

Clinical Research

Association of Myocardial Inotropic Reserve and Adrenergic Nerve Alterations in Idiopathic Dilated Cardiomyopathy: A Dobutamine Stress Echocardiographic and 123-I-MIBG Scintigraphic Study

FRANGISKOS I. PARTHENAKIS¹, ALEXANDER P. PATRIANAKOS¹, VASSILIOS K. PRASSOPOULOS², GEORGE F. DIAKAKIS¹, IOANNIS K. KARALIS¹, HERCULES E. MAVRAKIS¹, NIKOS S. KARKAVITSAS², PANOS E. VARDAS¹.

¹Department of Cardiology, ²Department of Nuclear Medicine², Heraklion University Hospital, Crete, Greece

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Address:

Panos E. Vardas

Cardiology Department,
Heraklion University
Hospital, Heraklion,
Crete, Greece
e-mail:
cardio@med.uoc.gr

Introduction: The aim of this study was to assess the relationship between myocardial inotropic reserve and cardiac sympathetic innervation in patients with idiopathic dilated cardiomyopathy (IDC) and their correlation to exercise capacity.

Methods: Baseline and dobutamine stress echocardiography and radiotracer studies with 123-I-Metaiodobenzylguanidine (MIBG) provided quantitative assessment of left ventricular (LV) wall motion and heart to mediastinum uptake ratio and washout, in 37 patients with IDC and LV ejection fraction (EF) < 45 %. A cardiopulmonary exercise test was performed in all patients.

Results: According to median MIBG uptake at 4 hours patients were divided into two groups: Group I, who showed late MIBG ≥ 1.47 and Group II with late MIBG < 1.47 . No significant differences were found in baseline NYHA functional class, LV dimensions or LVEF between two groups. However, Group I patients showed increased maximal oxygen consumption at peak exercise (PVO_2) compared to Group II ($p=0.04$). Late MIBG was correlated with LV rest motion score index (WMSI) ($r=-0.39$), systolic wall stress ($r=-0.34$) and PVO_2 ($r=0.37$). WMSI increased in both groups under dobutamine, with a higher increase in group I ($p<0.001$). WMSI changes under dobutamine were correlated significantly with early ($r=0.69$), late ($r=0.71$) MIBG, washout ($r=-0.38$) and LVEF changes ($r=0.56$) but not with other echocardiographic parameters. Multivariate analysis revealed that the late MIBG uptake was independently associated with WMSI improvement ($p<0.001$).

Conclusions: Myocardial inotropic reserve is significantly associated with the myocardial adrenergic innervation in dilated cardiomyopathy. Late MIBG cardiac uptake may predict cardiac inotropic reserve and exercise capacity in those patients.

Evaluation of myocardial contractile reserve in patients with heart failure provides useful information concerning the underlying disease process and contributes towards identifying the risk for poor exercise tolerance and prognosis.^{1,2}

The adrenergic nervous system plays a major role in regulating cardiac function, stimulating cardiac contractility and contributing significantly to the pathophysiology of congestive heart failure.³ Decreased response to beta-adrenergic stimulation due to a reduction in beta-adre-

nergic receptors is considered to be one of the major mechanisms leading to systolic dysfunction in this condition.⁴ The decrease in beta-receptors has been evaluated from their response to beta-agonist inotropic stimulation.^{5,6}

Dobutamine, a mainly beta₁-adrenergic agent, has been used to assess the myocardial inotropic reserve in patients with congestive heart failure,⁵ which depends not only on the amount of viable myocardium but also on the degree of neuroadrenergic activation.⁷

Non-invasive scintigraphy with 123-I-Metaiodobenzylguanidine (MIBG), an analogue of norepinephrine that shares the same re-uptake pathways within the cardiac synapse,⁸ was developed to visualize sympathetic innervation and thus has the potential to mirror the whole myocardial adrenergic pathway disintegrity.^{9,10} Decreased cardiac MIBG uptake and increased washout rate have been found in patients with heart failure, both correlating with alterations in left ventricular function^{8,11} and life duration.¹²

We assumed that in patients with idiopathic dilated cardiomyopathy (IDC) myocardial inotropic reserve could be correlated with cardiac adrenergic nerve activation, as both of these are associated with adrenergic receptor mechanisms.

