

Cardiac ^{123}I -MIBG Uptake in Idiopathic Ventricular Tachycardia and Fibrillation

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Patients with idiopathic ventricular tachycardia or fibrillation have no additional structural or functional myocardial abnormalities. However, the inducibility of typical tachyarrhythmias by physical or mental stress or by catecholamine infusion suggests the involvement of the adrenergic system in the pathogenesis of these potentially life-threatening diseases. **Methods:** 45 patients with idiopathic right ventricular outflow tract tachycardia (RVO-VT), 25 patients with idiopathic left ventricular tachycardia (ILVT), 15 patients with idiopathic ventricular fibrillation (IVF) and 10 age-matched control patients were investigated in this study. Diagnoses were made on the basis of detailed evaluation of the results of two-dimensional echocardiography, left and right ventricular angiography, coronary angiography and endomyocardial biopsy. Local presynaptic norepinephrine re-uptake was assessed using the norepinephrine analog ^{123}I -metaiodobenzylguanidine (MIBG), SPECT and semiquantitative 33-segment bull's-eye analysis. **Results:** Locally reduced ^{123}I -MIBG uptake was found in 27 of 45 RVO-VT patients (60%), 5 of 15 ILVT patients (33%) and 17 of 25 IVF patients (68%). Unlike ILVT patients, RVO-VT and IVF patients had significantly reduced segmental ^{123}I -MIBG uptake of the posterior wall compared with control patients. **Conclusion:** Patients with idiopathic tachycardia and fibrillation show abnormal ^{123}I -MIBG uptake, which indicates presynaptic sympathetic dysfunction. RVO-VT and IVF patients exhibit significantly reduced ^{123}I -MIBG uptake in the posterior left ventricular wall, whereas ILVT patients do not.

Key Words: cardiac sympathetic innervation; idiopathic ventricular tachycardia; idiopathic ventricular fibrillation; ^{123}I -metaiodobenzylguanidine SPECT

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Ventricular tachyarrhythmias lead to palpitation, dizziness, syncope and sometimes sudden cardiac death. In most cases, these arrhythmias are due to structural heart diseases such as coronary heart disease or cardiomyopathy. In contrast, there are patients without structural or other functional myocardial abnormalities who suffer from ventricular tachyarrhythmias. For example, in patients with

idiopathic tachycardia and fibrillation (1-4), a primary involvement of the cardiac sympathetic nervous system (primary cardioneuropathy) is suggested by frequently inducible tachyarrhythmias under physical or mental stress and/or during catecholamine infusion (5,6). Additionally, these arrhythmias can be successfully suppressed by antiarrhythmic drugs such as β -blockers (7).

Impairment of presynaptic catecholamine re-uptake, which can be assessed by using the norepinephrine analog ^{123}I -metaiodobenzylguanidine (MIBG) and either planar scintigraphy or SPECT (8-10), has been found in a variety of diseases associated with primary or secondary cardioneuropathy: dilated and hypertrophic cardiomyopathy (11,12), heart failure of other causes, hypertension, diabetes, coronary heart disease (13-15), arrhythmogenic right ventricular cardiomyopathy (16,17) and long-QT syndrome (18,19).

In this study, cardiac sympathetic innervation was evaluated using ^{123}I -MIBG scintigraphy in patients with idiopathic right ventricular outflow tract tachycardia (RVO-VT) (1-3), idiopathic left ventricular tachycardia (ILVT) (20) and idiopathic ventricular fibrillation (IVF) (1,21).

MATERIALS AND METHODS

Patients

We studied 85 patients who had a history of tachyarrhythmias and were undergoing ^{123}I -MIBG SPECT assessment. Some patients (13 of 98) were excluded because of inadequate image quality (i.e., lung uptake exceeded 30% of heart uptake, or liver uptake interfered). The study population consisted of 45 patients with RVO-VT (29 women and 16 men, median age 42 y, range 16-70 y), 25 patients with ILVT (7 women and 18 men, median age 32 y, range 19-64 y) and 15 patients with IVF (5 women and 10 men, median age 31 y, range 16-58 y).

