Abnormal Iodine-123-MIBG Images in Healthy Volunteers

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We have encountered two healthy volunteers with significant reductions of myocardial [^{123}I]MIBG (metaiodobenzylguanidine) uptake and rapid clearance. In one of these subjects (a 31-yr-old man), we performed additional examinations to clarify the mechanism of the abnormal myocardial MIBG uptake. There was no abnormality on orthostatic test, maximal exercise test (bicycle ergometer) or in plasma norepinephrine concentration. Nevertheless, power spectral analysis (PSA) of heart rate variability revealed that the percent low frequency component (%LF), an index of sympathetic nerve activity, was increased. Furthermore, [^{123}I]MIBG scintigraphy after oral administration of an α_2 agonist (guanabenz acetate; 4 mg) demonstrated that myocardial uptake and clearance of MIBG returned to normal, as did the %LF. These results suggest that reduced uptake and rapid clearance of myocardial MIBG in this subject was strongly related to the increased release of norepinephrine from sympathetic nerve terminals due to augmented sympathetic activity. This subject illustrated that unsuspected, subclinical variants of normal or abnormal sympathetic functions may pose a diagnostic pitfall in interpretating myocardial MIBG images.

Key Words: iodine-123-MIBG; sympathetic nerve activity; α_2 receptor blocker

J Nucl Med 1996; 37:1686–1688

Iodine-123-MIBG scintigraphy has been widely used to assess myocardial sympathetic nerve distribution and function (*1–4*). We studied MIBG images in normal volunteers to establish the range and variability of these images. Iodine-123-MIBG scintigraphy was performed in 15 normal volunteers, and we observed two subjects with reduced myocardial MIBG uptake and rapid clearance. In one subject, we performed additional examinations to evaluate the origin of these image abnormalities.

CASE REPORT

Iodine-123-MIBG scintigraphy was performed in a 31-yr-old male volunteer with no past medical history. Anterior planar images were acquired using a three-headed gamma camera at four time points: 15, 60, 110 and 240 min after intravenous injection of [^{123}I]MIBG (145 MBq). Image acquisition time was 300 sec. Power spectral analysis (PSA) of heart rate variability was performed simultaneously, with image acquisition at 15 min postinjection to evaluate autonomic nerve activity; %LF, a percentage of the power spectral density of low-frequency component (0.05–0.15 c/b), and HF, the power spectral density of high-frequency component (0.15–0.4 c/b), were calculated as indices of sympathetic nerve activity and parasympathetic nerve activity, respectively (*5*).

There were marked differences between the MIBG images in this subject (Fig. 1B) when compared with the other normal volunteer (Fig. 1A). Specifically, in contrast to other subjects, there was disproportionately higher washout of tracer from the heart relative to the lungs.

When corrected for the injected dose, there were no differences between the time course of mean radionuclide counts of this subject and those of 1 of 13 normal volunteers in the upper mediastinum, liver and lung as defined by regions of interest (Fig. 2). However, myocardial MIBG accumulation was severely depressed and disappeared rapidly in this subject. The washout rate from the heart (calculated as the percentage of the radionuclide counts at 240 min compared with 15 min postinjection) was high (55.1%) compared with that in the remaining 13 normal volunteers (32.4% ± 5.4%; mean ± s.d.). The washout rates in the upper mediastinum and the liver were also higher than those in normals. The %LF in the first examination was 77.4%, indicating augmented sympathetic nerve activity (Fig. 3). The HF value was 359 msec^2.

Laboratory examination revealed no significant abnormalities relating to diabetes mellitus or renal dysfunction. No drugs were administered that might affect myocardial MIBG uptake. Additional examinations, including chest radiograph, echocardiography,