The aim of our study was to examine the relationship between the myocardial response to dobutamine during stress echocardiography and the sympathetic nerve alterations assessed by MIBG scintigraphy as well as their correlation with cardiopulmonary exercise capacity in patients with heart failure secondary to IDC.

Methods

Patients

We studied 37 patients (22 men and 15 women, mean age 56 ± 11 years) with IDC and stabilized their congestive heart failure, which was referred to our heart failure clinic for further evaluation. Functional capacity was class I-IV according to the New York Heart Association classification and patients had a reduction in left ventricular (LV) ejection fraction (EF) to <45%.

The diagnosis of IDC was based on LVEF <45%, LV end diastolic diameter >5.5 cm on echocardiography and absence of significant coronary artery disease on coronary angiography.

Patients with uncontrolled systemic hypertension, primary valvular heart disease, chronic systemic dis-

ease involving the heart, congenital heart disease, cor pulmonare or diabetes mellitus were excluded.

Cardiac medication during the study period included angiotensin converting enzyme inhibitors and diuretics in all patients, digoxin (n=18), coumarin (n=4) and nitrates (n=3). No patient received spironolactone, beta-blockers, beta-agonists or tricyclic antidepressants, which are known to reduce the concentration of the myocardial MIBG.

All patients were in sinus rhythm and none had left bundle branch block or severe mitral valve regurgitation.

Our institution's ethical committee approved this study and patients gave informed consent before they entered the study.

Echocardiographic study

M-mode, two-dimensional and Doppler echocardiography were performed in all patients at baseline and at the end of dobutamine infusion using a Hewlett-Packard Sonos 2500 echocardiograph device (Andover, Massachusetts, USA) with a 2.5 MHz wide-angle phased-array transducer.

All examinations were recorded on videotape and calculations were made offline, using the internal analysis software of the echocardiographic device.

All measurements were made according to the recommendations of the American Society of Echocardiography.¹³ Left ventricular volumes were measured from the apical two-dimensional echocardiogram using a modified Simpson's rule algorithm, while ejection fraction and LV systolic wall stress¹⁴ were calculated. Regional systolic wall thickening was assessed with a sixteen-segment model. For each segment, systolic wall thickening was visually graded with a quantitation scoring system in which 1=normal, 2=hypokinetic, 3=akinetic and 4= dyskinetic.

Global wall motion score index (WMSI) was calculated by adding individual segment scores and dividing by the total number of segments analyzed. Two independent investigators analyzed the LV wall motion abnormalities. In the case of a disagreement, a third investigator reviewed the findings and a majority decision was reached. Those analyzing the echocardiographic data were blinded to the other data. Data were analyzed as the mean of three cardiac cycles.

Dobutamine administration

Intravenous dobutamine was administered by infusion pump, starting at 2.5 µg/kg/min and increasing

to 5, 7.5 and 10 µg/kg/min at 3-minute intervals in all patients. A continuous 12-lead electrocardiogram was recorded throughout the test and blood pressure was recorded every 3 minutes.

