Clin. Cardiol. 20, 61–66 (1997)

Relation of Iodine-123 Metaiodobenzylguanidine Myocardial Scintigraphy to Endomyocardial Biopsy Findings in Patients with Dilated Cardiomyopathy

KATSUTOSHI MURATA, M.D., SHOZO KUSACHI, M.D., TAKASHI MURAKAMI, M.D., KUNIO NOGAMI, M.D., MASAHIRO MURAKAMI, M.D., SATOSHI HIROHATA, M.D., YOUKOU TOMINAGA, M.D., ISSEI KOMATSUBARA, M.D., TAKAO TSUJI, M.D.

The First Department of Internal Medicine, Okayama University Medical School, Okayama, Japan

Summary

Background: Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) concentrates in adrenergic neurons and has been developed for evaluation of the sympathetic nervous system. Recent studies have demonstrated that the normal heart is clearly visualized by ^{123}I-MIBG cardiac scintigraphy, whereas abnormal ^{123}I-MIBG myocardial uptake and washout have been demonstrated in patients after myocardial infarction and in patients with congestive cardiomyopathy, long QT syndrome, and ventricular tachycardia.

Hypothesis: Based on evidence from recent studies, it can be hypothesized that ^{123}I-MIBG uptake is related to histopathologic changes in the myocardium.

Methods: The relation of ^{123}I-MIBG uptake to the histologic findings for the heart was studied in 24 patients with dilated cardiomyopathy (DCM). The study group did not include patients with complicating disorders that primarily affect the adrenergic nervous system. The ^{123}I-MIBG uptake was visually assigned one of four grades using the two criteria of the mean score for six regional uptake grades (mean score) and the global score obtained by visual evaluation of the entire image (global score). The ^{123}I-MIBG uptake score was also determined for the region at which the biopsy specimen was obtained (biopsy region score). The histologic findings were evaluated by assigning one of four grades for each of the following five factors: myocyte hypertrophy, myocardial fibrotic change, myocyte degeneration and necrosis, mononuclear cell infiltration, and myocyte disarray. The sum for all grades was defined as the total score, and the global score was also assigned to the overall histologic findings.

Results: All of the global, mean, and biopsy region scores for ^{123}I-MIBG uptake correlated significantly with the global and total scores for the histologic findings. Among the histologic factors, myocyte degeneration showed score correlated with all global, mean, and biopsy region scores for the uptake. Myocyte hypertrophy was associated weakly with the ^{123}I-MIBG uptake scores.

Conclusion: These results indicate that ^{123}I-MIBG uptake imaging is associated with histopathologic abnormalities in patients with DCM.

Key words: dilated cardiomyopathy, histopathology, degeneration, fibrosis, beta receptor, nuclear medicine

Introduction

Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG), an analog of norepinephrine, concentrates in adrenergic neurons[1] and has been developed for evaluation of the sympathetic nervous system.[2,3] Studies in animals[2] and in humans[3,4] have demonstrated that the normal heart is clearly visualized by ^{123}I-MIBG cardiac scintigraphy, whereas abnormal ^{123}I-MIBG myocardial uptake and washout have been demonstrated in patients after myocardial infarction[5,6] and in patients with congestive cardiomyopathy,[7,8] long QT syndrome,[9] and ventricular tachycardia.[10]

Adrenergic innervation and catecholamine depletion have been demonstrated in experimental[11] and human congestive heart failure.[12,13] A recent study demonstrated decreased beta$_1$ receptor density and attenuated sensitivity to catecholamine stimulation, that is, downregulation of adrenergic beta receptor, in the heart in idiopathic dilated cardiomyopathy (DCM).[14] Decreased norepinephrine concentration in the myocardium in relation to downregulation of beta receptor has also been found in DCM.[15] Experimental studies have indicated that this downregulation is caused by long-term exposure of the myocardium to catecholamine in response to heart failure.[16,17]

It is well known that myocyte degeneration, necrosis, and cardiac fibrosis are critical features in the heart in DCM.[18] Moreover, the same histologic abnormalities, especially myocyte degeneration and necrosis, also occur following long-term catecholamine exposure.[19–21]

Address for reprints:

Shozo Kusachi, M.D.
The First Department of Internal Medicine
Okayama University Medical School
2-5-1, Shikata-cho
Okayama 700, Japan

Received: January 16, 1996
Accepted with revision: September 6, 1996

Based on these lines of evidence, it can be hypothesized that ^{123}I-MIBG uptake is related to histopathologic changes in the myocardium. Accordingly, we examined the relation of myocardial ^{123}I-MIBG uptake to histopathologic abnormalities observed in endomyocardial biopsy specimens from patients with DCM.