The conditions of idiopathic ventricular tachycardia and fibrillation were diagnosed on the basis of documented sustained or unsustained ventricular tachycardia or fibrillation in the absence of morphological, functional and structural heart disease (3,4). Coronary artery disease, hypertrophic or dilated cardiomyopathy and congenital, valvular or inflammatory heart disease were excluded in all patients on the basis of diagnostic evaluation of the results of two-dimensional echocardiography, left and right ventricular angiography, coronary angiography and endomyocardial biopsy (7,17). All patients had sinus rhythm with normal resting 12-lead electro-

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cardiograms. In particular, no patient had a bundle branch block, electrocardiographic signs of left ventricular hypertrophy or a prolongation of the QT interval. In accordance with previously published data in control subjects (22), signal-averaged electrocardiogram results were inconspicuous in 89% of the investigated patients. As reported previously, each patient underwent an invasive electrophysiological study with programmed ventricular stimulation, including up to three extrastimuli and additional isoproterenol infusion (7,17).

In the patients with ventricular tachycardia, RVO-VT was diagnosed on the basis of left bundle branch block morphology and inferior QRS axis of the ventricular tachycardia and by endocardial catheter mapping during an electrophysiological study that confirmed the origin of the ventricular tachycardia in the right ventricular outflow tract. Patients with ILVT were diagnosed on the basis of right bundle branch block morphology and superior QRS axis of the tachycardia originating in the left ventricle.

Controls

An age-matched group of 10 patients (5 women and 5 men, median age 43 y, range 25–62 y, $P = ns$), who had medullary carcinoma of the thyroid and were undergoing ^{123}I -MIBG scintigraphy to exclude pheochromocytoma in the setting of multiple endocrine neoplasia (MEN), served as controls. Control patients had no history of cardiac disease, low risk profiles and normal physical examinations. All had normal resting electrocardiograms.

Data Acquisition

Patients imaged were off antiarrhythmic medication for at least 24 h. Patients on amiodarone and/or other drugs that may affect ^{123}I -MIBG uptake (23) were excluded from this study. In all patients, cardiac norepinephrine re-uptake was evaluated by blocking the thyroid gland with 300 mg perchlorate and then intravenous injection of 300 MBq ^{123}I -MIBG (Mallinckrodt Diagnostics, Petten, The Netherlands; specific activity 280–420 MBq/mg). To allow for clearance of nonspecific tissue uptake, cardiac SPECT images were acquired 4 h after injection using a one-head gamma camera (Orbiter; Siemens Medical Systems, Chicago, IL) equipped with a LEAP collimator. Thirty-two projections, 60 s each, were acquired over a 180° rotation in a 64 × 64 matrix and reconstructed by filtered back-projection using a Shepp-Logan-Hanning filter with a cutoff frequency of 0.5. Patients whose ^{123}I -MIBG scans were of poor image quality due to high lung or liver uptake were excluded from this study, as described earlier.

To exclude myocardial perfusion abnormalities on a small-vessel level, despite normal coronary angiogram results, an additional routine myocardial ^{201}Tl stress-redistribution SPECT was initially performed on a subgroup of 12 patients (5 RVO-VT, 3 ILVT and 4 IVF patients) within 2–5 d after the ^{123}I -MIBG study (24). Because of normal ^{201}Tl results in these patients and normal coronary angiogram results in all patients, this part of the investigation was not performed in the whole patient group to minimize radiation exposure.

Data Analysis

In each individual study, local ^{123}I -MIBG uptake (MIBG_{loc}) of the left ventricular myocardium was measured semiquantitatively in a 33-segment bull's-eye analysis as percentage uptake relative to the segment with maximal uptake (100%). For each segment of the bull's-eye, the mean ($\text{mean}_{\text{control}}$) and SD ($\text{SD}_{\text{control}}$) of MIBG_{loc} of all studies in the control group was calculated. A segment of the

bull's-eye analysis in a patient study was considered abnormal if MIBG_{loc} was less than $\text{mean}_{\text{control}} - 2 \times \text{SD}_{\text{control}}$. A result of a patient study was classified as abnormal if it showed at least three adjacent abnormal segments and was not exclusively located in the most basal bull's-eye segments (25).

All data are means \pm SD. Nonparametric Mann-Whitney U tests were used to assess the intergroup differences of number, extent and mean uptake of segments with reduced MIBG_{loc} of all ^{123}I -MIBG studies classified as abnormal. Intergroup differences of the incidence of abnormal ^{123}I -MIBG scintigrams were tested using a nonparametric Kolmogorov-Smirnov two-sample test. $P < 0.05$ was considered significant. Results of MIBG_{loc} were compared between controls and patients using a nonparametric Mann-Whitney U test. After Bonferroni's correction for multiple testing (33 segments), $P < 0.002$ was considered significant.

