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Assessment of Left Ventricular Performance in Patients with Variable States of Hypertrophy Secondary to Essential Hypertension Using a New Load-Independent Index, E'_{max}/V_{100}*)

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ABSTRACT

The left ventricular (LV) contractile performance in left ventricular hypertrophy (LVH) induced by chronic pressure overload was assessed in 87 essential hypertensive (EHT) patients. They were classified by the presence of LVH as measured by the sum of LV end-diastolic posterior wall thickness and interventricular septal thickness on echocardiogram, and the presence of ST-T changes on electrocardiogram into a H1-subgroup (H1) consisting of patients with neither LVH nor ST-T changes, a H2-subgroup (H2) with LVH but without ST-T changes and a H3-subgroup (H3) with both LVH and ST-T changes. Thirty-two normal subjects were used as a normal control group (N).

The relation between the peak systolic pressure and LV end-systolic volume normalized by volume intercept at 100 mmHg peak systolic pressure, E'_{max}/V_{100}, was used for expression of the LV inotropic state. The peak systolic pressure was measured with a cuff sphygmomanometer and the LV-end systolic volume was determined by echocardiography. To validate whether E'_{max}/V_{100} was insensitive to loading condition, E'_{max}/V_{100} obtained during dynamic responses to acute LV afterload reduction by nifedipine (NIF group) was compared with that obtained by isosorbide dinitrate-induced preload reduction (ISDN group). E'_{max}/V_{100} obtained in the NIF and ISDN groups showed similar values in analogous subgroups, indicating the independence of this index on acute reduction in cardiac load.

In the NIF group, E'_{max}/V_{100} in H3, 0.13 ± 0.04 mmHg/ml^2, was significantly lower than that in H2, 0.23 ± 0.05 ($p<0.01$), and the value in H2 was significantly lower than that in H1, 0.36 ± 0.17 ($p<0.01$). Similarly, the ISDN group showed that E'_{max}/V_{100} in H3, 0.15 ± 0.07 mmHg/ml^2, was significantly decreased from that in H2, 0.21 ± 0.05 ($p<0.05$) and the value in H2 was significantly less than that in H1, 0.40 ± 0.17 ($p<0.01$). Both the NIF and ISDN groups showed no difference in the value of E'_{max}/V_{100} in H1 from N, indicating a normal level of LV contractility. The value of E'_{max}/V_{100} obtained in both the NIF and ISDN groups did separate the three EHT subgroups (H1, H2 and H3) with a lower LV contractility from those with a normal contractile state.

These findings indicate that in LVH induced by pressure overload the LV contractile state is depressed and becomes further impaired when ST-T changes accompanied LVH. Clinically it is reasonable to assume that the classification of EHT as in this manner

*) Hamed Oemar：新左室機能指標，E'_{max}/V_{100}を用いた高血圧性肥大心における左室機能評価

is a simple and accurate way to evaluate LV performance. It is also concluded that E'_{max}/V_{100}, which is easily determined noninvasively, can be used as a load-independent index of LV contractility.

INTRODUCTION

Evaluation of the left ventricular (LV) function in patients with essential hypertension (EHT) is immensely important in determining the therapy and predicting their prognosis clinically. In EHT patients, chronic pressure overload is a predominant cause of concentric LV hypertrophy (LVH) which is well regarded to occur as a compensatory mechanism for maintaining adequate cardiac pump function[19]. At present, though the effects of compensatory hypertrophy on cardiac performance are still controversial[41], previous investigation in terms of the end-systolic wall stress—diameter relation confirmed that the LV function was depressed in LVH[41]. In their study, however, classification of EHT patients was based only on the presence or absence of LVH using echocardiography.

LV performance is determined by the interaction of four physiologic variables; preload, afterload, myocardial contractile state and LV myocardial mass[3]. Preload and afterload of the human LV can be estimated with reasonable accuracy, but the measurement of myocardial contractility has proved elusive. In recent reports[9,18,31,41], it has been pointed out that contractility indices derived from analysis of the end-systolic pressure—volume relation or end-systolic wall stress—diameter relation appears more promising than those derived from analysis of isovolumic contraction[18] or from typical ejection phase indices[21,31,36]. The former two indices are independent of the end-diastolic volume (preload), incorporate afterload and vary directly with alterations in a myocardial contractile state[39], while the latter two are influenced by both preload and afterload[17,30]. Therefore, in both experimental and clinical studies, the slope of the end-systolic pressure—volume relation (E_{max})[30,31,39] or peak systolic pressure—end-systolic volume relation (E'_{max})[20] has been advocated as a useful measure in evaluating the contractile state of the heart.

Grossman et al.[9] have suggested the importance of the extrapolated value of end-systolic volume at zero pressure (V_0) in assessing the LV function, but others[2,21,39] claimed that V_0 was not a sensitive index of myocardial performance. Sagawa[31] and Noble[23] proposed that simultaneous consideration of V_0 and E_{max} would add more informational value to the end-systolic pressure—volume relation, allowing estimation of the position of the relation. The slope of the entire end-systolic pressure—volume relation shifts when there is an alteration of the inotropic state[2,35,39]. Thereby, the steepness of the slope alone does not necessarily reflect the ventricular contractile state[2,41]. Recently, to obtain a relative position of the slope noninvasively, the peak systolic pressure—end-systolic volume relation normalized by volume intercept at 100 mmHg, E'_{max}/V_{100}, has been proposed and it was used for expression of the contractile state[25]. However, the quantification of this analysis has to be elucidated in order to provide a new clinical approach to the assessment of LV contractile performance under an acutely changing loading condition in man.

The purpose of the present study is (1) to evaluate the LV performance in variable states of hypertrophy in a simple manner using echocardiographic and electrocardiographic methods in patients with essential hypertension, by analyzing the peak systolic pressure—end-systolic volume relation normalized by volume intercept, and (2) to prove that this index is not affected by an acute change in afterload and preload, which are obtained during dynamic responses to acute pressure and volume reduction by nifedipine and isosorbide dinitrate administration respectively.

SUBJECTS AND METHODS

Patients. A single-blind protocol of the investigation procedure was designed in hypertensive out- and in-patients and normal volunteers. Patients having blood pressure (BP) equal to or higher than 165/95 mmHg and belonging to WHO grade I and II were chosen. All patients were diagnosed having EHT after exclusion of secondary hypertension, and have sinus rhythm. No patient was associated with a valvular heart disease and congestive heart

Table 1. Classification of normotensive group (N) and essential hypertensive subgroups (H1, H2 and H3) according to the echocardiographic (UCG) and electrocardiographic (ECG) findings in nifedipine (NIF) and isosorbide dinitrate (ISDN) intervention groups.

