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Assessment of Hypertrophied Left Ventricular Function in Patients with Essential Hypertension Using New Noninvasive Index, E'_{max}/V_{100}: Comparison between non-hypertrophied and hypertrophied hearts with and without ST-T changes*)

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ABSTRACT

In forty-one essential hypertensive (EHT) patients with and without left ventricular hypertrophy (LVH), the left ventricular (LV) contractile performance was determined noninvasively using echocardiography. Classification was made with respect to the LVH, as measured by the sum of end-diatolic posterior wall thickness and interventricular septal thickness, and the presence of ST-T changes on electrocardiogram. Patients who had neither LVH nor ST-T changes formed H1-subgroup (H1; n=22), those who had LVH without ST-T changes served as H2-subgroup (H2; n=8), and those with LVH accompanied by ST-T changes constituted H3-subgroup (H3; n=11), Sixteen normal volunteers served as normal control (N).

LV systolic phase indices such as ejection fraction (EF), mean velocity of circumferential fiber shortening (mVcf) and end-systolic wall stress (ESWS), and diastolic indices such as isovolumic relaxation time (IVRT) and PR-AC interval were compared among each subgroup and normal subjects. All systolic and diastolic indices showed a depressed LV function in H3. Of these variables, the only IVRT could separate H2 from H1, suggesting deteriorated diastolic function at an early stage of hypertrophy.

By altering LV systolic loading, peak systolic pressure—end-systolic volume relation, E'_{max}, and E'_{max}-volume intercept at 100 mmHg peak systolic pressure ratio, E'_{max}/V_{100}, were designated and these indices were used for the expression of the myocardial contractile state. E'_{max} and E'_{max}/V_{100} were significantly lower in H2 and H3 than in the control group, indicating depressed myocardial contractility. The value of these variables in H1 did not differ from N, indicating a normal level of inotropic state. E'_{max}/V_{100} in H3, 0.13 ± 0.04 mmHg/ml^2, was significantly less than in H2, 0.23 ± 0.05 ($p<0.01$), and the value in H2 was significantly lower than that in H1, 0.36 ± 0.07 ($p<0.01$), indicating a validity of E'_{max}/V_{100} to differentiate each EHT subgroup.

It is concluded that in patiens with LVH induced by pressure overload the LV function

*) ハメッド・オエマル，末田　隆，土岡由紀子，松浦秀夫，鍒　寛之，梶山梧朗：非侵襲的新指標である E'_{max}/V_{100} を用いた高血圧性肥大心の左室機能評価。非肥心，ST-T 変化を伴わない肥大心および ST-T 変化を伴う肥大心における比較検討

is declined, furthermore, LV contractile performance is more impaired when LVH is accompanied by ST-T changes. E'_{max}/V_{100} is highly sensitive in identifying the presence of LV contractile impairment and may be a useful approach to the quantitation of LV performance.

INTRODUCTION

Concentric left ventricular hypertrophy (LVH) in essential hypertension associated with chronic pressure overload is a compensatory mechanism for maintaining an adequate cardiac pump function[14,18]. However, the effects of hypertrophy on myocardial performance are controversial[14,21,32,45]. Some experimental and clinical researches have shown some abnormalities on left ventricular (LV) systolic and diastolic functions in LVH due to systemic arterial hypertension[1,5,41], while others found the systolic function remained normal in basal state[11,15,27]. LV systolic and diastolic phase indices they used are relatively insensitive in detecting an early stage of LV contractile impairment[24,34,39,40], because these indices have been reported to be load-dependent[12,16,34].

Recently, the LV end-systolic pressure—volume relation has been shown to be a sensitive indicator of the myocardial contractile state[22,24,43] (Fig. 1). This relationship can be obtained by using noninvasive peak systolic pressure instead of LV end-systolic pressure and the LV end-systolic volume derived from echocardiogram[19].

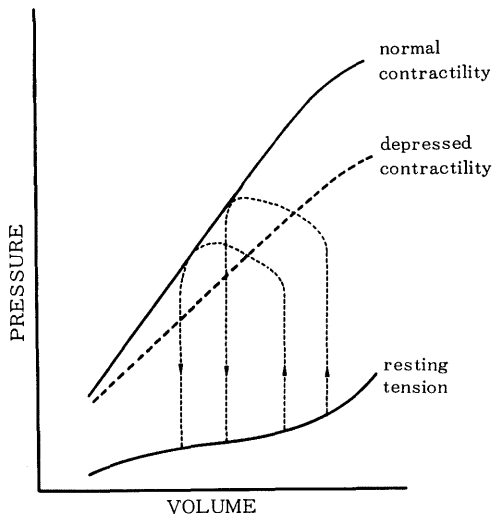

Fig. 1. End-systolic pressure-volume relation based on the Frank-Starling diagram. The end points of all LV contractions coming from any point on the resting tension are best described by a straight line, where the degree of its slope (E_{max}) is a sensitive index of myocardial contractility.

The aim of the present study was, therefore, to assess the contractile state of the LVH with and without electrocardiographic (ECG) abnormalities in patients with essential hypertension by analyzing the noninvasive peak systolic pressure—end-systolic volume relation normalized by volume intercept.

PATIENTS AND METHODS

Study patients. Forty-one patients (25 men and 16 women) with essential hypertension (EHT) were examined for this study. All had sinus rhythm and belonged to WHO grade I to II. Of these patients, 22 (mean age 45.5± 11.6 years, range 23 to 62) who had no ST-T changes on ECG and the sum of end-diastolic posterior wall thickness (PWTd) and end-diastolic interventricular septal thickness (IVSTd) less than 24 mm formed H1-subgroup (H1). Eight patients (mean age 47.6±8.7 years, 34 to 62) who had no ST-T changes but their PWTd+IVSTd above 24 mm served as H2-subgroup (H2). Eleven other patients (mean age 49.6±11.3 years, range 33 to 68) with ST-T changes on ECG and PWTd+IVSTd above 24 mm constituted H3-subgroup (H3) (Table 1). No patient in this subgroup had suffered from valvular heart disease and congestive cardiac failure. The echocardiographic study revealed no evidence of LV asynergy in all patients.

