Relationship between myocardial ^{123}I-metaiodobenzylguanidine scintigraphic uptake and heart rate variability in patients with syndrome X

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Key words:
Syndrome X; Autonomic function; ^{123}I-metaiodobenzylguanidine myocardial scintigraphy; Heart rate variability.

Background. **We have recently demonstrated a striking impairment in cardiac uptake of ^{123}I-metaiodobenzylguanidine (MIBG) in most patients with syndrome X. In this study we investigated the relationship between cardiac MIBG defects and cardiac autonomic activity in these patients.**

Methods. **MIBG myocardial scintigraphy and time-domain and frequency-domain heart rate variability (HRV) were compared in 11 syndrome X patients and 10 healthy controls. Cardiac MIBG uptake was assessed by the heart/mediastinum ratio and a cardiac MIBG uptake defect score (higher values = lower uptake).**

Results. **The heart/mediastinum ratio was lower (1.71 – 0.6 vs 2.19 – 0.3, p = 0.03) and MIBG uptake score higher (37.1 – 32 vs 4.0 – 2.5, p = 0.005) in syndrome X patients, whereas average HRV values did not differ between the two groups. However, while there were no correlations between MIBG uptake and HRV in controls, in syndrome X patients both the heart/mediastinum ratio and MIBG uptake score correlated significantly with two HRV parameters, specific for vagal activity: the square root of the mean squared differences of consecutive RR intervals (r = 0.73, p = 0.01, and r = -0.67, p = 0.02, respectively), and high frequency (r = 0.64, p = 0.03, and r = -0.74, p = 0.009, respectively).**

Conclusions. **In patients with syndrome X, the impairment in cardiac MIBG uptake was associated with a reduction in HRV indexes mainly reflecting vagal modulation of sinus node, thus suggesting that a predominance of cardiac adrenergic activity may be present in those with abnormal cardiac MIBG scintigraphy.**

(Ital Heart J 2000; 1 (3): 221-225)

Received January 28, 2000; revision received March 1, 2000; accepted March 2, 2000.

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Patients with syndrome X have effort anginal pain, ischemic-like ST-segment depression on exercise testing and normal coronary arteries at angiography[1,2]. Although the causes of the syndrome are controversial[3-7], the occurrence of ST-segment depression during anginal pain and the documentation of a dysfunction of small coronary arteries strongly suggest a cardiac ischemic origin in at least a group of these patients[8-10]. Previous studies suggested that such patients exhibit an abnormal predominance of sympathetic nerve activity[11-16], which may contribute to the pathogenesis of the syndrome.

We have recently demonstrated that cardiac sympathetic nerve function is abnormal in most patients with syndrome X, showing a striking impairment in cardiac uptake of ^{123}I-metaiodobenzylguanidine (MIBG)[17], a guanethidine analogue compound which shares the same uptake, storage and release mechanisms of noradrenaline at sympathetic nerve endings[18,19]. These findings, however, lend themselves to different interpretations, as they could be due to either an increase or a decrease in adrenergic activity. In the attempt to clarify this point, we correlated the results of MIBG studies with measures of cardiac autonomic function, obtained by heart rate variability (HRV) analysis, an accepted clinical indicator of cardiac autonomic activity[20-22].

Methods

Study groups. Twelve patients fulfilling strict diagnostic criteria for syndrome X were enrolled in the study on MIBG up-

take[17]. All patients had effort-related anginal pain, both ST-segment depression and anginal pain on exercise testing, and angiographically normal coronary arteries. They had no evidence of other cardiac or noncardiac diseases, including hypertension and diabetes mellitus. Standard 12-lead electrocardiogram and echocardiographic study were normal in all patients, who also had negative ergonovine test. All investigations in these patients were carried out after appropriate wash-out of medications; β-blockers, in particular, were withdrawn at least 15 days before each test.

