

Washout rate of ^{123}I -metaiodobenzylguanidine increased by posture change or exercise in normal volunteers

Takashi YANO, Hiroshi YAMABE and Mitsuhiro YOKOYAMA

First Department of Internal Medicine, Kobe University School of Medicine

^{123}I -metaiodobenzylguanidine (MIBG) imaging detects sympathetic nerve function in the heart. The present study was conducted to clarify whether posture change or exercise affects ^{123}I -MIBG kinetics in normal volunteers. Seven subjects underwent three ^{123}I -MIBG studies, i.e., supine protocol, sitting protocol and exercise protocol. Planar ^{123}I -MIBG images were obtained at 15 minutes, 1 hour and 4 hours after injection of ^{123}I -MIBG. The washout rate (WR) from 15 minutes to 1 hour in the supine position in all subjects was similar for all three protocols, whereas the WR from 1 hour to 4 hours was significantly augmented in the sitting protocol and the exercise protocol as compared to the supine protocol ($p < 0.05$ and $p < 0.01$). The serum concentration of noradrenaline was significantly increased from the baseline to the 4 hour sampling in the sitting protocol and the exercise protocol (both $p < 0.01$), but was not altered in the supine protocol. The WR from 1 hour to 4 hours significantly correlated with the noradrenaline concentration in 4 hour sampling ($r = 0.59$, $p < 0.01$). It also significantly correlated with an increase in the noradrenaline concentration from the baseline to the 4 hour sampling ($r = 0.53$, $p < 0.05$). It is concluded that posture change or exercise affects the WR of ^{123}I -MIBG in normal healthy subjects.

Key words: sympathetic nerve, upright position, supine position, noradrenaline

INTRODUCTION

THERE IS INCREASING EVIDENCE that ^{123}I -MIBG scintigraphy detects cardiac sympathetic function in various heart diseases.¹⁻⁴ Sympathetic activation is linked to the severity of heart failure and indicates the patients' prognosis.^{5,6} ^{123}I -MIBG scintigraphy is useful in evaluating patients with heart failure.⁷⁻¹⁰ But no attention has been paid to posture or physical activity during ^{123}I -MIBG scintigraphy, in spite of the fact that posture change or exercise affects the activity of autonomic nerves.^{11,12} It is important to clarify whether posture change or exercise alters ^{123}I -MIBG kinetics or not. The present study was conducted with normal volunteers.

Received September 9, 1998, revision accepted January 11, 1999.

For reprint contact: Takashi Yano, M.D., Department of Internal Medicine, Shinko Kakogawa Hospital, 797-295, Isshiki, Kakogawa-cho, Kakogawa 675-0115, JAPAN.

MATERIALS AND METHODS

Subjects

Seven healthy volunteers were studied. All were males. Their age was 29 to 44 years (36 ± 5 years). None of them had any symptoms of cardiac disease, coronary risk factors, or taking medicines. The purpose and details of the study were explained, and informed consent was obtained from each subject. The study protocol was approved by the Institutional Research Committee of the Kobe University School of Medicine.

Study Design

All subjects underwent three study protocols in random order: supine, sitting and exercise protocols. Figure 1 shows an outline of the protocols. In the supine protocol, subjects were in the supine position throughout the examination. They strictly maintained the supine position except when they went to the toilet. ^{123}I -MIBG images were obtained at 15 minutes, 1 hour and 4 hours after the injection. In the sitting protocol, the subjects were in the

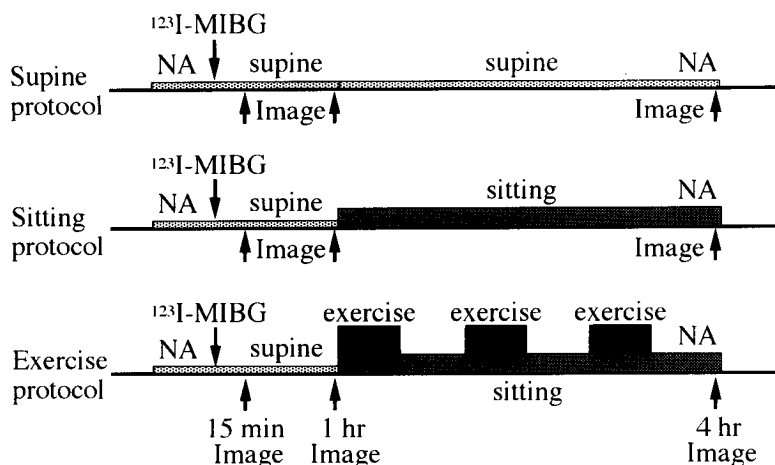


Fig. 1 Study protocol. All subjects underwent three protocols at random order. Detail was described in the manuscript.