Group & Subgroup	NIF intervention group						ISDN intervention group					
	No.	Age (year)	Sex	mean BP (mmHg)	UCG PWTd+IVSTd (mm)	ECG ST-T change	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)	(−)	16	24-56 (40.0±10.3)	12 M 4 F	(92.2±10.6)	(18.6± 1.6)	(−)
H1	22	23-62 (45.5±11.6)	11 M 11 F	(121.7±10.5)	(20.7± 1.4)	(−)	22	27-68 (43.8±11.8)	10 M 12 F	(126.2±11.3)	(19.4± 1.5)	(−)
H2	8	34-62 (47.6± 8.7)	6 M 2 F	(126.3± 9.7)	(27.0± 0.9)	(−)	11	20-60 (44.2±14.4)	6 M 5 F	(127.2±12.1)	(26.8± 2.0)	(−)
H3	11	33-68 (49.6±11.3)	8 M 3 F	(127.4± 9.8)	(25.4± 1.8)	(+)	13	35-64 (50.0± 8.4)	7 M 6 F	(125.5± 9.7)	(27.9± 1.5)	(+)

All values are mean±standard deviation

Abbriviations: No.=number of subjects; BP=blood pressure; PWTd=end-diastolic left ventricular posterior wall thickness; IVSTd=end-diastolic interventricular septal thickness; M=male; F=female (−)=absence; (+)=presence.

failure in this study. The echocardiographic study revealed no evidence of LV asynergy in all patients. All antihypertensive drugs or other medications were withdrawn 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.

Groups. Eighty-seven EHT patients included in this study consisted of 41 patients (25 males and 16 females) (mean age: 47.2±10.9 years) in the nifedipine (NIF) intervention group and 46 patients (23 males and 23 females) (mean age: 46.0±12.2) in the isosorbide dinitrate (ISDN) intervention group (Table 1). In both the intervention groups, the EHT patients were then classified into three subgroups dependent on the echocardiographic and electrocardiographic findings: 22 patients (mean age: 45.5± 11.6, range 23 to 62) in the NIF group and 22 patients (mean age: 43.8±11.8, range 27 to 68) in the ISDN group who had the sum of posterior wall thickness at end-diastole (PWTd) and interventricular thickness at end-diastole (IVSTd) less than 24mm without ST-T changes on ECG formed a H1-subgroup (H1). Eight patients (mean age: 47.6±8.7, range 34 to 62) in the NIF group and 11 patients (mean age: 44.2±14.4, range 20 to 60) in the ISDN group who had PWTd+ISVTd above 24 mm without ST-T changes served as a H2-subgroup (H2). Eleven other patients (mean age: 49.6±11.3, range 33 to 68) in the NIF group and 13 patients (mean age: 50.0±8.4, range 35 to 64) in the ISDN group with PWTd+IVSTd above 24 mm and ST-T changes on ECG constituted a H3-subgroup (H3).

Sixteen normotensive volunteers (10 males and 6 females) in the NIF group and 16 others (12 males and 4 females) in the ISDN group without an evidence of a heart disease served as a normal control group (N). Their averaged age was 41.4±9.5 years (range 29-56) in the NIF group and 40.0±10.3 years (range 24-56) in the ISDN group.

Protocol. After a resting period of 30 min, echocardiography was performed on all the subjects with a Sector Scanner TOSHIBA model SSH-11A using a 22.5-MHz transducer focused at 7.5 cm. M-mode scanning was recorded with a Honeywell visicorder at 50- and 100-mm/sec paper speed.

With the patients laid 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 had been performed. The transducer was kept in place throughout the study and the echogram was continuously checked to assure that all recordings came from the same level in the ventricle. Lead II of the ECG, phonocardiogram from the second left intercostal space and carotid pulse tracing (CPT) were recorded simultaneously with the echocardiogram. The LV end-systolic dimension (ESD) and end-systolic posterior wall thickness (PWTs) were measured at the onset of the second heart sound (A2). The LV end-diastolic dimension (EDD), PWTd and IVSTd were obtained at the Q wave of the ECG using the leading edge method[32]. Data were analyzed as the mean of at least five consecutive cardiac cycles. Adequate echocardiograms were defined as those in which the M-mode scanning could be clearly measured. In all the patients and normal subjects BP was measured in triplicate using a standrad cuff sphygmomanometer. Mean BP was defined as diastolic BP+1/3 pulse pressure and heart rate (HR) was obtained from ECG.

After the basal echocardiographic and cuff pressure data were obtained, hemodynamic load was altered with sublingual administration of either 10 mg of NIF or 10 mg of ISDN to determine the peak systolic pressure—end-systolic volume relation. Data were included in the analysis only when mean BP obtained 30 min after NIF and 20 min after ISDN showed a change of at least 10 mmHg.

Measurements and calculations. For evaluation of the LV systolic and diastolic functions, the following indices were derived from the echocardiograms. The LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from the echocardiographic dimensions using the method of Teichholz et al.[43]. The LV stroke volume (SV) was calculated as; EDV−ESV. All the ventricular volumes were reported as volume indices, that is, ml/m^2 body surface area (EDVI, ESVI and SVI, respectively). The left ventricular ejection fraction (EF) was calculated as;

$$EF\ (\%)=\frac{SV}{EDV}\times 100.$$

The LV mean velocity of circumferential fiber shortening (mVcf) was calculated from the formula,

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

where LVET represents measurement of the LV ejection time (sec) which was obtained from the upstroke of the CPT to the nadir of its dicrotic notch. The cardiac output (CO) was calculated as; SV × HR and was then divided by the body surface area as a cardiac index (CI). The systemic vascular resistance (SVR) was calculated as;

$$SVR\ (dyn\cdot sec\cdot cm^{-5})=\frac{mean\ BP}{CO}\times 80.$$

The mean normalized systolic ejection rate (MNSER) was calculated by the method of Karliner et al.[13] as;

$$MNSER(sec^{-1})=\frac{SV}{EDV\times LVET}.$$

The end-systolic circumferential midwall stress (ESWS) was calculated from the modified LaPlace equation[27],

$$ESWS\ (dyn/cm^2)=\frac{(SBP\times ESD/2)}{PWTs}\left\{1-\frac{ESD}{8\,(ESD+PWTs)}\right\}\times 1334,$$

where SBP is systolic blood pressure (mmHg), ESD is a LV dimension at end-systole (cm) and PWTs is a LV posterior wall thickness at end-systole (cm). The 1334 is a conversion factor to obtain dyn/cm^2. The LV mass was calculated according to the method of Bennet and Evans[1] and was then divided by the body surface area to give a LV mass index (LVMI), expressed in gram/m^2.

The LV isovolumic relaxation time (IVRT), obtained from the dual-echocardiogram (Fig.1), was measured as an interval from the aortic valve closure and the opening of the mitral valve leaflet. The PR-AC interval (Fig. 1) was defined as an interval between point A and the termination of mitral valve closure or point C; and then subtracted from the interval between the onset of P wave to the beginning of the QRS complex, as described by Konecke et al.[15]. The measured LVET, IVRT and PR-AC interval were then corrected to the heart rate of 60 beats/min using the Bazett's formula; the measured interval was divided by the square root of the RR interval in seconds.