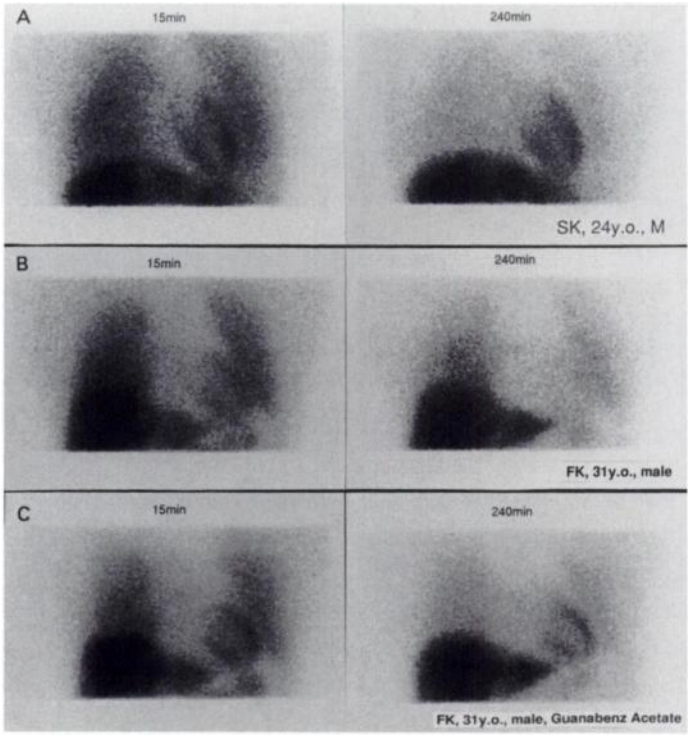

FIGURE 1. Iodine-123-MIBG scintigraphy in one normal volunteer and in a healthy 31-yr-old man. (A) Planar (anterior) images at 15 and 240 min postinjection in a normal volunteer. Myocardial uptake is distinct from the lung in the 15-min image (left panel) and appears more pronounced at 240 min (right panel). (B) Comparison images in our 31-yr-old male subject. Myocardial activity is low at 15 min with faster washout. (C) Images postadministration of the α_2 agonist.

Received Aug. 24, 1995; revision accepted Dec. 28, 1995.
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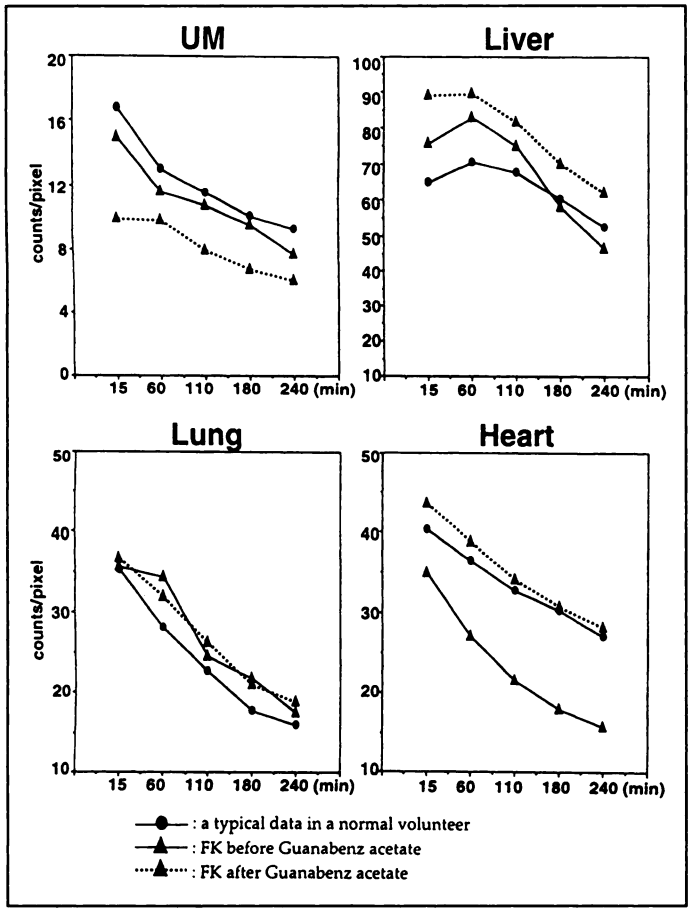

FIGURE 2. Mean radionuclide counts obtained 240 min postinjection in one normal volunteer and in our 31-yr-old subject. Activity in the upper mediastinum (UM), lung, liver and heart was shown. Solid line and dotted line with triangles represent activity in the subject before and after administration of the α_2 agonist. Solid line with circles represents typical time course in the normal volunteer shown in Figure 1A.

electrocardiogram at rest and symptom-limited maximal exercise test by bicycle ergometer, showed no abnormalities. Epinephrine, norepinephrine, dopamine and renin activity in plasma levels measured at baseline and at peak exercise during exercise testing were all within normal limits. Heart rate and blood pressure response in orthostatic tests were also within normal limits.

