

Effect of exercise-induced activation of sympathetic nerve activity on clearance of ^{123}I -MIBG from the myocardium

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The effect of exercise on the cardiac kinetics of ^{123}I -MIBG was investigated in the present study. ^{123}I -MIBG was administered intravenously at rest in 6 healthy male volunteers, and anterior planar and SPECT images were obtained 15 minutes, and 2 and 4 hours after administration (protocol A). After 4 weeks, ^{123}I -MIBG was again administered intravenously at rest, and images were obtained 15 minutes later. After imaging, the subjects ran 10 km in approximately 1 hour, and anterior planar and SPECT images were obtained 2 and 4 hours after administration of ^{123}I -MIBG (protocol B). The heart-to-mediastinum uptake ratio (H/M) was calculated from each anterior planar image, and the mean ^{123}I -MIBG clearance from 15 minutes to 2 hours, and from 2 hours to 4 hours was calculated with a bull's eye display. The H/M was much lower after exercise. The mean clearance rate between 15 minutes and 2 hours in protocol B was significantly higher than that between 2 hours and 4 hours, and that between 15 minutes and 2 hours in protocol A. It was concluded that the clearance rate of ^{123}I -MIBG may be a useful index of cardiac sympathetic nerve activity.

Key words: ^{123}I -MIBG scintigraphy, exercise, cardiac sympathetic nerve function, clearance rate

INTRODUCTION

CARDIAC SYMPATHETIC NERVE function imaging with ^{123}I -metaiodobenzylguanidine (MIBG) has been useful for evaluating the pathophysiology of various heart diseases¹⁻⁴ and making a prognosis in patients with congestive heart failure.⁵ The clearance rate (washout rate) and heart-to-mediastinum uptake ratio are frequently used as quantitative indices for cardiac sympathetic nerve function in ^{123}I -MIBG myocardial scintigraphy.⁶⁻⁸ Accelerated ^{123}I -MIBG clearance has been reported in various heart diseases, such as dilated cardiomyopathy,^{5,9} hypertrophic cardiomyopathy,^{10,11} hypertension,⁴ ischemic heart disease¹² and valvular heart disease.^{13,14} Although these indices are thought to reflect cardiac sympathetic nerve activity, whether or not the activation of cardiac sym-

thetic nerve activity accelerates ^{123}I -MIBG clearance from the heart in humans remains unclear. In the present study, the effect of exercise that physiologically activates cardiac sympathetic nerve activity on ^{123}I -MIBG clearance was investigated.

MATERIALS AND METHODS

Subjects

The subjects were six healthy male volunteers (average age: 36 ± 5 years). No subjects suffered from hypertension or diabetes and the results of physical examinations, chest X rays, electrocardiography and echocardiography were normal.

^{123}I -MIBG study

At rest 111 MBq of ^{123}I -MIBG [Daiichi Radioisotope Laboratories (Japan); non-carrier-added; specific activity: $45-55 \mu\text{Ci}/\mu\text{g}$] was administered intravenously. Anterior planar and single photon emission computed tomography (SPECT) images were obtained 15 minutes, 2 hours and 4 hours after administration (protocol A). After 4 weeks,

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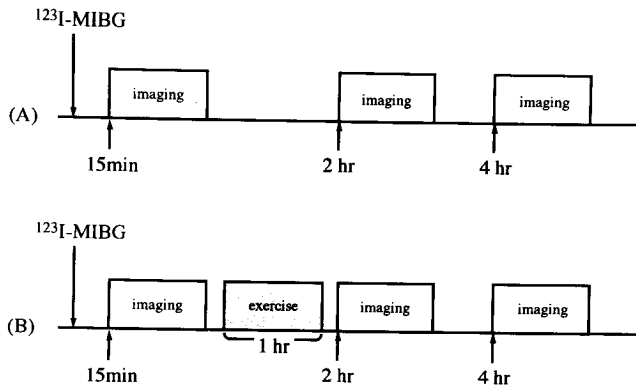


Fig. 1 Schema of ^{123}I -MIBG imaging. ^{123}I -MIBG images were obtained 15 minutes, and 2 and 4 hours after administration (protocol A: upper). ^{123}I -MIBG images were obtained 15 minutes after administration. After imaging, subjects ran 10 km in 1 hour, and images were obtained 2 and 4 hours after administration (protocol B: lower).

111 MBq of ^{123}I -MIBG was again administered intravenously at rest. Anterior planar and SPECT images were obtained 15 minutes later. Immediately after imaging, the subjects ran 10 km in approximately 1 hour, and then anterior planar and SPECT images were obtained 2 and 4 hours after administration (protocol B) (Fig. 1).

