Impairment of Cardiac Neuronal Function in Childhood Dilated Cardiomyopathy: An ^{123}I-MIBG Scintigraphic Study

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Abnormalities of norepinephrine uptake have been found to reflect impairment of cardiac adrenergic neuronal function in adults with heart failure. To our knowledge, no data on childhood dilated cardiomyopathy (DCM) are available. The aim of this study was to assess the cardiac neuronal function using ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy in children with idiopathic DCM. **Methods:** We studied 26 patients (mean age, 44 ± 50 mo) with DCM and left ventricular dysfunction and 12 control subjects (mean age, 49 ± 65 mo) with normal left ventricular function. All subjects underwent planar cardiac imaging after intravenous injection of 20–75 MBq ^{123}I-MIBG. A static anterior view was acquired 4 h after injection. The heart-to-mediastinum count ratio was measured as described previously. **Results:** On the basis of a reduction of the heart-to-mediastinum count ratio, cardiac neuronal uptake of ^{123}I-MIBG was significantly decreased in patients with DCM compared with cardiac uptake in control subjects (172% ± 34% versus 277% ± 14%; $P < 0.0001$). A significant correlation was found between left ventricular ejection fraction and ^{123}I-MIBG cardiac uptake in patients with DCM ($y = 2.5x + 113.3$; $r = 0.80$; $P < 0.0001$). **Conclusion:** Cardiac adrenergic neuronal function is impaired in children with idiopathic DCM. ^{123}I-MIBG cardiac scintigraphy is a useful tool to assess cardiac neuronal function in childhood DCM.

Key Words: cardiac neuronal function; cardiomyopathy; pediatrics; metaiodobenzylguanidine; scintigraphy

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Assessment of cardiac adrenergic innervation is clinically useful in adults with heart failure (idiopathic dilated and ischemic cardiomyopathy) (1–5) or pheochromocytoma (6) using ^{123}I-metaiodobenzylguanidine (MIBG) cardiac imaging. The natural history in childhood dilated cardiomyopathy (DCM) remains unclear. Prognosis varies from death to complete recovery. Potential risk factors such as age, arrhythmias, and hemodynamic and histologic parameters are controversial in childhood DCM (7–17).

MIBG is an analog of guanethidine that is taken up by the adrenergic nerve endings and appears to share common uptake and storage mechanisms with those of norepinephrine (18). When labeled with ^{123}I, MIBG allows assessment of myocardial adrenergic uptake in humans (19,20). The aim of this prospective study was to assess the cardiac neuronal function in children with idiopathic DCM using ^{123}I-MIBG cardiac scintigraphy.

MATERIALS AND METHODS

Study Population

Between October 1996 and June 1998, 26 consecutive patients with idiopathic DCM were included. All patients had a hypokinetic left ventricle on 2-dimensional echocardiography (ejection fraction < 50%); none had a hypertrophic left ventricle. DCM was idiopathic without identifiable cause (toxic, metabolic, or ischemic).

The 26 patients (17 females, 9 males) were 44 ± 50 mo old (age range, 2–175 mo). All patients underwent equilibrium radionuclide angiography and ^{123}I-MIBG cardiac scintigraphy. No patient had diabetes mellitus or chronic renal failure disease. The patients were treated with diuretics and captopril. They received no inotropic drugs for 2 wk before the examination; no one received β blockers.

Ten patients referred for suspicion of neuroblastoma and 2 patients with Recklinghausen's disease but no pheochromocytoma served as control subjects and underwent ^{123}I-MIBG scintigraphy. The 12 control subjects (4 females, 8 males) were 49 ± 65 mo old (age range, 1–192 mo). They had no history of cardiac disease, no cardiac symptoms, normal electrocardiogram, and normal left ventricular function. Norepinephrine and epinephrine urinary excretion rates were within a normal range.

Planar ^{123}I-MIBG Imaging

The pharmacologic precursor, metaiodobenzylguanidium sulfate, was obtained commercially (CIS Biointernational, Gif-sur-Yvette, France). The radiochemical purity of the radioisotope was guaranteed by the manufacturer to exceed 99.8% at the time of delivery. The specific activity was 37 MBq/mL. Thin-layer chromatography showed that the radiopharmaceutical purity of each dose exceeded 90%.

All sympathomimetic medicines that could potentially interfere with the MIBG uptake were discontinued for at least 5 half-lives before the scintigraphic examination. To block the thyroid uptake

of free ^{123}I, patients were given Lugol's solution 2 d before and 2 d after administration of the radiopharmaceutical. A dose of 20–75 MBq ^{123}I-MIBG was injected intravenously. Scanning was performed 4 h later on a γ camera equipped with a low-energy, all-purpose, parallel-hole collimator. Energy discrimination was provided by a 20% window centered on the 159-keV photopeak of [123]I. The matrix size format was 64 × 64. The chest was imaged in anterior view for 10 min.

