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Myocardial Catecholamines in Hypertrophic and Dilated (Congestive) Cardiomyopathy: A Biopsy Study

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A high performance liquid chromatographic method was used to determine myocardial norepinephrine and epinephrine concentrations in 66 biopsy specimens obtained from the right or left ventricle during routine diagnostic cardiac catheterization of 45 patients with dilated (congestive) or hypertrophic cardiomyopathy, or with heart disease other than cardiomyopathy, such as acute perimyocarditis, postmyocarditis and constrictive pericarditis. The validity of catecholamine determination in a 2 to 6 mg biopsy specimen to assess overall ventricular myocardial catecholamines was demonstrated.

Norepinephrine concentrations in the myocardium were inversely correlated with the grade of hypertrophy in patients with congestive cardiomyopathy or heart disease other than cardiomyopathy, but not in patients with hypertrophic cardiomyopathy. The fact that the myocardial norepinephrine concentration was always lower in the left than in the right ventricle of the same patient may be explained by the simple dilution of sympathetic nerve endings in the left ventricle.

There were some cases of hypertrophic cardiomyopathy in which the concentration of myocardial norepinephrine was exceptionally high, although its mean value was not significantly higher than that in patients with other types of heart disease who served as a control group without cardiomyopathy. Some patients with dilated cardiomyopathy had lower levels of myocardial norepinephrine than would be expected for the degree of interstitial fibrosis and the severity of heart failure. The mean plasma norepinephrine and epinephrine levels were significantly elevated in patients with dilated cardiomyopathy.

The term "noradrenosis" was proposed by Pearse (1) in 1964 to describe a significant increase in the level of fluorescent noradrenaline in myocardial specimens removed at operation from the outflow tract of the left ventricle in patients with hypertrophic obstructive cardiomyopathy. However, the hypothesis of an increased noradrenaline content and augmented sympathetic nerve supply to the interventricular septal myocardium in cases of hypertrophic obstructive cardiomyopathy has not been substantiated. In 1971, Van Noorden et al. (2) failed to confirm the presence of noradrenaline by microspectrofluorimetric methods in samples of myocardium obtained from the area of greatest obstruction during open heart surgery in cases of hypertrophic obstructive cardiomyopathy. However, the myocardial noradrenaline content of patients with congestive cardiomyopathy has never been reported, because these patients rarely undergo cardiac surgery.

This report describes the myocardial catecholamines in biopsy specimens removed from the right and left ventricles during diagnostic cardiac catheterization in an attempt to elucidate the role of myocardial catecholamines and sympathetic nervous activity in the pathogenesis of cardiomyopathy.

Methods

Patients. Biopsy specimens were obtained during routine diagnostic cardiac catheterization after premedication with 5 mg of diazepam (Cercine). Specimens were taken from the right ventricular side of the septum or left ventricular free wall, or both, by the Konno-Sakakibara (3) or Kawai (4) biopsy catheter in 34 patients with cardiomyopathy (10 congestive [dilated] and 24 hypertrophic) and in 11 patients with other types of heart disease (2 with acute perimyocarditis, 6 with postmyocarditis, 1 with constrictive pericarditis, 1 with coronary arteriovenous fistula and 1 with

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alcoholism). The use of any catecholamine or vasodilating agent was forbidden for either therapeutic or diagnostic purposes for a least 24 hours before the procedure. The diagnosis of congestive (dilated) and hypertrophic cardiomyopathy was made according to the definition and classification proposed by the World Health Organization/ International Society and Federation of Cardiology task force (5). The last group of patients served as a control group without cardiomyopathy. All the patients gave written consent before the study.