Patients and Methods

Patients

Among 37 consecutive patients who underwent endomyocardial biopsy after providing informed consent, a total of 24 patients in whom a diagnosis of DCM was established were studied. The group studied included no patient with a complicating disorder that primarily affects the autonomic nervous system, including the cardiac adrenergic nervous system, such as diabetes mellitus. The 13 patients excluded were 2 patients with associated hypertrophic cardiomyopathy (HCM) with preserved left ventricular (LV) function; 3 with HCM that had progressed to DCM-like conditions; 3 with hypertensive heart disease with heart failure; and 1 each with QT prolongation syndrome, hypothyroidism, convalescent stage of acute myocarditis, ischemic DCM, and right-sided heart failure. The clinical characteristics of the 24 patients studied are listed in Table I. The symptoms in relation to the cardiac condition at the time of biopsy examination were determined according to New York Heart Association (NYHA) functional class.[22] Endomyocardial biopsy was performed to determine whether there was underlying heart disease that caused LV dilation with reduced wall motion. Beta blockade and drugs that affect catecholamine metabolism were not administered to any of the patients examined. Conventional 12-lead electrocardiography (ECG), plain chest x-ray, and echocardiography with pulsed Doppler examination were performed in all patients. Associated primary valvular disease was not present in any of the patients. Coronary angiography, performed in all patients, revealed no stenotic lesion in any of them. Dilated cardiomyopathy was diagnosed according to the diagnostic criteria of the World Health Organization/International Society and Federation of Cardiology Task Force,[23] with demonstration of histologic findings for the biopsy specimens consistent with DCM.

^{123}I-MIBG Myocardial Scintigraphy

Image collection: For blocking of the thyroid uptake of free iodine, Lugol's solution (containing 10 mg iodine and 20 mg potassium iodine per 1 ml) was administered orally; 10 drops were given daily for 5 days before the scintigraphic examination. After a 15-min rest period, a 111-MBq bolus of ^{123}I-MIBG (Daiichi Radioisotope Co. Ltd., Tokyo) was injected intravenously. Twenty min after the bolus injection of ^{123}I-MIBG, 5-min static acquisitions (early image) were performed with a tomographic gamma camera with a high-resolution, low-energy parallel collimator (SNC-510R, Shimazu Co. Ltd., Kyoto). Projection images were corrected for 45 s each at 6° increments over 180° circular orbits from 45° right anterior oblique to 45° left posterior oblique. The delayed image was acquired 4 h after the first image collection. Collected images were reconstructed by filtered back projection with a Butterworth filter combined with a Wiener filter. Vertical long-axis, short-axis, and trans-axis images (6 mm/pixel) were extracted from the reconstructed volume. Another 8 × 8 pixel region of interest was positioned over the upper mediastinum area. The heart-to-mediastinum ratio (H/M ratio) for the ^{123}I-MIBG activity in anterior planar image collection acquired 4 h after the first image collection was computed in 18 patients, and this ratio served for statistical analysis. Because of the lack of planar image due solely to incidental procedural error, the H/M ratio could not be obtained in six patients. The H/M ratio obtained from 18 patients was compared with the global and mean scores for ^{123}I-MIBG uptake, obtained as described below, in order to test the validity of the visual ^{123}I-MIBG uptake scoring system employed in this study.

Scoring of ^{123}I-MIBG uptake: The three sets of vertical long-axis, short-axis, and transverse-axis images were acquired, each comprised of 14 slices. Each tomographic image was divided according to anatomic landmarks into the six regions of anterior, septal, inferior, posterior, lateral, and apical. Delayed images of ^{123}I-MIBG uptake in each division were visually evaluated by two investigators who were blinded to all clinical and histopathologic information about the patients. The interobserver and intraobserver reliabilities were assessed. The histologic findings were visually scored into four grades, and the ^{123}I-MIBG uptake in each division was also visually graded as follows: 0, uptake not reduced compared

