. 1 Protocol. Scintigrams were obtained 15 minutes and 240 minutes after the injection of 111–148 MBq of ^{123}I-MIBG at rest. During the analysis of heart rate, rest electrocardiography and echocardiography were performed. To evaluate the autonomic nerve activity, plasma catecholamine level was also measured.

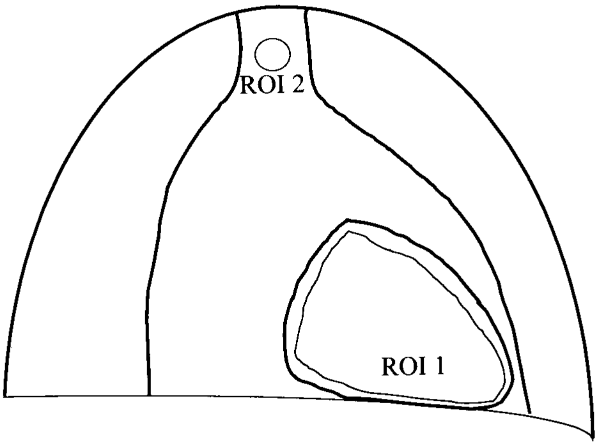

Fig. 2 For the analysis of MIBG accumulation, two regions of interest (ROIs) were defined on planar images (upper mediastinum and heart). Location of ROIs set in anterior planar image. ROI 1 indicates ROI in the heart. ROI 2 indicates ROI in the upper mediastinum.

Image analysis
As indices of myocardial MIBG accumulation, the ratio of MIBG uptake in the heart to that in the upper mediastinum (H/M ratio) on the delayed planar image (Fig. 2) and the decreased counting rate as the washout rate in the heart normalized by the count at 15 minutes after injection were used.

Statistical analysis
The data were reported as the mean ± one standard deviation. Results were analyzed by a Mann-Whitney U test. A p value of less than 0.05 was considered statistically significant.

Table 1 Subjects baseline characteristics

	Professional cycle racers	Healthy volunteers
Number of subject	11	11
Age (yr)	39.4 ± 5.5	43 ± 6.2
Body height (cm)	171.0 ± 4.6	168.5 ± 5.0
Body weight (kg)	75.4 ± 5.8*	63.4 ± 5.6
Systolic blood pressure (mmHg)	123.3 ± 9.5	118.8 ± 15.0
Diastolic blood pressure (mmHg)	74.4 ± 8.1	70.4 ± 12.5
Blood glucose (mg/d*l*)	96.6 ± 11.5*	83.0 ± 5.4
Plasma noradrenaline concentration (ng/m*l*)	0.235 ± 0.087	0.310 ± 0.137
Intraventricular septal thickness (mm)	10.9 ± 1.6*	8.3 ± 0.9
Posterior wall thickness (mm)	10.8 ± 1.5	9.6 ± 1.2
Left ventricular systolic dimension (mm)	32.4 ± 4.7*	26.8 ± 3.4
Left ventricular diastolic dimension (mm)	50.2 ± 2.9*	45.8 ± 2.0
Leftventricular ejection fraction (%)	69.2 ± 9.7	72.4 ± 6.6
Left ventricular mass (g)	228.5 ± 45.2*	156.6 ± 20.6

Values are expressed as mean ± SD. *Significant difference ($p < 0.05$).

Table 2 Time and frequency domain indices of heart rate variability in professional cycle racers and healthy volunteer

	Professional cycle racers	Healthy volunteers
R-R interval (sec)	1.08 ± 0.10*	1.00 ± 0.12
ln LF (ms^2)	6.69 ± 0.54	6.19 ± 0.68
ln HF (ms^2)	6.13 ± 0.64*	5.53 ± 0.68
LF/HF	1.10 ± 0.11	1.13 ± 0.12

Values are expressed as mean ± SD. *Significant difference ($p < 0.05$).

RESULTS

Professional cycle racers (Keirin racers) had increased body weight and increased heart volume. Significant difference between professional cycle racers and healthy volunteers was observed in the body weight, IVST, LVDs, LVDd, and LV mass (Table 1). The mean R-R interval in professional cycle racers was significantly longer than that in healthy volunteers ($p < 0.05$) (Table 2). And HF power in professional cycle racers was significantly higher than that in healthy volunteers ($p < 0.05$) (Table 2). The mean H/M ratio on the planar image obtained at 4-hr post-injection in professional cycle racers was significantly lower than that in healthy volunteers ($p < 0.01$) (Fig. 3A). There was no significant difference between the washout rate of MIBG in professional cycle racers and healthy volunteers (Fig. 3B). The H/M ratios of professional cycle racers showed a significant correlation with the R-R interval ($r = 0.80$, $p < 0.01$) (Fig. 4A), whereas the H/M ratios of healthy volunteer showed no significant correlation with the R-R interval ($r = -0.26$, n.s.) (Fig. 4B).