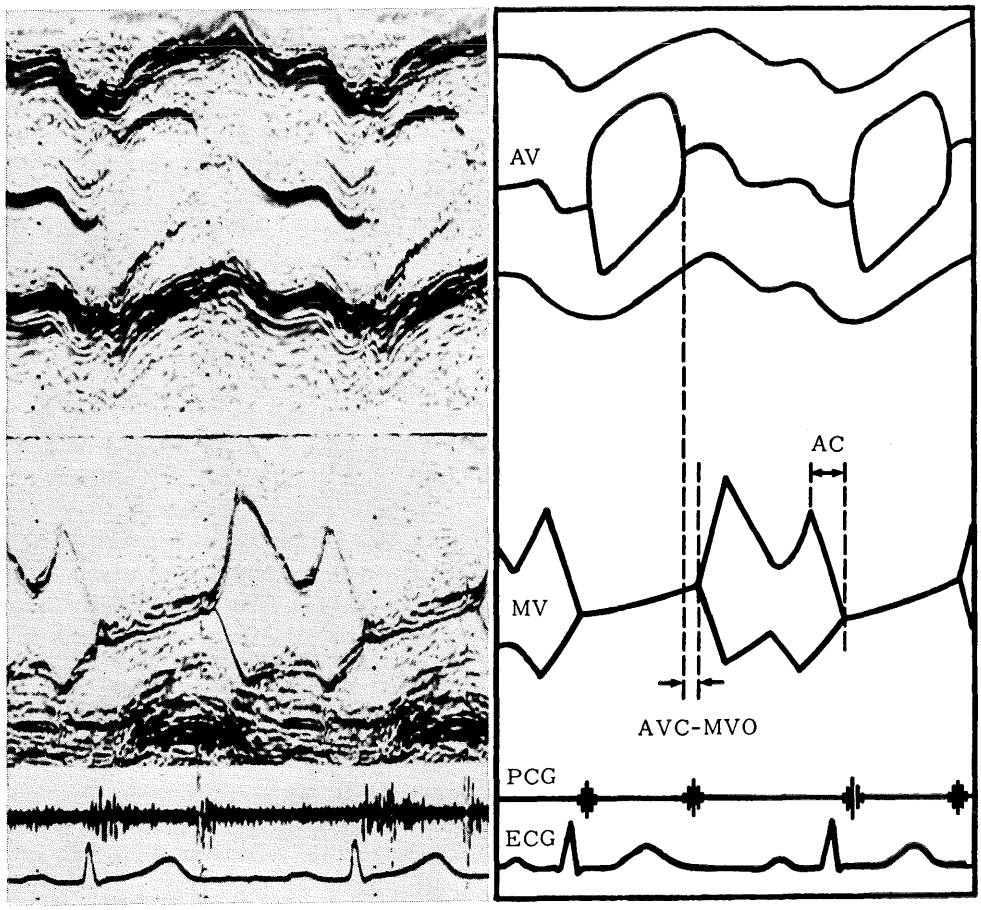

Fig. 1. Dual M-mode echocardiogram of the aortic root and the mitral valve (left panel) and schematic representation (right panel) of the isovolumic relaxation time, the interval from the aortic valve closure (AVC) to mitral valve opening (MVO), and the AC interval. AV=aortic valve; MV=mitral valve; PCG=phonocardiogram; ECG=electrocardiogram.

End-systolic pressure—volume determination. Because only noninvasive measurements were available, the slope of the linear relation between the peak systolic pressure obtained with a cuff sphygmomanometer and the end-systolic volume from the echocardiogram was used as an index of the inotropic state. The slope (E'_{max}) was calculated as;

$$E'_{max}\ (\text{mmHg/ml}) = \frac{\Delta PSP}{\Delta ESV},$$

where ΔPSP and ΔESV are changes in the peak systolic blood pressure and end-systolic volume respectively, after either NIF or ISDN intervension (Fig. 2). Previous studies in man[21,35] and in animal experiments[39,40] have shown that the LV end-systolic pressure—volume relation is linear. According to the end-systolic formula used by Grossman et al.[9],

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

where P_{ES} and V_{ES} are LV end-systolic pressure and volume respectively, m is the slope of the line and V_0 is the volume at $P_{ES}=0$, a modified formula was constructed as;

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

where P_{PS} is a peak systolic pressure. By solving the regression equation for $P_{PS}=100$ mmHg, V_{100} was calculated. It has been reported that the position of the slope of end-systolic pressure—volume relation may reflect the LV inotropic state under basal condition[2,35,41]. To avoid applying a negative V_0 value found in this study, E'_{max} was normalized by volume intercept at 100 mmHg peak systolic pressure as a new index of the myocardial contractile state and expressed as mmHg/ml[2], E'_{max}/V_{100} (Fig. 2)[25].

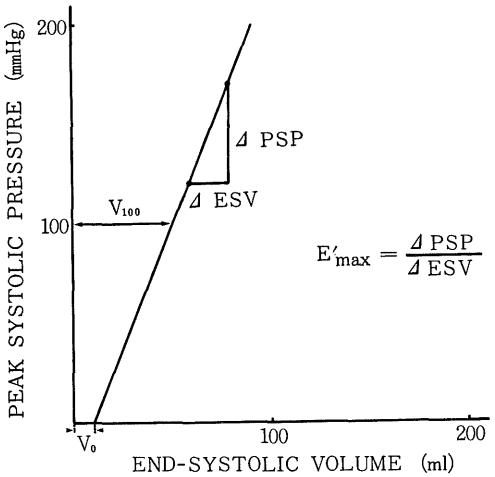

Fig. 2. Schematic diagram of methodology in calculation of E'_{max} and E'_{max}/V_{100}. ΔPSP =change in peak systolic pressure; ΔESV= change in end-systolic volume; V_0=volume at zero pressure; V_{100}=volume at 100 mmHg peak systolic pressure.

Statistical analysis. Correlations were calculated by linear and multiple regression analyses. Student's t test was used for statistical evaluation of paired data. Group and subgroup comparisons were assessed using the Mann-Whitney U test. The level of significance was set at $p<0.05$.

RESULTS

Evaluation of LV function in NIF group (Table 2).

The hemodynamic data in the normotensive subjects and each of three essential hypertensive subgroup before NIF intervention is shown in Table 2. HR was not statistically different among all the group and EHT subgroups. Among H1, H2 and H3, systolic (166.3±11.7 mmHg, 165.6±11.0 mmHg and 172.7±19.4 mmHg, respectively), diastolic (98.0±12.1, 107.2 ±10.5 and 105.0±10.5, respectively) and mean BP (121.2±10.2, 126.2±9.7 and 127.6±9.8, respectively) were not significantly different but the levels of systolic, diastolic and mean BP in each EHT subgroup were significantly higher than those in N (116.4±7.2, 71.7±7.8 and 86.4±7.5 respectively; all $p<0.01$).

