Evaluation of cardiac sympathetic neuronal integrity in diabetic patients using iodine-123 metaiodobenzylguanidine

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Abstract. Autonomic dysfunction is associated with increased mortality in diabetic patients. To evaluate the cardiac autonomic dysfunction in these patients, a prospective study was undertaken using iodine-123 metaiodobenzylguanidine (MIBG) single-photon emission tomography (SPET). The study groups consisted of ten diabetic patients with cardiac autonomic neuropathy (group I) and six without autonomic neuropathy (group II). Autonomic nervous function tests, thallium scan, radionuclide ventriculographic data including ejection fraction and wall motion study, and 24-h urine catecholamine levels were evaluated. ¹²³I-MIBG SPET was performed at 30 min and 4 h following injection of 3 mCi of ¹²³I-MIBG in groups I and II and in normal subjects (n=4). On planar images, the heart to mediastinum (H/M) ratio was measured. Defect pattern and severity of MIBG uptake were qualitatively analysed on SPET. Compared with control subjects, diabetic patients had a reduced H/M ratio regardless of the presence of clinical autonomic neuropathy. There was no difference in H/M ratio between groups I and II. On SPET images, focal or diffuse defects were demonstrated in all patients in group I and in five of the six patients in group II. The extent of defects tended to be more pronounced in group I than in group II. In conclusion, ¹²³I-MIBG scan was found to be a more sensitive method than clinical autonomic nervous function tests for the detection of autonomic neuropathy in diabetes.

Key words: Iodine-123 metaiodobenzylguanidine scan – Cardiac sympathetic nervous function – Diabetes mellitus


Introduction

As a guanethidine analogue, metaiodobenzylguanidine (MIBG) shares many of the cellular transport properties of norepinephrine (NE). Both MIBG and NE enter the adrenergic neuronal cells through the same uptake system, are stored in granules and are secreted in response to acetylcholine [1–3]. In patients with congestive heart failure and dilated cardiomyopathy, radiolabelled MIBG scan was soon recognized as a promising diagnostic modality in the assessment of sympathetic neuronal integrity [4–6]. Decreased myocardial MIBG uptake is associated with autonomic dysfunction in diabetic patients as well, and such autonomic dysfunction is linked with increased mortality [7, 8]. The clinical tests evaluating autonomic nervous dysfunction only indirectly reflect the autonomic regulation of the heart and peripheral circulation (mainly the parasympathetic function) [9]. In addition, in its early stages, diabetic autonomic neuropathy (ANP) is often symptomless; therefore there is a need for a sensitive test to detect early changes and sympathetic function. In this study, we investigated iodine-123 MIBG cardiac imaging for the early detection of sympathetic nerve dysfunction in diabetic patients.

Material and methods

Subjects

Sixteen patients (mean age 57.9 years, range 39–72 years, six males) with diabetes mellitus were included in the study. The duration since diagnosis of diabetes mellitus ranged from 20 days to 26 years (mean 8.3 years). The diabetic patients were initially screened using clinical autonomic nervous function tests (ANFTs) such as heart rate response during the Valsalva manoeuvre and deep-breathing and stand-up tests as previously described [9]. Clinical ANP was defined as an abnormal response during any one of these three tests. Based on these clinical criteria, ten out of 16 diabetic patients had cardiac ANP (group I) and six did not show evidence of ANP (group II). In group I, six patients were treated with oral hypoglycaemic drugs, two with insulin alone and two with a combination of insulin and an oral hypoglycaemic
Radionuclide ventriculography