We used a Toshiba GCA 901A gamma-camera fitted with a collimator dedicated to ^{123}I with a 20% energy window centered on the 159-keV photon peak of ^{123}I . In the planar studies, each image was obtained for 5 minutes and the data were stored on a 256×256 matrix. In the SPECT studies, projection images were taken for 40 seconds at 6° increments over 180° circular orbits starting 45° from the left posterior oblique projection and ending 45° from the right anterior oblique projection. The images were recorded at a digital resolution of 64×64 matrix. Recordings were made at regions of interest over the left ventricular myocardium and upper mediastinum areas. The heart-to-mediastinum uptake ratio (H/M) was calculated as the average count per pixel in the left ventricular myocardium divided by the average count per pixel in the upper mediastinum and used as an index of myocardial ^{123}I -MIBG uptake from the planar image. Short axis SPECT images (15 minutes, 2 hours and 4 hours) were reconstructed and a bull's-eye polar map was generated from the apical to basal short-axis slices. After correction for the physical decay of ^{123}I , mean ^{123}I -MIBG clearance from the myocardium was calculated as the percent change in activity between 15 minutes and 2 hours and between 2 hours and 4 hours after administration.

Data analysis

All data were expressed as the mean \pm SD. Statistical analyses were performed by repeated measure ANOVA or paired t-test. A p value < 0.05 was considered statistically significant.

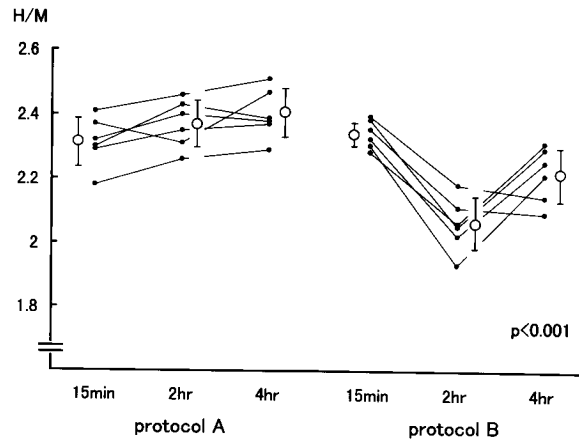


Fig. 2 The heart to mediastinum uptake ratio (H/M) at 15 minutes, 2 hours, and 4 hours in protocols A and B.

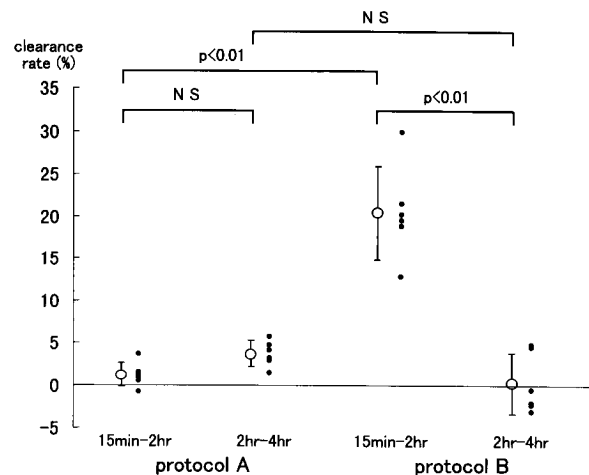


Fig. 3 Clearance rate of ^{123}I -MIBG from 15 minutes to 2 hours, and from 2 hours to 4 hours in protocols A and B.

RESULTS

(1) The H/M 15 minutes, 2 hours and 4 hours after administration in protocol A was 2.31 ± 0.06 , 2.37 ± 0.07 and 2.41 ± 0.08 , respectively. The H/M 15 minutes, 2 hours and 4 hours after administration in protocol B was 2.33 ± 0.04 , 2.06 ± 0.08 and 2.22 ± 0.07 , respectively. The H/M after exercise lowered significantly (Fig. 2).

(2) The mean clearance rates between 15 minutes and 2 hours and between 2 hours and 4 hours after administration in protocol A were $1.2 \pm 1.2\%$ and $3.7 \pm 1.4\%$ respectively, and these values did not significantly differ. The mean clearance rates between 15 minutes and 2 hours and between 2 hours and 4 hours in protocol B were $20.3 \pm 5.6\%$ and $0.2 \pm 3.4\%$, respectively. The mean clearance rate between 15 minutes and 2 hours in protocol B was significantly higher than that between 2 hours and 4 hours. The mean clearance rate between 15 minutes and 2 hours in protocol B was significantly higher than that in protocol A (Fig. 3).