All antihypertensive drugs were discontinued at least one week prior to the study. Informed consent was obtained from each patient, and no complication occurred as a result of this study.

Control group. Sixteen normotensive subjects (10 men and 6 women) with no evidence of heart disease served as normotensive control group, N group (N), (mean age 41.4±9.6 years, range 29 to 56).

Study protocol. After an initial resting period of 30 min in all subjects, echocardiogram was performed with a Sector Scanner TOSHIBA model SSH-11A using a 2.25-MHz tran-

Table 1. Classification of the normotensive group (N) and the three essential hypertensive subgroups (H1, H2 and H3) according to the echocardiographic (UCG) and electrocardiographic (ECG) findings, with number of cases, age, sex and mean blood pressure (BP).

Group & Subgroup	No.	Age (year)	Sex	mean BP (mmHg)	UCG PWTd+IVSTd (mm)	ECG ST-T change
N	16	29-56 (41.4± 9.5)	10 M 6 F	(84.9± 7.3)	(19.7± 1.8)	(−)
H1	22	23-62 (45.5±11.6)	11 M 11 F	(121.7±10.5)	(20.7± 1.4)	(−)
H2	8	34-62 (47.6± 8.7)	6 M 2 F	(126.3± 9.7)	(27.0± 0.9)	(−)
H3	11	33-68 (49.6±11.3)	8 M 3 F	(127.4± 9.8)	(25.4± 1.8)	(+)

All values are mean ±standard deviation (SD). Abbreviations: PWTd=left ventricular end-diastolic posterior wall thickness, IVSTd=end-diastolic interventricular septal thickness, M=male, F=female, (−)=absence, (+)=presence.

sducer focused at 7.5 cm. M-mode scanning was recorded with a Honeywell visicorder at 50- and 100- mm/sec paper speed.

With the subject lying in a left lateral supine position the echocardiogram was recorded at the standard left ventricular position at the level of the chordae tendinae, after long-axis and transverse scans were performed. The transducer was kept in place throughout the study and the echocardiogram was continuously checked to assure that all recordings came from the same level in the ventricle. ECG, phonocardiogram and carotid pulse tracing (CPT) were recorded simultaneously with the echocardiogram. LV end-systolic dimension (ESD) and end-systolic posterior wall thickness (PWTs) were measured at the onset of the second heart sound (A2). LV end-diastolic dimension (EDD), PWTd and IVSTd were obtained at the Q wave of the ECG using the leading edge method[36]. Data were analysed as the mean of at least five consecutive cardiac cycles. The unclearly recorded echocardiogram was excluded. The blood pressuse of all patients and normal subjects was obtained with a standard cuff sphygmomanometer. After basal echocariographic and cuff pressure data were obtained, hemodynamic load was altered with sublingual administration of 10 mg nifedipine for the determination of peak systolic pressure—end-systolic volume relation.

Measurements and Calculations. For evaluation of LV systolic and diastolic functions, the following indices derived from echocardiogram were obtained. The LV ejection fraction (EF) was calculated according to the standard formula[28], whereas LV end-diastolic volume (EDV) and end-systolic volume (ESV) were estimated from echocardiographic dimensions by the method of Teichhotz et al.[46]. The LV mean velocity of fiber shortening (mVcf) was calculated as:

$$\text{mVcf (circ/sec)} = \frac{\text{EDD} - \text{ESD}}{\text{LVET} \times \text{EDD}}$$

where LVET represents measurement of the LV ejection time (sec) which was obtained from the CPT by the standard technique.

In order to normalize ejection phase index to preload, mVcf was divided by EDVI (end-diastolic volume index), mVcf/EDVI. The LV mass was calculated according to the method of Bennet and Evans[2] and was then divided by the body surface area to give LV mass index (LVMI). End-systolic circumferential midwall stress (ESWS) was calculated from the modified LaPlace equation[31]

$$ESWS=\frac{(SBP\times ESD/2)}{PWTs}\left\{1-\frac{ESD}{8(ESD+PWTs)}\right\},$$

where SBP is the peak arterial systolic pressure in mmHg, ESD and PWTS are in cm. The result obtained by this formula was converted to dyne/cm^2 by multiplying by a conversion factor of 1334.

LV isovolumic relaxation time (IVRT), obtained from the dual-echocardiogram (Fig. 2), was measured as the interval between the end of aortic valve closure and opening of the mitral valve leaflets. PR-AC interval (Fig. 2) was defined as the interval between A point, which is the onset of closure of the mitral valve, and the termination of valve closure or C point; and then this interval was subtracted from PR interval, as described by Konecke et al.[13]. The measured LVET, IVRT and PR-AC interval were then corected to heart rate of 60 beats/min with Bazett's formula, with which the corrected each interval is derived by dividing the measured interval by the square root of the PR interval in seconds.

End-systolic pressure—volume determination. Because only noninvasive measurements were available, systolic cuff pressure was substituted for end-systolic pressure; these data therefore actually represent a peak pressure—end-systolic volume relation, E'_{max}. LV end-systolic pressure—volume relation is linear in human[17,22,24,38] as well as in animal studies[23,34,42], such as a formula used by Grossman et al.[7]:

$$P_{ES}=m(V_{ES}-V_0)$$

where P_{ES} and V_{ES} are left ventricular end-systolic pressure and volume, respectively, m is the slope of the line and V_0 is the volume