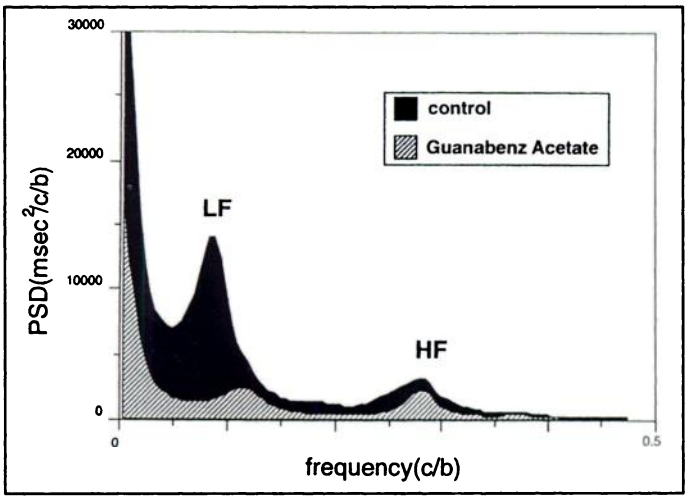

FIGURE 3. Power spectral density (PSD) curve of heart rate variability performed in our 31-yr-old subject. Low frequency (LF) and high frequency (HF) components are shown. The %LF at baseline was abnormally high (77.4%) and returned to normal levels (14.4%) after guanabenz administration.

To elucidate the mechanism of abnormalities in this subject, we repeated MIBG scintigraphy after a single oral administration of the α_2 agonist, guanabenz acetate (4 mg) (*6*). Guanabenz changed blood pressure and heart rate from 126/84 mmHg and 68 bpm to 110/50 mmHg and 55 bpm, respectively. Myocardial MIBG uptake increased, and its washout rate decreased (Figs. 1C, 2), coupled with a reduction of %LF to 14.4% (Fig. 3). These results suggest that the abnormalities in the MIBG images may be caused by the activation of sympathetic nerve activity and not by denervation or a disturbance in the uptake at nerve terminals.

DISCUSSION

Abnormalities in myocardial MIBG images have been reported in subjects with various diseases since the development of [^{123}I]MIBG, which accumulates in myocardial sympathetic nerve terminals (*7–10*). We performed MIBG scintigraphy in 15 healthy volunteers to obtain the normal range in MIBG images and encountered two subjects with decreased myocardial accumulation of MIBG and rapid washout. We performed further evaluations of the autonomic nervous system in one of the subjects. In that subject, %LF, an index of sympathetic nerve activity, was quite high compared with other normal volunteers, and administration of an α_2 agonist, which inhibits the release of norepinephrine from myocardial sympathetic nerve terminals, normalized almost completely myocardial MIBG accumulation and washout as well as the %LF. These results suggest that decreased myocardial MIBG accumulation was associated with augmented myocardial sympathetic nerve activity. Nevertheless, there were no abnormalities in other tests of autonomic nerve function.

Three mechanisms can be proposed for the poor myocardial MIBG accumulation. The first is denervation due to loss of sympathetic nerve terminals, including central nerve disease. However, this was not supported since the orthostatic test and maximal exercise test were normal. Moreover, other tests for general disorders, including congestive heart failure or diabetes mellitus, showed no abnormalities. The changes in the MIBG images after administration of an α_2 agonist also weighed against this mechanism. The second mechanism is dysfunction of the norepinephrine reuptake pathway consisting of uptake-1 and norepinephrine storage vesicles. The changes in MIBG images after administration of an α_2 agonist demonstrated that there was no complete loss in uptake function of MIBG into sympathetic nerve terminals, but an incomplete loss of the function may relate to poor myocardial accumulation of MIBG. The third mechanism is activation of sympathetic nerve function. This was strongly supported by the PSA results and changes in the MIBG images after administration of an α_2 agonist. However, we propose that the increase in sympathetic nerve activity may be mild since other tests of sympathetic activity showed no abnormalities.

Other published studies of MIBG uptake in normal subjects have not reported this phenomenon (*11,12*). Our subject demonstrates that unsuspected, subclinical variants of normal or abnormal sympathetic functions may pose a diagnostic pitfall in the interpretation of myocardial MIBG images. The α_2 agonist may be a useful discriminator among the various causes of decreased MIBG uptake and retention.