Catecholamine determination in myocardial biopsy specimens. Biopsy specimens, weighing approximately 2 to 6 mg, were divided into two parts: one for histologic study and the other for catecholamine determination by high performance liquid chromatography which has been developed recently in our institution (6–9). The other section of the biopsy specimen was quickly weighed and frozen in liquid nitrogen. The specimen was homogenized in 100 μl of freshly prepared cold 0.4 N perchloric acid/mg wet weight of the tissue containing 5 m*M* reduced glutathione in a microhomogenizer submerged in an ice bath and then centrifuged in a refrigerated centrifuge at 4°C for 20 minutes at 30,000 *g*. An aliquot (10 to 100 μl) of the clear supernatant was directly injected into the double column, which was composed of an upper anion exchange column of CDR-20 (quarternary ammonium anion exchanger with average particle size 9 μm) (Mitsubishi Chemical Co.) and a lower cation exchange column of Zipax SCX (Du Pont Instruments Co.). The mobile phase was 0.07 N, sodium phosphate (NaH_2PO_4) with a flow rate of 0.8 ml/min. The separated catecholamines then entered a continuous flow system described previously (6), and the reagents for the trihydroxyindole method were added sequentially at a constant flow rate with the use of a proportioning pump. Because perchloric acid caused no adverse effect on the detector system (trihydroxyindole reaction), tissue extracts were used without neutralization. Finally, the fluorescent products were applied to a highly sensitive spectrofluorophotometer.

The plasma catecholamine concentrations were determined by the high peformance liquid chromatographic method described in a previous report (7). The blood samples for the determination of catecholamines were drawn through an indwelling catheter in a peripheral vein after the patient had been resting for at least 30 minutes on a day close to the cardiac catheterization study.

Histologic study. For histologic studies, the biopsy specimen was fixed in 10% formalin, dehydrated with graded ethanol and embedded in paraffin. The paraffin block was cut in 4 μ sections by a microtome, and the sections were stained with hematoxylin-eosin, elastic Van Gieson, periodic acid-Schiff or Masson trichrome.

The shortest diameters of cardiocytes were measured only in nucleated transverse sections. More than 30 myocardial cells in each specimen were measured by an ocular micrometer disc with a linear scale, and the average cell diameter of each specimen was calculated.

Fibrosis was graded as follows: Grade 0 signified no apparent fibrosis with the exception of small islets of fibrous tissue around the capillaries. Focal and minimal fibrosis was grade I and moderate to severe fibrosis of nearly 30 to 50% of the area of the entire specimen was classified as grade II. All the histologic studies were performed by observers who were ignorant of the source of the specimen.

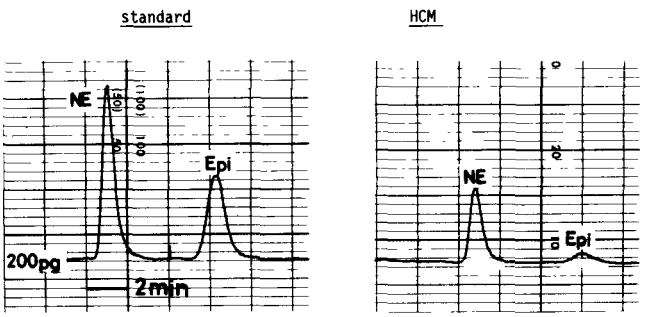
Statistical analysis. Paired or unpaired *t* tests and analyses of variance followed by multiple comparison tests were used in the statistical analysis. Values are expressed as the mean ± standard deviation. Statistical significance is defined as a probability (p) value of less than 0.05.

Results

Reliability, reproducibility and sensitivity of the method for determining myocardial catecholamine concentration. There was a linear relation between fluorescence intensity (peak height) and catecholamine concentration from 0 to 1,000 pg, the highest concentration tested. Within-run and day to day coefficients of variation were 1.0 and 1.6% for norepinephrine and 1.0 and 1.8% for epinephrine, respectively ($n = 10$). A significant correlation ($p < 0.001$) was observed between measurements ($n = 10$) in the two assays for both norepinephrine (correlation coefficient [r] = 0.98) and epinephrine ($r = 0.94$). Analytical recovery of norepinphrine and epinephrine on the basis of the recovery rate from samples fortified with 100 pg of each standard catecholamine was about 100%. With this chromatographic system, the lowest detection limit for each catecholamine in the myocardium is about 10 pg.