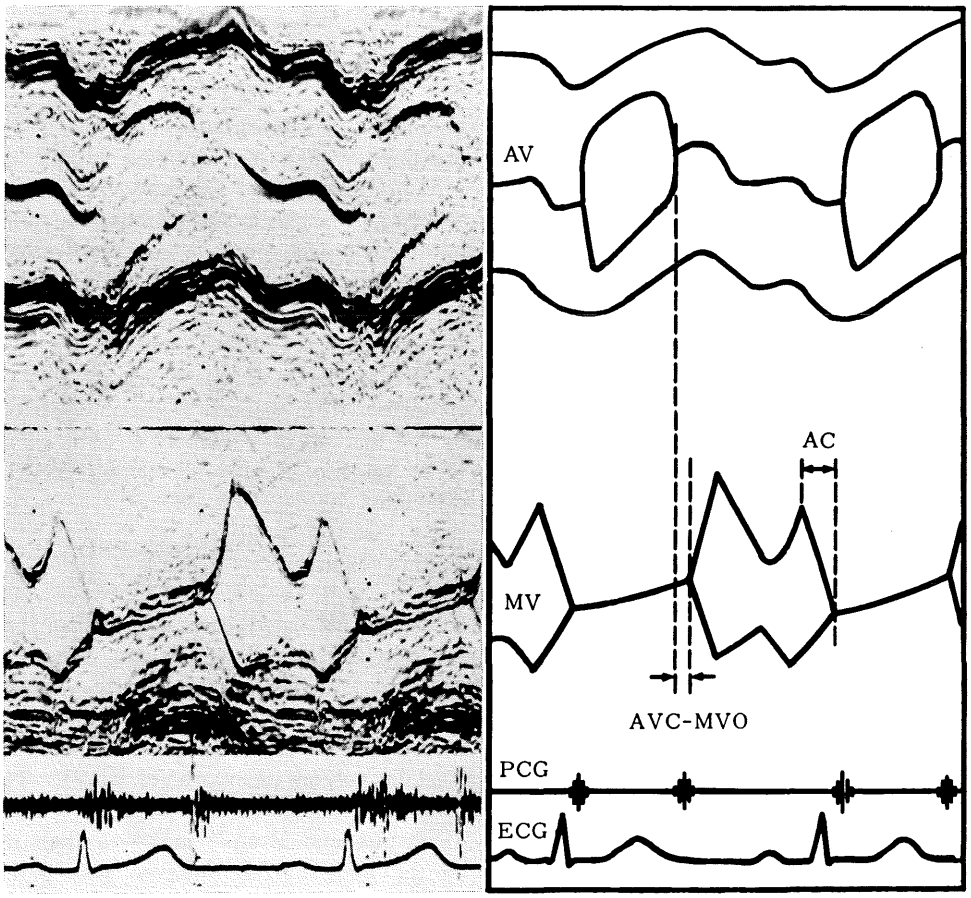

Fig. 2. Dual M-mode echocardiogram of the aortic root and the mitral valve (left panel) and schematic representation (right panel) of the isovolumic relaxation tfme, the interval from the aortic valve closure (AVC) to the mitral valve opening (MVO), and the AC intereval. AV=A ortic valve, MV=mitral valve; PCG=phonocardiogram; ECG=electrocardiogram.

at $P_{ES}=0$. However, a study with animal models demonstrated by Suga[44] showed that end-systolic pressure—volume relation is actually linear at pressure range 50 to 150 mmHg. Since volume intercept V_0 varies with the state of the heart[7], and to avoid applying negative V_0 values found in the present study, we designate a simultaneous evaluation of E'_{max} with volume intercept at 100 mmHg peak pressure, V_{100}, as a new index of myocardial contractille state; i. e. E'_{max}/V_{100} (Fig. 3).

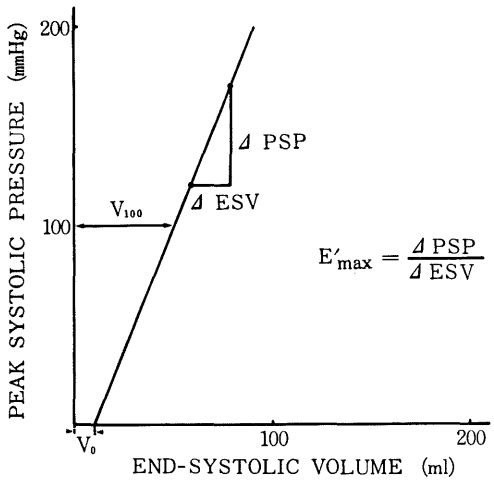

Fig. 3. Schematic diagram of methodology in calculation of E'_{max} and E'_{max}/V_{100}. △PSP= change in peak systolic pressure; △ESV=change in end-systolic volume; V_{100}=volume at 100 mmHg peak systolic pressure.

Statistics. Statistical comparisons among the subgroups were performed with a Mann-Whitney test, whereas the correlations among different indices of contractile state, systolic and diastolic function were compared by using multiple regression analysis. The level of significance was taken at $p<0.05$.

RESULTS

Left ventricular systolic and diastolic functions. The basal hemodynamic data in normotensive subjects and each of three EHT subgroups are shown in Table 2. HR was not statistically different among hypertensive subgroups and between each subgroup and normal control group. Systolic and diastolic BP were not significantly different among subgroups. EDD and ESD in N (47.5 ± 3.6 and 27.7 ± 3.7 mm, respectively) were similar to those in H1 (48.2 ± 4.2 and 28.7 ± 3.6, respectively) or in H2 (46.5 ± 4.3 and 28.0 ± 4.5, respectively), but these values in H3 (52.2 ± 5.8 and 34.0 ± 4.8, erspectively) were significantly larger than in N ($p<0.05$ and $p<0.01$, respectively). Among hypertensive subgroups, EDD and ESD in H3 were significantly larger than those in H2 (both $p<0.05$) or in H1 (NS and $p<0.05$, repectively). The values of LV end-diastolic index (EDVI) and end-systolic volume index (ESVI) were also insignificantly different among N, H1 and H2, while H3 showed a significant enlarge in these values as compared with N ($p<0.05$ and $p<0.01$, respectively) as well as either with H2 (both $p<0.01$) or with H1 (NS and $p<0.01$, respectively).

