—Case Report—

A Case of "Disease of the Intercalated Disc" Demonstrated in Obstructive Cardiomyopathy*

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DURING the past 10 years, considerable attention has been focused on the clinical entity consisting of a muscular obstruction to the outflow of ventricle, and various clinical and hemodynamic features have been detailed by many investigators.¹⁻³⁵

However, the histological aspect of the disease is highly nonspecific^{2, 18, 23, 26, 36} and it has been included in "cardiomyopathy" which principally affects the myocardium.³⁷⁻³⁹

More recently, a new concept of "disease of the intercalated disc" has been advanced on an ultrastructural basis.⁴⁰ The correlation of this morphological disarrangement with the hemodynamic aspect is still obscure. It is our purpose to report one case of obstructive cardiomyopathy demonstrating this subcellular alteration and to review its hemodynamic features.

CASE REPORT

A 20 year old female was admitted to Tenri hospital on August 14, 1967, with complaints of exertional dyspnea and a syncopal attack. She was first noted as having heart disease at

6 years of age. She had enjoyed normal school life only with restriction of hard physical exercise. Since 15 years old, exertional dyspnea had become intensified gradually, and at 19 years of age, she began to have difficulty in climbing stairs without rest. Ten days prior to admission she had a sudden syncopal attack while at work. She has never noticed chest pain or peripheral edema.

Physical examination revealed a well nourished, somewhat small female. She was acyanotic. The radial pulse was 92 per minute, regular with a quick rise and fall. The jugular venous pulse was normal. The blood pressure was 100/20 mm Hg. A systolic thrill was felt along the upper left sternal border. On auscultation of the heart, the first heart sound was decreased in intensity. Both the aortic and pulmonic components of the second sound were also decreased but normally split with normal respiratory change. The third sound was not heard. The fourth sound was loud and best heard at the apex. There was a grade 6/6 systolic murmur of ejection type, which was maximal at the second intercostal space to the left of the sternum and radiated widely both to the apex and to the left axilla, but less to the carotid artery. A low pitched presystolic murmur of grade 2/6 was heard at the apex (Fig. 1, 2). No rales nor wheezes were heard in the lungs. The liver was not palpable. Peripheral edema was not noted.

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Fig. 1. Phonocardiogram recorded at the apex, exhibits the fourth heart sound. The third sound is not recorded. There are a mid-systolic, diamond-shaped ejection murmur, and low pitched presystolic murmur.

Conventional roentgenography revealed a considerable cardiomegaly with globular appearance. The cardio-thoracic ratio was 0.61. The ascending aorta appeared to be of normal size (Fig. 3).

The electrocardiogram showed regular sinus rhythm. The mean electrical axis was $+30^\circ$.

There was no distinct P wave abnormality. PQ interval was prolonged to 0.22 sec. There was distinct evidence of left ventricular hypertrophy. Abnormal Q waves were seen in III and aVF, which were attributed to depolarization of a hypertrophied septum (Fig. 4).

Selective Angiocardiography:

Fig. 2. Indirect carotid arterial pulse and a simultaneous phonocardiogram recorded at the second intercostal space to the left of the sternum. The ejection murmur is most prominent. There is a short upstroke time, mid-systolic dip and a late systolic plateau on an arterial pulse.

Fig. 3. Chest plane film showing enlargement of the cardiac silhouette.

Left ventriculography revealed filling defects which were produced by localized areas of myocardial hypertrophy and by that of papillary muscles, just beneath the aortic valve. The left ventricular cavity formed a tongue-like shape in the lateral projection and there were irregular indentations in the anterior portion of the left ventricular outflow tract (Fig. 5). In the frontal plane, the left ventricular cavity presented a biconcave configuration (Fig. 6). The left superior filling defect was attributed to the localized hypertrophy of the free wall, and concavity of the right inferior wall resulted from bulging of the hypertrophied interventricular septum. The deformed area narrowed further during ventricular systole. Mitral regurgitation was not observed.

Selective angiocardiogram with right atrial injection showed extreme obstruction of the right ventricular outflow tract at end-systole

(Fig. 7). The right ventricle was generally shifted to the right. The right atrium was moderately enlarged and pushed anteriorly and to the right, presumably by the adjacent large left atrium. The main pulmonary artery was dilated.

Arterial Pulse:

The indirectly recorded carotid arterial pulse exhibited a rapid rise and mid-systolic dip followed by a late systolic plateau. The ejection period was moderately prolonged to 0.38 sec. The upstroke time was found to be 0.082 sec (Fig. 2).

Cardiac Catheterization:

The data are summarized in Table I. A systolic pressure gradient of 28 mm Hg was recorded within the right ventricular outflow tract. Pulmonary arterial pressure was moderately elevated and pulsus alternans was observed in the PA and RV pressure distal to

Fig. 4. Electrocardiogram showing abnormal Q waves in lead III and aVF. The precordial leads exhibit clockwise rotation and the voltage criteria for left ventricular hypertrophy.

the obstruction (Fig. 8).