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Bartter's Syndrome: Renal Scintigraphic Appearance after Captopril Administration

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We report a case of Bartter's syndrome, a rare disease characterized by hypokalemia, increased plasma renin and angiotensin II levels with normal blood pressure. During the diagnostic work-up, the patient had renal scintigraphy in baseline and after captopril administration. Pharmacological blockade of the renin-angiotensin system with captopril resulted in bilateral and symmetrical renal abnormalities (increase of parenchymal transit time, time to maximum activity and retained cortical activity, with cortical trapping of the radiopharmaceutical). Baseline scintigraphy was normal. The findings are consistent with Bartter's syndrome pathogenesis. Captopril renography may be useful to differentiate Bartter's syndrome from other covert causes of hypokalemia.

Key Words: Bartter's syndrome; renal scintigraphy; technetium-99m-MAG3

J Nucl Med 1996; 37:1688–1690

Bartter's syndrome is a rare disease (*1*) characterized by chronic hypokalemia due to renal potassium wasting, increased plasma renin and angiotensin II levels, secondary hyperaldosteronism and normal blood pressure.

Onset of the disease is usually presented during childhood with poor stature-ponderal growth, suggestive facies, polyuria, polydypsia and weakness (*2*). In 30% of patients however, there is a late onset with symptoms related to hypokalemia (cramps, diarrhea, asthenia, palpitations) (*3*). It is even occasionally discovered on routine evaluation (*1*).

No single symptom is specific for the disease. A differential diagnosis requires exclusion of other causes of hypokalemia such as Gitelman's syndrome, vomiting, magnesium deficiency, laxative abuse and diuretics intoxication (*4,5*). The physiopathology is still not completely understood (*3*) and various hypotheses have been put forward. Several of these hypotheses include: reduced vascular response to angiotensin II (*6*), defects in sodium (*7*) and chloride (*8*), re-absorption by the thick ascending limb of Henle's loop, increased production of atrial natriuretic factor (*9*) and abnormal membrane permeability to sodium (*10*).

Regardless of Bartter's primary cause, pathogenesis includes bilateral hyperplasia of juxtaglomerular apparatus, which causes excess renin production with volume depletion and stimulated aldosterone production (*3*). Blood pressure levels are maintained within normal limits due to the counteracting effects of prostaglandins, bradykinin and angiotensin II.

Elevated levels of angiotensin II are also present in renovascular hypertension, a secondary form of hypertension caused by activation of renin-angiotensin system due to renal artery stenosis (RAS) (*11*). In this latter condition, angiotensin-converting enzyme blockade has been shown to alter renal handling of radiopharmaceuticals such as ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA, eliciting typical abnormalities of renographic studies (*12*) when the renin-angiotensin system is activated.

CASE REPORT

A 27-yr-old woman was admitted with weakness, postural hypotension, polydypsia and methrorragy. One month earlier, a blood test performed for reasons unrelated to hospital admission had revealed hypokalemia.

At admission, the patient was 160 cm tall and weighed 46 kg. Blood pressure levels were well within normal limits: serum electrolytes: Na 141 mEq/liter; Ca 9.3 mEq/liter; P 3.9 mEq/liter; Cl 99 mEq/liter; Mg 1.7 mEq/liter. Renal function was normal (creatinine 88 μmole/liter); plasma renin activity resulted to be $>$ 25 ng/ml with aldosterone levels up to 904 pg/ml on repeated measurements; cortisol and ACTH levels slightly exceeded normal limits. Abdominal ultrasound failed to show any abnormal finding.

During diagnostic work-up, she was referred for captopril renal scintigraphy (*13*). The patient received 50 mg captopril orally and was injected 1 hr later with 100 MBq ^{99m}Tc-MAG3. Images were obtained with the patient and the camera head under the table. Computer acquisition was obtained at a rate of 1 frame/10 sec for 20 min. The same procedure, except for captopril administration, was repeated the next day.

Captopril renography revealed bilaterally delayed tracer transit through both kidneys with late appearance of the pelvi-calyceal system, increased tracer parenchymal transit times and high resid-

Received Feb. 9, 1995; revision accepted Jan. 13, 1996.
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