As compared with that in N (122.1 ± 22.1 g/m^2), LV mass index (LVMI) in hypertensive subgroups was progressively increased from H1 (137.5 ± 25.4, NS) to H2 (197.2 ± 35.6, $p<0.05$) to H3(211.4 ± 40.1,$p<0.01$). The value of LVMI in H2 and H3 were significantly higher than that in H1 ($p<0.05$ and $p<0.01$, respectively). LVMI in H3 tended to be higher than that in H2, though a statistically significant difference was not recognized.

Stroke volume index (SVI) was similar in three subgroups and normotensive subjects. While LV ejection fraction (EF) gradually declined in hypertensive supgroups from H1 ($70.0\pm6.4\%$) to H2 (65.0 ± 8.4) to H3 (60.1 ± 8.7), the level of statistical significance among subgroups was observed only between H3 and H1 ($p<0.05$) and between H3 and N (72.2 ± 8.9, $p<0.05$). Mean velocity of circumferential fiber shortening (mVcf) also gradually decreased from N to the hypertensive subgroups H1, H2, H3, while the only significant difference was found between N and H3 ($p<0.05$) and between H1 and H3 ($p<0.05$) (Fig. 4A). To minimize the dependency of preload toward systolic phase index, mVcf/EDVI was plotted in hypertensive subgroups and normotensive subjects (Fig. 4B). This value was significantly smaller in H3 ($14.6\pm4.1\times10^{-3}$ circ/sec·ml·m^2) than in H2 (19.7 ± 4.3, $p<0.05$), or in H1 (20.3 ± 4.5, $p<0.01$), as well as in N (21.3 ± 4.6, $p<0.01$). However, this value failed to demonstrate a statistical significance among N, H1 and H2.

ESWS in each subgroup was significantly higher than that in normal subjects (H1 vs N, $p<0.01$; H2 vs N, $p<0.05$ and H3 vs N, $p<$

Table 2. Hemodynamic data for the normotensive subjects and three essential hypertensive subgroups

Variable	Normotensives	Essential Hypertensives			p	p′	p″
	N (n=16)	H1 (n=22)	H2 (n=8)	H3 (n=11)			
Heart rate, HR (beat/min)	64.5±7.6	62.4±10.6	65.4±7.3	70.1±8.3	NS	NS	NS
Systolic blood pressure, SBP (mmHg)	116.4±7.1	166.3±11.7**	165.6±11.0**	172.7±19.4**	NS	NS	NS
Diastolic blood pressure, DBP (mmHg)	71.7±7.8	98.0±12.1**	107.2±10.5**	105.0±10.5**	NS	NS	NS
LV end-diastolic dimension, EDD (mm)	47.5±3.6	48.2±4.2	46.5±4.3	52.2±5.8*	NS	NS	<0.05
LV end-systolic dimension, ESD (mm)	27.7±3.7	28.7±3.6	28.0±4.5	34.0±4.8**	NS	<0.05	<0.05
LV end-diastolic volume index, EDVI (ml/m^2)	64.3±10.2	69.3±13.2	63.0±13.1	79.4±16.1*	NS	NS	<0.01
LV end-systolic volume index, ESVI (ml/m^2)	19.1±6.9	21.3±5.0	21.5±7.4	32.4±8.1**	NS	<0.01	<0.01
LV mass index, LVMI (g/m^2)	122.1±22.1	137.5±25.4	197.2±35.6*	211.4±40.1**	<0.05	<0.01	NS
Stroke volume index, SVI (ml/m^2)	45.2±9.8	49.3±11.6	41.5±11.4	47.3±10.5	NS	NS	NS
LV ejection fraction, EF (%)	70.5±8.9	70.0±6.4	65.0±8.4	60.1±8.7*	NS	<0.05	NS
Mean velocity of circumferential fiber shortening, mVcf (circ/sec)	1.37±0.15	1.36±0.16	1.22±0.18	1.14±0.22*	NS	<0.05	NS
LV end-systolic wall stress, ESWS ($\times 10^3$ dyn/cm^2)	140.3±17.3	187.5±31.9**	163.7±29.3*	222.6±65.4**	NS	<0.01	<0.01
Isovolumic relaxation time, IVRT (msec)	72.37±10.80	78.33±15.15	94.25±16.01*	108.84±17.37**	<0.05	<0.01	NS
PR interval minus AC interval, PR-AC (msec)	89.24±12.87	84.80±19.03	71.05±16.05*	56.18±15.25**	NS	<0.01	NS
Peak systolic pressure—end-systolic volume relation, E'_{max} (mmHg/ml)	8.42±2.25	7.02±1.98	3.85±1.87**	3.48±1.78***	<0.01	<0.01	NS
Peak systolic pressure—end-systolic volume relaton/Volume at 100 mmHg peak systolic pressure, E'_{max}/V_{100} ($mmHg/ml^2$)	0.37±0.11	0.36±0.17	0.23±0.05**	0.13±0.04***	<0.01	<0.001	<0.01

All values are mean±standard deviation (SD).

Abbreviations: NS=not significant,

p =difference from values in patients in subgroups H1 and H2,
p′ =difference from values in patients in subgroups H1 and H3,
p″=difference from values in patients in subgroups H2 and H3,