All patients underwent ECG-gated radionuclide ventriculography (RVG) to assess the regional myocardial contractility and to measure the left ventricular ejection fraction (LVEF). Thirty minutes after an injection of 1 mg of pyrophosphate, 20 mCi (740 MBq) of technetium-99m pertechnetate was injected into the antecubital vein. Anterior, left anterior oblique (LAO) and lateral views at the short-axis view of single-photon emission tomography (SPET) images were obtained at 40 s/view with a 5.6° of angular increment. The projection data were reconstructed by the filtered back-projection method using a Butterworth filter (Nyquist frequency 0.35 cycle/cm, order no. 5). Short-axis, vertical long-axis and horizontal long-axis views were then obtained by re-orientation of the transaxial images. On planar images at 30 min and 4 h after MIBG injection, planar anterior views were acquired at a preset count of 200 kcounts on a dual-headed gamma camera equipped with low-energy high-resolution parallel-hole collimators (ADAC, Milpitas, USA) in 64x64 matrices. A 20% energy window centered on 159 keV was used for imaging. SPET images were obtained at 40 s/view with a 5.6° of angular increment. The projection data were reconstructed by the filtered back-projection method using a Butterworth filter (Nyquist frequency 0.35 cycle/cm, order no. 5). Short-axis, vertical long-axis and horizontal long-axis views were then obtained by re-orientation of the transaxial images. On planar images at 30 min and 4 h after MIBG injection, regions of interest (ROIs) were placed over the heart and mediastinum and the heart to mediastinum (H/M) activity ratio was calculated. The baseline value of cardiac MIBG uptake was determined in four non-diabetic subjects. The early and delayed H/M ratios in each of the groups were compared using statistical analysis on a computer with an SAS program package (SAS Institute, North Carolina). Significance was accepted at the P <0.05 level.

The defect pattern and severity were visually assessed based on the short-axis view of single-photon emission tomography (SPET) images by two independent observers who did not know the clinical history of the study subjects. In cases of discordance, a consensus was reached.

The findings were grouped as follows:
1. Defect pattern: focal or diffuse
2. Defect extent: grade 0 (no defect)
   grade 1 (defect less than 50%)
   grade 2 (defect more than 50%)
   grade 3 (non-visualized myocardium)

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Catecholamine assays

Twenty-four hour urinary NE and epinephrine were measured using high-performance liquid chromatography with electrochemical detection [10].

Results

The urinary concentration of NE was within the normal range. In group I, it was 36.21±16.88 (8.32-61.96) µg/day, and in group II, 25.02±15.68 (6.58-48.24) µg/day. The urinary concentration of epinephrine was also within the normal range [12.42±9.89 (3.5-22.4) µg/day for group I, and 18.47±7.5 (10.5-25.4) µg/day for group II]. RVG showed normal LVEF [57.13%±5.19% (48%-65%) for group I, and 58.17%±2.93% (57%-63%) for group II] and regional wall motion. There was no perfusion defect on 201TI SPET in any of the patients.

Intra- and interobserver differences for H/M ratio measurements and visual assessment for the defect pattern and severity were not significant (P >0.05).

In group I, early and delayed H/M ratios were 1.70±0.24 (1.45–2.08) and 1.61±0.27 (1.18–2.08) respectively. In group II, early and delayed H/M ratios were 1.80±0.26 (1.38–2.03) and 1.71±0.25 (1.36–1.93). Normal controls showed ratios of 2.01±0.24 (1.90–2.08) and 1.95±0.25 (1.83–2.07) respectively (Table 1).

The mean H/M ratio was significantly reduced in the diabetic groups at both 30 min and 4 h compared with the non-diabetic control groups (P <0.05). Two of six patients without clinical ANP showed markedly decreased H/M ratios and defects (Fig. 1). The washout of MIBG from the heart was not significant different between the diabetic groups and normal controls (P >0.05).

On SPET, control subjects showed homogeneous uptake without any focal defects (Fig. 2). In contrast, all but one of the diabetic patients showed focal or diffuse defects (diffuse in four, focal in 11) (Fig. 3). The defects tended to be larger in group I than in group II; however, this difference was not statistically significant. No correlation between H/M ratios and the presence of ANP was demonstrated (P >0.05).

Thallium-201 scintigraphy

Within a week of RVG or 123I-MIBG scintigraphy, pharmacological stress thallium SPET was performed to rule out coronary artery disease. After an intravenous injection of dipyridamole (0.56 mg/kg over 4 min), 3 mCi of thallium-201 was injected into the antecubital vein. Tomographic images were obtained as with 123I-MIBG SPET. When the stress images were normal, the resting study was omitted.