123-I-MIBG scintigraphy

On the day of the 123-I-MIBG scintigraphy all patients and controls were instructed to fast for six hours. Lugol's iodine solution 1 ml was given orally two hours before a slow intravenous injection of 5 mCi 123-I-MIBG (Mallinckrodt Inc, St Louis, Missouri, USA); specific activity 74 MBq/mg. At 10 minutes and four hours after the tracer injection, a 10 minute static acquisition was performed in the anterior view of the chest, using a General Electric (GE Medical Systems) large field of view, single head gamma camera fitted with a low energy, all purpose, parallel hole collimator. A 20% energy window centred on 157 keV and a 128 x 128 matrix size were used. Thirty-two projections (50 seconds each) were obtained over a 180° arc, from left posterior oblique to right anterior oblique, and the images were stored using a 64 x 64 matrix. Trans-axial, sagittal, and oblique tomograms were obtained using a nuclear medicine computer (software: GENIE v. 2.5H, 99224, rev. 137, GE medical systems). Cardiac uptake was quantified in all planar views. A 7 x 7 pixel region of interest was drawn over the cardiac region and another 7 x 7 region of interest over the upper mediastinum area. The heart to mediastinum (H/M) activity ratio, introduced by Merlet and colleagues,¹² was then computed to quantify cardiac 123-I-MIBG accumulation. Two independent observers measured the H/M ratio, and the average of the two measurements was taken as the datum. The MIBG washout rate from the myocardium was calculated as follows:

$$\frac{\text{Initial myocardial MIBG uptake} - \text{Delayed myocardial MIBG uptake}}{\text{Initial MIBG uptake}} \times 100$$

Two independent experts with no knowledge of the clinical and angiographic results examined MIBG scintigrams. The MIBG uptake and washout data of our patients were compared with those of ten, age-matched, normal individuals with no cardiovascular disease or diabetes mellitus, who were not on any medication and comprised the control group.

Exercise testing protocol and gas exchange analysis

All patients underwent an exercise test, using a Marquette treadmill device Max-1 (GE medical systems, USA), after at least 3 hours without food, coffee or cigarettes. A graded, symptom-limited test was performed using a Naughton protocol. A 12-lead ECG was monitored continuously, with recordings every 2 minutes at the end of each stage. Blood pressure was measured with a sphygmomanometer during the final 30 seconds of each work stage. Gas exchange data were collected continuously with an automated breath-by-breath system (Oxycon A, version 3.1, Jaeger, Netherlands). These instruments were calibrated before every test using standard gases.

The exercise duration was defined as the time from the start of exercise until its cessation because of dyspnea or fatigue. Oxygen consumption at peak exercise (PVO_2) was calculated as the average VO_2 value over the final 30 seconds of exercise. The test was performed within a mean 10 ± 5 days before or after the rest-stress echocardiographic and MIBG study.

Statistical analysis

Continuous variables are summarized as mean \pm standard deviation. One-way analysis of variance was used to compare MIBG uptake across the patient and control groups. Comparisons of the means in two groups were performed using the Student t-test. The relation between MIBG and other parameters of interest were assessed with Pearson two-tailed correlation methods. Multivariate stepwise linear regression analysis was used to determine the variables independently associated with changes in WMSI. The criterion for significance was set at 5%.

Results

Both early (at 10 min) and late (at 4 hours) cardiac MIBG uptake ratio was significantly reduced in the patients compared to normal individuals (1.6 ± 0.15 vs. 2.08 ± 0.20 , $p < 0.001$ and 1.48 ± 0.17 v 2.05 ± 0.20 , $p < 0.001$). The washout rate was also significantly increased in the patients compared to the control group ($7\% \pm 4\%$ vs. $2\% \pm 3\%$, $p < 0.001$). Late MIBG uptake was found to correlate with rest WMSI ($r = -0.39$, $p = 0.01$), washout ($r = -0.60$, $p < 0.001$) and LV end-systolic wall stress ($r = -0.34$, $p = 0.03$). Ten-