* $p<0.05$
** $p<0.01$
*** $p<0.001$

} compared with normotensive subjects

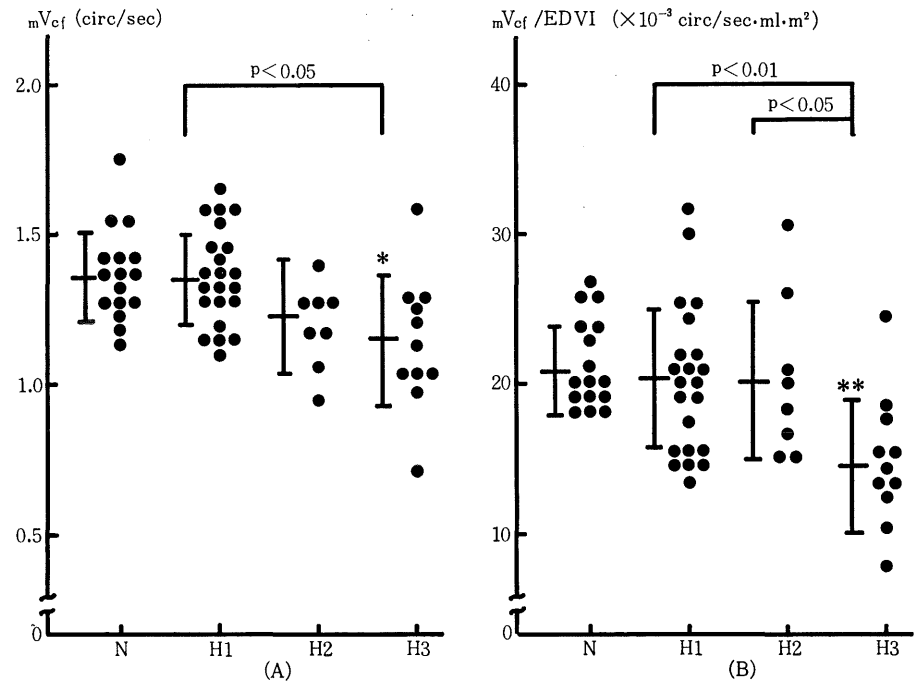

Fig. 4. Mean velocity of circumferential fiber shortening (mVcf, A) and mean velocity of circumferential fiber shortening/end-diastolic volume index ratio (mVcf/EDVI, B) in normotensive subject (N) and in three essential hypertensive subgroups (H1, H2 and H3). *p<0.05, **p<0.01 compared with N.

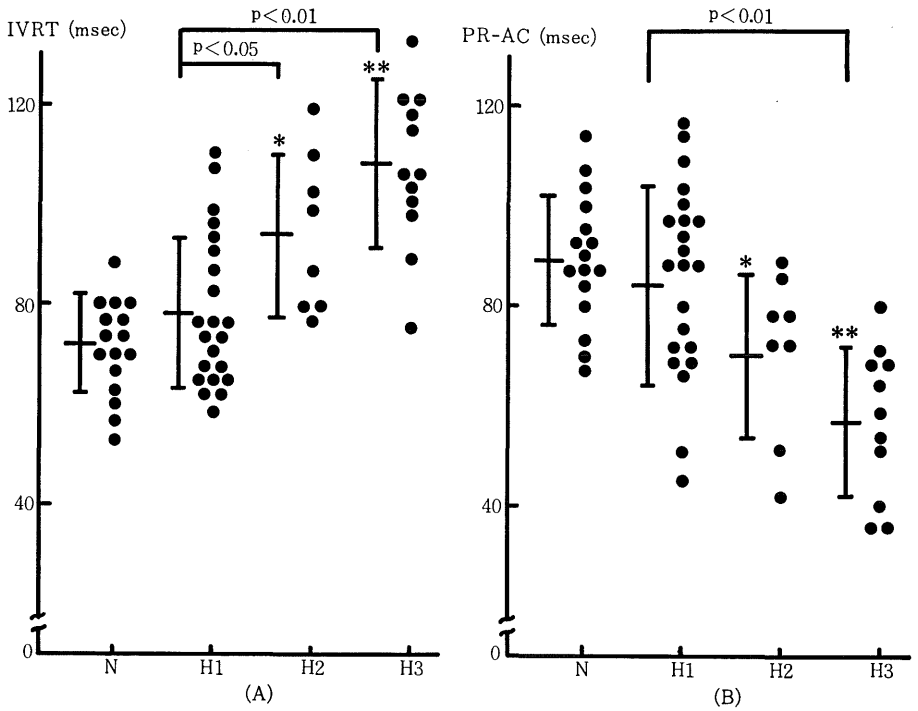

Fig. 5. Isovolumic relaxation time (IVRT, A) and PR-AC interval (B) in the control group (N) and in the three essential hypertensive subgroups (H1, H2 and H3). *p<0.05, **p<0.01 compared with N.

0.01). Among hypertensive subgroups, however, ESWS significantly increased in H3 and tended to decrease in H2 as compared with that in H1 ($p<0.01$ and NS, respectively). Moreover, a significant difference in this value between H2 and H3 ($p<0.01$) was recognized.

Representative LV diastolic phase in normal subjects and in each hypertensive subgroup are shown in Fig. 5. Although indual value of IVRT in three hypertensive subgroups was considerably overlapped, significant differences between the value in H1 and H2 ($p<0.05$) and between H1 and H3 ($p<0.01$) were recognized except between H2 and H3 (NS). When the value of IVRT in each subgroup was compared with that in normal subjects, H2 and H3 showed a significant prolongation ($p<0.05$ and $p<0.01$, respectively), while in H1, a tendency of prolongation in IVRT was noted (Fig. 5A, Table 2). As compared with normal subjects, PR-AC interval in hypertensive subgroups showed a progressive decline in H1, H2 and H3 (NS, $p<0.05$ and $p<0.01$, respectively), while among subgroups, the level of statistical significance in PR-AC interval was recognized neither between H1 and H2 nor between H2 and H3 (Fig. 5B, Table 2).

A correlation was observed between LVMI

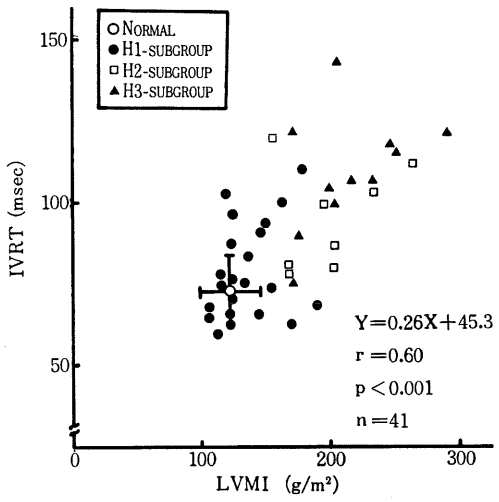

Fig. 6. Relationships between left ventricular mass index (LVMI) and isovolumic relaxation time (IVRT) in essential hypertensive patients. Open circle represents the control value (±SD) of these indices.

