CARDIOMYOPATHY

Clinical, Pathological and Theoretical Aspects

Edited by
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Preface

This relatively small yet comprehensive volume on cardiomyopathy concentrates on very wide-ranging and important aspects of the subject. Many experts in cardiology were gathered in Tokyo on the occasion of the VIIIth World Congress of Cardiology, and the opportunity seemed too good to be missed to invite those actively engaged in the study of cardiomyopathy to present their up-to-date experience. A post-congress symposium was therefore arranged, and this book is the result of that meeting. At a glance it can be seen that many world-renowned experts in the subject of cardiomyopathy have contributed. Each contributor has expanded his or her topic to include basic information so that each chapter is an authoritative full account of the special aspect with which it deals.

We felt that this approach would enable the reader not too familiar with the subject, as well as the specialist, to derive some benefit.

The book is divided into 5 major sections. The first deals with non-invasive and some invasive techniques for defining clinically the major types of cardiomyopathy. Pathomorphological, biochemical and immunological aspects are discussed in the second section, and the role of endomyocardial biopsy by means of the catheter technique—first developed in Japan in 1962—is critically analyzed. The important subject of up-to-date medical and surgical treatment is discussed in the third section. Recent possible etiologic factors are considered both in human and experimental studies in the fourth section. The last section deals with genetic aspects of cardiomyopathy.

In each section, additional papers which were on the initial program but could not be presented at the symposium have been included in order to widen the coverage of this volume. Whenever it was thought that points raised during the discussion were relevant and highlighted a particular aspect, they were included in the relevant section after the appropriate chapter.

We hope that this book will be of great value not only to those workers actively engaged in the study of cardiomyopathy but also to the student who would like to learn more about this subject. We also hope that some readers will be stimulated into initiating new research to advance our knowledge in this exciting and rapidly expanding field of cardiology.

M. S.
E. G. J. O.

Abbreviations

AHCM	Apical hypertrophic cardiomyopathy
ASH	Asymmetric septal hypertrophy
BMHD	Bizarre myocardial hypertrophy with disorganization
CCM	Congestive cardiomyopathy = COCM
CI	Cardiac index
COCM	Congestive cardiomyopathy = CCM
CTR	Cardiothoracic ratio
DCR	Diastolic closure rate
DDR	Diastolic descent rate
Dd	Diastolic dimension
Ds	Systolic dimension
Dv	Diastolic volume
ECG	Electrocardiogram
EF	Ejection fraction
EFE	Endocardial fibroelastosis
EMF	Endomyocardial fibrosis
HCM	Hypertrophic cardiomyopathy
HNOCM	Hypertrophic nonobstructive cardiomyopathy = Hypertrophic cardiomyopathy without obstruction
HOCM	Hypertrophic obstructive cardiomyopathy
ICM	Idiopathic cardiomyopathy
IHSS	Idiopathic hypertrophic subaortic stenosis
IRT	Isometric relaxation time
IVS	Interventricular septum
LAO	Left anterior oblique
LBBB	Left bundle branch block
LCM	Latent cardiomyopathy
LV	Left ventricle, Left ventricular
LVEDV	Left ventricular end-diastolic volume
LVEDP	Left ventricular end-diastolic pressure
LVET	Left ventricular ejection time
LVH	Left ventricular hypertrophy
PEP	Preejection period

PW	Posterior wall
RA	Right atrium, right atrial
RAO	Right anterior oblique
RBBB	Right bundle branch block
RV	Right venticle, right ventricular
SAM	Systolic anterior motion
SD	Standard deviation
SEM	Scanning electronmicroscopy
SV	Stroke volume
TEM	Transmission electronmicroscopy

Contents

Studies on Cardiomyopathy in Japan

Chuichi KAWAI

During the last 15 years, idiopathic cardiomyopathy, defined as heart muscle disorder of unknown cause or association, has been the topic of world-wide study in the field of cardiology. So far, very few cases have been clarified in terms of pathogenesis or etiology. With the aid of a research grant from the Ministry of Health and Welfare, a multi-center cooperative study on cardiomyopathy has been carried out in Japan for the past 5 years. Fifteen to 20 cardiologists representing the leading institutions throughout the country have been appointed to the committee (Chairman: Chuichi Kawai, M.D.). Divided into subcommittees for epidemiology, pathogenesis or etiology, pathology, pathologic physiology, criteria for diagnosis, and treatment, the committee has undertaken extensive studies on cardiomyopathy. This paper will discuss two representative studies by the Committee. Other Japanese co-workers will supplement this report.