Table 1 Results of the ^{123}I -MIBG scintigraphy and serum noradrenaline

	H/M			WR (%)			Noradrenaline (pg/ml)	
	15 min	1 hr	4 hr	15 min-1 hour	1 hour-4 hour	15 min-4 hour	Before	4 hours
Supine protocol	1.84 ± 0.08	1.95 ± 0.10	2.14 ± 0.09	2.63 ± 4.48	15.97 ± 4.59	18.17 ± 6.04	180 ± 30	172 ± 52
Sitting protocol	1.84 ± 0.14	2.00 ± 0.13	2.17 ± 0.13	1.80 ± 5.98	20.44 ± 3.71*	21.88 ± 5.84	216 ± 73	414 ± 166 [†]
Exercise protocol	1.87 ± 0.12	1.98 ± 0.14	2.07 ± 0.16	3.30 ± 4.37	23.80 ± 2.73**	26.25 ± 5.34*	187 ± 72	541 ± 117 [†]

H/M = heart/mediastinum ratio, WR = washout rate, * $p < 0.05$, ** $p < 0.01$ versus supine protocol, [†] $p < 0.01$ versus supine protocol

supine position before injection of ^{123}I -MIBG until the imaging 1 hours later, then they were in the sitting position until the imaging at 4 hours. In this protocol, patients did not leave the chair except when they went to the toilet. In the exercise protocol, the subjects were in the supine position before the injection of ^{123}I -MIBG until the imaging at 1 hour, then they exercised intermittently three times for 30 minutes and rested in the sitting position at intervals. The subjects underwent a bicycle exercise on an electrically braked instrument (Colival-400, Load Co. Ltd., Holland). The exercise load was set to maintain the heart rate at 120 beats per minute in each subject. None of the protocol subjects took meals. Blood sampling for measurement of serum noradrenaline was performed through an indwelling catheter before the injection of ^{123}I -MIBG and before 4 hour imaging. Noradrenaline was measured with a fully automated catecholamine analyzer (HLC, Toso Co. Ltd., Japan).

^{123}I -MIBG Scintigraphy

Potassium iodide (300 mg daily) was given orally to block the uptake of ^{123}I -MIBG by the thyroid gland on the day before the ^{123}I -MIBG injection. Each subject was given 111 MBq ^{123}I -MIBG via an antecubital vein in the supine position in all protocols. Anterior planar cardiac images were acquired 15 minutes (15 minute image), 1 hour (1 hour image) and 4 hours (4 hour image) post-injection with a standard field gamma camera equipped with a medium energy collimator. The energy window was set at 159 keV ± 20%. Data acquisition time was 5 minutes for

each imaging in the supine condition. All data were recorded by a computer (Scintipac 2400, Shimadzu Medical System, Japan) for display and quantitative analysis. The analysis was performed with raw data. The myocardial ^{123}I -MIBG uptake and washout rate (WR) were measured as follows. Regions of interest delineating the upper mediastinum and global heart were selected. The size of the region of interest on the mediastinum was 5 × 5 pixels with a 64 × 64 matrix size. Myocardial uptake was assessed by calculating the heart/mediastinum count ratio (H/M ratio), defined as (the global heart counts per pixel)/(the mediastinum counts per pixel). The WR was calculated as, for example that from 15 minutes to 1 hour, {(15 minute heart counts - 15 minute mediastinum counts) - (1 hour heart counts - 1 hour mediastinum counts)} / (15 minute heart counts - 15 minute mediastinum counts). WR (1 hour to 4 hours) and WR (15 minutes to 4 hours) were calculated in a similar manner. The decay correction of ^{123}I was not accounted for.

Statistical Analysis

The difference between protocols in parameters was analyzed by paired t-test. A p value less than 0.05 was regarded as significant.

