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Anti-tachycardia therapy can improve altered cardiac adrenergic function in tachycardia-induced cardiomyopathy

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We investigated whether anti-tachycardia therapy might improve the altered cardiac adrenergic and systolic function in tachycardia-induced cardiomyopathy (TC) in contrast to dilated cardiomyopathy (DCM). The subjects were 23 patients with heart failure, consisting of 8 patients with TC (43.6 ± 10.0 yrs) and 15 with DCM (45.3 ± 8.2 yrs). TC was determined as impairment of left ventricular function secondary to chronic or very frequent arrhythmia during more than 10% of the day. All patients were receiving anti-tachycardia treatment. Cardiac ^{123}I-MIBG uptake was assessed as the heart/mediastinum activity ratio (H/M) before and after treatment. LVEF was also assessed. In the baseline study, H/M and LVEF showed no difference between TC and DCM (2.21 ± 0.44 vs. 2.10 ± 0.42, 35.3 ± 13.1 vs. 36.0 ± 10.9%, respectively). After treatment, the degree of change in H/M and LVEF differed significantly (0.41 ± 0.34 vs. 0.08 ± 0.20, 20.5 ± 14.4 vs. −2.1 ± 9.6%, $p < 0.01$). In TC, heart failure improved after a shorter duration of treatment ($p < 0.05$). In conclusion, anti-tachycardia therapy can improve altered cardiac adrenergic function and systolic function in patients with TC over a shorter period than in those with DCM.

Key words: tachycardia-induced cardiomyopathy, iodine-123-metaiodobenzylguanidine (^{123}I-MIBG), adrenergic function, dilated cardiomyopathy, congestive heart failure

INTRODUCTION

CHRONIC or very frequent tachycardia has been clearly shown to cause congestive heart failure, so-called tachycardia-induced cardiomyopathy (TC).[1,2] The development of this form of cardiomyopathy is characterized by significant chamber dilatation, reduced wall thickness, and impairment of systolic function. It is very similar to dilated cardiomyopathy (DCM) before treatment. At present, the diagnosis of TC can be confirmed only retrospectively after control of the arrhythmia. The prevalence of supraventricular or ventricular arrhythmias among patients with heart failure is high. Many reports have demonstrated that patients with TC have a significant improvement of ventricular function, either partial or complete, after normalization of the heart rate.[3–8] Other reports have also demonstrated that experimental pacing-induced cardiomyopathy models have an improvement of ventricular function after finishing pacing.[9–11] In chronically paced animals, the response to beta-adrenergic stimulation is blunted.[11–13] As in human dilated cardiomyopathy, this may be related to a decrease in the density of beta-adrenergic receptors.[12,13] In addition, these studies suggested that tachycardia may result in a reversible form of TC. It is important to properly recognize patients with heart failure in whom TC may be present.

Schofer et al. established DCM with Iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) imaging which can non-invasively assess cardiac adrenergic function, and demonstrated altered cardiac adrenergic function in patients with DCM,[14] but there are no reports on the

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results of ^{123}I-MIBG imaging in TC.

In this study, we evaluated cardiac adrenergic function in TC with ^{123}I-MIBG, and investigated whether anti-tachycardia therapy might improve the altered cardiac adrenergic function in TC, and the possibility of distinguishing TC from DCM with ^{123}I-MIBG.

MATERIALS AND METHODS

Patients and evaluation

Twenty-three patients (Tables 1, 2) with heart failure were identified retrospectively between 1993 and 2000, consisting of 8 patients with TC (43.6 ± 10.0 years old) and 15 patients with DCM (45.3 ± 8.2 years old) at our institution. All patients had dyspnea and/or abnormalities on echocardiography. No patient had suffered a recent myocardial infarction or unstable angina. There were no cases of uncorrected valvular heart disease.