I. MULTI-CENTER COOPERATIVE STUDY[1)]

A) Patient's profile

Out of 540 cases, most of which were adult, uniform data sheets for idiopathic cardiomyopathy were completed in 15 cardiology divisions of university or national hospitals in Japan. Three hundred and forty cases were selected for the present study when at least one of the following types of data was available: (1) autopsy confirmation; (2) biopsy findings and one or more supportive findings such as increased left ventricular end-diastolic volume (LVEDV), decreased cardiac index (CI), (3) supportive angiocardiographic and/or hemodynamic findings; and (4) typical echocardiogram. The cases thus selected were classified into 3 clinical subgroups following the system of Goodwin *et al.*: namely, congestive (CCM), hypertrophic non-obstructive (HNOCM), and hypertrophic obstructive (HOCM) cardiomyopathies.

Categorization of the diagnosis of each patient was as follows: (1) definite, (2) probable, or (3) undetermined, according to the certainty of the diagnosis.

Department of Internal Medicine, Faculty of Medicine, Kyoto University, Kyoto, Japan

When categorization into a subgroup was difficult, the patient was placed under "Undetermined" although the diagnosis of cardiomyopathy was certain. Restrictive or obliterative cardiomyopathies were not included in the present study because of infrequent occurrence. As shown in Table 1, there were 84 definite cases of CCM, 57 of HNOCM, and 52 of HOCM; and clinical features of these patients were analyzed (Table 1). It is to be noted that the numbers of cases of hypertrophic cardiomyopathy, including HNOCM and HOCM, exceeded those of CCM. This finding may partly be due to the fact that patients with asymptomatic hypertrophic cardiomyopathy are frequently found in Japan because of the popular annual physical examination.

TABLE 1. Numbers of Cases in Subgroups

	Definite	Probable	Undetermined	Total
CCM	84(43.5%)	19(37.3%)	29(30.2%)	132(38.8%)
HNOCM	57(29.5%)	15(29.4%)	25(26.0%)	97(28.5%)
HOCM	52(27.0%)	17(33.3%)	21(21.9%)	90(26.5%)
Unknown			21(21.9%)	21(6.2%)
Total	193	51	96	340(100.0%)

TABLE 2. Sex Distribution

	Total	Male	Female	Male/Female
CCM	84	64	20	3.2
HNOCM	57	46	11	4.2
HOCM	52	35	17	2.1
Total	193	145(75%)	48(25%)	3.0

Among the 193 patients with definitely diagnosed cardiomyopathy, 145 (75%) were male and 48 (25%) were female (M/F ratio = 3:1). The mean age of the definite group was 34.1. Differences in the mean ages between the subgroups were statistically insignificant (Table 3).

TABLE 3. Mean Age

	Definite	Probable
CCM	37.8	31.8
HNOCM	31.6	33.7
HOCM	30.7	25.0
Total	34.1	30.0

B) Clinical features

In congestive cardiomyopathy (CCM) (upper panel, Fig.1), patients were more severely symptomatic than in the other subgroups; dyspnea was the most common symptom, followed in frequency by palpitation, edema, chest oppression, arrhythmia, and chest pain. Among these symptoms, dyspnea, edema, and arrhythmia were characteristic in this subgroup. There was an increased incidence of congestive heart failure.

In hypertrophic non-obstructive cardiomyopathy (HNOCM) (middle panel, Fig. 1), many patients were asymptomatic. When symptoms were present, palpitation considered to be totally nonspecific was frequent.