RESULTS

All ^{123}I -MIBG scans in the control group showed homogeneous uptake in the whole left ventricular myocardium. In the patients, 397 of the total of 2805 segments (14.2%) showed significant reduction of MIBG_{loc} . According to the classification criteria described earlier, 49 of 85 scintigrams (58%) were classified as abnormal. ^{201}Tl stress-redistribution images revealed homogeneous ^{201}Tl -uptake in all 12 patients investigated, whereas 9 of these showed significantly reduced MIBG_{loc} (4 RVO-VT, 3 ILVT and 2 IVF patients). Figure 1 illustrates typical findings of ^{123}I -MIBG SPECT and ^{201}Tl stress-redistribution SPECT in a patient with RVO-VT.

Idiopathic Right Ventricular Outflow Tract Tachycardia

In RVO-VT patients, 224 of 1485 segments (15.1%) showed significant reduction of MIBG_{loc} , resulting in 27 of 45 scintigrams (60.0%, $P = 0.006$ versus controls) being classified as abnormal. In these patients, 8.3 ± 3.9 segments, representing a bull's-eye area of $25.1\% \pm 12.2\%$, were found to show significant reduction of MIBG_{loc} . The mean

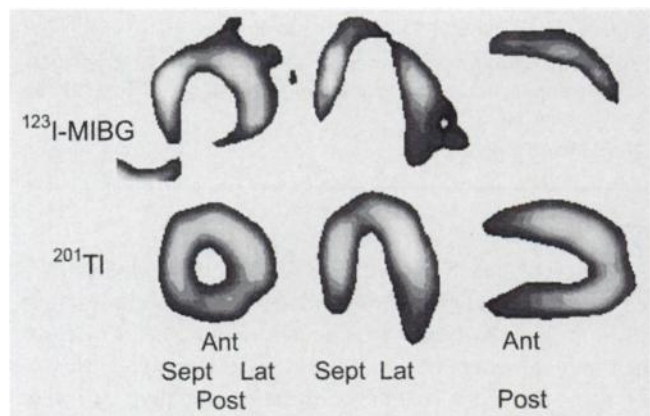


FIGURE 1. Short axis (left), horizontal long axis (middle) and vertical long axis (right) slices of ^{123}I -MIBG SPECT (top) and matching ^{201}Tl stress-redistribution SPECT (bottom) of patient with idiopathic right ventricular outflow tract tachycardia: ^{123}I -MIBG uptake is locally reduced in posterior and posterolateral myocardial walls despite homogeneous myocardial stress flow. Ant = anterior; Lat = lateral; Post = posterior; Sept = septal wall.

TABLE 1
¹²³I-MIBG Uptake in Idiopathic Tachycardia and Fibrillation

Condition	No.	MIBG		Segments	
		Percentage (%)	n	Area (%)	Uptake (%)
RVO-VT	27/45	60.0	8.3 ± 3.9	25.1 ± 12.2	59.3 ± 7.2
ILVT	5/15	33.3	8.2 ± 4.4	24.6 ± 12.3	55.5 ± 11.2
IVF	17/25	68.0	7.8 ± 3.9	23.5 ± 11.6	56.8 ± 12.1

MIBG = incidence of abnormal ¹²³I-MIBG; segments = segments (n) with significantly reduced ¹²³I-MIBG uptake; area = bull's-eye area with significantly reduced ¹²³I-MIBG uptake; uptake = mean uptake in segments with significantly reduced ¹²³I-MIBG uptake; RVO-VT = right ventricular outflow tract tachycardia; ILVT = idiopathic left ventricular tachycardia; IVF = idiopathic ventricular fibrillation.

MIBG_{loc} in these defect areas was 59.3% ± 7.2% (Table 1). Segments with reduced MIBG_{loc} were located mainly in the basal and midventricular parts of the posterior wall and the inferior septum and in the apical and midventricular portion of the anterior wall. In two segments of the basal inferior wall, MIBG_{loc} was significantly lower in RVO-VT patients than in control patients ($P < 0.002$), whereas the reduction of MIBG_{loc} in the anterior and inferoseptal regions attained only borderline significance ($P < 0.05$) (Fig. 2).