Systolic and diastolic indices. The values of EDVI and ESVI were significantly higher in H3 than those in H2, H1 and N (H3 vs H2, both $p<0.01$; H3 vs H1, NS and $p<0.01$ respectively; and H3 vs N, $p<0.05$ and $p<0.01$ respectively). In the hypertensive subgroups, LVMI was progressively increased from H1 (137.5±25.4 g/m²) to H2 (197.2±35.6) and to H3 (211.4±40.1). The values in H2 and H3 were significantly higher compared to that either in H1 ($p<0.05$ and $p<0.01$ respectively) or normotensive subjects (122.1±22.1, $p<0.05$ and $p<0.01$ respectively).

SVI and CI were similar in the EHT subgroups and normotensive group. EF and mVcf showed gradual decline in the hypertensive subgroups in the order of H1, H2 and H3 (70.0± 6.4% and 1.36±0.16 circ/sec in H1, 65.0± 8.4 and 1.22±0.18 in H2 and 60.1±8.7 and 1.14±0.22 in H3), but a significant difference was only found between H1 and H3 (both $p<0.05$). These values were significantly lower in H3 than in N (70.5±8.9 and 1.37±0.15, both $p<0.05$). LVET was similar in the EHT subgroups and normotensive subjects. SVR was significantly higher in the EHT subgroups than normal subjects. MNSER gradually declined in the order of H1, H2 and H3. ESWS was significantly increased in the EHT subgroups than in the normotensive subjects; among the EHT subgroups, H3 showed a significant increase in this value compared with other two subgroups (both $p<0.01$).

IVRT was gradually prolonged in the hypertensive subgroups in the order of H1, H2 and H3, whereas a significant difference was found between H1 and H2 ($p<0.05$) and between H1 and H3 ($p<0.01$). The value of IVRT in H2 and H3 was significantly larger compared with that in N ($p<0.05$ and $p<0.01$ respectively). The PR-AC interval was also gradually shortened in N and EHT subgroups; N>H1>H2> H3, and the significant difference in this parameter was evident between H1 and H3 ($p<0.05$), while the values in H2 and H3 were significantly lower than that in N ($p<0.05$ and $p<0.01$ respectively). The overall systolic and diastolic indices could not clearly separate three EHT subgroups.

Contractility indices by NIF intervention. To determine the peak systolic pressure—end-systolic volume relation in this group, hemodynamic load was altered with NIF. The values of E'_{max} and E'_{max}/V_{100} were progressively decreased from the normotensive subjects to the three EHT subgroups (H1, H2 and H3).

Table 2. Hemodynamic data in normotensive group and essential hypertensive subgroups before nifedipine intervention

	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
Mean blood pressure, MBP (mmHg)	86.4 ± 7.5	121.2 ± 10.2**	126.2 ± 9.7**	127.6 ± 9.8**	NS	NS	NS
LV end-diastolic volume index, EDVI (ml/m²)	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/m²)	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/m²)	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/m²)	45.2 ± 9.8	49.3 ± 11.6	41.5 ± 11.4	47.3 ± 10.5	NS	NS	NS
Cardiac index, CI (L/min/m²)	2.96± 0.70	3.07± 0.62	2.65± 0.69	3.29± 0.98	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)	1.34± 0.15	1.36± 0.16	1.22± 0.18	1.14± 0.22*	NS	<0.05	NS
LV ejection time, LVET (msec)	301.4 ± 15.1	298.4 ± 21.0	304.0 ± 25.1	305.4 ± 27.1	NS	NS	NS
Systemic vascular resistace, SVR (dyn·sec·cm^{-5})	1506 ±358.5	2092 ±572.5**	2410 ±706.5**	1881 ±435.1*	NS	NS	<0.05
Mean normalized systolic ejection rate, MNSER (sec^{-1})	2.34± 0.38	2.35± 0.24	2.14± 0.29	1.97± 0.30**	NS	<0.01	NS
LV end-systolic wall stress, ESWS (×10³ dyn/cm²)	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)	72.4 ± 10.8	81.3 ± 15.2	94.3 ± 16.0*	108.8 ± 17.4**	<0.05	<0.01	NS
PR interval minus AC interval, PR-AC (msec)	89.2 ± 12.9	84.8 ± 19.0	71.1 ± 16.1*	56.2 ± 15.3**	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 relation/ Volume at 100 mmHg peak systolic pressure, E'_{max}/V_{100} (mmHg/ml²)	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
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 N
Abbreviations: NS=not significant; H1, 2 and 3=essential hypertensive subgroups; LV=left ventricular

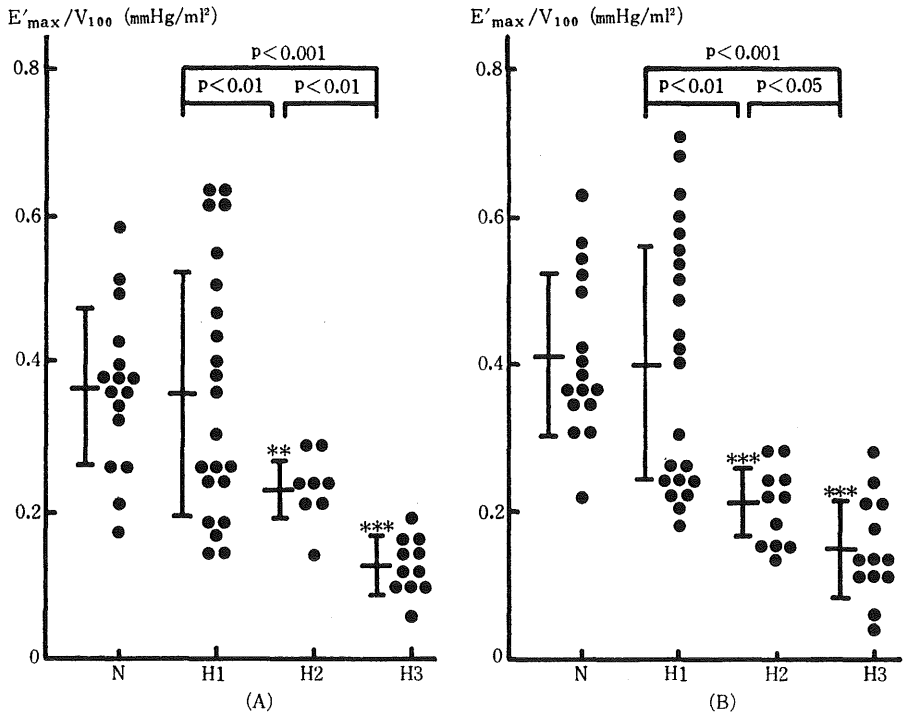

Fig. 3. Peak systolic pressure—end-systolic volume relation/volume intercept at 100 mmHg peak systolic pressure, E'_{max}/V_{100} obtained by nifedipine (A) and isosorbide dinitrate (B) interventions in normotensive subjects (N) and essential hypertensive subgroups (H1, H2 and H3). **p<0.01, ***p<0.001 compared with N.