Figure 1 (right panel) shows a representative catecholamine chromatogram of a myocardial biopsy specimen from the left ventricle of a patient with hypertrophic cardiomyopathy. The left panel demonstrates the standard sample containing 200 pg of norepinephrine and epinephrine. Con-

Figure 1. A representative catecholamine chromatogram of biopsied myocardium obtained from a patient with hypertrophic cardiomyopathy (HCM) (**right**) and that of a standard sample containing a known amount of catecholamines (**left**). Epi = epinephrine; NE = norepinephrine.



centrations of norepinephrine and epinephrine in this specimen are 920 and 340 pg/mg wet weight, respectively. These values are lower for norepinephrine and higher for epinephrine than is usual in hypertrophic cardiomyopathy.

Catecholamine concentrations in myocardial biopsy specimens (Tables 1 to 4). Myocardial and plasma catecholamine concentrations, diameters of myocytes and grade of fibrosis in each subgroup of patients are shown in Tables 1 to 4. The mean norepinephrine concentration in the left ventricular myocardium was significantly lower ($p < 0.05$) in congestive than in hypertrophic cardiomyopathy. There was no significant difference in the mean norepinephrine concentration in either the right or left ventricular myocardium between the patients with hypertrophic cardiomyopathy and those with other heart disease. The mean myocardial epinephrine concentration showed no significant difference among the three subgroups.

Biopsy specimens were removed from both the right and left ventricle in 14 patients. Norepinephrine concentration was always significantly higher in the right than in the left ventricle ($p < 0.01$). The mean diameter of the cardiocytes was 17 ± 3 μm in the right ventricle and 22 ± 3 μm in the left. This difference was also statistically significant ($p < 0.001$).

Plasma catecholamine concentrations in patients of each subgroup (Tables 1 to 4). The mean plasma norepinephrine and epinephrine concentrations in patients with heart disease other than cardiomyopathy (noncardiomyopathy group) were 177 ± 47 and 16 ± 3 pg/ml, respectively, which are within the normal range by our method. In patients with congestive cardiomyopathy, the concentrations were 402 ± 151 and 78 ± 58 pg/ml, respectively, which were significantly higher than those in patients with hypertrophic cardiomyopathy (207 ± 58 and 22 ± 14 pg/ml, respectively) ($p < 0.001$ for norepinephirine and < 0.05 for epinephrine). The mean plasma norepinephrine and epinephrine levels were also significantly higher in patients with congestive cardiomyopathy than in patients with other heart disease ($p < 0.001$ for norepinephrine and < 0.05 for epinephrine).

Relation between myocardial norepinephrine concentration and diameter of myocardial cells (Fig. 2 to 4). The myocardial norepinephrine concentration showed a close inverse correlation ($r = -0.86$, $p < 0.005$; regression equation: $Y = 4{,}223 - 201X$) with the diameter of the myocardial cells obtained from the patients with heart disease other than cardiomyopathy (Fig. 2). The inverse relation was also statistically significant, but less so in patients with congestive cardiomyopathy ($r = -0.55$, $p < 0.05$; regression equation: $Y = 1{,}416 - 40X$) (Fig. 3). There was no significant inverse correlation in patients with hypertrophic cardiomyopathy (Fig. 4). There were two patients (Cases 12 and 13) with hypertrophic cardiomyopathy with exceptionally high levels of myocardial norepinephrine, regardless of the mean fiber width of the myocardial cells. The mean diameters of cardiocytes in the right ventricle were significantly larger in the patients with congestive and hypertrophic cardiomyopathy than in those with other heart disease ($p < 0.05$) (Table 4).

Relation between myocardial norepinephrine concentration and grade of interstitial fibrosis (Fig. 5). Generally, as the grade of interstitial fibrosis increases, myocardial norepinephrine concentration decreases. There were six specimens, two from the left ventricle and four from the right ventricle in five patients with congestive cardiomyopathy, in which low concentrations of myocardial nor-