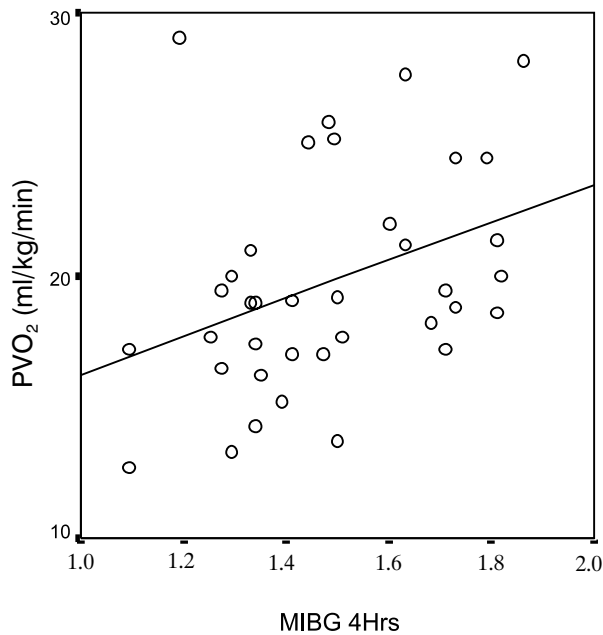


Figure 1. Relationship between MIBG at 4 hours and oxygen consumption at peak exercise (PVO_2) in patients with idiopathic dilated cardiomyopathy.

minute MIBG cardiac uptake was also correlated with resting WMSI ($r=-0.38$, $p=0.02$).

When we examined the relationship of MIBG and cardiopulmonary exercise parameters, we found that late MIBG uptake was correlated with PVO_2 ($r=0.37$, $p < 0.02$; Figure 1).

Based on median MIBG cardiac uptake at 4 hrs (1.47) our patients were divided into two groups. The first included those in whom the late MIBG uptake was greater than or equal to the median value (Group I, 19 patients) and the second contained those with late MIBG uptake < 1.47 (Group II, 18 patients).

The clinical and echocardiographic parameters of the study groups are illustrated in Table 1. No significant differences in baseline demographic or echocardiographic chamber dimensions or function were found between the two groups.

There were no significant differences in resting WMSI (2.06 ± 0.29 vs. 2.21 ± 0.34 , $p=NS$) or in LV end-systolic wall stress (191.2 ± 43.4 vs. $201.6 \pm 49.9 \times 10^3$ dynes/cm², $p=NS$) between Groups I and II, respectively.

Group I patients achieved better maximal PVO_2 compared to Group II ($p=0.04$).

No patient developed any major side effect during dobutamine infusion to interrupt the test, while all patients showed improvement in WMSI. Table 2 shows the effects of dobutamine on clinical and LV echocardiographic variables in all patients.

No significant differences between the two groups were apparent in heart rate changes, arterial systolic blood pressure or LV systolic wall stress changes under dobutamine infusion.

Although the LVEF increased significantly in both groups ($27 \pm 10.5\%$ and $18.5 \pm 8.4\%$ for Groups

Table 1. Baseline characteristics of study patients according to median cardiac MIBG uptake at 4 hrs.

Baseline variables	Late MIBG cardiac uptake ≥ 1.47 (Group I)	Late MIBG cardiac uptake < 1.47 (Group II)	p value
No.	19	18	
Age (years)	54.7 ± 11.9	55.2 ± 12.3	0.90
NYHA class	2.6 ± 0.55	2.75 ± 0.7	0.61
LVEF (%)	31.1 ± 8.0	28.6 ± 7.6	0.35
WMSI	2.06 ± 0.29	2.21 ± 0.34	0.16
LVDD (mm)	60.8 ± 5.4	63.7 ± 8.1	0.20
LVSD (mm)	48.4 ± 5.7	52.3 ± 9.1	0.13
LA (mm)	43.3 ± 5.4	43.7 ± 4.9	0.81
Em (cm/s)	0.59 ± 0.19	0.64 ± 0.21	0.43
Am (cm/s)	0.64 ± 0.17	0.50 ± 0.23	0.04
Em/Am	1.11 ± 0.94	1.82 ± 1.43	0.09
LVWS (dynes/cm ²)	$191.2 \pm 43.4 \times 10^3$	$201.6 \pm 49.9 \times 10^3$	0.57
PVO_2 (ml/kg/min)	21 ± 3.9	18.2 ± 3.9	0.04