In all the subjects, the H/M ratios of MIBG showed a significant correlation with the LF power ($r = -0.45$, $p < 0.05$) (Table 3). In the group of professional cycle racers, the washout rate of MIBG showed a significant

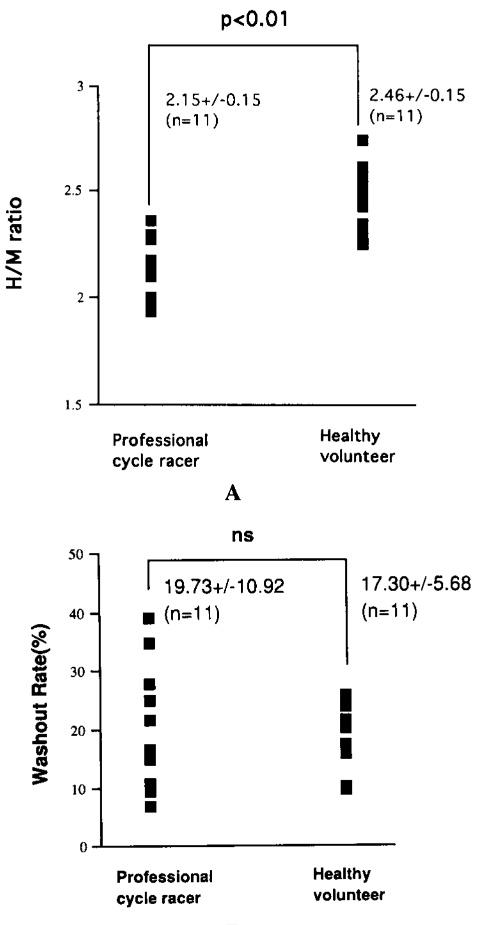

Fig. 3 ^{123}I-MIBG uptake in the heart. Heart to Mediastinum uptake ratio (H/M ratio) at 4-hr post-injection, (A) of ^{123}I-MIBG and washout rate of ^{123}I-MIBG (B) in professional cycle racers and healthy volunteers. The mean H/M ratio in professional cycle racers was significantly lower than that in healthy volunteers ($p < 0.01$). However there was no significant difference of washout rate of ^{123}I-MIBG between professional cycle racers and healthy volunteers.

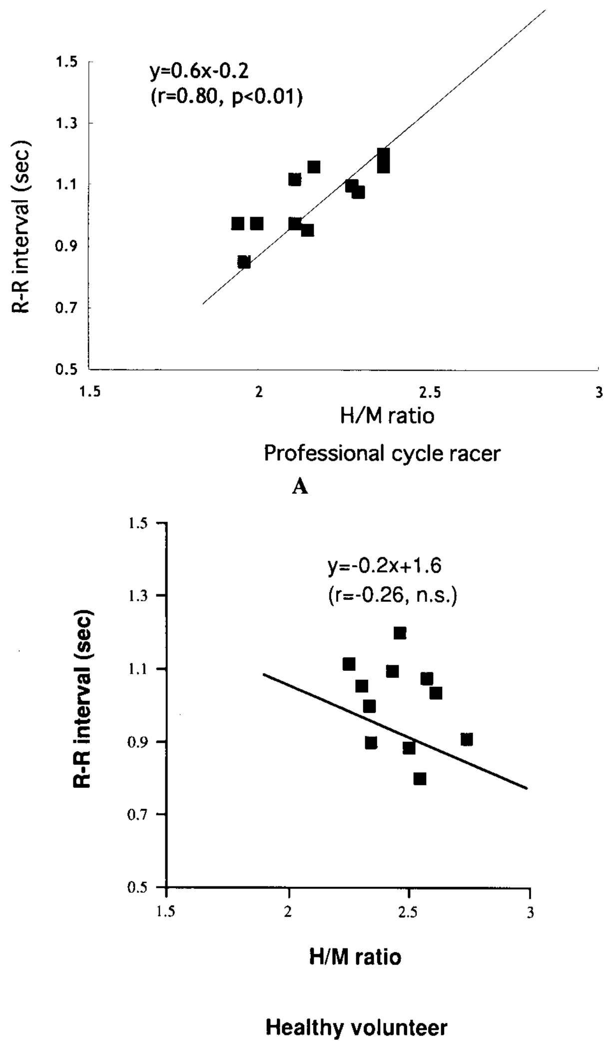

Fig. 4 Relation between ^{123}I-MIBG heart uptake and R-R interval of ECG in professional cycle racers (A) and healthy volunteers (B). The H/M ratios of professional cycle racers showed a significant correlation with R-R interval ($r = 0.80$, $p < 0.01$), while there was no significant correlation in healthy volunteers ($r = -0.26$, n.s.).

correlation with the LF power ($r = -0.60$, $p < 0.05$) (Table 3). But no significant correlation was observed between the LF/HF ratio and indices of myocardial MIBG accumulation in any group (Table 3). No significant correlation was noted between the HF power and indices of myocardial MIBG accumulation in any groups (Table 3).