Table 1. Results in 10 Patients With Congestive Cardiomyopathy

Case	Age (yr) & Sex	Myocardial Catecholamines (pg/mg wet weight) NE RV	NE LV	Epi RV	Epi LV	Diameter of Myocytes (μm) RV	LV	Grade of Fibrosis RV	LV	Plasma Catecholamines (pg/ml) NE	Epi	NYHA Functional Class On Admission	At Biopsy	EF (%)
1	44M	365	—	111	—	26	—	II	—	623	127	IV	II	27
2a	36M	819	203	8	4	18	26	0	II	352	74	III	II	40
2b		698		4		18		0						
3	38M	—	871	—	55	—	23	—	0	240	25	II	II	54
4	60F	312	—	5	—	18	—	II	—	702	213	II	II	—
5	58M	625	—	18	—	14	—	II	—	425	83	III	II	42
6a	37M	972	69	53	19	18	25	I	II	350	45	I	I	23
6b		833		45		19		0						
7	25M	1,100	—	8	—	16	—	I	—	295	37	IV	II	—
8	47M	900	600	10	8	18	25	I	II	295	42	II	II	26
9	58M	490	632	8	10	16	23	0	II	442	101	III	III	17
10	43M	1,016	232	5	4	12	19	I	0	298	40	II	II	37

EF = ejection fraction; Epi = epinephrine; F = female; I = slight fibrosis; II = moderate to severe fibrosis; LV = left ventricle; M = male; NE = norepinephrine; NYHA = New York Heart Association; RV = right ventricle; — = not measured; 0 = no fibrosis.

Table 2. Results in 24 Patients With Hypertrophic Cardiomyopathy

Case	Age (yr) & Sex	Myocardial Catecholamines (pg/mg wet weight)				Diameter of Myocytes (μm)		Grade of Fibrosis		Plasma Catecholamines (pg/ml)	
		NE		Epi							
		RV	LV	RV	LV	RV	LV	RV	LV	NE	Epi
1a	55M	1,400	868	25	21	20	20	I	I	185	12
1b		1,020		20		20		I			
2	52M	1,950	1,337	26	17	20	23	0	I	143	25
3	31M	706	—	11	—	20	—	I	—	192	18
4	47M	2,160	—	8	—	17	—	0	—	112	14
5	39M	1,004	—	15	—	20	—	I	—	222	15
6	19M	1,404	—	14	—	20	—	I	—	—	—
7	37M	—	920	—	340	—	26	—	I		
8	52M	1,516	1,110	22	26	20	21	I	I	135	18
9a	37M	1,238	1,110	7	17	14	18	I	I	141	12
9b			1,143		13		18		I		
10	44M	620	460	18	15	18	29	I	II	285	24
11	58M	64	—	4	—	25	—	II	—		
12	57M	1,760	(4,810)	250	(20)	14	(18)	0	II	218	19
13	34M	(7,930)	500	—	10	(15)	18	II	I		
14	50M	708	—	60	—	17	—	I	—	158	21
15	49M	653	—	9	—	17	—	I	—	254	15
16	52M	438	—	10	—	16	—	II	—	—	—
17	47M	626	—	8	—	16	—	I	—	252	18
18a	55M	1,094	—	5	—	17	—	II	—	184	16
18b											
19	58M	—	1,188	—	8	—	22	—	II	218	19
20	50M	469	—	8	—	17	—	II	—	223	40
21	42M	—	250	—	5	—	22	—	II	356	72
22	50F	1,963	—	10	—	17	—	0	—	235	16
23	48M	1,200	1,062	8	3	20	24	II	I	194	15
24	50M	1,000	556	10	13	18	20	II	II	225	32

Figures in parentheses indicate values not included for statistical analysis. Abbreviations as in Table 1.

epinephrine were present despite minimal interstitial fibrosis. The mean value of norepinephrine concentration in these specimens was 657 ± 250 pg/mg wet weight, definitely lower than that in the specimens from the patients with hypertrophic cardiomyopathy and other heart disease with minimal interstitial fibrosis. The mean value in the latter group was 1,959 ± 142 pg/mg wet weight. The average diameter of the myocardial cells was 19 μm in the former and 14 μm in the latter group.

Discussion

Methodologic problems. The recent introduction of highly sensitive, specific techniques for measuring catecholamines has allowed us to determine the concentration of myocardial norepinephrine and epinephrine in a small piece of biopsy specimen obtained from the right or left ventricle during routine diagnostic cardiac catheterization.