TABLE I Patient characteristics

No. of patients	M:W	Age (years)	Echocardiography LVDd (mm)	Echocardiography LVEF (%)	Chest x-ray CTR (%)	NYHA class
24	15:9	62 ± 10	62 ± 10	31 ± 13	53 ± 7	Class I n = 7 Class II n = 7 Class III n = 7 Class IV n = 3

Abbreviations: M = men, W = women, LVDd = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, CTR = cardiothoracic ratio, NYHA = New York Heart Association.

with that in normal positive controls; 1, mildly reduced uptake; 2, severely reduced uptake; and 3, complete or almost complete absence of uptake. Both the mean score for the six regional uptake grades (mean score) and the global score obtained by visual evaluation of the entire image (global score) were assigned. The score for ^{123}I-MIBG uptake was also determined for the region from which the biopsy specimen was obtained (biopsy region score). These grading values were then subjected to the statistical analysis described below.

Endomyocardial Biopsy and Histologic Analysis

After obtaining informed consent from the patients, we obtained three to five endomyocardial biopsy specimens from the right side of the septum and/or the posterolateral wall of the left ventricle using a biotome (Bicep 6110, Boston Scientific Corp., Natick, Mass., USA). Each biopsy specimen was fixed with 10% buffered formalin and embedded in paraffin, and the paraffin-embedded specimens were then cut into 6-μm sections; these were stained with hematoxylin-eosin and Azan-Mallory stains. The specimens were evaluated histologically according to well-established histopathologic procedures[24–26] and then assessed for the following five factors: myocyte hypertrophy, myocardial fibrotic change, myocyte degeneration, mononuclear cell infiltration, and myocyte disarray. Each factor was scored as follows: 0, not observed; 1, slight but apparent; 2, moderate; and 3, severe. The sum of the grades for all five factors (total score) was determined. The global score was assigned as follows: 0, minimal changes with mild hypertrophic findings; 1, hypertrophic findings with mild intracellular fibrotic change; 2, in addition to the changes in 1, moderate myocyte degeneration with replacement fibrotic change; and 3, severe myocyte degeneration with myocyte necrosis and replacement fibrotic changes. The histopathologic grading was evaluated by two investigators who were blinded to all clinical and scintigraphic information about the patients. Interobserver and intraobserver reliabilities were assessed.

Statistical Analysis

As the scoring method employed a ranking scale for both ^{123}I-MIBG myocardial uptake and grading of endomyocardial histologic findings, we employed nonparametric analysis for correlation by ranks to examine the relation of myocardial scintigraphic ^{123}I-MIBG uptake to endomyocardial histologic findings. The relation of ^{123}I-MIBG uptake and endomyocardial histologic findings to the NYHA functional class was also examined using the same correlation analysis. A p value of < 0.05 was considered to be a statistically significant difference. All values are expressed as mean ± standard deviation.

Results

^{123}I-MIBG Uptake and Endomyocardial Biopsy Findings

Table II shows the distribution of patients classified by the ^{123}I-MIBG uptake scores. Regional ^{123}I-MIBG uptake difference ≥ two grades was observed in only two patients. Segmental defect was not observed in any patients studied. There

TABLE II Patient distribution by scoring system for ^{123}I-MIBG uptake and histologic findings

A: MIBG uptake

Total number of patients	Mean score	Number of patients	Score	Number of patients						
				Global	Anterior	Septum	Inferior	Posterior	Lateral	Apex
	Score 0≤ <1	7	Score 0	2	8	7	2	1	8	1
			Score 1	10	5	5	3	6	5	5
24	Score 1≤ <2	6								
			Score 2	7	9	8	6	5	8	8
	Score 2≤ <3	11	Score 3	5	2	4	13	12	3	10

B: Histologic findings

Total number of patients	Mean score	Number of patients	Score	Number of patients					
				Global	Myocyte hypertrophy	Myocardial fibrosis	Myocyte degeneration	Mononuclear cell infiltration	Myocyte disarray
	Score 0≤ <3	2	Score 0	1	0	0	2	14	0
	Score 3≤ <6	11	Score 1	6	14	12	8	8	16
24									
	Score 6≤ <9	10	Score 2	13	9	10	13	2	8
	Score 9≤ <12	1	Score 3	4	1	2	1	0	0

Abbreviations: MIBG = I-123-metaiodobenzylguanidine.

was a significant correlation between the global and mean scores for ^{123}I-MIBG uptake ($r=0.91$, $p<0.01$). Moreover, the global and mean scores for ^{123}I-MIBG uptake correlated significantly with the H/M ratio (-0.71, $p<0.01$; -0.87, $p<0.01$, respectively). Representative sets of ^{123}I-MIBG scintigraphic images are shown in Figure 1. Table II also shows the distribution of patients classified by the scores for endomyocardial biopsy findings. There was a significant correlation between the global and total scores ($r=0.71$, $p<0.01$).