DISCUSSION

¹²³I-MIBG myocardial imaging has been used to evaluate cardiac sympathetic nerve function, and represents a non-invasive method to examine physiological conditions. This imaging has also been suggested to have prognostic value in patients with congestive heart failure.⁵ The clearance rates (washout rates) for early and delayed images and the heart to mediastinum uptake ratio for ¹²³I-MIBG on anterior planar images are frequently utilized as quantitative indices for cardiac sympathetic nerve function.^{4,8,9} Furthermore, these indices are correlated with the severity of diseases such as dilated cardiomyopathy,⁹ hypertrophic cardiomyopathy,^{10,11} mitral stenosis,¹³ aortic regurgitation and mitral regurgitation.¹⁴ As it was reported that myocardial ¹²³I-MIBG uptake was significantly related to the myocardial norepinephrine concentration,¹⁵ decreased myocardial ¹²³I-MIBG uptake in patients with congestive heart failure may reflect exhaustion of intramyocardial norepinephrine. Brush et al.¹⁶ reported that norepinephrine uptake is reduced in the cardiac sympathetic nerve endings of patients with hypertrophic cardiomyopathy, which suggests that the acceleration of ¹²³I-MIBG clearance may reflect the impairment of norepinephrine reuptake in sympathetic nerve endings.

Myocardial ¹²³I-MIBG uptake is thought to be associated with intravesicular components (uptake 1) and extravesicular components (uptake 2) of sympathetic nerve endings.¹⁷ According to Nakajo et al., because the clearance of ¹²⁵I-MIBG from the intravesicular components is slow and that from the extravesicular components is fast,¹⁸ delayed images (consisting mainly of specific accumulation in the sympathetic nerves) are thought to accurately reflect cardiac sympathetic nerve function, but since the specific activity of ¹²³I-MIBG used in Japan is high, early images as well as delayed images may reflect primarily specific accumulation (uptake 1). It was suggested by Dae et al. that the uptake 2 mechanism is not significant in human myocardium, because ¹²³I-MIBG accumulation is not seen in the early images of transplanted hearts.¹⁹ In the present study, the mean clearance rate in healthy individuals between 15 minutes and 4 hours after administration at rest was relatively low, and this agrees with the results of previous studies.⁷ This finding also suggests that the early images of ¹²³I-MIBG primarily consist of uptake 1 and a small quantity of fast-clearing uptake 2.

The objective of the present study was to investigate the effect of activation of the cardiac sympathetic nerve on ¹²³I-MIBG clearance, but because no physiological methods that selectively activate the sympathetic nerve in the human heart exist, subjects were asked to run for 1 hour. The results of the H/M and clearance rate in protocols A and B demonstrated that clearance of ¹²³I-MIBG that was accumulated in the myocardium following intravenous injection at rest was accelerated by exercise. Although

¹²³I-MIBG behaves in a similar manner to norepinephrine, it is not metabolized by catechol-O-methyl transferase or monoamine oxidase and does not act as a transmitter to the postsynaptic receptor. Therefore, the acceleration of ¹²³I-MIBG clearance was thought to be the result of both release and reuptake. If the early images primarily reflect uptake 1, then the result of both release and reuptake of ¹²³I-MIBG in cardiac sympathetic nerve endings is thought to be accelerated by exercise. Recent advances in micro-neurography that have enabled direct observation of sympathetic nerve activity during exercise in humans, have confirmed the acceleration of sympathetic nerve activity during exercise.²⁰ Although no direct evidence of accelerated cardiac sympathetic nerve activity due to exercise has been reported, other findings such as increases in heart rate and cardiac contractility during exercise support the hypothesis that cardiac sympathetic nerve activity is accelerated by exercise. Consequently, the acceleration of ¹²³I-MIBG clearance from the myocardium during exercise is thought to reflect an acceleration in the release of ¹²³I-MIBG from storage vesicles in sympathetic nerve endings caused by the activation of the cardiac sympathetic nerves. Although the plasma concentration of catecholamines was not measured in the present study, Nakajo et al.²¹ found an inverse relationship between the accumulation of ¹³¹I-MIBG in the heart and the plasma concentration of catecholamines, suggesting competitive uptake of MIBG by the heart and circulating catecholamines. Future research should focus on the plasma concentration of catecholamines during exercise and assessing the effects of exogenous administration of norepinephrine on ¹²³I-MIBG clearance.

The results of the present study demonstrated that the clearance of ¹²³I-MIBG from the myocardium is accelerated by exercise and that the clearance rate of ¹²³I-MIBG may be a useful marker of cardiac sympathetic nerve activity.

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