Pulmonary capillary wedge pressure was elevated (18 mm Hg) with giant A wave. The peak systolic pressure gradient across the left ventricular outflow tract was 108 mm Hg in the basal resting state. There was a distinct notch on the upstroke of the left ventricular pressure curve proximal to the obstruction and a mid systolic dip was noted on the distal pressure pulse. LV end-diastolic pressure was increased to 24 mm Hg (Fig. 9).

This patient was selected for surgery on the basis of persistent exertional dyspnea and repeated syncope. The operation was undertaken by *Dr. Tatsuta* and his associates, using heart lung bypass, on September 24, 1968. The interventricular septum was approached through a right ventriculotomy. Exploring finger was introduced into left ventricular outflow tract through aortotomy, which disclosed the septal thickening to be about 3 cm. Myocardium of 11 grams was resected from the surface of the interventricular septum, preserving the attachments of the chorda tendinae of the tricuspid valve, until the guiding fingers proved the thickness of the septum to be 1 cm under bimanual control.

She did not show striking clinical improvement after the operation, and remained in functional class III in spite of the use of propranolol in doses of 30 to 60 mg per day. She died suddenly on March 13, 1970. Unfortunately, facilities for an autopsy were not available.

Pathologic findings of the resected septal myocardium:

Light microscopy revealed thickened muscle fibers with different sized vacuolation. The nuclei were in various stages of degeneration. There was localized overgrowth of fibrous tissue, surrounding the capillaries and partially extending to the interstitial space. There was no significant inflammatory reaction in the myocardium. (Fig. 10)

Electron microscopic examination did not disclose any significant change in the subcellular fractions such as mitochondria or muscle elements. There were numerous vacuoles which were presumably part of the sarcoplasmic reticulum or increased fat deposits. The former

Fig. 5. Left ventricular angiogram in the lateral projection exposed at end-systole (left) and end-diastole (right). Note the tongue-like appearance of the left ventricular cavity, (left) and the greatly hypertrophied papillary muscles. (right)

Fig. 6. Frontal view of left ventricular angiogram exposed during diastole. There are inward concavities at the midportion of the right inferior and left superior margin.

Fig. 7. Selective angiogram with right atrial injection. Dotted lines denote the narrowing of the right ventricular outflow tract.

were often distended to cystic proportion. Dense granular and myelinated structures were seen in the sarcoplasm which suggested significant changes in myocardial cells. However, one of the characteristic aspects was the widening of the intercellular space at the intercalated disc as shown in figure 11.

DISCUSSION

Two types of obstruction to the outflow tract of the left ventricle have been considered. One is the true organic type of subaortic stenosis which is now better termed "Hypertrophic obstructive cardiomyopathy"¹⁻²⁰ The most prominent feature of this condition is massive hypertrophy of the septum, resulting in impairment of ventricular ejection. From the pathologic aspect, the syndrome is now

accepted as a form of primary myocardial disease in which the disease process has localized predominantly in the interventricular septum.³⁷⁻³⁹ The second type is characterized by a functional obliteration of the left ventricular cavity.²¹⁻³⁵ The latter is distinguished from the former type by a changeable and often absent pressure gradient during the course of left heart catheterization or on repeated studies. Sometimes, no obstruction is found at operation or at autopsy in the patients with large pressure gradients. The generally accepted term for this disorder is "Idiopathic hypertrophic subaortic stenosis". The functional obstruction is shown to increase with the inotropic intervention which enhances the force of contraction or by the procedure which diminishes the amount of venous return to the left ventricle.^{27-30, 41-45} However, opinions are

TABLE I DATA OF CARDIAC CATHETERIZATION

	<i>s</i>	<i>d</i>	<i>ed</i>	<i>m</i>	<i>O₂ Vol.%</i>
SVC				-2	9.63
IVC				0	12.75
SIVC					11.50
RA mid.				-2	11.13
RV inf.	70	5	9		
RV outf.	42	2	5		
m PA	40	17		24	9.59
l PA	39	14		23	9.58
l PC				18	
Ao	80	44		63	15.59 (94.4%)
LV outf.	82	0	22		
LV inf.	190	8	24		
SAB					16.50 (100%)
Cardiac output 5.23 L/min					
Cardiac index 4.02 L/min/M ²					
Stroke volume 80 ml/beat					
Pulmonary arterial resistance 61 dynes.sec.cm ⁻⁵					

divided concerning the mechanism which is responsible for the intraventricular pressure gradient, between obstruction from the extreme narrowing of the outflow tract³⁰ and catheter entrapment by contracting muscle.²⁹

In the case presented in this report, a considerable degree of pressure gradient was observed within the outflow tract of both ventricles in the basal resting state, and this case is in agreement with the reported findings of the former type in all respects.

The histological examination is not conclusive in this condition, for the myocardium presents inconsistent and highly nonspecific features as in the idiopathic disease of the myocardium. Cardiomegaly is mainly due to hypertrophy of the muscle fibers and to a variable increase in the connective tissue.