Whether catecholamine levels in a small piece of biopsy specimen represent those of the entire ventricle is a substantial problem in biopsy studies. Norepinephrine concentrations in the specimens removed from different sites of the right or left ventricle in the same patient showed little variation (coefficient of variation 7.6%, n = 6, Tables 1 to 3). However, some heterogeneities of myocardial innervation, particularly in hearts that are heavily fibrosed, may cause an inevitable risk that the biopsy specimen does not represent myocardial catecholamine concentrations throughout the ventricle. Moreover, there may be a sampling error in that the histologic features of one sample and the catecholamines measured in a separate sample in the same patient might not match.

In previous studies (10,11), very low concentrations of norepinephrine were demonstrated in atrial tissues and ventricular muscles removed during operation on patients with heart failure. The norepinephrine concentration was also markedly depressed in papillary muscles removed from the left ventricle of patients undergoing mitral valve replacement who had been in severe left ventricular failure (12).

The role of catecholamines appears to be important in determining the pathogenesis of cardiomyopathy. Determination of the norepinephrine concentration in the myo-

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Table 3. Results in 11 Patients With Other Heart Diseases

Case	Age (yr) & Sex	Myocardial Catecholamines (pg/mg wet weight) NE RV	NE LV	Epi RV	Epi LV	Diameter of Myocytes (μm) RV	LV	Grade of Fibrosis RV	LV	Plasma Catecholamines (pg/ml) NE	Epi
					Acute Perimyocarditis						
1	18M	1,367	—	17	—	12	—	I	—	113	13
2	19M	1,472	—	16	—	14	—	I	—	234	21
					Postmyocarditis						
3	34F	529	—	15	—	20	—	II	—	185	14
4	28M	720	—	5	—	17	—	II	—	127	15
5	14M	889	—	7	—	16	—	I	—	232	16
6a	45M	564	400	4	3	16	19	II	I	221	15
6b		608	476	3	8	15	18	II	I		
7	25M	883	—	5	—	16	—	I	—	—	—
8	57F	1,960	—	145	—	10	—	0	—	—	—
					Constrictive Pericarditis						
9	53M	2,690	—	32	—	11	—	I	—	132	21
					Coronary Arteriovenous Fistula						
10	44F	1,474	—	5	—	15	—	I	—	199	15
					Alcoholism						
11	42M	1,024	—	6	—	13	—	I	—	154	18

Abbreviations as in Table 1.

cardium removed at operation, however, may be meaningless because of the influence of anesthesia and other nonphysiologic procedures. Biopsy specimens obtained during routine diagnostic cardiac catetherization certainly provide information under far more physiologic circumstances. Morever, myocardial catecholamines can be investigated only in biopsy specimens in patients with congestive cardiomyopathy, in whom cardiac surgery is rarely indicated.

Myocardial norepinephrine concentration in congestive cardiomyopathy. The mean myocardial norepinephrine concentration in mg wet weight of tissue in the left ventricular myocardium was lower in patients with conges-

Table 4. Myocardial Norepinephrine Concentrations, Diameters of Cardiocytes and Plasma Catecholamines (mean ± standard deviation)

	Myocardial Norepinephrine (pg/mg wet weight) RV	LV	Cardiocyte Diameter (μm) RV	LV	Plasma Catecholamines (pg/ml) NE	Epi
CCM	739 ± 265 (n = 11)	435 ± 311 (n = 6) *	18 ± 4	24 ± 3	402 ± 151 (n = 10) †	78 ± 58 (n = 10) *
HCM	1095 ± 562 (n = 21)	875 ± 348 (n = 12)	18 ± 3 *	22 ± 3	207 ± 58 † (n = 19)	22 ± 14 * (n = 19)
Other	1182 ± 649 (n = 12)	438 (n = 2)	15 ± 3 *	19	177 ± 47 (n = 9)	16 ± 3 (n = 9)
Total	n = 44	n = 20				

*p<0.05. †p<0.001.