The ^{123}I-MIBG cardiac uptake was semiquantified with a 4 × 4 pixel region of interest (ROI). The ROI was drawn in the cardiac area and a same-sized ROI was drawn in the upper mediastinum area to standardize cardiac uptake as described (2,3). The ROIs were placed by two independent observers who were unaware of clinical status. To determine the control data, ^{123}I-MIBG imaging was performed on control subjects using the same protocol.

Equilibrium Radionuclide Angiography

Equilibrium radionuclide angiography was performed on the same γ camera following a standard protocol. The left ventricular ejection fraction (LVEF) cutoff was 50%. ^{123}I-MIBG imaging was performed on the next day.

Statistical Analysis

Data are expressed as mean ± 1 SD. Unpaired Student's t test was used to evaluate differences between data of patients with DCM and of control subjects. Linear regression analysis with calculation of Pearson's correlation coefficient was performed to determine whether the ^{123}I-MIBG cardiac uptake was related to the LVEF. $P < 0.05$ was considered significant.

RESULTS

MIBG and LVEF Imaging

^{123}I-MIBG cardiac uptake was observed in all patients with DCM, with a heart-to-mediastinum count ratio (HMR) of 172% ± 34% 4 h after injection (range, 121%–255%). The HMR in control subjects was 277% ± 14% (range, 256%–298%; $P < 0.0001$), and the relationship between HMR and age was $r = 0.09$ ($P = $ not significant).

Figure 1A shows a scintigraphic image of ^{123}I-MIBG cardiac uptake in a patient with DCM (HMR = 132%). Figure 1B shows a scintigraphic image of ^{123}I-MIBG cardiac uptake in a control subject (HMR = 279%).

The radionuclide LVEF was assessed in 22 of 26 patients with DCM. The LVEF was 23% ± 11% (range, 10%–48%). The relationship between ^{123}I-MIBG cardiac uptake and LVEF in patients with DCM was $r = 0.80$ (y = 2.5x + 113.3; $P < 0.0001$) (Fig. 2).

Reproducibility of MIBG Results

The intraobserver correlation for HMR calculation was $r = 0.99$ ($P < 0.0001$) and the interobserver correlation was $r = 0.94$ ($P < 0.0001$) for the 26 patients with DCM. For the 12 control subjects, the intraobserver correlation for HMR calculation was $r = 0.98$ ($P < 0.0001$) and the interobserver correlation was $r = 0.94$ ($P < 0.0001$).

DISCUSSION

To our knowledge, assessment of cardiac neuronal function using ^{123}I-MIBG scintigraphy in childhood DCM has not been reported previously. This study showed an impairment of MIBG cardiac uptake in childhood DCM. This reduction was related to the left ventricular dysfunction.

MIBG Metabolic Pathway

MIBG, a guanethidine analog, is thought to share the same uptake, storage, and release mechanisms as norepinephrine in the adrenergic nerve terminals but is not metabolized by monoamine oxidase or catechol-O-methyltransferase (18). Several studies have shown the affinity of MIBG for the adrenal medulla and the adrenergic nerves, and ^{123}I-MIBG myocardial scintigraphy can be used to assess the cardiac adrenergic neuronal function in humans (19,20).

MIBG Cardiac Uptake in Healthy Subjects

Estorch et al. (21) showed that ^{123}I-MIBG myocardial uptake is related to age; a decrease in ^{123}I-MIBG myocardial uptake was observed with aging, especially in patients older than 60 y. Patients younger than 20 y (mean age, 17 ± 1 y) had a mean HMR of 207% ± 26%. For the 12 control subjects of this study, the mean HMR was 277% ± 14% for an average age of 49 ± 65 mo. No relationship was found between HMR and age.

Morozumi et al. (22) reported a heterogeneous MIBG distribution in the left ventricle using ^{123}I-MIBG SPECT and a mean HMR of 302% ± 47% 4 h after injection.

### MIBG Cardiac Uptake in Adults with Heart Failure

Decreased myocardial accumulation of MIBG has been described in conditions in which norepinephrine content or uptake was reduced (e.g., myocardial infarction (23,24); congestive heart failure (25,26); cardiac denervation (27,28); chronic renal failure (29); and diabetic autonomic neuropathy (30)). However, when the circulating norepinephrine level was increased (e.g., pheochromocytoma), ^{123}I-MIBG cardiac uptake was also decreased (6).

In the chronic stage of DCM, decreased MIBG uptake may reflect neuronal injury or adrenergic dysfunction (1–3). Glowniak et al. (27) reported decreased uptake of MIBG and faster washout of MIBG in DCM. Decreased ^{123}I-MIBG cardiac uptake in these patients suggested sympathetic nerve dysfunction, whereas rapid washout could reflect increased sympathetic nerve activity.