As seen in Table 2, the value of E'_{max} was relatively higher in N (8.42±2.25 mmHg/ml) and became gradually smaller in the subgroups in the order of H1, H2 and H3. E'_{max} in H1 (7.02±1.98) 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). No significant difference in E'_{max} was observed between H2 and H3. E'_{max} in H1 had no significant difference from N but those in H2 and H3 were significantly lower than in N ($p<0.01$ and $p<0.001$ respectively).

On the other hand, the values of E'_{max}/V_{100} in the hypertensive subgroups were progressively decreased as LVH occurred (from 0.36± 0.17 mmHg/ml² in H1 to 0.23±0.05 in H2) and attained the lowest value in H3 (0.13± 0.04). The intersubgroup differences in E'_{max}/V_{100} were found to be highly significant (H1 vs H2, $p<0.01$; H2 vs H3, $p<0.01$; and H1 vs H3, $p<0.001$) (Fig. 3A). It is obvious that each hypertensive subgroup can be significantly differentiated by E'_{max}/V_{100}. However, this index cannot separate H1 from the normal control (0.37±0.11). Figure 4A shows a positive correlation between E'_{max} and E'_{max}/V_{100} which were determined with NIF intervention ($r=0.79$, $p<0.001$, $n=41$) in the EHT patients. The systolic and diastolic indices except ESWS as well as contractility indices in the NIF group did not show any significant difference between N and H1.

Evaluation of LV function in ISDN group (Table 3).

The hemodynamic state in the normotensive subjects and three EHT subgroups before ISDN intervention is shown in Table 3. No significant difference in HR was found among the hypertensive subgroups and between each subgroup and normotensive subjects. In the EHT subgroups, H1, H2 and H3, the levels of systolic (174.1±18.2 mmHg, 175.5±18.0 mmHg and 178.6±13.3 mmHg respectively), diastolic (98.3±23.2, 103.4±13.2 and 100.8±8.7 respectively) and mean BP (126.2±11.3, 127.2± 12.1 and 125.5±9.7 respectively) were similar, while the levels of these indices in each EHT subgroup were significantly higher than those

Table 3. Hemodynamic data in normotensive group and essential hypertensive subgroups before isosorbide dinitrate intervention

	Normotensives	Essential Hypertensives			p	p′	p″
	N (n=16)	H1 (n=22)	H2 (n=11)	H3 (n=13)			
Heart rate, HR (beat/min)	69.2 ± 7.5	72.1 ± 9.3	71.3 ± 11.0	63.8 ± 7.1	NS	NS	NS
Systolic blood pressure, SBP (mmHg)	121.6 ± 13.5	174.1 ± 18.2***	175.5 ± 18.0***	178.6 ± 13.3***	NS	NS	NS
Diastolic blood pressure, DBP (mmHg)	77.3 ± 10.0	98.3 ± 23.2***	103.4 ± 13.2***	100.8 ± 8.7***	NS	NS	NS
Mean blood pressure, MBP (mmHg)	92.2 ± 10.6	126.2 ± 11.3***	127.2 ± 12.1***	125.5 ± 9.7***	NS	NS	NS
LV end-diastolic volume index, EDVI (ml/m^2)	66.6 ± 8.6	62.1 ± 12.3	65.3 ± 14.6	77.5 ± 17.5	NS	<0.01	NS
LV end-systolic volume index, ESVI (ml/m^2)	22.7 ± 4.6	20.9 ± 5.7	21.9 ± 5.3	35.5 ± 10.7**	NS	<0.01	<0.05
LV mass index, LVMI (g/m^2)	130.7 ± 24.6	129.7 ± 24.1	209.2 ± 47.5**	266.9 ± 47.2***	<0.01	<0.001	<0.05
Stroke volume index, SVI (ml/m^2)	43.9 ± 7.9	41.7 ± 8.7	43.5 ± 7.8	42.0 ± 9.2	NS	NS	NS
Cardiac index, CI ($L/min/m^2$)	3.04± 0.69	3.01± 0.62	3.11 ± 0.70	2.68± 0.74	NS	NS	NS
LV ejection fraction, EF (%)	67.9 ± 7.4	68.2 ± 6.7	66.6 ± 9.7	57.4 ± 11.4*	NS	<0.05	NS
Mean velocity of circumferential fiber shortening, mVcf (circ/sec)	1.30± 0.21	1.28± 0.20	1.26± 0.27	1.04± 0.28*	NS	<0.05	NS
LV ejection time, LVET (msec)	293.0 ± 14.2	295.0 ± 17.2	291.1 ± 29.2	303.2 ± 22.8	NS	NS	NS
Systemic vascular resistance, SVR ($dyn \cdot sec \cdot cm^{-5}$)	1499 ±400	2181 ±490**	2036 ±512**	2357 ±740**	NS	NS	NS
Mean normalized systolic ejection rate, MNSER (sec^{-1})	2.37± 0.24	2.31± 0.19	2.33± 0.21	1.90± 0.24*	NS	<0.05	<0.05
LV end-systolic wall stress, ESWS ($\times 10^3$ dyn/cm^2)	159.4 ± 20.4	202.4 ± 37.4**	223.8 ± 51.4**	258.1 ± 42.0***	NS	<0.01	NS
Isovolumic relaxation time, IVRT (msec)	57.6 ± 17.9	81.1 ± 21.6	91.1 ± 20.2**	101.0 ± 21.9***	NS	<0.05	NS
PR interval minus AC interval, PR-AC (msec)	87.3 ± 18.5	81.2 ± 23.8	75.4 ± 20.1	62.7 ± 16.2*	NS	<0.05	NS
Peak systolic pressure—end-systolic volume relation, E'_{max} (mmHg/ml)	8.04± 1.8	7.94± 2.96	3.87± 1.62***	3.04± 2.28***	<0.01	<0.001	NS
Peak systolic pressure—end-systolic volume relation/ Volume at 100 mmHg peak systolic pressure, E'_{max}/V_{100} ($mmHg/ml^2$)	0.41± 0.11	0.40± 0.17	0.21± 0.05***	0.15± 0.07***	<0.01	<0.001	<0.05

Significances and Abbreviations see Table 2.

in N (121.6±13.5, 77.3±10.0 and 92.2±10.6, all $p<0.001$).

Systolic and diastolic indices. The values of EDVI and ESVI in H3 were larger than those in N (NS and $p<0.01$ respectively) or in H1 (both $p<0.01$) or in H2 (NS and $p<0.05$ respectively). LVMI in H1 (129.7±24.1 g/m²) was similar to that in N (130.7±24.6, NS). Among the EHT subgroups, H3 (266.9±47.2) showed a maximum value of LVMI as compared either with that in H2 (209.2±47.5, $p<0.05$) or H1 ($p<0.001$).