Relation of ^{123}I-MIBG Uptake to Histologic Findings

The results of the correlation analysis are summarized in Table III. All of the global, mean, and biopsy site scores for ^{123}I-MIBG uptake correlated with both the global and total scores for endomyocardial histologic findings. Among the five histologic factors, myocyte degeneration score showed correlations with all global, mean, and biopsy region scores for ^{123}I-MIBG uptake. The score for myocyte hypertrophy was weakly associated with these scores for ^{123}I-MIBG uptake, but the myocardial fibrosis score did not obviously correlate with ^{123}I-MIBG uptake scores.

Relation to NYHA Classification

Table IV summarizes the results of correlation analysis of ^{123}I-MIBG uptake and of endomyocardial histologic findings with NYHA functional class. Both the global and mean scores for ^{123}I-MIBG uptake correlated significantly with NYHA class. The global score for endomyocardial histologic findings also correlated with NYHA class, but correlation was weaker than that of ^{123}I-MIBG uptake to NYHA functional class.

Discussion

The major findings of this study were that the myocardial ^{123}I-MIBG uptake of patients with DCM is related to endomyocardial biopsy histopathologic findings. The ^{123}I-MIBG uptake also correlated significantly with myocyte degeneration and associated weakly with myocyte hypertrophy.

The delayed image acquired 4 h after the early image was used for the evaluation of myocardial ^{123}I-MIBG uptake. Previous studies[27, 28] demonstrated that the non-neural myocardial uptake of ^{123}I-MIBG contributes mainly to the early image and disappears rapidly, while the neural uptake contributes to the delayed image. These findings indicate that the delayed image represents adrenergic nervous system function more faithfully than does the early image. In fact, increases in washout of ^{123}I-MIBG have been reported in severe DCM.[8] Use of the delayed image for evaluation of the adrenergic nervous system was thus considered theoretically reasonable.

We evaluated ^{123}I-MIBG uptake visually using the two methods of obtaining the mean score for each of six segments