LVEF = left ventricular ejection fraction, WMSI = wall motion score index, LVDD = left ventricular end-diastolic diameter, LVSD = left ventricular end-systolic diameter, LA = left atrium, Em = Doppler mitral early filling wave velocity, Am = mitral atrial filling wave velocity, LVWS = left ventricular end-systolic wall stress, PVO_2 = maximal oxygen consumption at peak exercise.

Table 2. Changes in hemodynamic and echocardiography parameters in response to dobutamine.

Variables	Group I		Group II		p value
	Rest	Stress	Rest	Stress	
HR (beats/min)	81.1 ± 7.3	86.7 ± 7.7	79.2 ± 6.7	85.5 ± 6	
ΔHR (%)		-7 ± 6		-8 ± 10	0.54
SBP (mmHg)	130.3 ± 17.2	138.9 ± 17.4	131.7 ± 11.8	139.8 ± 15.1	
ΔSBP (%)		-7 ± 14		-6 ± 7	0.77
LVDV (ml)	144.4 ± 32.9	131.4 ± 25.9	180.2 ± 79.2	156.4 ± 68.8	
ΔLVDV (%)		7.3 ± 15.5		12.9 ± 7.8	0.18
LVSV (ml)	100.8 ± 31.3	76.6 ± 21.5	129.2 ± 72.9	104.3 ± 59.3	
ΔLVSV (%)		22.5 ± 12.8		19.4 ± 11.6	0.43
WMSI	2.06 ± 0.29	1.22 ± 0.23	2.21 ± 0.34	1.64 ± 0.31	
ΔWMSI (%)		40.4 ± 7.2		25.9 ± 7.1	<0.001
EF (%)	31.1 ± 8.3	42.2 ± 7.6	28.6 ± 7.6	35.2 ± 9.3	
ΔLVEF (%)		27 ± 10.5		18.5 ± 8.4	0.01
LVWS (dynes/cm ² x10 ³)	191.2 ± 43	223.7 ± 51	199.6 ± 49.22	5.5 ± 57	
ΔLVWS %		17 ± 10		13 ± 8	0.12

HR = heart rate, SBP = systolic blood pressure, LVEF = left ventricular ejection fraction, WMSI = wall motion score index, LVDV = left ventricular end-diastolic volume, LVSV = left ventricular end-systolic volume, LVWS = left ventricular wall stress, Δ = change under dobutamine, p values refer to differences between Δ values in the two groups.

I and II, respectively, the magnitude of the increase was higher in Group I (p=0.01).

The change in WMSI under dobutamine (ΔWMSI) was also higher in group I compared to group II patients (40.4 ± 7.2 vs. 25.9 ± 7.1%, p <0.001; Figure 2).

A significant correlation was found between the ΔWMSI and early MIBG (r=0.69, p<0.001), late

MIBG (r=0.71, p<0.001; Figure 3), washout (r=-0.38, p=0.02; Figure 4) and LVEF changes (r=0.56, p<0.001) but not with other echocardiographic variables.

When we entered all the above parameters into a multivariate stepwise linear regression analysis, we found that the MIBG uptake at 4 hours was independently associated with the ΔWMSI, indicating a rela-