A control group of 10 healthy volunteers, well-matched for sex and age to patients, was enrolled in the study. All subjects had no history of any type of chest pain, nor evidence of heart or systemic diseases. They also had normal electrocardiogram, echocardiographic study and symptom-limited exercise testing, and were not taking any type of drugs.

Study investigations. All laboratory investigations were performed in the two groups, after written informed consent had been obtained.

Holter monitoring. Twenty-four-hour Holter recordings were obtained with Oxford Medilog MR-45 2-channel tape recorders, monitoring the CM5 and CM3 leads. Transient ST-segment depression was defined as a horizontal or downsloping ST shift > 1 mm 0.08 s after the J point, lasting at least 1 min and separated from previous episodes by at least 1 min of isoelectric ST.

Cardiac autonomic activity was assessed by measuring 24-hour HRV both in time and frequency domain. The mean RR interval (RR, ms), the standard deviation of all normal RR intervals (SDNN, ms), the percentage of the absolute differences between each normal RR interval and the previous one > 50 ms (pNN50, %), and the square root of the mean squared differences of consecutive RR intervals (RMSSD, ms) were obtained as time-domain HRV measures. HRV in the frequency domain was evaluated by fast Fourier transform spectral analysis in the range of frequencies from 0 to 0.5 Hz, with a spectral resolution of 0.0005 Hz. The amplitude values of low frequency (LF = 0.04-0.15 Hz, ms) and high frequency (HF = 0.15-0.40 Hz, ms) were obtained, and the LF/HF ratio, which was considered an index of sympatho-vagal balance in previous studies[20-22], was calculated.

MIBG scintigraphy. MIBG scintigraphy was performed using a protocol which has previously been described in detail[17]. Briefly, 5 mCi (185 MBq) of high specific activity MIBG (3.7 MBq/μg) were injected intravenously in 1 min through an indwelling catheter in a fasting state and after at least 1 hour of rest, both in patients and controls. Planar scintigraphic images of the chest were obtained by a single head gamma-camera (Elscint 409 ECT, Haifa, Israel). Images were recorded in anterior view 30 min and 1, 2, 3, and 18 hours after MIBG injection. Following the 3-hour planar scan, a SPECT acquisition was performed by rotating the camera by 6 increments, collecting 30 views for 30 s each. For the purposes of the study, only data of MIBG uptake at 3 hours after injection were analyzed, as earlier time-points have been shown to be less reliable for the assessment of adrenergic cardiac function by MIBG uptake[23]. The heart/mediastinum ratio, which is considered an index of global cardiac MIBG uptake[24], was calculated on planar MIBG images using regions of interest positioned around the heart and on the mediastinal area. When the heart silhouette was not clearly identifiable, a region of interest was centered in the anatomic site of the heart.

Transverse tomographic images were reoriented on the short axis and on the vertical/horizontal long axis of the left ventricle. Slice thickness was normalized to 1 cm. For purposes of analysis, 5 short-axis slices (from the most proximal to the most distal but excluding the apex) and the midventricular vertical and horizontal slices were selected. In order to evaluate regional tracer uptake the left ventricle was divided into 24 anatomical segments[17]. Semiquantitative MIBG uptake for each segment was obtained by a threshold method based on an 8-level color scale, each level corresponding to 12.5% of the maximal pixel value. Segments were scored as follows: 0 = normal (tracer uptake > 87.5% of maximum); 1 = mild defect (uptake > 75 to 87.5%); 2 = moderate defect (uptake 50 to 75%); 3 = severe defect (uptake < 50%). A global MIBG uptake defect score was obtained as the sum of all segmental scores for each patient.

Statistical analysis. Comparisons of continuous variables were performed by Mann-Whitney U test. Correlation analyses were carried out by Spearman rank test and proportions were compared by Fisher exact test. Values are reported as mean – 1 SD. A $p < 0.05$ was always considered statistically significant.