All patients underwent physical, electrocardiographic and radiographic examination (Table 2). Fifteen of the 23 patients underwent cardiac catheterization, and 11 patients underwent myocardial biopsy. No patient had significant coronary stenosis, of more than 50% of the lumen diameter. All patients had perfusion scintigraphic imaging. The images were analyzed with respect to the extent of the perfusion defect as the defect score (DS) by using 20 segments of LV (Fig. 1), which consisted of 6 segments of 3 cuts in the short-axis (apical, midventricular and basal) and 2 additional apical segments of a vertical long-axis cut. Each segment was evaluated on a 4-grade scale (0 = normal, 1 = mild perfusion defect, 2 = moderate perfusion defect, 3 = severe perfusion defect).

The diagnosis of DCM was made on the basis of evaluations that included electrocardiography, chest roentgenography, and echocardiography. Ten of 15 underwent cardiac catheterization, and 11 cases underwent endomyocardial biopsy. TC was determined retrospectively according to the criteria of Fenelon et al.[9]: impairment of left ventricular function secondary to chronic or very frequent cardiac arrhythmia that occurred more than 10–15% of the day.

Treatment

Patients were treated with digitalis, diuretics, vasodilators, angiotensin converting enzyme inhibitors, β-blockers, or anti-arrhythmic agents. Among 8 patients with TC, 2 were treated with radiofrequency catheter ablation (RFCA) and 3 underwent direct-current cardioversion (DC). The patients were studied before and after anti-tachycardia treatment (Table 3), when the symptoms of heart failure had improved and were confirmed to be stable.

SPECT imaging technique

First ^{123}I-MIBG myocardial scintigraphy was performed within 3 months after the development of heart failure. In a steady state after blockade of thyroid uptake of free ^{123}I-MIBG by sodium perchlorate and fasting, 111 MBq (3 mCi) ^{123}I-MIBG was intravenously injected, and anterior planar images were obtained 4 hours after injection, with a low-energy general purpose collimator attached to a single-headed rotating gamma camera (Starcam 3000 XC/T, General Electrics, Milwaukee, Wisconsin). Analysis of the tomographic data was performed with a computer system in a 128 × 128 matrix, and data were stored in a personal computer. Uptake of ^{123}I-MIBG by the heart was quantified within the region of interest (ROI). The ROI was placed in the left ventricular myocardium, and another ROI was placed in the upper mediastinum area to standardize cardiac uptake, as previously described.[15,16] On planar images, the heart to mediastinum activity ratio (H/M) was determined from the cardiac ^{123}I-MIBG uptake, which was obtained as the average count of the ROI of the heart. And the washout rate was calculated as the percent change in cardiac ^{123}I-MIBG activity from early

Table 1 Clinical characteristics and parameters of the paients recorded at baseline (n = 23)

	TC (n = 8)	DCM (n = 15)	p
Age (years old)	43.6 ± 10.0	45.3 ± 8.2	ns
Gender (M/F)	7/1	11/4	ns
NYHA class	1.88 ± 1.13	1.60 ± 1.12	ns
Baseline LVEF (%)	35.3 ± 13.1	36.4 ± 13.1	ns
Baseline H/M	2.21 ± 0.44	2.10 ± 0.42	ns

Abbreviations: TC, tachycardia-induced cardiomyopathy; DCM, dilated cardiomyopathy; M/F, male/female; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; H/M, heart-to-mediastinum uptake ratio.

Table 2 Underlying diseases of the patients

	TC (n = 8)	DCM (n = 15)	p
Ischemic Heart Disease	0	0	ns
Diabetes Mellitus	1 (12.5%)	3 (20.0%)	ns
Hypertention	2 (25.0%)	1 (6.7%)	ns
Hyperuricemia	2 (25.0%)	4 (26.7%)	ns
Hyperlipidemia	3 (37.5%)	4 (26.7%)	ns
Valvular Disease (MR)	0	1 (6.7%)	ns

Abbreviations: TC, tachycardia-induced cardiomyopathy; DCM, dilated cardiomyopathy; MR, mitral valve regurgitation.

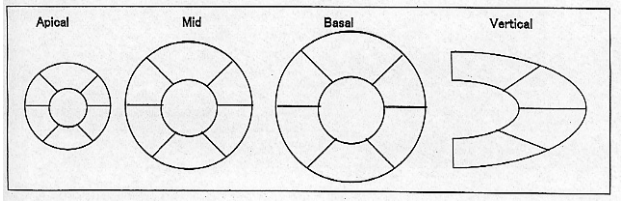

Fig. 1 Myocardial segmentations used to scoring of perfusion defects.