CCM = congestive cardiomyopathy; Epi = epinephrine; HCM = hypertrophic cardiomyopathy; NE = norepinephrine, other = other diseases; other abbreviations as in Table 1

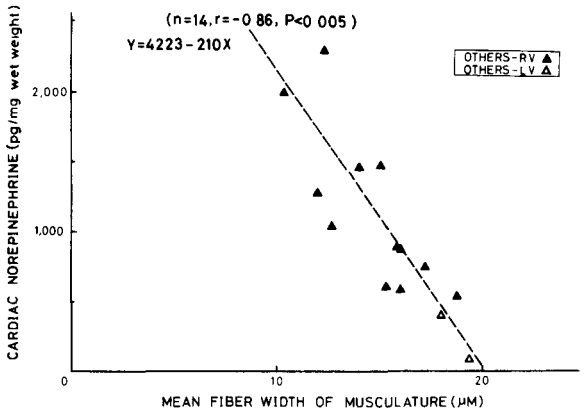


Figure 2. Relation between myocardial norepinephrine concentration and mean fiber width of cardiocytes in 11 patients (14 biopsy specimens) with heart diseases other than cardiomyopathy (noncardiomyopathy group). LV = left ventricular and RV = right ventricular biopsy.

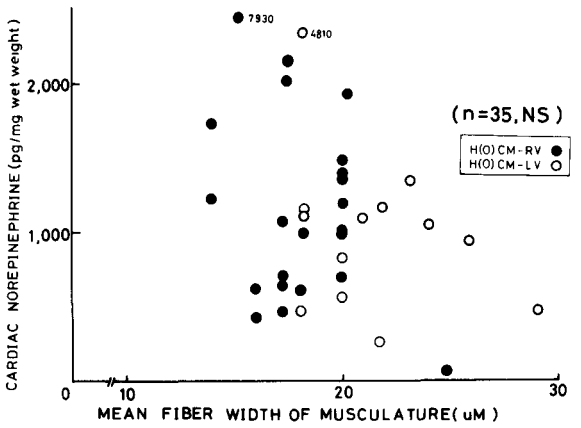


Figure 4. Relation between myocardial norepinephrine concentration and mean fiber width of cardiocytes in 24 patients (35 biopsy specimens) with hypertrophic cardiomyopathy (H[O]CM).

tive than in those with hypertrophic cardiomyopathy. However, the present study failed to show larger stores of myocardial norepinephrine in patients with hypertrophic cardiomyopathy than in those with noncardiomyopathic heart disease.

Decreased myocardial levels of norepinephrine stores in congestive cardiomyopathy may well be the result of heart failure. This is supported by the fact that the mean plasma norepinephrine and epinephrine levels were significantly higher in patients with congestive cardiomyopathy than in those with hypertrophic cardiomyopathy or other heart disease. It is conceivable, therefore, that patients with congestive cardiomyopathy were at least in latent heart failure, although there was no obvious evidence of heart failure at the time of the study.

Mechanism of myocardial norepinephrine depletion in heart failure. The mechanism of cardiac norepinephrine depletion in heart failure is still controversial. In dogs with right ventricular failure, the reduction of cardiac norepinephrine concentration was shown not to be the result of a simple dilution of sympathetic nerve endings in a hypertrophied muscle mass, because the total ventricular content of norepinephrine was lower in both the hypertrophied right and nonhypertrophied left ventricle (13). Marked reduction in the activity of tyrosine hydroxylase was considered to be responsible for the cardiac norepinephrine depletion through decreased biosynthesis (14). On the other hand, in cardiomyopathic Syrian hamsters the rate constant for cardiac norepinephrine turnover was much higher than in the control group. Thus, in the late stage of hamster cardiomyopathy,

Figure 3. Relation between myocardial norepinephrine concentration and mean fiber width of cardiocytes in 10 patients (17 biopsy specimens) with congestive cardiomyopathy (CCM). Abbreviations as in Figure 2.

