Architectural Alteration of the Myocardium and Asymmetry in Left Ventricular Hypertrophy of Known Etiologies with Special Reference to Correlation with Electrocardiographic Changes

RYOZO OKADA, M.D.

IT is well known that modes of hypertrophy of the left ventricle vary in accordance with hemodynamic conditions, such as volume overload or pressure overload, as well as with the type of basic disease, e.g., aortic or mitral valvular failure. The aim of this report is to define general rules applicable in various types of dilatation and hypertrophy, which may eventually induce specific architectural changes in the myocardium and an asymmetry of wall thickness, which lead to corresponding electrocardiographic (ECG) changes.

In addition, careful analysis of the modes of hypertrophy of known etiologies would seem to provide some valuable information for the clarification of asymmetric hypertrophy in cardiomyopathy, the etiology and significance of which still remain obscure.

Architectural Alteration of the Myocardium in Hypertrophy¹

Eighty-five autopsied hearts with left ventricular hypertrophy were studied macroscopically and histologically. They consisted of cases of mitral regurgitation (MR), aortic regurgitation (AR), combined valvular disease (CVD), hypertensive heart disease (HHD) and ischemic heart disease without gross myocardial infarction (IHD). In addition, 23 hearts, normal and with

mitral stenosis (MS), were selected as the controls.

Each heart was weighed and ventricular size was determined by measuring both the base-apex distance (A) and the width of the ventricles at the median portion (B) after formalin fixation. The left ventricular (LV) volume was measured by the water volume which filled an ice bag inserted into the left ventricle. The wall thickness was determined by the thickness of the stratum compactum at the median portion of the anterior wall. The measured values in females were adjusted by multiplying by the female to male conversion factor (1.1 for heart weight, ventricular size and wall thickness; 1.3 for LV volume). Thus, all our results should be interpreted as data for males.

For microscopic examination, blocks, including vertical sections from the base to the apex, and horizontal sections were taken from the anterior wall; they were cut into 7- μ m slices after being embedded in paraffin. These slices were stained by hematoxylin and eosin, azan or by Masson's, and Weigert-van Gieson's methods.

Ante-mortem ECG records were carefully checked. At least two records were utilized in each case: one taken one month or more prior to death and the other within one week before death. High voltages of QRS, defined as Rv_5 or $6 + Sv_1$ of more than 3.5 mV, and ST-T changes were estimated at the left precordial leads. Cases of bundle branch blocks were excluded from the ST-T estimation.

Data obtained by macroscopic examination is listed in Table I. The shape of the left ventricle

Key Words:

- Left ventricular hypertrophy
- Asymmetry of hypertrophy
- ECG of LV hypertrophy
- Architecture of the myocardium
- Shape of the ventricular septum

Department of Internal Medicine, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Fig.1. Frontal view of a normal heart with macroscopic dissection of three layers of the ventricular myocardium.

A: outer oblique layer; B: median circular layer; C: inner oblique layer

is quite different in each disease. Globular enlargement in MR and CVD and elongated enlargement in AR are easily differentiated. Heart weight increases markedly in AR and CVD, moderately in MR and slightly in HHD and IHD. Wall thickness of the LV is the greatest in HHD and AR. The most marked increase of LV volume is seen in CVD and AR and the second largest in MR and HHD.

Results of microscopic study are summarized in Table II. Categories made according to ECG findings are listed horizontally, and vertical columns correspond to the basic disease. Each pathological finding, such as hypertrophy, degeneration or fibrosis, is counted as 3 for +, 6 for ++ and 10 for +++ lesions, as well as 10 for a normal state. The myocardial index is presented as a number that is calculated by subtracting the degeneration plus the fibrosis counts from

the sum of the normal plus the hypertrophy counts. A positive index indicates a good condition of the myocardium and a negative index means an altered state. The estimation was made separately for the three layers,² i.e., the outer oblique, median circular and inner oblique layers of the myocardium.