SVI and CI were similar in the three subgroups and normotensive subjects. While EF and mVcf were gradually diminished in the hypertensive subgroups from H1 (68.2±6.7% and 1.28±0.20 circ/sec respectively) to H2 (66.6±9.7 and 1.26±0.27 respectively) and to H3 (57.4±11.4 and 1.04±0.28 respectively). The values of EF and mVcf in N (67.9±7.4 and 1.30±0.21 respectively) were similar to those in H1. No significant difference in LVET was found among the normal control and EHT subgroups. SVR was significantly higher in the EHT subgroups than the normal subjects. MNSER was similar among N, H1 and H2, but the level of this index in H3 was significantly lower than that either in N ($p<0.05$) or H1 ($p<0.05$) or H2 ($p<0.05$). ESWS in each subgroup was significantly higher than that in the normal subjects (H1, $p<0.01$; H2, $p<0.01$ and H3, $p<0.001$). Among the hypertensive subgroups, ESWS increased progressively from H1 to H2 and to H3 whereas a statistical significance was found between H1 and H3 ($p<0.01$).

IVRT was prolonged gradually from N to the hypertensive subgroups consecutively, H1 to H2 and to H3. When compared with N, the IVRT value in each subgroup was significantly increased (H2, $p<0.01$ and H3, $p<0.001$), but an intersubgroup difference was found only between H1 and H3 ($p<0.05$). The PR-AC interval was found to be gradually shortened in the order of H1, H2 and H3, and this value was significantly shortened in H3 compared with that in N and H1 (both $p<0.05$). It was also noted in the ISDN group that all the systolic and diastolic indices except ESWS could not distinctly differentiate each EHT subgroup.

Contractiliy indices by ISDN intervention. The LV contractile state indices, E'_{max} and E'_{max}/V_{100}, showed progressive decreases from H1 to H2 and to H3. E'_{max} in H1 (7.94±2.96 mmHg/ml) showed a significant difference

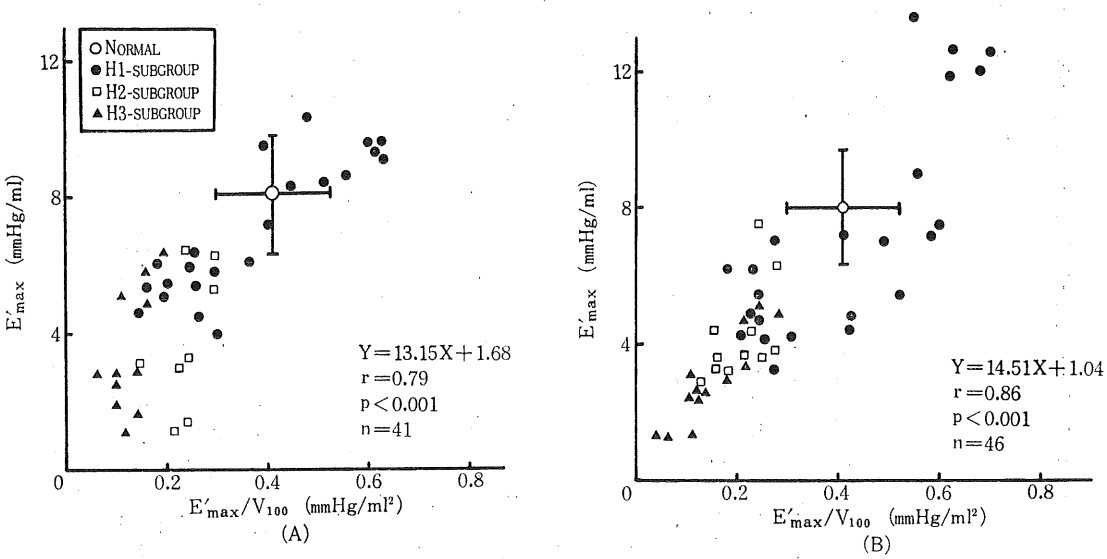

Fig. 4. Relationship between peak systolic pressure—end-systolic volume relation/volume intercept at 100 mmHg peak systolic pressure (E'_{max}/V_{100}) and peak systolic pressure—end-systolic volume relation (E'_{max}) obtained by nifedipine (A) and isosorbide dinitrate (B) interventions in essential hypertensive patients. Open circle represents the control value (±SD) of these indices.

Table 4. Average percent changes in hemodynamic data after nifedipine intervention

	N group		H1-subgroup		H2-subgroup		H3-subgroup		p′	p″	p‴
	% Change	p	% Change	p	% Change	p	% Change	p			
Heart rate, HR (beat/min)	5.6	<0.05	14.0	<0.01	10.8	<0.01	9.0	<0.01	NS	NS	NS
Systolic blood pressure, SBP (mmHg)	−15.0	<0.01	−21.6*	<0.001	−20.7*	<0.001	−22.8*	<0.001	NS	NS	NS
Diastolic blood pressure, DBP (mmHg)	−11.0	<0.01	−18.0*	<0.001	−17.0*	<0.001	−18.3*	<0.001	NS	NS	NS
Mean blood pressure, MBP (mmHg)	−13.0	<0.01	−20.1*	<0.001	−18.4*	<0.001	−20.0*	<0.001	NS	NS	NS
LV end-diastolic volume index, EDVI (ml/m²)	3.1	NS	− 0.1	NS	− 4.2	NS	− 6.8**	<0.01	NS	<0.05	NS
LV end-systolic volume index, ESVI (ml/m²)	−11.0	<0.01	−19.3	<0.01	−23.0*	<0.01	−26.0*	<0.01	NS	<0.05	NS
Stroke volume index, SVI (ml/m²)	9.0	<0.05	5.0	NS	9.0	<0.01	11.0*	<0.01	NS	<0.05	NS
Cardiac index, CI (L/min/m²)	15.0	<0.01	19.0	<0.01	21.0	<0.001	25.2	<0.001	NS	NS	NS
LV ejection fraction, EF (%)	5.1	<0.05	6.5	<0.01	14.8*	<0.001	16.0*	<0.001	<0.05	<0.05	NS
Mean velocity of circumferential fiber shortening, mVcf (circ/sec)	3.0	<0.05	5.5	<0.01	14.0*	<0.01	19.0*	<0.01	<0.05	<0.05	NS
LV ejection time, LVET (msec)	3.2	<0.01	3.0	<0.01	3.6	<0.05	3.0	<0.05	NS	NS	NS
Systemic vascular resistance, SVR (dyn·sec·cm^{-5})	−22.1	<0.01	−33.2	<0.001	−35.4	<0.001	−42.5	<0.001	NS	NS	NS
Mean normalized systolic ejection rate, MNSER (sec^{-1})	2.1	NS	4.2	<0.05	11.0	<0.01	14.0	<0.01	NS	<0.01	NS
LV end-systolic wall stress, ESWS (×10³ dyn/cm²)	−9.8	<0.05	−33.9**	<0.001	−29.1**	<0.001	−34.6**	<0.001	NS	NS	NS
Isovolumic relaxation time, IVRT (msec)	−2.2	NS	−21.5*	<0.01	−20.0*	<0.01	−39.2***	<0.001	NS	<0.01	<0.01
PR interval minus AC interval, PR-AC (msec)	6.1	NS	11.0	<0.05	31.5**	<0.01	57.8***	<0.001	<0.05	<0.01	<0.05

p = Significance of the change
p′ = Significance of the differences in changes in each parameter, between H1- and H2-subgroups
p″ = Significance of the differences in changes in each parameter, between H1- and H3-subgroups
p‴ = Significance of the differences in changes in each parameter, between H2- and H3-subgroups
* p<0.05, ** p<0.01, *** p<0.001 } compared with N
Abbreviations: NS=not significant; N=normotensive; H1, 2, and 3=essential hypertensive subgroups; LV=left ventricular