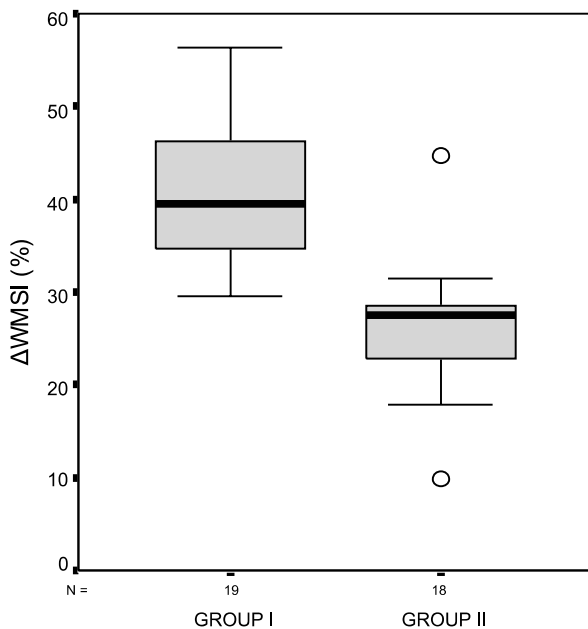


Figure 2. Left ventricular wall motion score index changes under dobutamine (ΔWMSI) in the two groups separately.

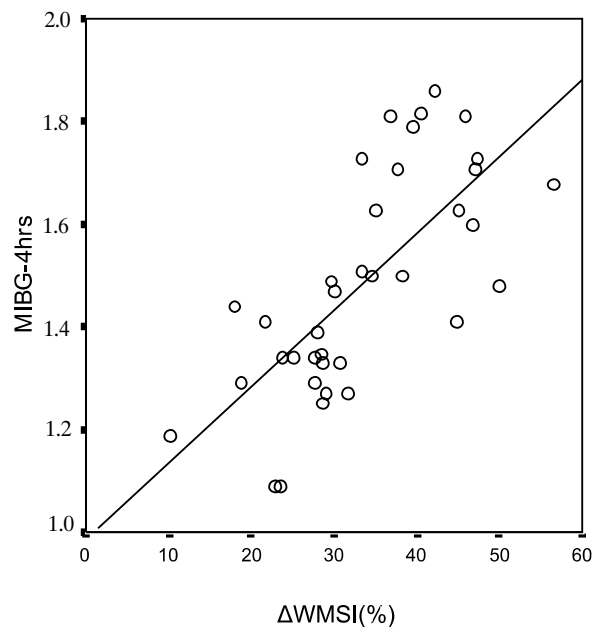


Figure 3. Correlation between left ventricular wall motion score index changes (ΔWMSI) under dobutamine and cardiac MIBG uptake at 4 hours.

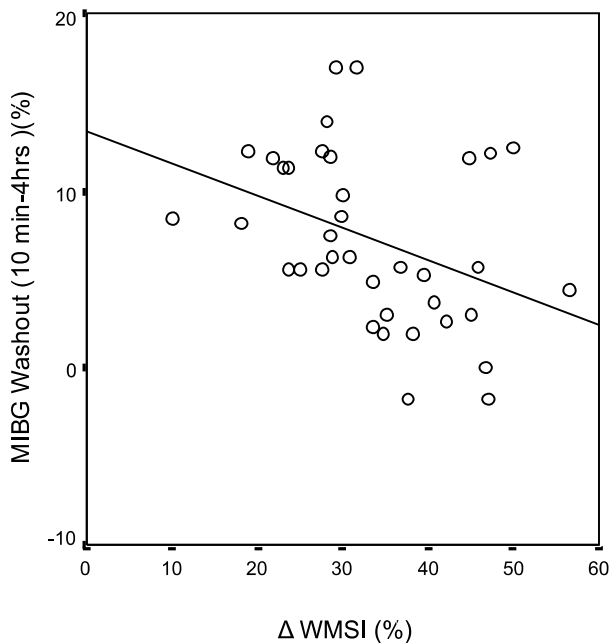


Figure 4. Correlation of MIBG washout rate with left ventricular wall motion score index changes (Δ WMSI) under dobutamine.

relationship between cardiac contractile reserve and myocardial adrenergic innervation. More specifically, the relation of late MIBG and WMSI changes with dobutamine can be described by the equation of the least square line:

$$\Delta\text{WMSI} = -17.1 + 34.05 \times \text{MIBG at 4 hours} \quad (\text{R square} = 0.51)$$

The washout rate correlated with the magnitude of Δ WMSI, suggesting a possible association of sympathetic nerve activity and cardiac contractile reserve.