MIBG Cardiac Uptake in Children with Heart Disease

To our knowledge, MIBG imaging in childhood DCM has not been reported. All ischemic, metabolic, or toxic cardiomyopathies, which could alter the MIBG metabolism, were excluded, so the idiopathic DCM population was very homogeneous. The ^{123}I-MIBG cardiac uptake was decreased and left ventricular systolic function was impaired. The strength of the study was the comparison with control subjects, which showed a severe impairment of cardiac neuronal function in patients with DCM. These findings indicated the presence of an abnormal function of efferent cardiac sympathetic nerve endings.

Several mechanisms are involved in ^{123}I-MIBG cardiac uptake abnormalities detected in children with heart disease.
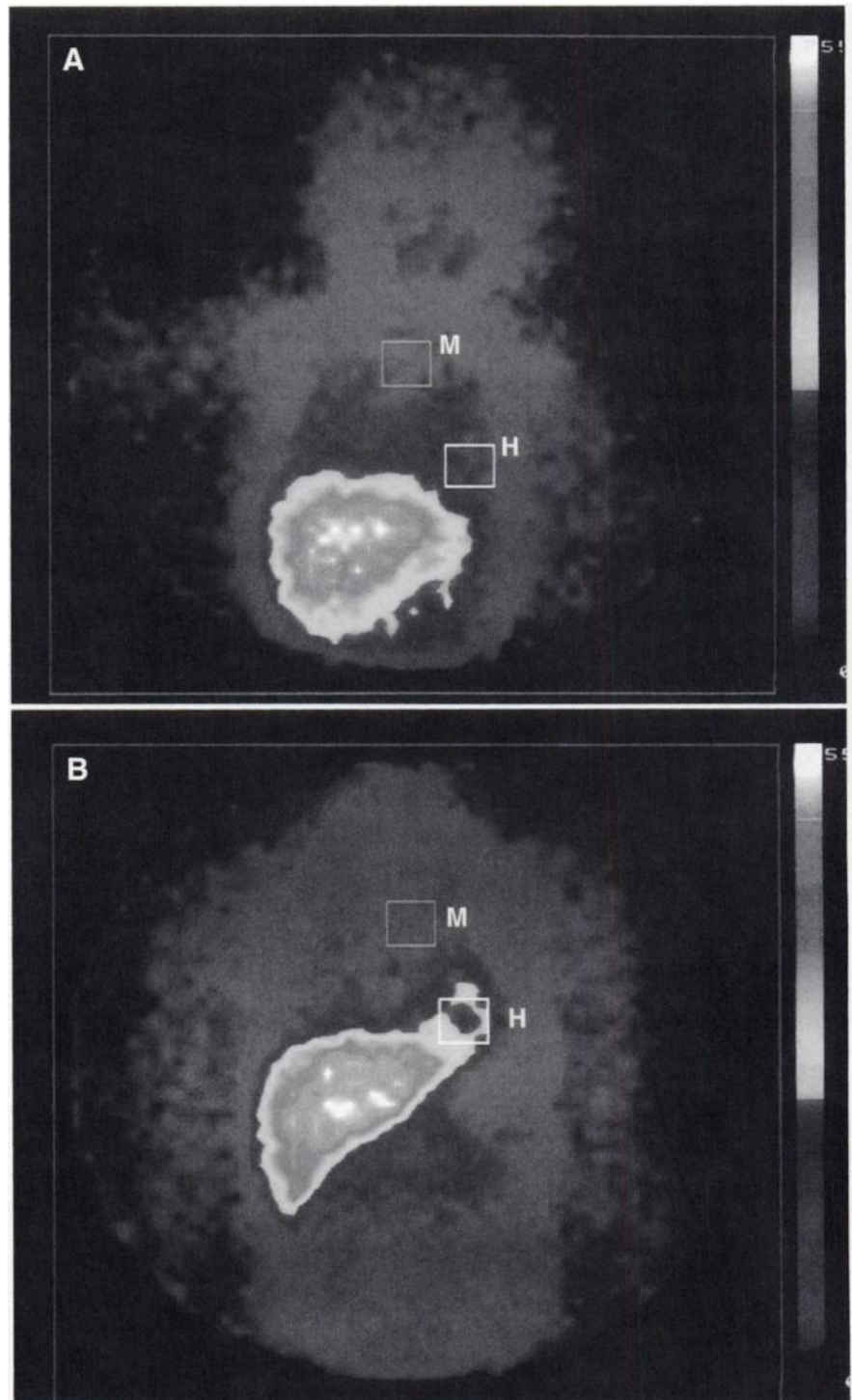
FIGURE 1. Anterior view of chest 4 h after ^{123}I-MIBG injection in patient with idiopathic DCM (A) and in control subject (B). Heart (H) and mediastinum (M) were selected as shown to measure HMR. Significant decrease in ^{123}I-MIBG cardiac uptake was observed in patient with idiopathic DCM (A) compared with ^{123}I-MIBG cardiac uptake in control subject (B).