The three-layer structure of the ventricular myocardium is easily presented using the macroscopic dissection method. Figure 1 shows a frontal view of normal ventricles, in which muscle bundles are stripping superficially (A), intermediately (B) or deeply (C) from left to right. The outer oblique layer has a muscle-bundle orientation originating the right upper area extending in the left lower direction, the median circular layer has a horizontal orientation and the inner oblique layer has a orientation originating from the left upper area extending in

TABLE I SHAPE AND SIZE OF THE LEFT VENTRICLE

	Normal	MS	MR	AR	CVD	HHD	IHD
Shape
	RV	RV	RV	RV	RV	RV	RV
Heart weight (g)	272	438	501	620	618	469	451
A (Length) (cm)	10.4	11.3	12.2	13.0	12.7	11.3	11.5
B (Width) (cm)	8.4	8.4	11.0	10.8	10.3	9.8	9.8
LV wall (cm)	1.03	0.91	1.26	1.41	1.21	1.48	1.39
LV volume (ml)	27	27	38	59	71	35	34
Blood pressure	norm	norm	norm	syst high	norm	high	some high

Abbreviations: MS = mitral stenosis, MR = mitral regurgitation, AR = aortic regurgitation, CVD = combined valvular disease, HHD = hypertensive heart disease, IHD = ischemic heart disease without infarction

TABLE II HISTOLOGY OF THE LEFT VENTRICULAR MYOCARDIUM AND ECG FINDINGS AT THE LEFT PRECORDIAL LEADS

ECG	Disease	N	MS	MR	AR	CVD	HHD	IHD	Total	Average score					Index (N+H)-(D+F)	Major lesions
										m	N	H	D	F		
Normal		8	5				1		14	i 4 m 5 o 6	1 0 0 1 0 0	1 1 1 1 0 1	1 1 1 1 1 1		+3 +3 +4	normal
ST↓		1			1	1			3	i 0 m 0 o 0	1 1 1 1 0 0	6 3 5 2 3 1			-8 -6 -4	i > m > 0
T→		3	3	1		1	1		9	i 6 m 1 o 6	1 0 0 4 1 1	1 3 4 2 1 2			+3 -5 +4	median
T↓				2				3	5	i 0 m 0 o 0	2 1 1 6 1 1	5 5 5 5 4 4			-8 -10 -4	i < m > 0
ST↓, T↓				1	1			3	5	i 0 m 0 o 0	4 2 2 5 4 3	5 7 5 5 4 4			-8 -8 -3	i = m > 0 H
HiV		1		1			1	1	4	i 0 m 3 o 0	3 2 2 3 3 3	3 3 3 2 3 2			-3 0 -2	balanced, H
HiV, ST↓		1		2	2	1			6	i 0 m 0 o 0	4 3 3 4 3 2	6 6 5 5 4 4			-8 -6 -3	i > m > 0 H
HiV, T→				1	1	3			5	i 0 m 0 o 0	4 5 1 5 4 1	5 5 3 3 3 3			-6 -7 0	i < m H
HiV, ST↓, T→			1	1	2	6	3		13	i 0 m 1 o 0	4 2 2 4 4 3	5 7 4 4 3 3			-8 -5 -2	i > m H
HiV, ST↓, T↓				2	6	3	3	2	16	i 0 m 0 o 0	3 2 2 5 4 2	6 6 5 5 3 3			-9 -8 -1	i = m oH
cBBB						5			5	i 0 m 0 o 0	2 0 0 6 1 4	8 4 6 4 4 4			-14 -10 -7	i > m > 0 +++
Total		14	9	11	13	20	9	9	85	Histological findings are graded as -, +, ++, +++ for each lesion, and scores 0 for -, 3 for +, 6 for ++ and 10 for +++, as well as 10 for normal myocardium, are given for the calculation of the myocardial index.						
Normal	i	5	2	1	0	0	0	0								
	m	3	3	3	0	0	1	0								
	o	5	6	2	0	0	1	0								
Hypertrophy	i	1	1	3	3	3	3	3								
	m	0	0	2	3	1	2	1								
	o	0	1	3	5	3	4	3								
Degeneration	i	2	2	5	7	5	4	5								
	m	3	2	4	5	4	4	6								
	o	1	1	3	2	2	2	2								
Fibrosis	i	0	3	7	7	6	5	7								
	m	0	2	5	4	4	3	5								
	o	0	2	4	3	3	2	4								
Index (N+H)-(D+F)	i	+4	-2	-8	-11	-8	-6	-9								
	m	0	-1	-4	-6	-7	-4	-10								
	o	+4	+4	-2	0	-2	+1	-3