Discussion

By utilizing dobutamine stress echocardiography and ^{123}I -MIBG scintigraphy we investigated the relation between the myocardial neuroadrenergic activation and contractile reserve in patients with idiopathic dilated cardiomyopathy.

Our results showed that the cardiac response to beta-inotropic stimulation was inversely related to cardiac adrenergic nerve activity. Although all patients in heart failure showed reduced values of MIBG uptake, patients with lower values of MIBG uptake exhibited lower inotropic response to dobutamine stimulation.

123-I-MIBG uptake in heart failure

The compensatory mechanisms that have been described in the pathophysiology of heart failure

include, among others, early activation of the sympathetic nervous system. Norepinephrine is synthesized directly within the myocardium, acts in an autocrine and paracrine manner¹⁵ and its increased levels in the vicinity of the receptors mediate the down-regulation of cardiac beta-adrenergic receptors.¹⁶ Furthermore, several abnormalities of the sympathetic nervous system have been demonstrated in dilated cardiomyopathy¹⁷ and a reduction in the density of membrane-associated beta-adrenoreceptors is believed to be a consequence of the development of anti-beta-adrenoreceptor auto-antibodies.¹⁸ The enhanced adrenergic activity is marked by attenuation in cardiac responsiveness to beta-adrenergic stimuli and prolonged sympathetic activation may ultimately contribute to the progression of heart failure.¹⁹

The elevated levels of circulating norepinephrine are thought to participate in the evolution of congestive heart failure.²⁰ However, plasma norepinephrine is derived throughout the whole body and is therefore not a specific index of cardiac adrenergic activity.²¹ Noninvasive scintigraphy with ^{123}I -MIBG imaging provides the opportunity to explore the cardiac nerve integrity function, as it is a norepinephrine analogue.²²

We found a significant association between MIBG uptake and improvement in LV segmental wall contractility, indicating that the degree of neuroadrenergic activation influences the magnitude of contractile reserve in these patients. Bengel et al²³ found that in dilated cardiomyopathy the alterations of cardiac sympathetic innervation are associated with impaired contractile function, suggesting a common pathogenic pathway.

Previous studies^{22,24} have shown that the non-neuronal myocardial MIBG uptake mainly contributes to early images and disappears rapidly, whereas the neural uptake contributes to delayed images. These findings suggest that delayed images represent adrenergic nerve function more faithfully than early images. Therefore we mainly evaluated delayed cardiac MIBG uptake.

Since the MIBG washout rate is standardized by the initial myocardial uptake of MIBG, regardless of the amount of viable myocardium,²⁵ this measurement could more accurately represent sympathetic nervous system activity. We found a relationship between MIBG washout and Δ WMSI, suggesting that the increased sympathetic nerve activity in heart failure leads to reduced inotropic cardiac reserve due

to down-regulation or desensitization of cardiac beta-adrenergic receptors.

We also found a significant correlation between MIBG uptake and cardiopulmonary exercise variables. This suggests that the alteration in cardiac adrenergic function may participate in the alteration of exercise response in patients with dilated cardiomyopathy.

Cohen-Solal et al,²⁶ who showed a good correlation between MIBG uptake and PVO_2 , have reported similar findings to those of this part of our study in patients with chronic heart failure.

Beta-contractile responsiveness

The detection of the contractile reserve of dobutamine stress echocardiography in asynergic segments requires up to 50% of viable myocytes²⁷ but is also influenced by the degree of myocardial neuroadrenergic status.⁷

In the failing myocardium, the beta-adrenergic receptor pathway is altered. Changes in the beta-adrenergic receptor/G Protein /adenylyl cyclase pathways have been extensively described^{6,28} and all result in impairment of contractile capacity. Although assessment of these alterations in humans is complex, pharmacological studies provide a reliable measurement to explore such alterations.