DISCUSSION

"Athlete's heart" is a term used to describe the cardiovascular effects of long-term conditioning observed in highly trained competitive athletes.[10] As structural features of athlete hearts determined by echocardiography, the IVST, LVDs, LVDd, and LV mass in athletes were greater than those in non-athletes.[8] Echocardiographic assessment

Table 3 Correlation between time and frequency domain indices of heart rate variability and indices of myocardial MIBG accumulation

(Professional cycle racers)	H/M ratio	WR
R-R interval (sec)	0.80*	−0.26
ln LF (ms^2)	−0.03	−0.60*
ln HF (ms^2)	0.47	−0.42
LF/HF	−0.54	−0.02
(Healthy volunteers)	H/M ratio	WR
R-R interval (sec)	−0.26	−0.11
ln LF (ms^2)	−0.54	−0.08
ln HF (ms^2)	−0.14	−0.34
LF/HF	−0.37	0.38
(Whole subjects)	H/Mratio	WR
R-R interval (sec)	−0.11	−0.07
ln LF (ms^2)	−0.45*	−0.24
ln HF (ms^2)	−0.20	−0.24
LF/HF	−0.20	0.08

ln, natural logarithm; H/M ratio, heart to mediastinum uptake ratio of ^{123}I-MIBG; WR, washout rate of ^{123}I-MIBG; HF, high frequency power (> 0.15–0.4 Hz); LF, low frequency power (0.05–0.15 Hz). *Significant correlation ($p < 0.05$).

revealed that professional cycle racers involved in this study have athlete's heart (Table 1).

Iodine-123 labeled MIBG is the analogue of the potent antihypertensive-agent guanethidine sulphate, and has been used to evaluate cardiac sympathetic nervous function.[11–13] The H/M ratio was employed as a semiquantitative index of cardiac MIBG uptake, which was reported to be significantly correlated with the myocardial norepinephrine concentration and left ventricle ejection fraction in patients with idiopathic dilated myocardiopathy.[14] In this study the H/M ratio in professional cycle racers was significantly lower than that of normal volunteers. Augmented plasma catecholamine levels are thought to reduce cardiac MIBG uptake,[15] but there was no difference between the serum norepinephrine levels of professional cycle racers and normal volunteers (Table 1). Therefore it is unlikely that the heart of professional cycle racers was in a condition of augmented sympathetic nerve activity. These results were inconsistent with the previous explanation of regulation of cardiac MIBG uptake in normal volunteers and patients with various heart diseases.[14–17] The possibility of attenuation caused by breast muscle or dilated cardiac cavity still exists, because no attenuation correction of breast muscle or dilated cardiac cavity was performed. In general, the cardiovascular adaptations of athlete's heart include vagotonia. Professional cycle racers involved in this study showed signs of sinus bradycardia based on training vagotony and their HF power was significantly higher than that of normal volunteers. Interestingly, cardiac MIBG uptake in professional cycle racers was closely correlated with indices of parasympathetic nerve activity such as R-R intervals, even if no significant correlation was observed in normal volunteers. These results suggested a contribution of parasympathetic nerve activity to cardiac MIBG uptake in athlete's heart. It has been reported that during parasympathetic stimulation the release of noradrenaline from the sympathetic axon terminals is presynaptically controlled through muscarinic receptors.[18–20] A previous report showed that LF power reflects both sympathetic activity and vagal activity. The LF/HF ratio is considered to mirror sympathovagal balance or to reflect the sympathetic modulation.[21] In this study the LF/HF ratio and the HF power were not significantly correlated with indices of myocardial MIBG accumulation in any group. It is similar to the previous report showing that the frequency domain indices of heart rate variability were not correlated with the left ventricular mass index.[22]

CONCLUSION

In the group of professional cycle racers, H/M MIBG uptake ratio was significantly lower than that in healthy volunteers, HF power was significantly higher than that in healthy volunteers, and the H/M ratio had a close correlation with the mean R-R interval. These results seem to indicate that parasympathetic nerve activity has an influence on MIBG uptake in cyclist's heart.

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