Abbreviations: ↓ = depression, → = flattening, HiV = high voltage, cBBB = complete bundle branch block, N = normal, H = hypertrophy, D = degeneration, F = fibrosis, i = inner layer, m = median layer, o = outer layer, > = more involved, oH = hypertrophy in outlayer

the right lower direction. These three layers are microscopically differentiated by the shapes of the myocytic cross sections and even the angles

of the muscle orientation, e.g., vertical, oblique or circular, can be grossly estimated by the ratio of length to width of the cut surface of the

Fig.2. Histological findings of the normal LV wall. Azan stain.

A: Panoramic view of vertically cut specimen, $\times 5$. Left side is the endocardium.

B: Inner layer, $\times 40$.

C: Median layer, $\times 40$.

D: Outer layer, $\times 40$.

Fig.3. Histological findings of the LV wall in MR. Azan stain.

A: Panoramic view of vertically cut specimen, $\times 5$. Direction is the same as in Fig.2.

B: Inner layer, $\times 40$.

C: Median layer, $\times 40$.

D: Outer layer, $\times 40$.

Fig.4. Histological findings of the LV wall in AR. Azan stain.

A: Panoramic view of vertically cut specimen, $\times 5$. Direction is the same as in Fig.2.

B: Inner layer, $\times 40$.

C: Median layer, $\times 40$.

D: Outer layer, $\times 40$.

Fig.5. Histological findings of the LV wall in HHD. Masson's stain.

A: Panoramic view of vertically cut specimen, $\times 5$. Direction is the same as in Fig.2.

B: Inner layer, $\times 40$.

C: Median layer, $\times 40$.

D: Outer layer, $\times 40$.

Fig.6. Distribution pattern of asymmetry indices in each disease group.

Abbreviations:

GI = disease of the GI tract, T = tumors, HT = hypertension between 150/90 and 220/130 mmHg, HN = renal hypertension (mostly chronic nephritis), SHT = severe hypertension of more than 220/130 mmHg, Sm = maximal thickness of the ventricular septum, Fm = free wall thickness at the median portion of the LV, Fb = free wall thickness at the basal portion of the LV, Fa = free wall thickness at the apical portion of the LV

myocytes.

Figure 2 shows a normal left ventricular free wall, vertically cut at the anterior papillary muscle. The top figure (A) is a low-power panoramic view of the wall from the left side of the endocardium to the right side of the epicardium. Whitish interstitial markings containing small vessels form a gentle concave curve. The bottom figures are medium-power views of the myocardium: the inner (B), median (C) and outer (D) layers from left to right, respectively. Shapes of the cross sections of the myocytes are quite varied depending on the layer. If the muscle bundle orientation deviates more vertically, the cut surface becomes more elongated, as shown in B and D; in contrast, a horizontal or circular orientation makes a round shape at the cut surface as shown in C. According to these criteria, the inner, median and outer layers occupy almost equal widths in the normal LV wall.

In the MS group, the outer layer has a more horizontal muscle bundle orientation than normal, and the combined thickness of the median and outer layers is slightly thinner than normal.

As to the quality of the myocardial cells, even in the control groups, the condition of the outer layer shows the best score of the myocardial index mentioned above, and that of the median and inner layers reflects some negative counts.

Figure 3 shows the left ventricular wall of a case of MR. The inner layer cells, running more vertically, are prominently hypertrophied, as shown in A and B. On the other hand, the median (C) and outer layer (D) cells are less hypertrophied with the orientation of the latter deviating more horizontally and seemingly with the reduced thickness. Degeneration and fibrosis predominate in the inner and median layers.