As expected, dizziness and syncope were more common in hypertrophic obstructive cardiomyopathy (HOCM) (lower panel, Fig. 1) than in the other subgroups. In addition patients frequently complained of palpitation in this subgroup. The frequencies of chest oppression and pain were low but were almost equally distributed among the other subgroups.

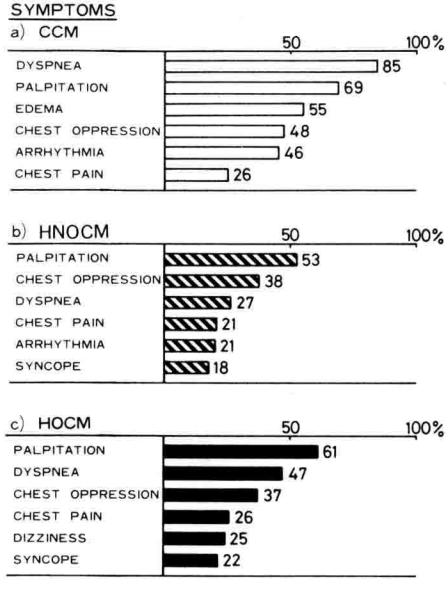

FIG. 1. Frequency of symptoms in patients with congestive (CCM), hypertrophic non-obstructive (HNOCM), and hypertrophic obstructive (HOCM) cardiomyopathies.

Nonspecific, abnormal electrocardiograms offer the first clue to the diagnosis of cardiomyopathy (Table 4). ST-T abnormalities were most frequently

observed in each of the subgroups: 88.5% in CCM, 90.3% in HNOCM, and 86.8% in HOCM. While a high percentage of patients with HNOCM and

TABLE 4. EKG Findings

	CCM	HNOCM	HOCM	Total
ST-T change	88.5%(85/96)	90.3%(65/72)	86.8%(59/68)	88.6%(209/236)
LVH	45.3%(43/95)	76.4%(55/72)	79.1%(53/67)	64.5%(151/234)
Abnormal P	50.5%(46/91)	26.8%(19/71)	30.9%(21/68)	37.4%(86/230)
LAD($< -30°$)	27.8%(27/97)	15.5%(11/71)	23.5%(16/68)	22.9%(54/236)
Abnormal Q	45.9%(45/98)	32.4%(23/71)	35.3%(24/68)	38.8%(92/237)
VPC	61.6%(61/99)	7.0%(5/71)	11.8%(8/68)	31.1%(74/238)
Low Voltage	18.1%(17/94)	1.5%(1/67)	3.0%(2/67)	8.8%(20/228)
Wide QRS $\geqq$ 0.12	23.1%(21/91)	3.1%(2/64)	10.6%(7/66)	13.6%(30/221)

LVH: left ventricular hypertrophy LAD: left axis dexiation

TABLE 5. Cardiothoracic Ratio (CTR)

CTR %	CCM	HNOCM	HOCM
49	1	26	15
50–54	7	18	21
55–59	30	16	16
60–	61	12	16
Total	99	72	68
Mean CTR	61.8	52.3	54.2
SD	6.4	7.4	6.4

TABLE 6. Auscultation

	CCM	HNOCM	HOCM	Total
S3	77.6%(66/85)	39.7%(25/63)	36.5%(23/63)	54.0%(114/211)
S4	61.8%(47/76)	69.2%(45/65)	75.8%(47/62)	68.5%(139/203)
Systolic M.	79.4%(73/94)	85.9%(61/71)	97.0%(64/66)	85.7%(198/231)
Diastolic M.	11.0%(8/73)	3.3%(2/61)	11.9%(7/59)	8.8%(17/193)

TABLE 7. N.Y.H.A. Classification

	CCM	HNOCM	HOCM	Total
I	8(8.1%)	30(42.2%)	20(29.9%)	58(24.5%)
II	32(32.3%)	33(46.5%)	39(58.2%)	104(43.9%)
III	42(42.4%)	8(11.3%)	8(11.9%)	58(24.5%)
IV	17(17.2%)	0	0	17(7.1%)
Total	99	71	67	237(100.0%)

HOCM satisfied the criteria for left ventricular hypertrophy (LVH), less than half the patients with CCM showed LVH. In CCM, low voltages in the limb and chest leads were more commonly seen than in the others. It should be noted that abnormal Q waves were observed in all subgroups: 45.9% in CCM, 32.4% in HNOCM, and 35.3% in HOCM. Differential diagnosis of idiopathic cardiomyopathy and ischemic heart disease is very important but often difficult. Ventricular premature contractions were encountered much more frequently in CCM than in the other subgroups. The high incidence of arrhythmia may be the reason for the high occurrence of sudden death in CCM.