Table 3 Treatments for the patients

	TC (n = 8)	DCM (n = 15)	p
Follow-up months	10.6 ± 7.8	25.5 ± 18.3	< 0.05
Medication			
ACE inhibitors	4 (50.0%)	11 (73.3%)	ns
β-blocker	6 (75.0%)	5 (33.3%)	ns
Ca-blocker	6 (75.0%)	5 (33.3%)	ns
Diuretics	5 (62.5%)	11 (73.3%)	ns
mexiletine	0	4 (26.7%)	ns
nitrate	1 (12.5%)	3 (20.0%)	ns
procainamide	0	1 (6.7%)	ns
pilsicainide	2 (25.0%)	1 (6.7%)	ns
Elective conversion	3 (37.5%)	0	0.03
Catheter ablation	2 (25.0%)	0	ns

Abbreviations: TC, tachycardia-induced cardiomyopathy; DCM, dilated cardiomyopathy; ACE, angiotensin converting enzyme.

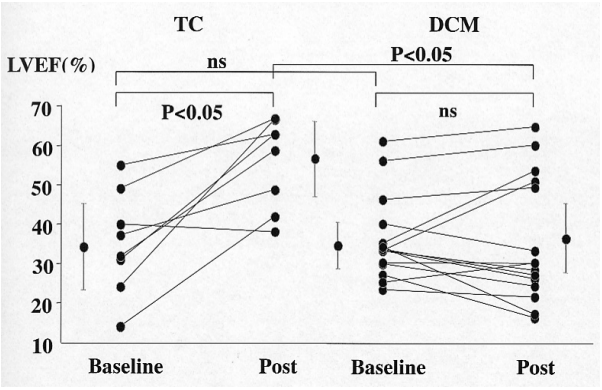

Fig. 2 Left ventricular ejection fraction before and after optimal treatment in patients with TC and DCM.

to delayed images. After optimal treatment, all patients underwent repeat ^{123}I-MIBG evaluation in the same way.

Echocardiography

Echocardiographic examination was performed with a commercially available scanner (Sonos 2500, Hewlett Packard Medical Products, Andover, Massachusetts) with a 3.75 MHz phase-array cardiac probe. The patient was positioned in the left lateral decubitus position. When an adequate precordial echocardiographic window was available, M-mode tracings of the left ventricle were recorded, and then end-systolic and end-diastolic measurements were obtained from the M-mode tracing according to previous recommendations.[17] The left ventricular ejection fraction (LVEF) was calculated from each pair of diameter measurements by using the Teichholz formula.[18]

Statistical analysis

Paired t-test was used to evaluate the significance of differences between TC and DCM in heart function and measurements. A p value of less than 0.05 was considered statistically significant. All parameters are expressed as the mean ± standard deviation (SD).

RESULTS

Clinical features

Before treatment, in 8 patients with TC (43.6 ± 10.0 years old, 7 male), one patient was in NYHA functional class IV, 1 was in class III, and 6 were in classes I–II (NYHA 1.88 ± 1.13). Five patients had atrial fibrillation (AF), one had ventricular tachycardia (VT) and very frequent premature ventricular contractions (PVCs), one had very frequent premature atrial contractions (PACs), and one had atrioventricular re-entry tachycardia (AVRT). In 15 patients with DCM (45.3 ± 8.2 years old, 11 male), 2 patients were in NYHA functional class IV, 2 were in class III, and 9 in classes I–II (NYHA 1.60 ± 1.12, ns). The perfusion images revealed more defects in patients with DCM than in those with TC (DS 16.3 ± 5.51 vs. 9.63 ± 5.50, $p < 0.05$).

Treatment

Patients were treated with digitalis, diuretics, vasodilators, angiotensin converting enzyme inhibitors, β-blockers, or anti-arrhythmic agents (Table 3). Among 8 patients with TC, 2 were treated with RFCA, and 3 received DC. TC patients required DC more often than DCM patients, with a statistically significant difference ($p = 0.03$), but other medications and procedures showed no significant difference between TC and DCM patients.