RESULTS

Results of ^{123}I -MIBG Analysis

Table 1 shows a summary of the results. There were no significant differences among the three protocols in the H/

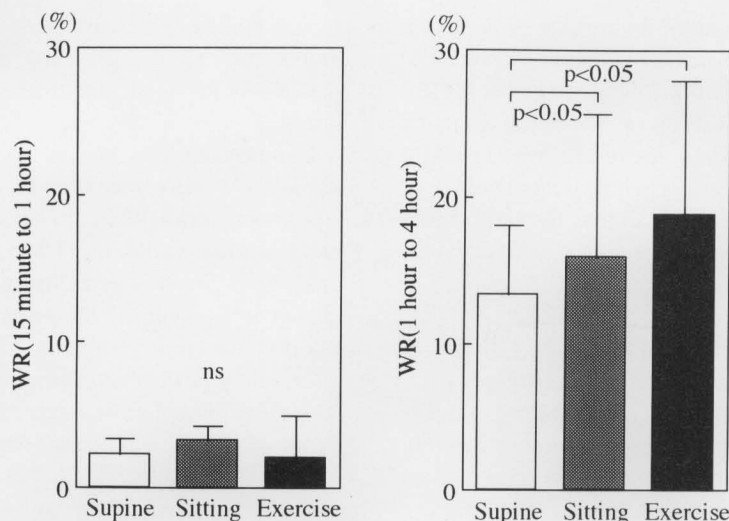


Fig. 2 Comparison of WRs of ^{123}I -MIBG between protocols. The left panel shows WRs (15 min to 1 hr) in three protocols. There was no significant differences among three protocols. The right panel shows WRs (1 hr to 4 hr). Those of the sitting protocol and the exercise protocol were significantly faster than that of the supine protocol ($p < 0.05$ and $p < 0.01$).

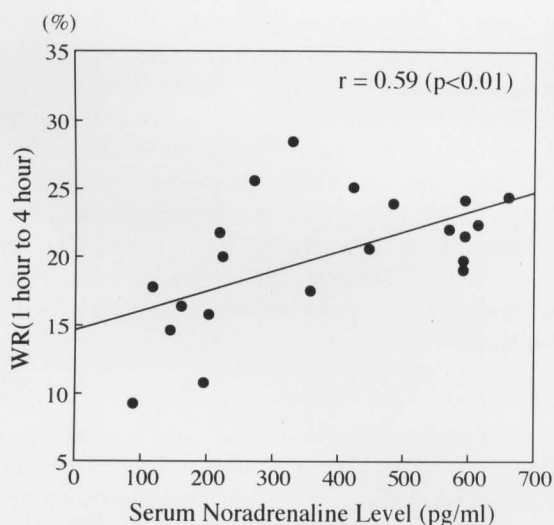


Fig. 3 Correlation between WR (1 hr to 4 hr) and the serum noradrenaline concentration at 4 hr. ^{123}I -MIBG WR from 1 hour to 4 hour significantly correlated with serum noradrenaline concentration at 4 hour sampling ($r = 0.59$, $p < 0.01$).

M ratios of all the 15 minute, 1 hour and 4 hour images (Table 1). The WR (15 minute to 1 hour) was similar for all three protocols, but the WRs (1 hour to 4 hours) in the sitting protocol and the exercise protocol were significantly greater than in the supine protocol ($p < 0.05$ and $p < 0.01$), as shown in Figure 2. Similarly, the WR (15 minutes to 4 hours) in the sitting protocol and the exercise protocol were also significantly greater than in the supine protocol ($p < 0.05$ and $p < 0.01$).

Quantitative analysis was also employed for the upper mediastinum counts. The WR of the upper mediastinum

was significantly faster than that of the myocardium ($p < 0.001$). Among the three protocols the WRs of the upper mediastinum were not significantly different, but the WR (1 hr to 4 hr) increased from the supine to the sitting, and to the exercise protocol, though it was not significant ($36.13 \pm 2.92\%$ vs. $37.55 \pm 4.26\%$ vs. $39.50 \pm 3.22\%$, $p = 0.09$: supine vs. exercise).

Change in Serum Noradrenaline Concentration

In the supine protocol, the serum concentration of noradrenaline did not significantly change from the baseline to the sampling at 4 hours (Table 1), but in the sitting protocol and the exercise protocol, the serum concentration of noradrenaline was significantly increased from the baseline to the sampling at 4 hours (both $p < 0.01$).