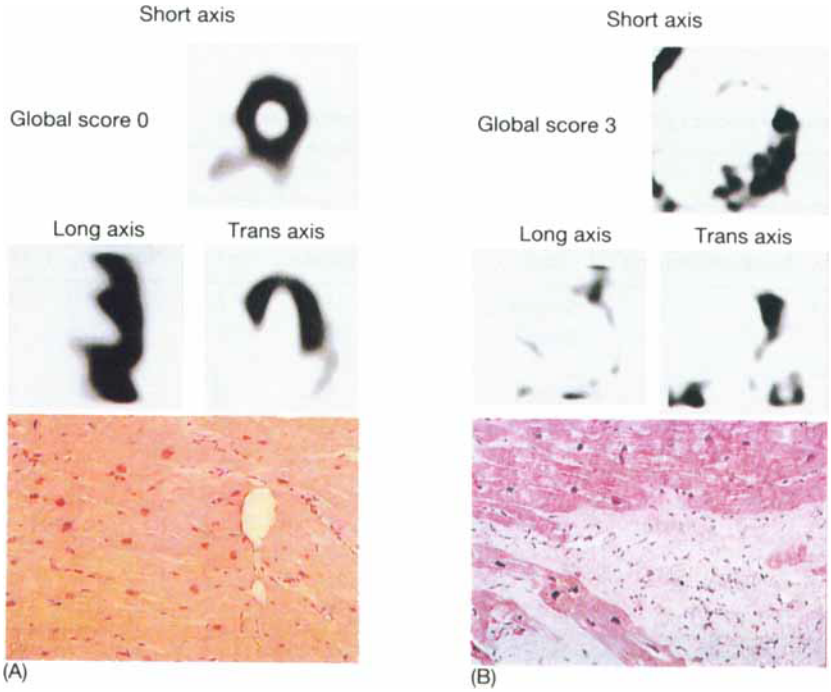

FIG. 1 Representative sets of ^{123}I-MIBG myocardial scintigraphic delayed images for two patients. (A) Normal ^{123}I-MIBG uptake (scores: global score, 0; mean score 0.5) is found in association with minimal histologic abnormalities (scores: global score, 0; myocyte hypertrophy, 1; myocardial fibrotic change, 0; myocyte degeneration, 0; mononuclear cell infiltration, 0; and myocyte disarray, 1). (B) In contrast, severely decreased ^{123}I-MIBG uptake (scores: global score, 3; mean score 2.83) is associated with considerable histopathologic abnormalities (scores: global score, 3; myocyte hypertrophy, 2; myocardial fibrotic change, 3; myocyte degeneration, 3; mononuclear cell infiltration, 0; and myocyte disarray, 2).

TABLE III Correlation coefficient of ^{123}I-MIBG uptake scores to endomyocardial histologic scores (n = 24)

			Histology				
^{123}I-MIBG uptake	Global score	Total score	Myocyte hypertrophy	Myocardial fibrosis	Myocyte degeneration	Mononuclear cell infiltration	Myocyte disarray
Global score	0.58[a]	0.42[b]	0.44[b]	0.31	0.56[a]	0.27	0.25
Mean score for segments	0.60[a]	0.49[b]	0.42[b]	0.36	0.58[a]	0.36	0.18
Score for biopsy site	0.67[a]	0.66[a]	0.49[b]	0.41[b]	0.65[a]	0.53[a]	0.39

[a] $p<0.001$.
[b] $p<0.05$.

TABLE IV Correlation coefficient of ^{123}I-MIBG uptake scores to endomyocardial histologic scores (n = 24)

	^{123}I-MIBG uptake		Histology	
	Global score	Mean score	Global score	Total score
NYHA	0.84[a]	0.87[a]	0.51[b]	0.36[c]

[a] $p<0.01$
[b] $p<0.05$.
[c] $0.05<p<0.10$.

and obtaining the overall score (global score). We also determined ^{123}I-MIBG uptake at the region of the biopsy site (biopsy region score). All scoring systems yielded essentially the same results. Both mean and global scores for ^{123}I-MIBG uptake correlated with the H/M ratio. Therefore, our methods for evaluation of ^{123}I-MIBG uptake seem to have high accuracy. Similarly to the ^{123}I-MIBG uptake scoring, the evaluation of endomyocardial biopsy findings was also performed using global scoring and scoring of individual histologic factors with the sum for each histologic score. Both scoring systems presented the same relation to ^{123}I-MIBG uptake. The present results obtained by different methods for evaluation of ^{123}I-MIBG uptake and histologic findings were thus considered to be valid.

The ^{123}I-MIBG uptake was associated with histopathologic biopsy findings, that is, myocardial damage. Myocyte hypertrophy was also weakly associated with decrease of ^{123}I-MIBG uptake. There are no reports available on the relation to myocardial damage, and accordingly we are not able to compare the results of this study with those of previous studies. One study, using binding assay of [^{3}H] dihydroalprenolol, demonstrated that beta-adrenergic receptors are located on the cell surface membrane of myocytes.[14] Thus, it would be logical to assume that loss of myocytes decreases ^{123}I-MIBG uptake, and, in fact, regional loss of ^{123}I-MIBG uptake has been reported in the myocardial infarct lesion[5, 6] where myocyte loss has occurred. In the heart in DCM, the major histopathologic characteristics are myocyte degeneration and necrosis.[18] On the other hand, downregulation of beta-adrenergic receptors has been demonstrated.[14] Other experimental studies[16, 17] have revealed that this downregulation is caused by long-term exposure of the myocardium to catecholamine. Many studies[19–21] have demonstrated that catecholamine administration can cause myocyte degeneration. The myocardium not only in congestive heart failure but also in the DCM heart would be under exposure to beta stimulant in response to hemodynamic failure, resulting in progression of histopathologic abnormalities of the myocardium, especially myocyte degeneration and necrosis. It is also well known that catecholamine causes myocyte hypertrophy. It is theoretically reasonable to assume that the NYHA functional class would reflect the extent of catecholamine exposure to the heart. In fact, as the present study disclosed significant correlation of NYHA functional class with myocardial ^{123}I-MIBG uptake, this relation of ^{123}I-MIBG uptake to the histologic findings may be at least partly explained by catecholamine exposure to the heart. These clinical and experimental findings could account for this significant relation.