In the TC group, one patient had VT and PVCs that decreased from 47,592 beats/day to 194 beats/day after RFCA, and one AVRT patient was also treated with RFCA and had no more attacks. Three AF patients received DC shock and remained in sinus rhythm subsequently. In patients with frequent PACs or AF, the heart rate was controlled with anti-tachycardial medication. The TC group required a shorter duration of treatment to achieve a stable condition and undergo evaluation post-treatment H/M than the DCM group (10.6 ± 7.8 vs. 25.5 ± 18.3 months, $p < 0.05$). After treatment, NYHA in the TC group was significantly improved (from 1.88 ± 1.13 to 0.75 ± 0.46, $p < 0.05$), but the DCM group showed no improvement (from 1.60 ± 1.12 to 1.53 ± 1.25, ns).

Echocardiography

Before treatment, LVEF showed no difference between TC and DCM (35.3 ± 13.1% vs. 36.0 ± 10.9%, ns). Indeed, the duration of treatment was shorter in TC, and after optimal treatment, LVEF significantly recovered in patients with TC (from 35.3 ± 13.1% to 55.8 ± 11.4%, $p < 0.01$, Fig. 2), whereas there was no change in patients with DCM (from 36.4 ± 10.6% to 35.4 ± 16.0%, ns, Fig. 2). Post-treatment LVEF and the change in LVEF were also significantly greater in TC (55.8 ± 11.4% vs. 35.4 ±

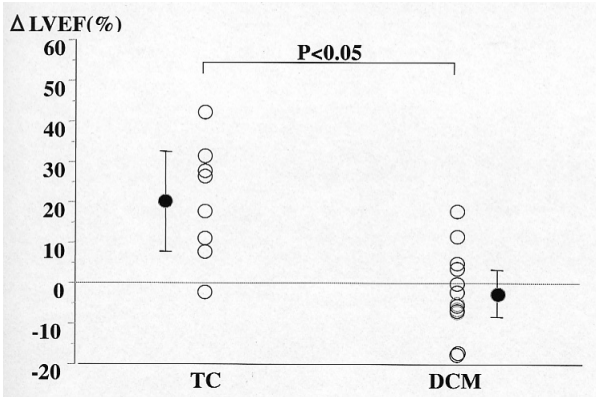

Fig. 3 Change of LVEF in patients with TC and DCM.

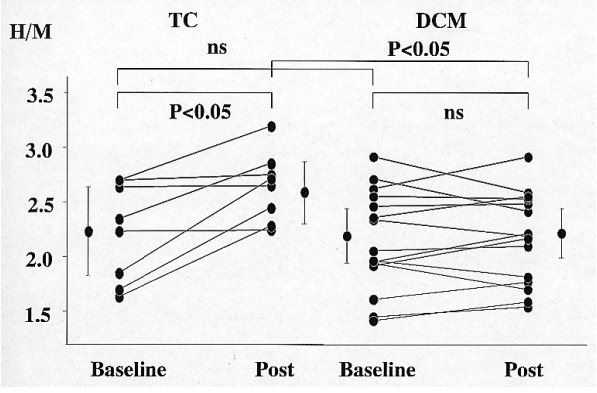

Fig. 4 Heart-to-mediastinum ^{123}I-MIBG uptake ratio before (*left*) and after (*right*) optimal treatment in patients with TC and DCM.

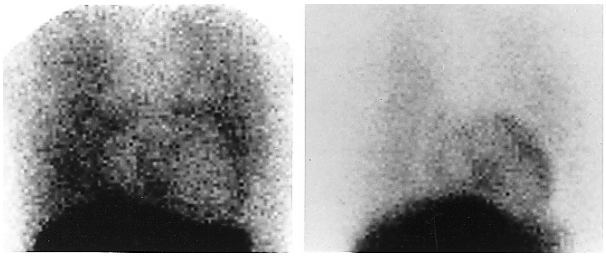

Fig. 5 ^{123}I-MIBG planar images before (*left*, H/M = 1.69) and after (*right*, H/M = 2.43) optimal treatment from a TC patient.