The cardiothoracic ratio (CTR) exceeded 55% in 91 of 99 patients (92%) with CCM. The mean CTR was 61.8% in CCM, 52.3% in HNOCM, and 54.2% in HOCM (Table 5). It should be mentioned that in the latter two subgroups the heart size on conventional radiography was within normal limits or was slightly enlarged in most cases.

A gallop rhythm, either a third or fourth sound, is common in cardiomyopathy (Table 6). A third sound was present in 66 of 85 patients (77.6%) with CCM, which was the highest among the subgroups. A fourth sound was most common in HOCM. A systolic murmur was frequently heard in each subgroup, especially in patients with HOCM. A diastolic murmur was rarely observed in any of the subgroups.

Fifty-nine of 99 patients (60%) with CCM were in functional classes III and IV (New York Heart Association), while most of the patients with HNOCM and HOCM were in classes I and II (Table 7). These results coincide with the fact that there were a number of asymptomatic patients with hypertrophic cardiomyopathy found incidentally at the time of an annual physical examination.

II. HLA AND HYPERTROPHIC CARDIOMYOPATHY

In Japan hypertrophic cardiomyopathy is found more frequently than congestive cardiomyopathy. Hypertrophic cardiomyopathy is often familial, and genetic factors have been considered in the pathogenesis of the disease[2,3]

Recently, several antigens of the HLA system (human leucocyte antigen, or human major histocompatibility complex) have been observed in association with diseases in which there is a high familial incidence or an immunologic basis.[4]

Thirty unrelated Japanese patients with hypertrophic obstructive and non-obstructive cardiomyopathy, 20 males and 10 females with an average age of 35, were studied to determine HLA typing by a lymphocytotoxicity micromethod.[5,6] Seventy antisera were used to define 21 major HLA specificities. Several HLA antigens such as A2, A9, A10 B7, and BW35 seemed to be more

common in patients, but there was no significant difference in frequencies between patients and controls (Table 8).

HLA typing was determined in two families in which many members had hypertrophic cardiomyopathy.

Family 1 (Fig. 2): The proband was a 41–year-old woman with hypertrophic non-obstructive cardiomyopathy. The proband carried a HLA-A9, B7 haplotype. This haplotype was also found in her mother and a younger brother, both affected. By contrast, her father and an elder brother, not carrying the A9, B7 haplotype, showed no cardiac abnormality. The proband's daughter, aged 10 years, had an A9, B7 haplotype. Her electrocardiogram showed inverted T waves in leads V_1 through V_3, although echocardiographic abnormalities were not yet evident.

Family 2 (Fig. 3): The proband was a 39–year-old woman with hypertrophic non-obstructive cardiomyopathy. Her mother, diagnosed as having "cardiac asthma," died suddenly at the age of 43. A younger sister, 36 years old, had

TABLE 8. Frequency of HLA in Hypertrophic Cardiomyopathy

Antigen	Patients $n = 30(\%)$	Controls $n = 176(\%)$
HLA-AI	0	0
A2	53.3	47.2
A3	0	0
A9 (AW24)	56.7	53.4
A10 (AW26)	33.3	19.9
A11	10.0	15.9
A28	0	0
AW19	16.7	19.3
HLA-B5	26.7	34.7
B7	13.3	8.0
B8	0	0
B12	10.0	17.6
B13	6.7	4.5
B15	10.0	18.2
BW16	3.3	10.2
BW17	6.7	0.6
BW21	0	0
BW22	13.3	5.1
BW54	6.7	14.2
BW35	36.7	19.3
BW37	0	0
BW40	30.0	35.2