We noted no obvious relation between ^{123}I-MIBG uptake and cardiac fibrosis. Reversible ^{123}I-MIBG uptake after beta-adrenergic receptor blockade therapy has been reported in one patient.[29] Similarly, we found an unchanged degree of myocardial fibrosis after beta-adrenergic receptor blockade therapy in one patient in this study, though improvement of ^{123}I-MIBG uptake was observed (data not shown). It is quite unlikely that myocardial fibrosis is markedly reduced by beta-adrenergic receptor blockade therapy, although improvement of myocardial function has been reported after such therapy.[30, 31] These reports are consistent with the absence we noted of a relation of ^{123}I-MIBG to the extent of myocardial fibrosis. Our results indicate that ^{123}I-MIBG reflects histologic changes in the myocytes themselves.

Although we found a significant correlation of ^{123}I-MIBG uptake with the endomyocardial histologic findings, the correlations were somewhat low. As we employed a four-grade scoring system for both ^{123}I-MIBG uptake and histologic findings, we believe that the relatively small number of grades might partly account for the somewhat low correlations.

There are clearly several limitations of this study. First, because endomyocardial biopsy was performed only in patients in whom myocardial disease could not be diagnosed by the

conventional approach, this study included a relatively small number of patients and lacked a normal control subject group. The use of more than one scoring system would have partly compensated for this limitation. Second, limited samples were obtained by endomyocardial biopsy. However, hearts with diffusely reduced wall motion were examined in this study and this sampling limitation thus would not have greatly affected overall the results obtained.

In conclusion, the present results indicate that myocardial ^{123}I-MIBG uptake is associated with the endomyocardial biopsy histopathologic findings, especially those for myocyte degeneration.