16.0%, $p < 0.005$, Fig. 2 and +20.5 ± 14.4 vs. –2.1 ± 9.6%, $p < 0.01$, Fig. 3). Rapid and significant LVEF recovery was observed in TC patients in comparison with DCM patients.

^{123}I-MIBG scintigraphy

Baseline H/M showed no difference between TC and DCM (2.21 ± 0.44 vs. 2.14 ± 0.45, ns, Fig. 4). After treatment, H/M was significantly improved in patients with TC (from 2.21 ± 0.44 to 2.62 ± 0.31, $p < 0.01$, Figs. 4, 5),

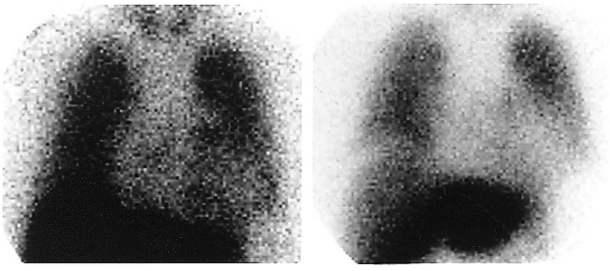

Fig. 6 ^{123}I-MIBG planar images before (*left*, H/M = 1.45) and after (*right*, H/M = 1.54) optimal treatment from a DCM patient.

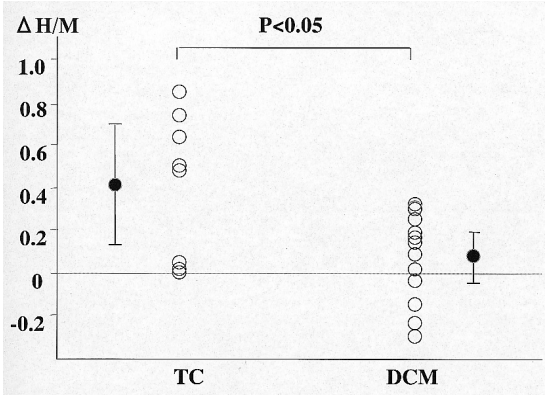

Fig. 7 Change in heart-to-mediastinum ^{123}I-MIBG uptake ratio in patients with TC and DCM.

but showed no change in patients with DCM (from 2.14 ± 0.45 to 2.16 ± 0.41, ns, Figs. 4, 6). Post-treatment H/M and change in H/M were also significantly greater in TC (2.62 ± 0.31 vs. 2.16 ± 0.41, $p < 0.05$, Fig. 3 and 0.41 ± 0.34 vs. 0.08 ± 0.20, $p < 0.01$, Fig. 7). Rapid and significant H/M recovery was observed in TC patients in comparison with DCM patients.

DISCUSSION

These data revealed the importance of cardiac adrenergic impairment as a factor in left ventricular dysfunction in tachycardia-induced cardiomyopathy (TC). In this study, we found reduced myocardial ^{123}I-MIBG H/M in patients with TC and patients with DCM. We also found that patients with TC had more rapid improvement of ^{123}I-MIBG H/M and cardiac systolic function after optimal treatment in comparison with DCM patients.

The term tachycardia-induced cardiomyopathy (TC) refers to the impairment of left ventricular function secondary to chronic or very frequent tachycardia, which is partially or completely reversible after normalization of the heart rate.[19] Since the specific mechanisms responsible for the development of TC are unclear, this broad definition is nonspecific, and may reflect various mechanisms by which chronic tachycardia may adversely affect

myocardial function in different subsets of patients. In animal models, atrial or ventricular pacing at a rate of around 240 beats/min for 3 weeks constantly results in low-output cardiac failure, very similar both hemodynamically and neurohumorally to heart failure in humans.[11,20–22] It is characterized by severe biventricular systolic and diastolic dysfunction, noticeable increased ventricular filling pressure,[23] chamber dilatation, and reduced wall thickness. In addition, intense neurohumoral activation is produced, with a noticeable rise in the plasma norepinephrine level[24,25] and noticeable depression of the left ventricular concentration of norepinephrine.[24,25] A progressive rise in plasma norepinephrine proved to be inversely related to the left ventricular concentration of norepinephrine in pacing models. Heart failure in animal pacing models is associated with activation of the sympathetic nervous system.[26,27]