Figure 4 shows an example of the AR group. The outer-layer cells, running more vertically, are markedly hypertrophied (A and D), and the

Fig.7. Shape of the ventricular septum. Frontal view of vertically cut surface.

inner (B) and median layer (C) cells show severe deterioration, i.e., myocytolysis and fibrosis.

The CVD group shows a similarity to MR, but with more advanced myocardial lesions.

Figure 5 is a thick wall of a cases of HHD. The cell orientation of each layer is essentially analogous to normal (A), though slightly exaggerated vertically at the inner (B) and outer (D) layers. The hypertrophy count is 4:2:3 from the outer to inner direction, and degeneration and fibrosis are concentrated in the inner region.

The IHD group has an essentially normal cell orientation, some hypertrophy in the inner and outer layers and severe cell deterioration in the inner and median layers.

From the viewpoint of ECG changes, ST depression corresponds to an inner layer deterioration and T changes indicate median layer involvement. Some cases with ST and T changes have normal QRS voltage in spite of the presence of histological hypertrophy. This observation could be explained by the cancellation of the high voltage by myocardial fibrosis with a substantial loss of muscle cells, as is often seen in IHD. As a rule, high voltage QRS correlates with hypertrophy at the outer layer, which is often associated with that of the inner layer. The bundle branch block group shows the most severe deterioration of the myocardium.

The layer selective myocardial lesions seem to be closely related to the shape and size of the ventricle and to the muscle bundle orientation. When the ventricular size is increased, overstretching of the myocardium can theoretically

cause median layer deterioration first³ because horizontally running muscle cells cannot avoid the stretching overload by changing intercellular or interfascicular distance⁴. When the ventricular shape is changed, the muscle bundle orientation should be altered to adapt to the new situation⁵. The globular MR-type enlargement makes the outer oblique layer more horizontally oriented, and elongated AR-type enlargement makes this layer more ventrically oriented than normal. The latter makes a sharp angulation between the hypertrophied outer layer and the fibrosing median layer, and this might augment mechanical stress that accelerates the median layer deterioration. Usually, the HHD and IHD groups show no particular alteration of the bundle orientation because very little dilatation is present.

The principle of a correlation between ECG and pathology presented here could be useful in ascertaining the nature of hypertrophy and hypertrophy-related myocardial lesions.

Asymmetry of Left Ventricular Hypertrophy

One hundred and eleven autopsied hearts with left ventricular hypertrophy, including the materials above-mentioned, were used in this study. The IHD group was omitted because of the case-by-case variations in the sites of the coronary stenosis. Cases with pulmonary disease or congenital heart anomaly and those younger than 17 were also excluded. The hypertension (HT) group was further divided into 3 subgroups: HT, ordinary hypertension of more than 150/90 and less than 220/130 mmHg; HN, renal hyperten-

Fig.8. Histological findings at the anterior and right side of the horizontally cut ventricular septum. Azan stain, $\times 13$.

- A: Type D₀ septum of a neoplasm case.
- B: Type D₁ septum of a gastrointestinal disease case.
- C: Type D₃ septum of a renal hypertension case.
- D: Type I septum of a mitral stenosis case.
- E: Type I septum of a mitral regurgitation case.
- F: Type C septum of an aortic regurgitation case.

sion; SHT, severe hypertension of more than 220/130 mmHg. Valvular diseases were categorized as MR, AR or CVD as in the previous section. Sixty control hearts consisted of cases with MS, gastrointestinal tract disease (GI) or neoplasms (T).

The number of items measured was also increased: Sm (the maximal thickness of the ventricular septum), Fb (the LV free wall thickness at the basal portion), Fm (the LV thickness at the median portion) and Fa (the LV thickness at the apical portion). The Sm:Fm, Fm:Fb and Fa:Fb ratios were calculated as asymmetry indices, i.e., increased Sm:Fm means asymmetrical septal hypertrophy, increased Fm:Fb asymmetrical median hypertrophy and increased Fa:Fb asymmetrical apical hypertrophy.