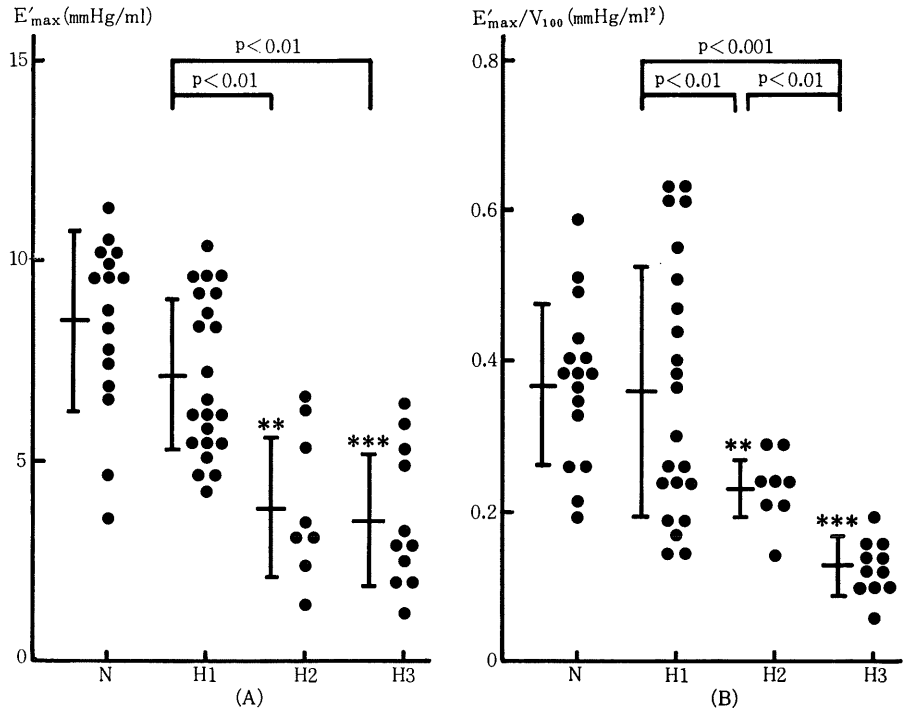

Fig. 7. Peak systolic pressure—end-systolic volume relation (E'_{max}, A) and peak systolic pressure—end-systolic volume relation/volume intercept at 100 mmHg peak systolic pressure ratio (E'_{max}/V_{100}, B) in normotensive subjects (N) and in three essential hypertensive subgroups (H1, H2 and H3). $^{**}p<0.01$, $^{***}p<0.001$ compared with N.

and IVRT in patients with essential hypertension ($r=0.60$, $p<0.01$) (Fig. 6). Patients with increased LVMI revealed a prolongation of IVRT associated with the abnormality of diastolic function, especially in H3.

The peak systolic pressure—end-systolic volume relation. The values of E'_{max} and E'_{max}/V_{100} in normal subjects and in hypertensive subgroups are plotted in Fig. 7. A progressive decrease in E'_{max} from H1 to H2 to H3 was observed. E'_{max} in H1 (7.02 ± 1.98 mmHg/ml) showed a significant difference from the values in H2 and H3 (3.85 ± 1.87, $p<0.01$ and 3.48 ± 1.78, $p<0.01$, respectively) (Fig. 7A). No significant difference in E'_{max} was observed between H2 and H3. E'_{max} in H1 had no significant difference to N (8.42 ± 2.25, NS) but that in H2 and H3 were significantly lower than in N ($p<0.01$ and $p<0.001$, respectively).

On the other hand, the value of E'_{max}/V_{100} in hypertensive subgroups progressively declined as LVH occurred (from 0.36 ± 0.17 mmHg/ml^2 in H1 to 0.23 ± 0.05 in H2) and achieved the lowest value when ST-T changes accompanied LVH ($H3=0.13\pm0.04$). This index showed high significant differences among subgroups (H1 vs H2, $p<0.01$; H2 vs H3, $p<0.01$ and H1 vs H3, $p<0.001$) (Fig. 7B). It is clear that E'_{max}/V_{100} is able to differentiate significantly each hypertensive subgroup. However, this index could not separate those in H1 from normal control.

The relation of E'_{max}/V_{100} to IVRT in patients with EHT is illustrated in Fig. 8. Patients having IVRT larger than 95 msec (N value-2SD) revealed an E'_{max}/V_{100} smaller than 0.15 mmHg/ml^2 (N value-2SD), while those who have IVRT less than 95 msec provided a wide range of E'_{max}/V_{100}. Fig. 9 is a plot of the relationship between E'_{max}/V_{100} and LVMI in EHT patients. The relation is best described by the exponential equation $Y=1.1.e^{-0.009X}$, $r=-0.72$. This relationship shows that patients with LVH as estimated from the high LVMI have a lower LV contractile state as judged from E'_{max}/V_{100}.

DISCUSSION

Cardiac hypertrophy resulting from mechanical overload is usually described according to three stages[20]. At the first stage, there is an increase of work per unit weight through physiologic hyperfunction, before any increase in cardiac mass occurs. When hypertrophy becomes established, the second stage of compensatory hypertrophy, without increasing contractile force per unit weight, is reached. The third stage of hypertrophy, that of cellular exhaustion, may develop eventually in association with cardiac failure. This concept is applicable not only to animal experiments but also to human with hypertrophy secondary to various types of heart disease[4]. However, the three stages of hypertrophy are clearly defined neither morphologically nor electrocardiographically. In the present study, since clinical hypertensive heart failure was excluded, left ventricular hypertrophy with (H3) or without (H2) ST-T changes is comparable as the second stage of compensatory hypertrophy. These ECG changes may be ascribed to unknown repolarization changes caused by increased muscle mass[45], however, H3 showed a tendency of decrease in measured wall thickness, though calculated LVMI was higher as compared with that in H2. The decrease in wall thickness may be explained by an increase in EDD which probaly caused a stretch in myocardial muscle cells. Thus, the presence of increased wall thickness itself does not necessarily indicate the severity of structural changes of myocardial cells that may alter the electrical activity on transmembrane action potential duration[47].