Table 5. Average percent changes in hemodynamic data after isosorbide dinitrate intervention

	N group		H1-subgroup		H2-subgroup		H3-subgroup		p′	p″	p‴
	% Change	p	% Change	p	% Change	p	% Change	p			
Heart rate, HR (beat/min)	2.2	NS	0.3	NS	2.6	NS	3.8	NS	NS	NS	NS
Systolic blood pressure, SBP (mmHg)	−18.0	<0.001	−21.0	<0.001	−20.1	<0.001	−19.8	<0.001	NS	NS	NS
Diastolic blood pressure, DBP (mmHg)	−8.5	<0.05	−10.5	<0.01	−9.1	<0.01	−13.4	<0.01	NS	NS	NS
Mean blood pressure, MBP (mmHg)	−13.2	<0.001	−17.1	<0.001	−14.0	<0.001	−14.6	<0.001	NS	NS	NS
LV end-diastolic volume index, EDVI (ml/m²)	−7.8	<0.05	−10.8	<0.01	−14.5*	<0.01	−16.2*	<0.01	NS	<0.05	NS
LV end-systolic volume index, ESVI (ml/m²)	−8.0	<0.01	−23.5	<0.001	−34.2*	<0.001	−39.4**	<0.001	NS	<0.01	NS
Stroke volume index, SVI (ml/m²)	−8.5	<0.01	−8.0	<0.05	−4.8	NS	4.0**	NS	NS	<0.01	NS
Cardiac index, CI (L/min/m²)	−6.5	<0.01	−8.6	<0.05	−3.0	NS	8.2**	NS	NS	<0.001	NS
LV ejection fraction, EF (%)	2.0	NS	4.0	<0.05	12.0	<0.05	19.0*	<0.05	NS	<0.01	NS
Mean velocity of circumferential fiber shortening, mVcf (circ/sec)	8.5	<0.05	13.4	<0.01	24.2	<0.01	28.0*	<0.01	NS	<0.01	NS
LV ejection time, LVET (msec)	−6.0	<0.01	−7.5	<0.01	−6.5	NS	−2.6	NS	NS	NS	NS
Systemic vascular resistance, SVR (dyn·sec·cm^{-5})	−3.0	NS	−10.0*	<0.05	−11.0*	<0.05	−5.0	NS	NS	<0.05	<0.05
Mean normalized systolic ejection rate, MNSER (sec^{-1})	4.0	<0.05	12.0	<0.01	17.0	<0.01	22.6*	<0.001	NS	<0.01	NS
LV end-systolic wall stress, ESWS (×10³ dyn/cm²)	−21.5	<0.001	−33.0	<0.001	−30.5	<0.001	−36.0	<0.001	NS	NS	NS
Isovolumic relaxation time, IVRT (msec)	15.0	<0.05	11.8	<0.01	12.0	<0.01	20.8*	<0.001	NS	<0.05	<0.05
PR interval minus AC interval, PR-AC (msec)	4.1	NS	4.6	NS	10.6	<0.05	24.0*	<0.001	NS	<0.05	<0.05

Significances and abbreviations see Table 4.

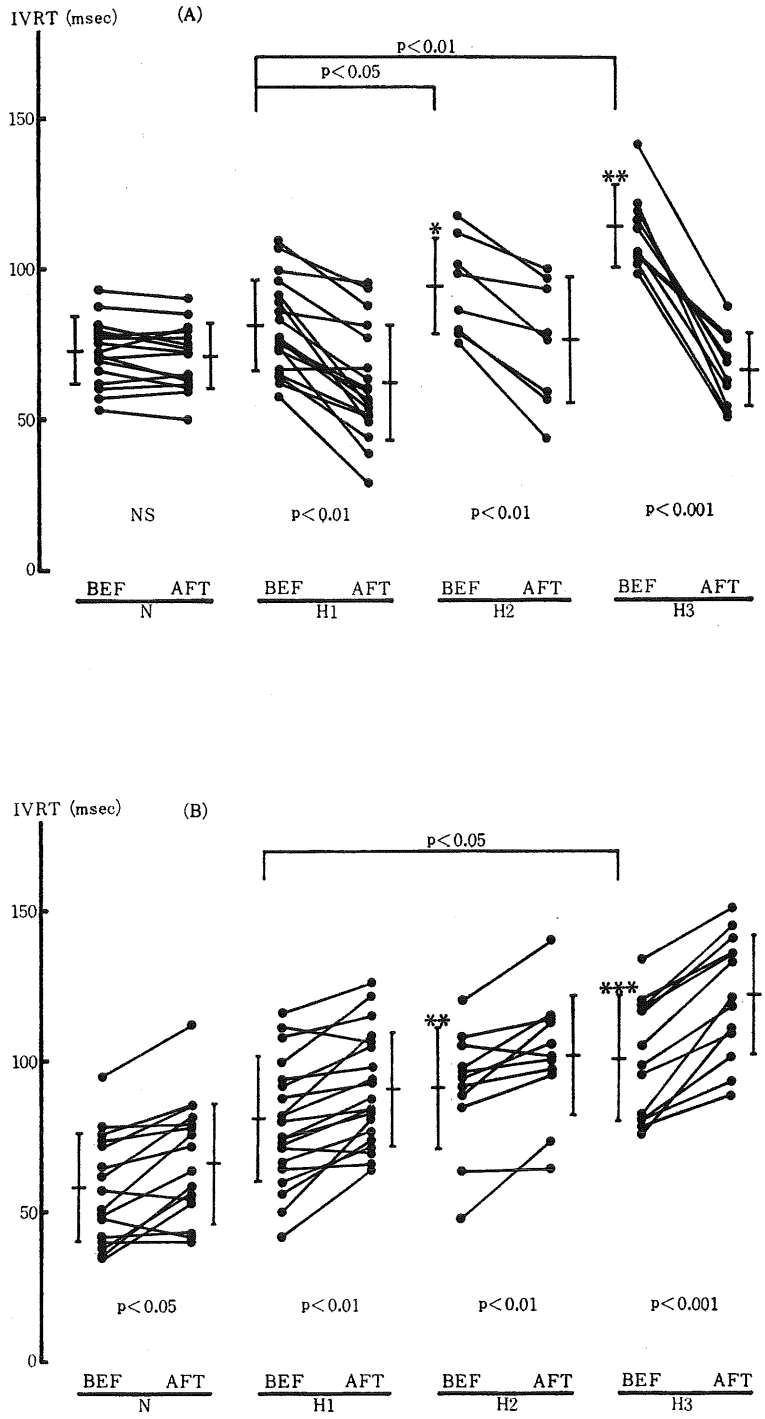

Fig. 5. Isovolumic relaxation time, IVRT, before (BEF) and after (AFT) nifedipine (A) and isosorbide dinitrate (B) interventions in normotensive subjects (N) and essential hypertensive subgroups (H1, H2 and H3). *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with N.

from the values in H2 and H3 (3.87 ± 1.62, $p<0.01$ and 3.04 ± 2.28, $p<0.001$, respectively). No significant difference in E'_{max} was noted either between N (8.04 ± 1.8) and H1 or between H2 and H3. The values or E'_{max} in H2 and H1 were significantly lower as compared to that in N (both $p<0.001$).