Correlation of ^{123}I -MIBG with Noradrenaline

The serum noradrenaline concentration at the baseline did not significantly correlate with any parameters of ^{123}I -MIBG analysis, but the serum noradrenaline concentration at 4 hour sampling significantly correlated with WR (1 hour to 4 hours) of ^{123}I -MIBG ($r = 0.59$, $p < 0.01$) as shown in Figure 3. In addition, the increase in the serum noradrenaline concentration from the baseline to the sampling at 4 hours also significantly correlated with the WR (1 hour to 4 hours) of ^{123}I -MIBG ($r = 0.53$, $p < 0.05$).

DISCUSSION

The present study demonstrated that the WR of ^{123}I -MIBG scintigraphy was significantly altered by a transient sympathetic activation caused by posture change or exercise in normal healthy subjects.

^{123}I -MIBG scintigraphy is a very useful method for

detecting the functional state of the cardiac sympathetic nerve in heart diseases, but the characteristics of ^{123}I -MIBG in physiological conditions has not been fully investigated. In the present study, we hypothesized that a transient change in autonomic nerve activity caused by posture change or exercise affects a quantitative marker of ^{123}I -MIBG scintigraphy. To elucidate the hypothesis healthy volunteers were enrolled, and WR analysis based on planar ^{123}I -MIBG images obtained at 15 minutes, 1 hour and 4 hours was employed.

The kinetics of ^{123}I -MIBG at nerve endings is similar to that of noradrenaline, but ^{123}I -MIBG is different from noradrenaline as to degradation by monoamine oxidase or catechol-*o*-methyltransferase. Noradrenaline is actively transported into nerve endings by an uptake-1 mechanism and stays in the storage vesicles. After release via exocytosis rapid re-uptake happens. Such kinetics suggests that a scintigraphically documented cardiac ^{123}I -MIBG uptake reflects the density of sympathetic nerve endings and the amount of noradrenaline in them.¹³ On the other hand, spillover of noradrenaline from the nerve endings is determined by the release and reuptake rate.^{14,15} Noradrenaline release is augmented by sympathetic activation, and the re-uptake rate is high in normal subjects.^{14,16,17} Since the WR of ^{123}I -MIBG is analogous to noradrenaline spillover, it is a function of sympathetic activation in normal subjects. A change in the physiological state induced by a posture change or by exercise can cause sympathetic activation. Studies of heart rate variation have shown that a low/high ratio of spectral power is related to sympathetic/parasympathetic balance during upright tilt,^{11,12} but there has been no evidence that such a physiological change can alter the kinetics of ^{123}I -MIBG.

In our study, the WR of ^{123}I -MIBG from 15 minutes to 1 hour in which period the subjects were in the supine position in all protocols did not differ among the three protocols, whereas the WRs at from 1 hour to 4 hours of the sitting protocol and the exercise protocol were significantly faster than that of the supine protocol. In this period; from 1 hour to 4 hours, the subjects were in the supine position, the sitting position or performed intermittent exercises. The latter two procedures caused a significant increase in the serum level of noradrenaline measured at the 4 hour sampling. In addition, the WR (1 hour to 4 hour) significantly correlated with the serum level of noradrenaline at the 4 hour sampling and also with its increase from baseline. These results suggested that a posture change from the supine position to the sitting position or exercise activated the sympathetic nerve, and they augmented the WR of ^{123}I -MIBG simultaneously. There was no difference between supine protocol and other protocols in the H/M ratio of the 4 hour imaging. This was unexpected because an increased WR could result in a reduced ^{123}I -MIBG accumulation in the 4 hour image. The WR of upper mediastinum, a background

factor, tended to increase from the supine to the sitting, and to the exercise protocol. This may be one of the reasons for no significant difference in the H/M ratio at 4 hours.