References

1. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S: Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987:28: 1620–1624
2. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu J-L, Clinthorne NH, Otto CA, Swanson DP, Beierwaltes WH: Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981;22:22–31
3. Kline RC, Swanson DP, Wieland DM, Thrall JH, Gross MD, Pitt B, Beierwaltes WH: Myocardial imaging in man with I-123 mataiodobenzylguanidine. *J Nucl Med* 1981;22:129–132
4. Sisson JC, Shapiro B, Meyers L, Mallette S, Mangner TJ, Wieland DM, Glowniak JV, Sherman P, Beierwaltes WH: Metaiodobenzylguanidine to map scintigraphically the adrenergic nervous system in man. *J Nucl Med* 1987;28:1625–1636
5. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock BH, Burt RW, Wellman HN, Zipes DP: Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123-metaiodobenzylguanidine. *J Am Coll Cardiol* 1989;14:1519–1526
6. McGhie AI, Corbett JR, Akers MS, Padmakur K, Sills MN, Kremers M, Buja LM, Durant-Reville M: Regional cardiac adrenergic function using I-123-metaiodobenzylguanidine tomographic imaging after acute myocardial infarction. *Am J Cardiol* 1991; 67:236–242
7. Henderson EB, Kahn JK, Corbett JR, Jansen DE, Pippin JJ, Kulkarni P, Ugolini V, Akers MS, Hansen C, Buja LM, Parkey RW, Willerson JT: Abnormal I-123 metaiodobenzylguanidine myocardial washout and distribution may reflect myocardial adrenergic derangement in patients with congestive cardiomyopathy. *Circulation* 1988;78:1192–1199
8. Glowniak JV, Turner FE, Gray LL, Palac RT, Lagunas-Solar MC, Woodward WR: Iodine-123 metaiodobenzylguanidine imaging of the heart in idiopathic congestive cardiomyopathy and cardiac transplants. *J Nucl Med* 1989;30:1182–1191
9. Gohl K, Feistel H, Weikl A, Bachmann K, Wolf F: Congenital myocardial sympathetic dysinnervation (CMSD): A structural defect of idiopathic long QT syndrome. *PACE* 1991;14:1544–1553
10. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, Zipes DP: Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. *J Am Coll Cardiol* 1993;22:1344–1353
11. Chidsey CA, Kaiser GA, Sonnenblick EH, Spann JF, Braunwald E: Cardiac norepinephrine stores in experimental heart failure in the dog. *J Clin Invest* 1964;43:2386–2393
12. Chidsey CA, Braunwald E, Morrow AG: Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Am J Med* 1965;39:442–451
13. Chidsey CA, Sonnenblick EH, Morrow AG, Braunwald E: Norepinephrine stores and contractile force of papillary muscle from the failing human heart. *Circulation* 1966;33:43–51
14. Bristow MR, Ginsburg R, Minobe W, Gubicciotti RS, Sageman WS, Lurie K, Billingham ME, Harrison DC, Stinson EB: Decreased catecholamine sensitivity and β-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982;307:205–211
15. Anderson FL, Port JD, Reid BB, Larrabee P, Hanson G, Bristow MR: Myocardial catecholamine and neuropeptide Y depletion in failing ventricles of patients with idiopathic dilated cardiomyopathy: Correlation with β-adrenergic receptor downregulation. *Circulation* 1992;85:46–53
16. Bobik A, Campbell JH, Carson V, Campbell GR: Mechanism of isoprenaline-induced refractoriness of the β-adrenoceptor-adenylate cyclase system in chick embryo cardiac cells. *J Cardiovasc Pharmacol* 1981;3:541–553
17. Fishman PH, Mallorga P, Tallman JF: Catecholamine-induced desensitization of adenylate cyclase in rat glioma C6 cells. *Mol Pharmacol* 1981;20:310–318
18. Schwarz F, Mall G, Zebe H, Blickle J, Derks H, Manthey J, Kübler W: Quantitative morphologic findings of the myocardium in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;51:501–506
19. Ferrans VJ, Hibbs RG, Black WC, Weinbaecher DG: Isoproterenol-induced myocardial necrosis. A histochemical and electron microscopic study. *Am Heart J* 1964;68:71–90
20. Ostadal B, Rychterova V, Poupa O: Isoproterenol-induced acute experimental cardiac necrosis in the turtle (*Testudo Horsfieldi*). *Am Heart J* 1968;76:645–649
21. Schenk EA, Moss AJ: Cardiovascular effects of sustained norepinephrine infusions. II. Morphology. *Circ Res* 1966;18:605–615
22. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis: *Disease of the Heart and Blood Vessels*, 6th ed., p. 110-114. New York: New York Heart Association/Little, Brown and Company, 1964
23. Brandenburg RO, Chazov E, Falase AO, Grosgogeat Y, Kawai C, Judez M, Orinius E, Goodwin JF, Olsen EGJ, Oakley CM, Pisa Z: Report of the WHO/ISFC task force on definition and classification of cardiomyopathies. *Circulation* 1981;64:437A–438A
24. Edwards WD: Pathology of endomyocardial biopsy. In *Pathology of the Heart and Great Vessels* (Ed. Waller BF), p. 191–275. New York: Churchill Livingstone, 1988
25. O'Connell JB, Silver MA: Cardiac disease diagnoses by endomyocardial biopsy. In *Pathology of the Heart and Great Vessels* (Ed. Waller BF), p. 277–291. New York: Churchill Livingstone, 1988
26. Edwards WD: Endomyocardial biopsy and cardiomyopathy. *Cardiovasc Rev Rep* 1983;4:820–851
27. Dae MW, Marco TD, Botvinick EH, O'Connell JW, Hattner RS, Huberty JP, Yuen-Green MS: Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts: Implication for clinical studies. *J Nucl Med* 1992;33:1444–1450
28. Yamakado K, Takeda K, Kitano T, Nakagawa T, Futagami Y, Konishi T, Hamada M, Nakano T, Ichihara T: Serial change of iodine-123 metaiodobenzylguanidine myocardial concentration in patients with dilated cardiomyopathy. *Eur J Nucl Med* 1992;19: 265–270
29. Yamamoto T, Furutani Y, Katayama K, Harada M, Ichioka T, Fujii T, Matszaki M: A case of dilated cardiomyopathy in which the effects of beta-blocker therapy were clearly demonstrated by 123-MIBG scintigraphy. *Respir Circ* 1994;42:989–993 (in Japanese with English abstract)
30. Heilbrunn SM, Shah P, Bristow MR, Valantine HA, Ginsburg R, Fowler MB: Increased β-receptor density and improved hemodynamics response to catecholamine stimulation during long-term metoprolol therapy in heart failure from dilated cardiomyopathy. *Circulation* 1989;79:483–490
31. Anderson JL, Gillbert EM, O'Connell JB, Renlund D, Yanowitz F, Murray M: Long-term (2 years) beneficial effects of beta-adrenergic blockade with bucindolol in patients with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol* 1991;71:1373–1381