Results

One patient with syndrome X was excluded from the present study because HRV analysis could not be performed reliably, due to frequent premature supraventricular beats in some periods of the day. Thus, HRV data were obtained from 11 syndrome X patients and the 10 control subjects, whose main clinical findings are shown in table I. There were no differences between the two groups in age, gender, resting heart rate, blood pressure and risk factor profile. Episodes of ST-segment depression on Holter monitoring were detected in 6 patients (54%) with syndrome X (range 1-24 per patient, median 7) and were associated with angina in only 10%. No significant ST-segment changes were found in controls.

Table I. Main clinical findings and results in patients with syndrome X and healthy control subjects.

	Syndrome X	Controls	p
Sex (M/F)	4/7	4/6	
Age (years)	52 – 10	54 – 5	0.70
HRV data*			
RR interval (ms)	868 – 109	816 – 97	0.31
(HR, b/min)	(69 – 7)	(74 – 8)	
SD (ms)	145 – 29	132 – 23	0.24
RMSSD (ms)	41 – 23	38 – 37	0.39
pNN50 (%)	8.0 – 5.7	4.5 – 2.6	0.16
LF (ms)	28.4 – 8.9	26.2 – 8.9	0.62
HF (ms)	16.4 – 6.4	13.7 – 4.5	0.40
LF/HF	1.82 – 0.4	1.93 – 0.3	0.58

HRV = heart rate variability. * see Methods for definition of HRV variables.

MIBG study. Global and/or regional abnormal findings were detected in 7 syndrome X patients (73%), while a mild regional inferior defect was only detectable in 1 control subject ($p < 0.01$). The heart/mediastinum ratio was 1.71 – 0.6 in syndrome X patients and 2.19 – 0.3 in controls ($p = 0.03$), while cardiac MIBG uptake defect score in the two groups was 37.1 – 32 and 4.0 – 2.5 ($p = 0.005$), respectively.

MIBG results and heart rate variability analysis. There were no significant differences between patients and controls in all HRV variables (Table I). However, while there was no correlation between MIBG results and HRV indexes in controls, in syndrome X patients the heart/mediastinum ratio and MIBG score showed, respectively, direct and inverse correlations with RMSSD and HF, two HRV indexes which have been found to largely depend on vagal activity[20-22] (Table II). There were no significant correlations in either groups between cardiac MIBG uptake and most clinical variables, such as age, heart rate, blood pressure, duration of symptoms, and exercise parameters (data not shown). There were also no differences in MIBG uptake between syndrome X patients with or without episodes of transient ST-segment depression on Holter monitoring.

Discussion

Several previous studies reported indirect evidence of an increased adrenergic activity in patients with syndrome X[11-16], including higher basal and daily heart rate[11], abnormalities in HRV and baroreflex sensitivity[13,15,16], prolonged QTc interval[14], hypercontractility of the left ventricle[25], and increased basal coronary blood flow[26]. Measures of systemic and coronary sinus plasma levels of catecholamines and β-adrenergic receptor analyses, however, gave either conflicting or negative results[11,17,27].

Table II. Correlation of heart/mediastinum ratio and MIBG uptake defect score with HRV indexes in syndrome X patients and controls.

	Syndrome X		Controls	
	r	p	r	p
Heart/mediastinum ratio				
RR interval	-0.45	0.15	-0.18	0.60
SD	-0.13	0.67	0.47	0.17
RMSSD	0.73	0.01	-0.08	0.83
pNN50	0.25	0.46	-0.05	0.88
LF	0.39	0.23	0.13	0.73
HF	0.64	0.03	0.04	0.92
LF/HF	-0.38	0.24	0.14	0.70
MIBG uptake defect score				
RR interval	0.39	0.23	0.31	0.38
SD	0.25	0.46	-0.06	0.86
RMSSD	-0.67	0.02	0.27	0.44
pNN50	-0.31	0.35	0.05	0.89
LF	-0.47	0.15	0.44	0.20
HF	-0.74	0.009	0.51	0.13
LF/HF	0.44	0.16	0.02	0.96

HRV = heart rate variability; MIBG = ^{123}I-metaiodobenzylguanidine. See Methods for definition of HRV variables.