Idiopathic Left Ventricular Tachycardia

Forty-one of 495 segments (8.3%) in the ILVT patient group had a significant reduction of MIBG_{loc}, resulting in 5 of 15 scintigrams (33.3%, $P = ns$ versus controls) being classified as abnormal. In these scintigrams, 8.2 ± 4.4 segments, representing a bull's-eye area of 24.6% ± 12.3%, had a significant reduction of MIBG_{loc}. Mean MIBG_{loc} in these defect areas was 55.5% ± 11.2% (Table 1). Compared with the control subjects, MIBG_{loc} in the ILVT group was not significantly reduced in any of the segments, and only a

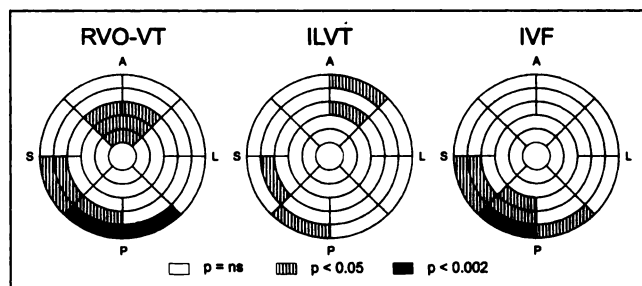


FIGURE 2. Bull's-eye display of differences of segmental ¹²³I-MIBG uptake between controls and patients with idiopathic right ventricular outflow tract tachycardia (RVO-VT), idiopathic left ventricular tachycardia (ILVT) and idiopathic ventricular fibrillation (IVF). Nonparametric Mann-Whitney *U* tests with Bonferroni correction for multiple testing were performed, and $P < 0.002$ was considered significant; $P < 0.05$ indicates borderline significance. A = anterior; L = lateral; P = posterior; S = septal wall.

few noncontiguous segments attained borderline significance ($P < 0.05$) (Fig. 2).

Idiopathic Ventricular Fibrillation

For IVF patients, 17 of 25 scintigrams (68.0%, $P = 0.003$ versus controls) were classified as abnormal, and 132 of the 825 total segments (16.0%) showed significant reduction of MIBG_{loc}. In these scintigrams, 7.8 ± 3.9 segments, representing a bull's-eye area of 23.5% ± 11.6%, had significant reduction of MIBG_{loc}. The mean MIBG_{loc} in these defect areas was 56.8% ± 12.1% (Table 1). Segments with reduced MIBG_{loc} were located mainly in the basal and midventricular parts of the posterior wall and the inferior septum. In IVF patients, MIBG_{loc} was significantly reduced in one segment of the basal inferior wall ($P < 0.002$), whereas the reduction of MIBG_{loc} in the inferoseptal regions reached borderline significance ($P < 0.05$) (Fig. 2).

Comparison Between Patient Groups

Statistical analysis revealed no significant differences between the three patient groups with regard to the incidence of abnormal ¹²³I-MIBG scintigrams as well as the number, extent (bull's-eye area) and mean uptake of segments with significantly reduced MIBG_{loc}.

DISCUSSION

The principal finding of this study is that idiopathic tachycardia and fibrillation are accompanied by cardiac reduction of local ¹²³I-MIBG uptake, indicating presynaptic sympathetic dysinnervation. Cardiac sympathetic nervous dysfunction has been described for several heart diseases associated with primary (idiopathic) or secondary cardioneuropathy: myocardial ischemia and infarction (15), dilated cardiomyopathy (11), hypertrophic cardiomyopathy (12), heart failure of other causes (13), long-QT syndrome (18,19) and arrhythmogenic right ventricular cardiomyopathy (16,17). In patients with structural heart disease, the alteration of the adrenergic nervous system is clearly secondary to structural and/or resulting functional abnormalities.

In contrast, structural or functional abnormalities other than tachyarrhythmia are absent in patients with idiopathic ventricular tachycardia or fibrillation, suggesting a primary involvement of the sympathetic nervous system in the arrhythmogenesis of these heart diseases. This is supported by findings of tachyarrhythmias that can be provoked by exercise (3,5) or catecholamine stimulation (e.g., isoproterenol infusion), the therapeutic efficacy of β -blockers and the present finding that significantly reduced MIBG_{loc} indicates dysfunction of presynaptic catecholamine re-uptake.

Pathophysiological Mechanism of Tachyarrhythmia in RVO-VT

One of the most likely pathophysiological mechanisms of idiopathic RVO-VT is a cyclic adenosine 5'-monophosphate (cAMP)-dependent increase in intracellular Ca²⁺ with subsequent delayed after-depolarization (26,27). This is supported indirectly by the pro-arrhythmic effect of β -adrenergic agonists (e.g., isoproterenol), which stimulate adenylyl

cyclase activity, as well as by the finding that in a subset of patients, the tachycardia can be terminated by adenylyl cyclase-inhibiting substances such as adenosine.