In patients with DCM, impairment of cardiac adrenergic function has also been detected. Change in the signal transmission pathway by which the β-receptors stimulate the contractile apparatus (G-protein system) has been found as one of the mechanisms of impairment. Inhibition of this system is enhanced in DCM patients, perhaps accounting for their depressed contractile function. In addition, an increase in the α subunit of the inhibitory guanine nucleotide-binding protein ($G_{i\alpha}$) has been reported to occur in the membranes of myocytes from failing hearts. The increase in $G_{i\alpha}$ might contribute to the reduced effects of endogenous catecholamines in DCM.[28] Meredith et al. suggested that the noticeable increase in norepinephrine spillover from the heart in heart failure results largely from an increase in sympathetic nerve firing and neuronal release of norepinephrine, and not from a failure to recapture released norepinephrine.[29] When minor extraneuronal ^{123}I-MIBG uptake in the human heart is included, the ^{123}I-MIBG clearance rate may reflect ^{123}I-MIBG release from sympathetic neurons, and the increase in the clearance rate may be due to increased cardiac sympathetic activity.

^{123}I-MIBG is now considered a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with heart failure.[14,15,30–32] ^{123}I-MIBG is subject to the same uptake and storage mechanisms as norepinephrine. ^{123}I-MIBG is internalized by neuronal cells through the uptake-1 system, a transporter- and energy-dependent system, whereas the compound enters myocytes through the uptake-2 system, the activity of which is very low in the human heart.[33] ^{123}I-MIBG imaging provides a means to noninvasively evaluate cardiac adrenergic nerve activity *in vivo*. Schofer et al. found a significant correlation between ^{123}I-MIBG H/M and myocardial norepinephrine content determined from endomyocardial biopsy samples. A positive correlation was also found between the left ventricular ejection fraction and H/M in patients with DCM.[14]

Our study showed reduced myocardial ^{123}I-MIBG uptake in patients with TC and DCM. This indicates existent abnormalities of the cardiac adrenergic nervous system, but the recovery process was different in these two groups. The TC group required a shorter duration of treatment to recovery H/M significantly, so that cardiac adrenergic impairment might have some effect on the different recovery processes of these two diseases, but the details are unclear from this study. It is important that the present ^{123}I-MIBG study showed impairment and rapid recovery of the adrenergic nervous system as evidenced by a change in H/M in patients with TC. Further studies are required to clearly elucidate the mechanism of the impairment of cardiac adrenergic function in TC.

Study limitations

These data are limited by the small number of patients and the retrospective nature of this study. Proof that chronic tachyarrhythmia results in impairment of the sympathetic nervous system and LV dysfunction requires demonstration of normal sympathetic nervous and LV function before the onset of tachyarrhythmia and subsequent deterioration documented by serial studies performed under constant loading conditions and heart rate after prolonged arrhythmia, but baseline H/M and LVEF before the onset of arrhythmia are not usually available. Following up symptomatic patients with serial assessment of sympathetic nervous and LV function before treatment is also unreasonable. In addition, it is difficult to identify DCM with tachyarrhythmia and TC without significant improvement of systolic function after successful antiarrhythmia therapy. Therefore in some cases, TC might be misdiagnosed as DCM or vice versa. Meanwhile, the perfusion images showed more defects in patients with DCM. Myocardial fibrosis or degeneration progressed in patients with DCM, and could influence the results of this study. Despite these limitations, we believe that the findings suggest that significant impairment of sympathetic nervous and LV function may follow chronic tachyarrhythmia in the absence of other cardiac disease. This warrants further consideration and study because the dysfunction appears to be reversible with complete control of the underlying arrhythmia.

CONCLUSION

Anti-tachycardia therapy can improve altered cardiac adrenergic function and systolic function in patients with TC over a shorter period than in those with DCM. The reduction and recovery of cardiac adrenergic and systolic function in TC within a short time differ significantly from the findings in DCM. These different changes can be detected with ^{123}I-MIBG. Therefore, cardiac adrenergic impairment might have some influence on the different progression and recovery process of these two diseases.

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