We have recently given direct evidence of abnormalities of cardiac adrenergic nerve function in most syndrome X patients, by demonstrating a marked reduction in global and/or regional cardiac uptake of MIBG[17], a guanethidine analogue compound which shares the same uptake/retention mechanisms as noradrenaline at sympathetic nerve terminals[18,19]. Cardiac defects of MIBG uptake, however, have different, and even possible contrasting interpretations. Indeed, they could be caused, theoretically, by a structural or functional impairment of sympathetic activity[28-34], possibly caused by ischemia[35-40], which in syndrome X has been proposed to be caused by microvascular dysfunction[8-10], but they could also be consequent to an increased release of noradrenaline, resulting in high intersynaptic concentrations and antagonistic competition for uptake with MIBG at nerve endings[23,34]. In the attempt to gain insights about the mechanism responsible for cardiac MIBG abnormalities in syndrome X, in this study we correlated scintigraphic MIBG results with cardiac autonomic tone, as assessed by 24-hour HRV analysis.

In agreement with our previous findings[41] and those of others[13,15], in this study we did not find any differences in average 24-hour values of HRV variables between patients with syndrome X and healthy control subjects. Nevertheless, while in control subjects there was no correlation between cardiac MIBG uptake, as assessed by either heart/mediastinum ratio or MIBG score, and HRV parameters, among syndrome X patients the degree of the impairment of cardiac MIBG uptake was significantly associated with lower values of HF and RMSSD, which have been shown to largely reflect vagal modulation of the sino-atrial node[20-22].

Thus, taken together, our findings suggest that, overall, modulation of cardiac autonomic activity may be set towards a prevalence of sympathetic activity in syndrome X patients. However, we cannot exclude that our data may reflect a simultaneous impairment in both sympathetic (indicated by the abnormal MIBG uptake) and vagal (indicated by the low HRV values) nerve function. The absence of differences in average values of HRV parameters between the two groups could be explained either by the heterogeneity of the population of syndrome X patients, making average values not significantly different from normal, or by possible compensatory or reflex adjustments of cardiac autonomic tone.

Some caution should also be used, however, in considering 24-hour HRV as simply correlated with cardiac autonomic function, as it might also be affected by other unrecognized factors[42].

The effects of adrenergic stimulation on coronary microvascular tone, on the other hand, are also complex and controversial. Sympathetic activation increases coronary flow indirectly through metabolic vasodilation secondary to an increase in heart rate and myocardial contractility[43] and, in part, to endothelium-mediated vasodilation[44]. On the other hand, it may have both direct vasodilator and vasoconstrictor effects through β-receptor and α-receptor stimulation, respectively[43], the net effect likely depending on the pathophysiologic state of small coronary arteries. Indeed, a heightened sympathetic stimulation could determine abnormal microvascular constriction in some conditions[43,45]. On the other hand, Di Carli et al.[46] have recently demonstrated that, in heart transplanted patients, myocardial areas with a lower uptake of the norepinephrine analogue [^{11}C]hydroxyephedrine, suggesting poor reinnervation, have blunted increase of coronary blood flow during sympathetic activation by cold pressor testing, compared to areas showing greater tracer uptake, suggesting higher degrees of sympathetic reinnervation. Thus, theoretically, both a reduced or increased sympathetic nerve activity could be associated with abnormalities in coronary blood flow in syndrome X.

It is worth noting that our data on MIBG results present some similarities with those reported by Meeder et al.[15]. As in our study, these authors did not observe any differences in average HRV values between syndrome X patients and controls. However, they found an inverse correlation between the heterogeneity of myocardial perfusion, as assessed by positron emission tomography, and vagal HRV indexes. Taken together, Meeder s data and ours suggest a possible relationship between abnormalities in coronary blood flow and those in cardiac nerve function. In which way they are correlated and the respective role in the pathogenesis of the syndrome, however, cannot be addressed from the data until now available and will require further investigation[47].

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