In this study, we have shown that MIBG_{loc} is reduced in the posterior wall of the left ventricular myocardium of patients with RVO-VT, indicating dysfunction of norepinephrine re-uptake, whereas in a subgroup, resting myocardial perfusion is normal. This finding is in agreement with that of reduced postsynaptic β -adrenoceptor density in the left ventricular myocardium of patients with RVO-VT (26), because a reduced presynaptic re-uptake of norepinephrine would lead to increased catecholamine levels in the synaptic cleft with subsequent downregulation of postsynaptic β -adrenoceptors. Ventricular tachycardia in RVO-VT patients can be triggered by exercise, which is accompanied by increased sympathetic activity, or by direct catecholamine administration (5). This suggests that, despite β -adrenoceptor downregulation, norepinephrine is still able to significantly increase the intracellular cAMP concentration (28), which may be explained by accompanying changes in the β -adrenoceptor-G-protein-adenylyl cyclase pathway. This pathophysiological process seems to act locally because the global plasma catecholamine levels in these patients are normal. The present data show that in patients with RVO-VT, impairment of MIBG_{loc} is predominantly located in the posterior wall of the left ventricle.

Pathophysiological Mechanism of Tachyarrhythmia in ILVT

ILVT differs from RVO-VT with respect to mechanism and pharmacological sensitivity. In patients with ILVT, the most likely underlying pathophysiological cause for the tachyarrhythmia is a left ventricular microentry mechanism in the posteroseptal left ventricular region with a QRS complex of right bundle branch block morphology and superior axis that is responsive to verapamil but not to adenosine (27). Because this mechanism seems not to be directly related to the sympathetic function, it is not surprising that in these patients the incidence of segments with significantly reduced MIBG_{loc} is lower than in patients with RVO-VT and IVF. Furthermore, in the ILVT group, no local preference of reduced ¹²³I-MIBG uptake was found.

Pathophysiological Mechanism of Tachyarrhythmia in IVF

IVF is defined as cardiac arrest in the absence of structural heart disease and other identifiable causes of ventricular fibrillation. The pathophysiology of this disease is still unknown (29,30). The data of the present study show a high incidence of reduced MIBG_{loc} in this patient group and predominant localization in the posterior wall, as in RVO-VT. In correlation with the inducibility of the tachyarrhythmias by catecholamine infusion or exercise, this finding strongly suggests involvement of the sympathetic nervous system in IVF patients. This field requires additional investigation.

Localization of Reduced MIBG_{loc}

The phenomenon of reduced MIBG_{loc} predominantly in the posterior wall is also detectable in patients suffering from other diseases, including hypertension (31). The reason for this alteration particularly in this region is unknown. Besides a mechanism directly related to the arrhythmogenic process or a higher vulnerability of the posterior nerve endings, the regional effects may be unspecific because of global reduction of norepinephrine re-uptake. The latter is supported by data of globally reduced norepinephrine re-uptake in RVO-VT patients (32). An unspecific process is further supported by the fact that the location of reduced ¹²³I-MIBG uptake is independent of the origin of the arrhythmias in patients with idiopathic ventricular tachycardia and in arrhythmogenic right ventricular cardiomyopathy (16,17,33).

Study Limitations

The uptake of ¹²³I-MIBG correlates well with the activity of the norepinephrine carrier (8). Nevertheless, because of its structural differences, ¹²³I-MIBG may over- or underestimate the changes in norepinephrine carrier activity in patients. In addition, the commercially available ¹²³I-MIBG used in this study contains significant amounts of cold MIBG, which leads to competition of both substances at the carrier site (34). It is not known whether this competition influences MIBG_{loc}.

All patients were off medication for 24 h. This excludes acute but not chronic pharmacological effects on the results.

Some of the segments may have been misclassified because of the relatively small number of controls. Nevertheless, because of the mismatch between homogeneous perfusion and reduced MIBG_{loc} in the patient subgroup investigated by both methods, the finding of reduced MIBG_{loc} is not likely to be an artifact caused by attenuation, for example.

CONCLUSION

Patients with idiopathic tachycardia and fibrillation show abnormal ¹²³I-MIBG uptake, indicating presynaptic sympathetic dysfunction. In contrast to the ILVT patients, RVO-VT and IVF patients exhibit significantly lower ¹²³I-MIBG uptake in the posterior left ventricular wall than control patients.

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