Although LV systolic and diasolic functions of hypertrophied heart have been reported[11,14,21,45], the effects of hypertrophy on LV performance remain controversial. In addition, available information about the contractile state in LVH, especially in LVH with ST-T changes, is scanty.

The systolic performance in LVH has been reported to be depressed[5], normal[11,41] or 'supranormal'[8,37]. In the present study systolic LV function, as judged from EF and mVcf, was not reduced in the hypertensive subgroups except in H3. Thus, a depressed systolic function does not seem an obligatory characteristic of pressure-induced hypertrophy unless ST-T changes occur.

Pathophysiology dealing with impaired relaxation in LVH is complex and poorly understood[26]. The relaxation abnormalities tended to occur at an earlier stage of hypertrophy than systolic impairment[26]. It has been also

reported that diastolic performance is a sensitive indicator of early impairment of LV function[10]. In the present study, IVRT did separate H1 from H2, while LV systolic phase indices such as EF, mVcf and ESWS provided a normal value for the two subgroups. IVRT in H3 tended to be prolonged compared with that in H2 but no statistical significance was observed (Fig. 5). Thus, this diastolic index is more sensitive in differentiating the early stage of impaired cardiac function than typical systolic phase indices.

Gaasch et al.[6] recently examined the mechanism responsible for altered LV chamber stiffness, derived from LV pressure-volume data, and myocardial stiffness, from muscle-strain analysis, in hypertrophied hearts. They suggested that abnormalities of chamber stiffness, as a main cause of changes in LV diastolic properties in cardiac hypertrophy, may be due to abnormalities of myocardial stiffness and/or increased myocardial mass *per se*. In this regard, Hess and associates[9] have previously studied diastolic function and myocardial structure in patients with LV hypertrophy. They concluded that myocardial stiffness appears not to be affected by LV mass or fiber size but increases in the presence of interstitial fibrosis of myocardial structure. Since nonsignificant difference in LVMI between H2 and H3 was observed in this study (Table 2), these findings indicate that decreased LV diastolic function in H3, as estimated by the prolonged IVRT, is probably related to the presence of myocardial interstitial fibrosis[6,26] in addition to that of increased myocardial mass (Fig. 6).

End-systolic pressure-volume relation (E_{max}), which generally approximated the length-tension relation, has recently been reported as a sensitive index for the assessment of myocardial contractile state in man[22,24,34,43]. This index has none of limitations of the ejection phase indices because it is independent of preload, incorporates afterload and varies directly with alterations in myocardial contractile state[42,43]. Recent studies[19,40] have reported that the end-systolic pressure can be replaced by the peak systolic pressure. In this study, systolic blood pressure obtained with a cuff sphygmomanometer was utilized as a close approximation of peak systolic LV pressure[40] as long as in the absence of valvular heart diseases. Therefore, peak systolic pressure—end-systolic volume relation (E'_{max}), which is easily obtained in clinical practice, was constructed as an index of contractile state. In addition, the peak systolic pressure-volume relation was best represented by a straight line[24,40], whereas the use of two points data for the construction of the E'_{max} in this study is in accordance with Mehmel et al.[22]. Since a positive inotropic stimulus with isoproterenol caused a leftward shift in the end-systolic pressure—volume relation[3,23,38] and the depression of inotropic state by propranolol shifted the relation rightward[38], both the value of the slope and its position should be used simultaneously as a new index of LV inotropic state under basal condition[25].

The intercept of the end-systolic pressure—volume line on the volume axis (theoretical volume V_0 in Fig. 3) has been considered as a possible additional index of LV contractility, because it might reflect the maximal pumping capacity of LV[7,17] and it should be independent of preload[7]. Experimental[35] and clinical studies[7] also pointed to a unique importance of V_0 in detecting LV function. In this study, however, V_0 value varied widely from patients to patients (-11 to 40 ml). Therefore, instead of applying negative V_0 value, E'_{max} was normalized for volume intercept at peak systolic pressure $=100$ mmHg (E'_{max}/V_{100}), as a new index of ventricular contractility (Fig. 3). Volume intercept V_{100} was selected as a parameter instead of V_0, first because the intercept of peak systolic pressure—end-systolic volume was able to disappear a negative value of V_{100} in this study, secondly because the level of peak systolic pressure at 100 mmHg is regarded as a normal range of peak LV pressure in normotensive subject, thirdly because in the range of 50–150 mmHg end-systolic pressure-volume relation can be approximated by a linear line[44]. In addition, the crossing point of each individual slope in majority of EHT patients did not occur above the level of 100 mmHg peak systolic pressure and a positive correlation between E'_{max} and E'_{max}/V_{100} in EHT patients studied was evidently recognized ($r=0.79$, $p<0.001$, $n=41$).

Several investigators have suggested that the relation of peak systolic pressure to end-systolic volume was more valuable than typical systolic phase indices such as EF and mVcf[7,19,24], since

the latter indices are dependent on preload as well as on changes in afterload in various degrees[16,34]. In this regard, the present study is in agreement with previous findings[39,40] where the EF and mVcf could not thoroughly evaluate the depressed LV contractile performance. As shown in Table 2, since SVI, EF and mVcf did not show any difference in value between H1 and H2, or between H2 and H3, these indices were unable to separate each hypertensive subgroup clearly. On the other hand, IVRT and E'_{max} showed a significant difference in values between H1 and H2, though they failed to separate the two LVH subgroups, which suggests a disturbance of LV diastolic properties as well as myocardial contractile state at an early stage of cardiac hypertrophy. With E'_{max}/V_{100}, however, a good separation between each hypertensive subgroup was recognized. These data indicate that E'_{max}/V_{100} may be a useful index in evaluating LV function more reliable than EF or mVcf or IVRT. In addition, IVRT, E'_{max} and E'_{max}/V_{100} could not separate H1 from normal control, indicating LV diastolic and contractile performance in H1 was normal.