The results are listed in Fig. 6. As to Sm:Fm,

the ratio ranges from 0.9 to 1.5 showing a one-peak pattern with the highest incidence about 1.1 in the control group. In the HT group, the peak of the distribution curve rises by 0.1, showing a mildly augmented septal hypertrophy. In the remaining groups studied, the distribution curve shows a two-peak pattern, which consists of a minor high-ratio group and a major low-ratio group. The minor peak indicates 1.3 (shown as in the Figure) of the Sm:Fm ratio in most groups, and 1.2 in the HN and CVD groups, both of which have the most marked dilatation of the LV. The major peak indicates 1.1 of the ratio in the SHT, MS and MR groups, 1.0 in the HN and AR groups and 0.9 in the CVD group. These results indicate that about 20 to 30% of the general population has a tendency to asymmetrical septal hypertrophy, whatever the etiologies

TABLE III INCIDENCE OF TYPES D, I AND C OF THE VENTRICULAR SEPTUM AND BASIC DISEASE

Basic disease	Shape of VS	No. of cases				%			%			Hemodynamic Condition
		D ₀	D ₁	D ₂	D ₃	D	I	C	D	I	C	
HT		0	19	10	0	85	15	0				Pressure load group
HN		0	7	2	1	62	19	19	78	17	5	
SHT		0	3	5	3	79	21	0				
MS		1	0	1	0	22	67	11				RV load
MR		1	1	0	0	22	56	22				Volume load group
AR		0	1	2	1	23	18	59	17	34	49	
CVD		0	0	2	0	10	38	52				
GI & T		7	32	2	0	80	20	0				Normal

TABLE IV HISTOLOGICAL SCORE OF THE MYOCARDIAL LESION, ECG FINDINGS AND SHAPE OF THE VENTRICULAR SEPTUM

Histology*		Shape of VS					
		D ₀	D ₁	D ₂	D ₃	I	C
Cullular hypertrophy		0.3	0.9	1.2	2.0	1.3	1.8
Degeneration and/or Fibrosis		0.9	0.8	1.2	1.1	1.1	1.6
Disarray		1.4	1.6	1.8	1.8	1.7	1.5
ECG*							
Chest leads	R ₁ ↑	0.3	0.5	1.1	3.0	0.9	2.2
	Sr ↓	0.9	1.1	1.8	3.0	1.2	2.2
	ST ↓	1.0	0.8	1.3	3.0	1.3	2.6
	T ↓	1.3	1.8	1.8	3.0	1.8	1.8

*score is the mathematical average of +: 1, ++: 2, +++: 3.

R₁ = R voltage at the left side of the precordial leads, Sr = S voltage at the right side of the precordial leads, ↑ = increased positive voltage, ↓ = increased negative voltage or depression

of the hypertrophy are. To avoid misunderstanding, it should be noted that the Sm:Fm ratio used here is more exaggerated than the S:F ratio obtained by ultrasound research on beating hearts, because, in the latter, F is measured as the thickness between Fb and Fm for technical reasons.

The asymmetrical median hypertrophy index, presented as Fm:Fb, shows a similar tendency to two-peak distributions in certain groups, including the HN, SHT, MR and CVD, although the separation of the peaks is less complete than in the Sm:Fm ratio.

The asymmetrical apical hypertrophy index has a minor high-ratio peak, with a good separation from the other major low-ratio group in the HN, MR and AR groups and with an incomplete

separation in the HT, SHT, MS and CVD groups.

In order to study the mechanism of the asymmetrical hypertrophy further, the shape of the ventricular septum was divided into D, I and C types from the frontal view, as shown in Fig. 7, using the same materials. Type D is defined as the septum projected left wards^{6,7} type I as not deviated and type C as projected rightwards. Type D was further subdivided by the maximal thickness of the septum into D₀, D₁, D₂ and D₃, each corresponding to less than 1.1, 1.2–1.5, 1.6–1.9 and more than 2.0 cm thick, respectively.

The incidence of types D, I and C is shown by each disease category in Table III. Type D is predominant in the normal and pressure hypertrophy groups, type C in the volume hyper-

trophy group and type I is intermediate between types D and C. In D, the pressure hypertrophy group is differentiated from the normal group by an increase of actual septal thickness, i.e., an increase in the D₂ and D₃ subgroups.