Reduction of MIBG uptake can be explained by functional mechanisms, such as increased cardiac spillover of norepinephrine (5), which results in competition with MIBG for uptake at nerve terminals. Therefore, a reduced number of sympathetic neurons with increased amounts of interstitial fibrotic tissue, together with increased MIBG turnover in dilated myocardium, could account for these phenomena. However, different mechanisms, such as denervation (31), reduced production of catecholamines, impaired storage in vesicles, impaired reuptake, or excessive release associated with increased sympathetic stimulation, can also be involved in heart failure. Wu et al. (32) showed that changes in noradrenaline level and lymphocyte β-adrenoreceptor density occur concurrently with the presence and severity of heart failure in children.

MIBG myocardial uptake may be modified by a variety of drugs such as labetalol and propranolol (33). However, in this study, patients received no such drugs at the time of
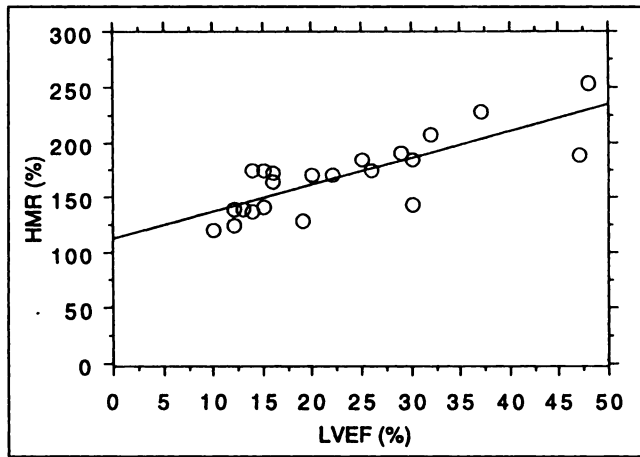
FIGURE 2. Correlation between ^{123}I-MIBG cardiac uptake expressed as HMR and LVEF in patients with idiopathic DCM ($y = 2.5x + 113.3$; $r = 0.80$; $P < 0.0001$).

radionuclide imaging. They were treated with diuretics and captopril, but no data were available concerning the effects of captopril on ^{123}I-MIBG cardiac uptake in childhood DCM. Enalapril reduced ^{123}I-MIBG cardiac release (34) and increased ^{123}I-MIBG myocardial uptake in adult patients with chronic heart failure (35). These studies were consistent with the fact that enalapril improved the clinical condition of the patients and, thus, the sympathetic adrenergic drive.

The HMR was highly reproducible despite difficulties of MIBG imaging in some patients associated with low ^{123}I-MIBG cardiac uptake. The position of ROIs was quite important in obtaining the HMR. A series of different ROI sizes was defined and tested in the anterior view. Finally, the 4 × 4 pixel ROI was found to be the best compromise to calculate the HMR.

Although a good correlation was found between ^{123}I-MIBG cardiac uptake and LVEF, the study could not assess whether the decreased MIBG uptake preceded the left ventricular dysfunction in childhood DCM.

Limitations of Study

Quantitation of ^{123}I-MIBG cardiac activity on scintigraphic images had technical limitations. Tomographic imaging provided an opportunity to study the myocardial distribution of ^{123}I-MIBG uptake in adults (22). In children with DCM, the decrease in ^{123}I-MIBG uptake induced difficulties for data processing, therefore hindering the use of tomographic imaging in routine examination. Consequently, planar imaging was used to quantify the MIBG cardiac uptake.

It was impossible to make any type of quantitative statement about sympathetic nerve activity on the basis of measurements at a single time point. Decreased activity at a single point could be associated with rapid washout of MIBG with normal initial uptake or decreased initial uptake with normal washout. The single measurement point was used in this study, as described in adult patients with heart failure (2,3).

Children in this study did not have sufficient follow-up to assess prognosis and to provide a cardiac cutoff value as described in adults with heart failure (3). Further studies of a larger population with long-term follow-up will help elucidate the role of MIBG imaging in childhood DCM.

CONCLUSION

^{123}I-MIBG cardiac scintigraphy can detect an impairment of cardiac neuronal function and, consequently, reflects an actual change in cardiac adrenergic metabolism in children with idiopathic DCM. These preliminary results are encouraging and should lead to adoption of ^{123}I-MIBG imaging as a key method for evaluating childhood DCM and perhaps an important factor in considering heart transplantation.

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