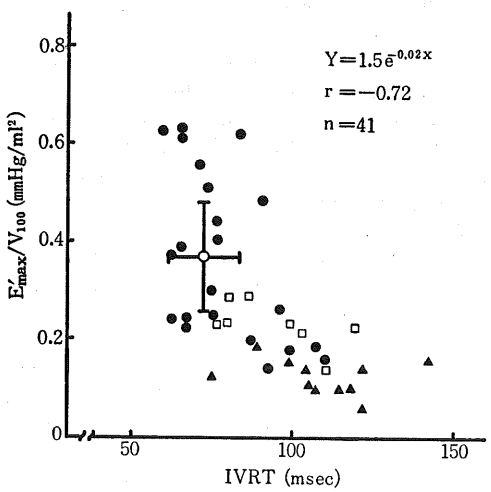

Fig. 8. Relationship between peak systolic pressure—end-systolic volume relation/volume intercept at 100 mmHg peak systolic pressure ratio (E'_{max}/V_{100}) and isovolumic relaxation time(IVRT) in essential hypertensive patients. Open circle represents the control value (±SD) of these indices. Symbols are the same as in Fig. 6.

As shown in Fig. 8, E'_{max}/V_{100} can differentiate the contractile state of the hearts which show the normal IVRT. Therefore, it suggest that a disturbance of LV function in hypertensive hearts, as estimated from the decrease in E'_{max}/V_{100}, appears earlier than an impairment of LV diastolic function, as judged from the prolongation of IVRT. Since the changes in IVRT and in PR-AC interval observed in this study were mainly caused by impaired LV relaxation[33], these data also indicate that impaired relaxation in patients with pressure-induced hypertrophy is due to depressed contractile state and, is found to be more deteriorate in LVH with ST-T changes.

Earlier studies on arterial hypertension[29] admitted no relationship beween LV function and LV mass. The lack of this relationship may be due to methodological differences in the parameters of LV function studied. In this study, an impairment LV contractility in patients with LVH as judged from E'_{max}/V_{100}, was closely related to the extent of hypertrophy (Fig. 9). Although there was a considerable overlap in LVMI between H2 and H3, E'_{max}/V_{100} in H3 was significantly lower than in H2. These findings indicate that in advanced LVH the contractile performance is impaired.

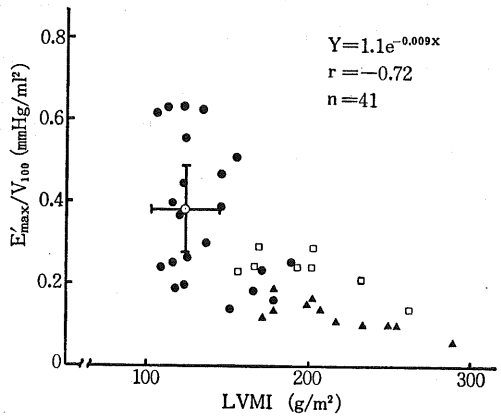

Fig. 9. Relationship between peak systolic pressure—end-systolic volume relation/volume intercept at 100 mmHg peak systolic pressure ratio (E'_{max}/V_{100}) and left ventricular mass index (LVMI) in essential hypertensive patients. Open circle represents the control value (±SD) of these indices. Symbols are the same as in Fig. 6.

It is generally believed that hypertrophy is a compensatory response permitting the ventricle to normalize wall stress. Unless the chamber enlargement has developed, ventricle systolic wall stress remain normal or near-normal in patients with LVH[30]. In this study, the difference in

the value of ESWS between H2 and H3 may be explained by the increase in ESD and SBP observed in H3 (Table 2).

Several limitations, inherent in the methods used in the present study, need to be elucidated. First, to identify the timing of minimal LV end-systolic dimension, the first high-frequency component of the aortic second heart sound was used as a uniform marker. This would disturb the volume calculation in the presence of mitral regurgitation in study population. Second, we used systolic cuff blood pressure to estimate the peak LV pressure. This would be unreasonable in case of the presence of aortic regurgitation or aortic stenosis because in this circumstance peak systolic blood pressure can not represent the peak LV pressure[22]. Since peak systolic pressure may be used instead of end-systolic pressure to calculate the slope of peak systolic pressure—end-systolic volume relation, E'_{max} value in this study would not greatly differ from the value of E_{max}, although the value tended to shift toward a steeper slope[39]. Third, it is assumed that LV contractile state remained uniform under the loading conditions. Although nifedipine has no direct cardiac inotropic effect *in vivo*[48], we cannot exclude the probability of sympathetic nerve reflex after vasodilator changed LV contractility. If this effect is really present, it would tend to increase the value of E'_{max} and E'_{max}/V_{100} that obscure the degree of myocardial impairment to some extent. Because this effect would be opposite to the present data it probably does not affect the validity of conclusion. Finally, in case a slope in N is not different from that in EHT, a calculation of V_{100} in this study may cause an inversion of E'_{max}/V_{100} value between individual normal subject and EHT patient, because the crossing point between each peak systolic pressure—end-systolic volume line in normotensive subject and that in hypertensive patient may occur above the level of 100 mmHg peak systolic pressure.

In conclusion, these findings suggest that in hypertensive LVH diastolic function tends to be depressed at an early stage of hypertrophy. By pharmacological intervention to alter cardiac hemodynamic load, the contractile state in LVH induced by essential hypertension was found to be depressed, and when the hypertrophy is followed by ST-T changes, a marked impairment is observed. A declined LV diastolic function is associated with changes in LV contractile state. E'_{max}/V_{100} did separate LV function of three EHT subgroups (H1, H2 and H3) clearly. This index detects LV depression more sensitively than E'_{max} alone or EF or mVcf under basal condition. Thus, clinically, it is reasonable to classify EHT into three subgroups as a way to evaluate LV function.

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