The grade of myocardial hypertrophy at the cellular level, degeneration and/or fibrosis of the myocardium, is estimated at the anterior wall of the LV, and cellular disarray is checked at the anterior portion of the septum. Each finding is counted as 1 for +, 2 for ++ and 3 for +++ lesions, and the index is calculated as an average of the score in each category. Figure 8 shows typical pathological findings at the anterior septum focusing attention on the cellular disarray. A is a localized mild disarray at the right side of the anterior septum of type D₀, B is an extensive moderate disarray with fibrosis of the D₁ septum and C is a severe fascicular disarray with hypertrophy of the D₃ septum. D shows a moderate disarray with advanced fibrosis of the I septum, E is a fatty replacement of the muscle cells that might have been disarrayed at the I septum and F is a mild disarray of the C septum.

The top half of Table IV shows a summary of the histological score by the shape of the septum. Cellular hypertrophy is most prominent in types D and C, degeneration and/or fibrosis is most severe in type C and disarray is prominent in types D₂ and D₃. The results suggest that the cellular disarray at a specific portion, such as the anterior septum,⁸ precedes septal thickening causing type D to become prominent and promotes asymmetrical septal hypertrophy, particularly in high Sm:Fm cases in types D₂ and D₃. After a decrease of the disarray, accompanied by either replacement by fatty or fibrous tissue or simple contraction, the septal shape may be transformed into type I or C, and symmetrical hypertrophy with dilatation becomes the most characteristic feature in this stage.

The bottom half of Table IV shows the correlation of ECG changes to the shape of the septum. A deep S at the right side of the precordial leads is prominent in types D₁ and D₂, while both a deep S at the right precordial leads and a high R at the left precordial leads are seen most markedly in type D₃ and less prominently in type C. Type I is situated in-between. A negative or flat T wave is prominent in type D₃, and depression of the ST segment is most marked in types D₃ and C. In a sense the score of the disarray shows a positive correlation with negative T and that of the cellular hypertrophy

correlates with depressed ST.

It has been reported that the cellular disarray at the ventricular septum coexists with asymmetrical septal hypertrophy in hypertrophic cardiomyopathy.⁹ The same evidence is seen in hypertrophy of known etiologies,¹⁰ though the degrees of the disarray and asymmetry are less marked in the known-etiology group. It is interesting that the disarray is specifically localized at the mysterious triangle area bordered by right and left ventricular components of muscle bundles at the anterior septum.⁸ Considering the abundance of nerve endings in this triangle, the existence of an active stimulation through autonomic nerve excitation, probably of a sympathetic nature which promotes hypertrophy, is suggested. If this mechanism is present, the septum hypertrophies asymmetrically causing type D to become prominent and inducing concentric or pressure hypertrophy, because the disarray is, as a rule, associated with cellular hypertrophy. If the disarray mechanism is burned out or inactive, insufficient hypertrophy may induce LV dilatation producing eccentric or volume hypertrophy. In any case, the deciding factor in the development and type of hypertrophy seems to be enclosed in the mysterious triangle at the anterior septum. It is, however, not certain whether the advancement to disarray is dependent on the nature of hemodynamic stress or on a personal sensitivity reaction. The two-peak distribution of the septal thickening shown in Fig. 6 may suggest that those individuals who react sensitively to asymmetrical hypertrophy form a minor group in the general population.

Asymmetrical apical hypertrophy is related to a whorled arrangement of the muscle cells around the apical vortex, which has a similarity to the disarray at the septum. The present correlative study using ECG changes reveals a high R with a less prominent S in the precordial leads and a negative T as the common features of this type of hypertrophy.

Asymmetrical median hypertrophy seems to be connected with a specific root-like arrangement of muscle bundles around the base of the papillary muscles. Corresponding ECG changes are not so characteristic except for a negative T at aV_L.

Asymmetry in hypertrophy may be a physiological process aiding the myocardium in adapting to increased hemodynamic stress, although individual differences in reactivity to the

disarray or hypertrophy exist. Careful ECG observation should be useful in making accurate diagnosis of asymmetrical hypertrophy of known etiologies and may promise further application to the study of cardiomyopathy.

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