Infusion of dobutamine, a beta-agonist, has been proposed as a more appropriate method for researching alterations in the beta-adrenergic receptor pathway.²⁹ One of the major findings of the present study was that patients with a low beta-adrenergic contractile responsiveness showed a lower augmentation of LV ejection fraction and reduced sympathetic innervation.

Patients with non-ischemic heart failure, such as those in our study, do not show contractile worsening during stress, but various degrees of improvement in most segments, which have been utilized for prognostic stratification.³⁰ This positive response to dobutamine however, is attenuated in some patients, suggesting impairment of contractile reserve.

The contractile reserve detectable with dobutamine is mainly influenced by scarring, patchy fibrosis,³¹ myocardial blood flow,²¹ depletion of myocardial norepinephrine,³² limitation of coronary flow reserve³³ and inappropriate elevation of myocardial wall stress during exercise.³⁴

The response of our patients to dobutamine was not related to baseline clinical or echocardiographic

characteristics. In this condition, the cardiac response to various inotropic agents has been found to be not strictly dependant on the baseline function.³⁵ The changes in heart rate, blood pressure and systolic wall stress in response to dobutamine were also similar in both groups. Thus, the myocardial inotropic response was the principle factor responsible for differentiating the patients with greater improvement in WMSI from the patients with an impaired response.

Other investigators have studied the prognostic usefulness of left ventricular response to dobutamine in patients with IDC.³⁶ Naqvi et al³⁷ found that dobutamine induced improvement in LV ejection fraction identifies patients with idiopathic dilated cardiomyopathy who exhibit substantial improvement in LV function, while Colucci et al³⁸ proved that the degree of adrenergic system activation may be one of the factors that are involved in the myocardial inotropic response to beta-adrenergic receptor stimulation.

Clinical implications

Although we did not study the prognosis of our patients according to our methodology, the present findings suggest that failing hearts which preserve their innervation are those that maintain the ability to recover their contractile function, and may constitute a marker for the prognosis of patients with idiopathic cardiomyopathy, as shown in other studies.^{23,39} Furthermore, patients who retain their sympathetic myocardial innervation are those who have more effective or less down-regulated beta₁-adrenergic receptors and may benefit from the use of beta-blockers.⁴⁰

The relationship between MIBG uptake, contractile reserve and cardiopulmonary exercise tolerance, suggests that the non-invasive assessment of alteration in the beta-adrenergic pathway may also be considered in the transplantation decision-making process.

Study limitations

The direct evaluation of neuroadrenergic system function via myocardial adrenoceptor density was not available in our study.

We did not measure plasma norepinephrine levels. Although previous studies have shown that in heart failure patients markedly elevated resting

plasma levels of norepinephrine concentration have a reduced myocardial inotropic reserve to beta-adrenergic stimulation,³⁸ these levels have been shown not to be high enough to activate myocardial adrenergic receptor mechanisms.²⁸

MIBG cardiac uptake has been found to correlate with myocardial content of norepinephrine but not with plasma norepinephrine concentration.²⁰ It therefore follows that MIBG uptake may be a more specific index of cardiac adrenergic dysfunction than that derived from measurements of plasma norepinephrine, which reflects the systemic adrenergic activity.

The number of patients in our study was limited. Further studies with larger study populations should therefore be undertaken.

Conclusions

Our study showed that in patients with heart failure, secondary to idiopathic dilated cardiomyopathy, cardiac adrenergic innervation is related to left ventricular contractile reserve and cardiopulmonary exercise tolerance.

MIBG scintigraphy and dobutamine stress echocardiography, which methods are both associated with beta-adrenergic receptor mechanisms, may identify patients who have preserved beta adrenergic receptor density.

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