The changes in subcellular elements were also not specific for obstructive cardiomyopathy. However, one of the striking features was shown in the cell boundaries, where the intercalated discs were partially dissociated.

The intercalated disc is structurally differentiated into four types and designated as follows:^{40, 46, 47}

1) Macula adherens or desmosome; A discontinuous button like structure which may function as a device for strengthening the intercellular cohesion in the myofibrillar insertion region.

2) Macula occludens, nexus or tight junction; The intercellular space was completely obliterated at tight junction and this is considered to be a site which is correlated with propagation of action potentials.

3) Fascia adherens or intermediate junction; This occupies the major part of transversely connecting surfaces. The I-band filaments of the end sarcomeres of the myocardial cells are inserted into the dense filamentous bands of this structure.

4) Non specialized region or normal intercellular gap region; This is probably a part of the sarcoplasmic reticulum.

Recently, attention has been paid to the pathologic changes of the intercellular junctional region. The intercalated disc has been shown to be partially separated under various experimental conditions. In man, three cases of disorder of the intercellular space have been reported in the literature (Poche,⁴⁸ Kawamu-

TABLE II LABORATORY FINDINGS AT ADMISSION

RBC	395 × 10	I. I.	4 u.
Hb	10.6 g/dl	Cholesterol	163 mg/dl
MCH	27 µg	GOT	19 u.
Thrombocytes	110/10 o.i.f.	GPT	16 u.
WBC	4400	Al-Phosphatase	1.0 u.
N. Band	4	CCF	—
N. Segment.	49	Cholinesterase	0.61
Eosinophil	1	BSP 30'	4%
Lymphocytes	39	NPN	23 mg/dl
Monocytes	7	Urea N	9.5 mg/dl
T. P.	7.1 g/dl	S-Creatinine	0.75 mg/dl
Albumin	56.3% 4.0 g/dl	U-Creatinine	9.1 mg/kg 0.39 g/d
α1-G	3.8%	PSP 15'	39%
α2-G	7.5%	30'	59%
β1-G	11.3%	60'	79%
β2-G	3.0%	120'	91%
γ-G	18.1%	Urine Pr.	—
Globulin	43.7% 3.1 g/dl	Gl.	—
A/G	1.3	Ur.	±
CRP	—	Sed.	n. p.
RAT	—	S Na	141 mEq/L
ASLO	166 T.u.	K	3.8 mEq/L
FBS	79 mg/dl	Cl	106 mEq/L
S-Fe	93 γ/dl	Ca	4.3 mEq/L
Wa R	—	ESR 1 hr.	3 mm
VC	2580 ml (104%)	2 hrs.	11 mm
FVC	60%	m	4.3 mm
%MBC	41%	Stool occ. bl.	—
MMF	1.47	paras. E.	—

ra,⁴ Burch⁴⁶). In each specimen, widening of the intercellular space was seen in the intermediate junction and in the non specialized region. The tight junction always remained unaffected. Under these circumstances, mechanical efficiency of the myocardial contraction would have been reduced, for the cell boundaries where the maximal tension is imposed were dissociated, while the velocity of excitation was left intact.

Kawamura and Konishi have recently proposed the concept of "disease of the intercalated disc" and suggested the electrophysiologic and hemodynamic disturbance related to this morphological dissarrangement.⁴⁰ In our patient, disturbance of the ventricular contraction which was evidenced by the pulsus alternans is compatible with these pathological events at the ultrastructural level, and this offers additional support to this concept.

SUMMARY

A case of obstructive cardiomyopathy has been presented. A pressure gradient was evident across the outflow tract of both ventricles under resting condition. Angiocardiology showed marked hypertrophy of the interventricular septum which bulged into the right ventricle as well as into the left. Ventriculomyotomy was carried out to relieve the obstruction. Special attention was directed to the ultrastructural findings of the resected myocardium, which showed dissociation of the intercalated disc. The condition offers additional support to the concept of "disease of the intercalated disc".

Fig. 8. Pressure tracings recorded in the RV cavity, in the RV outflow tract, and in the main pulmonary artery. Note the pulsus alternans in the PA and RV outflow tract pressure. Paper speed 25 mm/sec.

Fig. 9. Pressure tracings recorded in the LV cavity, in the LV outflow tract, and in the aorta. There is a notch on the upstroke of the ventricular pressure pulse proximal to the obstruction. Note a striking atrial kick and a mid-systolic dip with a secondary elevation late in systole on the distal curve. Paper speed 50mm/sec.

Fig. 10. Microphotographs of right ventricular septal myocardium, showing localized overgrowth of fibrous tissue, (upper HE $\times 100$) and the thickened muscle fibers with different sized vacuolation. (lower HE $\times 630$)

Fig. 11. Electron micrograph. ($\times 22000$) Note the widening of the intercellular space at the intercalated disc.

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