Sympathetic activity can be evaluated by heart rate variation.¹⁸ There have been several reports supporting a significant correlation between ^{123}I -MIBG scintigraphy and heart rate variation.²⁻⁴ The low/high ratio in power analysis is changed by an upright tilt, which suggests a change in the sympathetic/parasympathetic balance,^{11,12} but it is not known whether ^{123}I -MIBG scintigraphy is affected by posture change or exercise. An increase in serum noradrenaline, a marker of activated sympathetic nerve, was significantly correlated with the WR of ^{123}I -MIBG in our results. The WR of ^{123}I -MIBG is an integration of ^{123}I -MIBG release and faulty re-uptake at nerve endings. It means a spillover into blood, because ^{123}I -MIBG is not degraded by monoamine oxidase or catechol-*o*-methyltransferase. [^3H]-labeled noradrenaline studies^{14,15} have suggested that re-uptake of noradrenaline is decreased in patients with heart failure compared to normal controls, which agrees with an increased WR of ^{123}I -MIBG in patients with heart failure.¹ During exercise, noradrenaline spillover is reported to increase in normal humans,¹⁹ which agrees with our results. A variety of ^{123}I -MIBG findings have been reported in normal subjects. Age, gender and hypoxia are factors modifying ^{123}I -MIBG kinetics.²⁰⁻²⁴ Morozumi et al.²¹ demonstrated that ^{123}I -MIBG accumulation can be abnormal in normal volunteers and is corrected by alpha-2 agonist. This report suggests the ^{123}I -MIBG kinetics is a function of physiological states even in normal subjects and agrees with the findings of our study.

Study Limitation

In the present study we did not analyze the regional kinetics of ^{123}I -MIBG. It is well known that the inferoposterior region has less ^{123}I -MIBG uptake than the anterior region. A report on heart rate variation suggested that the ^{123}I -MIBG in the inferior wall is more likely to reflect parasympathetic activity than sympathetic activity.² Parasympathetic withdrawal may be the first step in a reaction to posture change or exercise. The regional ^{123}I -MIBG kinetics and comparison with heart rate variation remains an unsolved issue in our study.

Clinical Implication

Quantitative analysis of ^{123}I -MIBG kinetics has been reported to be a valuable marker in determining the prognosis of patients with heart failure.^{9,10} It has never been noticed to control posture and a physical activity during examination, so that the reported quantitative analysis values possibly included a variation caused by physical activity during examination. Patients with heart failure have an augmented noradrenaline spillover,¹⁴ which may cause an unexpectedly fast washout of ^{123}I -

MIBG under active conditions of a patient. We therefore propose to keep the posture being supine during examination. Controlling the posture and patient's activity promises more validity in ^{123}I -MIBG scintigraphy.

CONCLUSION

The WR of ^{123}I -MIBG is fastened by upright posture or exercise in normal healthy subjects. It is important to control the patient's posture and activity in ^{123}I -MIBG scintigraphy.