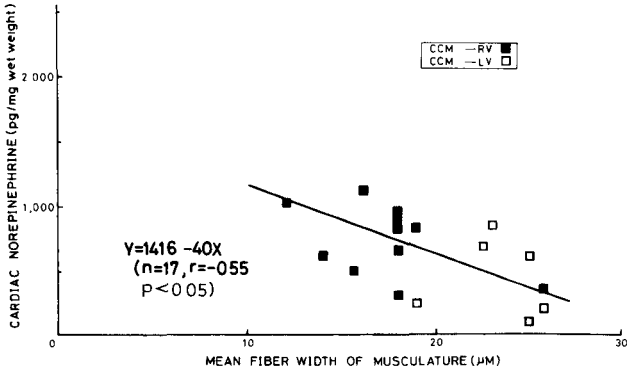
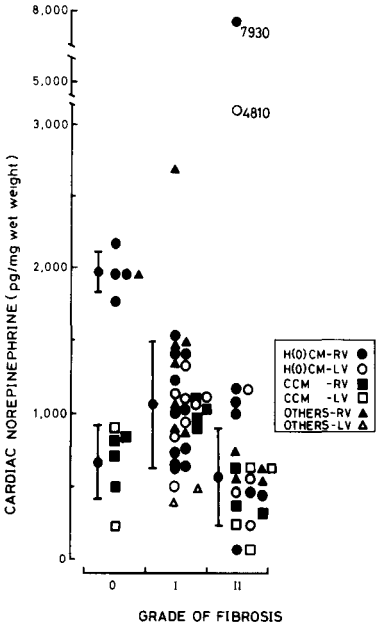


Figure 5. Relation between myocardial norepinephrine concentration and the grade of interstitial fibrosis in 45 patients (66 biopsy specimens). Abbreviations as before.



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the increase in cardiac sympathetic tone is responsible for the decrease in cardiac norepinephrine (15). Our results may also indicate that the myocardial norepinephrine level in no way provides us with a biochemical index of myocardial sympathetic activity. In the hamster with cardiomyopathy, moreover, there is an increase rather than a decrease of tyrosine hydroxlase activity during the development of heart failure (16). Although there is clear evidence of depletion in cardiac norepinephrine in heart failure, the specific mechanism responsible for it has not been clarified.

Role of myocardial hypertrophy and interstitial fibrosis. The present study indicates that the diameter of the myocardial cells (grade of myocardial hypertrophy) and the grade of interstitial fibrosis should always be taken into account in evaluating myocardial norepinephrine concentrations, because the reduction of norepinephrine concentration in the myocardium may be the result of a simple dilution of sympathetic nerve endings in a hypertrophied muscle mass (17) or an increase in interstitial fibrosis, or both. The lower value of the myocardial norepinephrine concentration in the left than in the right ventricle may be explained by the simple dilution of sympathetic nerve endings in the left ventricular myocardial cells, which have larger diameters than those in the right. It is worthwhile to note that the simple dilution theory holds true in patients with heart disease other than cardiomyopathy, whose myocardium showed fairly normal histologic features. In patients with hypertrophic cardiomyopathy, there was no significant inverse correlation between the diameter of the myocardial cells and myocardial norepinephrine concentrations. This is partly because there were some patients wich exceptionally high concentrations of myocardial norepinephrine, regardless of the cell diameter and the grade of interstitial fibrosis. In some patients with congestive cardiomyopathy, however, the level of myocardial norepinephrine was lower than would be expected for the degree of hypertrophy, interstitial fibrosis or severity of heart failure.

Implications. These findings suggest that abnormal myocardial norepinephrine (a depletion in congestive cardiomyopathy and an increase in some cases of hypertrophic cardiomyopathy) may be related to the development of cardiomyopathy. The regulation of beta-adrenergic receptor density in the myocardium and, therefore, sensitivity to catecholamine should also be clarified for a better understanding of its role in abnormal myocardial catecholamine activity in cardiomyopathy. The results of two recent important studies (18,19) on receptor density in failing hearts are conflicting. The obvious differences between these two studies appear to be the duration and cause of heart failure and the species examined. Further studies in this field are essential to elucidate more precisely the role of myocardial catecholamine in the pathogenesis of cardiomyopathy.

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