REFERENCES

1. Merlet P, Valette H, Dubois Rande JL, Mardon K, Pouillart F, Bourachot ML, et al. Iodine 123-labeled metaiodobenzylguanidine imaging in heart disease. *J Nucl Cardiol* 1: S79–85, 1994.
2. Morozumi T, Kusuoka H, Fukuchi K, Tani A, Uehara T, Matsuda S, et al. Myocardial iodine-123-metaiodobenzylguanidine images and autonomic nerve activity in normal subjects. *J Nucl Med* 38: 49–52, 1997.
3. Somsen GA, Szabo BM, VanVeldhuisen DJ, DeMilliano PA, DeGroot CA, Lie KI. Comparison between iodine ^{123}I metaiodobenzylguanidine scintigraphy and heart rate variability for the assessment of cardiac sympathetic activity in mild to moderate heart failure. *Am Heart J* 134: 456–458, 1997.
4. Merata K, Sumida Y, Murashima S, Matsumura K, Takeda H, Nakagawa T, et al. A novel method for the assessment of autonomic neuropathy in type 2 diabetic patients; a comparative evaluation of ^{123}I -MIBG myocardial scintigraphy and power spectral analysis of heart rate variability. *Diabet Med* 13: 266–272, 1996.
5. Zucker IH, Wang W, Brandle M, Schultz HD, Patel KP. Neural regulation of sympathetic nerve activity in heart failure. *Prog Cardiovasc Dis* 37: 397–414, 1995.
6. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 79: 1645–1650, 1997.
7. Imamura Y, Ando H, Mitsuoka W, Egashira S, Masaki H, Ashihara T, et al. Iodine-123 metaiodobenzylguanidine images reflect intense myocardial adrenergic nervous activity in congestive heart failure independent of underlying cause. *J Am Coll Cardiol* 26: 1594–1599, 1995.
8. Morozumi T, Ishida Y, Tani A, Sato H, Matsuyama T, Ozaki H, et al. Clinical significance of I-123 MIBG myocardial scintigraphy for evaluating the severity of congestive heart failure. *KAKU IGAKU (Jpn J Nucl Med)* 28: 271–280, 1991. (abstract in English)
9. Suzuki Y, Toyama T, Kanda T, Tsukagoshi J, Isobe N, Nagaoka H, et al. Prognostic significance of ^{123}I -metaiodobenzylguanidine scintigraphy in dilated cardiomyopathy. *KAKU IGAKU (Jpn J Nucl Med)* 32: 1207–1215, 1995. (abstract in English)
10. Merlet P, Valette H, Dubois Rande JL, Moysse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 33: 471–477, 1992.
11. Malliani A, Pagani M, Furlan R, Guzzetti S, Lucini D, Montano N, et al. Individual recognition by heart rate variability of two different autonomic profiles related to posture. *Circulation* 96: 4143–4145, 1997.
12. Saeki Y, Atogami F, Takahashi K, Yoshizawa T. Reflex control of autonomic function induced by posture change during the menstrual cycle. *J Auton Nerv Syst* 66: 69–74, 1997.
13. Schofer J, Spielmann R, Schuchert A, Weber K, Schluter M. Iodine-123 metaiodobenzylguanidine scintigraphy: a noninvasive method to demonstrate myocardial adrenergic nervous system disintegrity in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 12: 1252–1258, 1988.
14. Eisenhofer G, Friberg P, Rundqvist B, Quyyumi AA, Lambert G, Kaye DM, et al. Cardiac sympathetic function in congestive heart failure. *Circulation* 93: 1667–1676, 1996.
15. Bohm M, La Rosée K, Schinger RH, Erdmann E. Evidence for reduction of norepinephrine uptake sites in the failing human heart. *J Am Coll Cardiol* 25: 146–153, 1995.
16. Meredith IT, Eisenhofer G, Lambert GW, Dewar EM, Jennings GL, Esler MD. Cardiac sympathetic nervous activity in congestive heart failure. Evidence for increased neuronal norepinephrine release and preserved neuronal uptake. *Circulation* 88: 136–145, 1993.
17. Leuenberger U, Kenney G, Davis D, Clemson B, Zelis R. Comparison of norepinephrine and isoproterenol clearance in congestive heart failure. *Am J Physiol* 263: H56–60, 1992.
18. Ahmed MW, Kadish AH, Parker MA, Goldberger JJ. Effect of physiologic and pharmacologic adrenergic stimulation on heart rate variability. *J Am Coll Cardiol* 24: 1082–1090, 1994.
19. Rundqvist B, Eisenhofer G, Elm M, Friberg P. Attenuated cardiac sympathetic responsiveness during dynamic exercise in patients with heart failure. *Circulation* 95: 940–945, 1997.
20. Estorch M, Carrio I, Berna L, Lopez PJ, Torres G. Myocardial iodine-labeled metaiodobenzylguanidine 123 uptake relates to age. *J Nucl Cardiol* 2: 126–132, 1995.
21. Morozumi T, Fukuchi K, Uehara T, Kusuoka H, Hori M, Nishimura T. Abnormal iodine-123-MIBG images in healthy volunteers. *J Nucl Med* 37: 1686–1688, 1996.
22. Tsuchimochi S, Tamaki N, Tadamura E, Kawamoto M, Fujita T, Yonekura Y, et al. Age and gender differences in normal myocardial adrenergic neuronal function evaluated by iodine-123-MIBG imaging. *J Nucl Med* 36: 969–974, 1995.
23. Tsuchimochi S, Tamaki N, Shirakawa S, Fujita T, Yonekura Y, Konishi J, et al. Evaluation of myocardial distribution of iodine-123 labeled metaiodobenzylguanidine in normal subjects. *KAKU IGAKU (Jpn J Nucl Med)* 31: 257–264, 1994. (abstract in English)
24. Richalet JP, Merlet P, Bourguignon M, Le Trong JL, Keromes A, Rathat C, et al. MIBG scintigraphic assessment of cardiac adrenergic activity in response to altitude hypoxia. *J Nucl Med* 31: 34–37, 1990.