The value of E'_{max}/V_{100} was gradually and significantly declined from H1 (0.40 ± 0.17 mmHg/ml[2]) to H2 (0.21 ± 0.05) and further to H3 (0.15 ± 0.07). It was recognized that this index showed a highly significant difference among the EHT subgroups (H1 vs H2, $p<0.01$; H2 vs H3, $p<0.05$ and H1 vs H3, $p<0.001$). The value of E'_{max}/V_{100} in H1 was similar to that in the normal control (0.41 ± 0.11, NS) (Fig. 3B). The linear relation of E'_{max} to E'_{max}/V_{100} in patients with EHT (ISDN) is shown in Fig. 4B ($r=0.86$, $p<0.001$, $n=46$).

Effects of nifedipine and isosorbide dinitrate on LV hemodynamics (Tables 4 and 5).

Though the basal levels of HR, BP and LV volumes (EDVI and ESVI) in the analogous EHT subgroups of NIF and ISDN intervention groups were considerably equal (Tables 2 and 3), some different changes in hemodynamic variables were observed after these drugs interventions(Tables 4 and 5). In the normotensive subjects and EHT subgroups, HR was accelerated by NIF, but not altered by ISDN. The effect of NIF on BP reduction in the EHT subgroups was significantly higher than that in the normotensive group. But the decrement of BP after ISDN in the EHT subgroups was similar to that in the normal subjects. NIF did not change EDVI in the N and EHT subgroups, except in H3 in whom EDVI was decreased significantly. On the other hand, ISDN decreased EDVI significantly both in the N and EHT subgroups, showing a large decrement in H3.

ESVI was decreased significantly in and EHT subgroups both after NIF and ISDN with a gradual increment of percent change from N to H1 to H2 to H3. NIF augmented SVI and CI in N and EHT subgroups, while ISDN diminished these indices in all subgroups except in H3 who showed an increase in SVI and CI (both NS). Enhancement of CI after NIF was gradually greater from H1 to H2 to H3. However, after ISDN, decrement of CI was gradually smaller H1 to H2. NIF and ISDN increased EF, mVcf and MNSER in N and EHT subgroups. The percent rises in these indices were larger in H3 than those in N and H1.

NIF and ISDN showed an opposite alteration of IVRT in N and EHT subgroups. NIF shortened IVRT significantly in EHT subgroups, while ISDN prolonged it both in N and EHT subgroups (Fig. 5). On the other hand, PR-AC interval was significantly prolonged in EHT subgroups both after NIF and ISDN.

Comparison of contractility indices obtained by NIF and ISDN

The value of E'_{max}/V_{100} as well as E'_{max} obtained in each analogous subgroup by NIF and ISDN was found to be similar (Tables 2 and 3). In both the intervention groups, each EHT subgroup can be significantly and distinctly separated by only E'_{max}/V_{100} (Fig. 3).

DISCUSSION

The assessment of LV function in patients with essential hypertension is clinically important to choose the therapy and to predict the prognosis, especially in the presence of LVH. Since echocardiography (UCG) has been reported to be superior to electrocardiography (ECG) alone in identifying the presence of LVH in patients with systemic arterial hypertension[6], the application of UCG has proved to be the most reliable method to diagnose LVH and to measure LV mass[1]. However, unlike ECG, UCG does not permit evaluation of the existence of myocardial damages or ischaemia. Therefore, methods are needed that permits quantitative evaluation of variable states of LVH by means of a noninvasive technique which is easily obtained in clinical practice as previously reported from this laboratory[25].

Cardiac hypertrophy, which occurs in essential hypertension, is one of the fundamental mechanisms of adaptation to abnormal loading conditions[19,41]. However, studies on the effects of hypertrophy on myocardial performance are controversial. The systolic LV performance in LVH has been reported to be depressed[7], normal[14] or 'supranormal'[10]. Sasayama et al.[34] and Karliner et al.[14] reported that a successful hypertrophic response to chronic pressure overload did not result in depression of the myocardial inotropic state. On the other hand,

Takahashi et al.[41] recently concluded that myocardial contractility might be depressed in hypertensive patients with advanced LVH. The presence of these contrary results is probably firstly due to methodological differences in the parameters of LV function studied and secondly due to the absence of subclassification in EHT patients with LVH. In the present study, therefore, to evaluate the LV performance in patients with EHT, especially in the presence of LVH, a simple method to classify those patients by a noninvasive approach was designed.

Myocardial relaxation, the active process by which the ventricular muscle returns to its initial length and tension[37], has been extensively studied *in vitro*[37] and *in vivo* animal studies[8]. In man, LV relaxation has been assessed using indices such as the time course of isovolumic pressure decrease or the rate of changes in the LV volume or dimension during the rapid filling phase[12]. In this study, the IVRT and PR-AC interval were used to evaluate elasticity and compliance of the LV wall as the diastolic indices of LV function. The former index was markedly prolonged in both secondary forms of LVH and hypertrophic cardiomyopathy[12]. Recently, it has been reported that LV end-diastolic pressure inversely correlates with the PR-AC interval which has been claimed as an index of LV filling pressure[15,46]. They have also proposed that a shortened PR-AC interval is due primarily to abnormality of the ventricular diastolic function. The results of this study suggest that LV diastolic compliance may have been impaired in hypertensive LVH with and without ST-T changes, as estimated from the prolonged IVRT and shortened PR-AC interval (Tables 2 and 3). This finding is consistent with previous observations[12]. Nevertheless, the LV diastolic indices used in this study may not be adequate for separating EHT patients into subgroups.

The validity of the index used in the assessment of the LV performance depends on two factors, the sensitivity of index for evaluation of variable states of cardiac function prior to development of cardiac failure, and the independency of this index on changes in afterload and preload. Braunwald et al.[3] reported the usefulness of ejection phase indices such as EF, mVcf and MNSER in characterising the basal LV performance. The ejection phase indices remain relatively constant in a chronic pressure and volume overload state; however, they do vary with acute changes in the loading conditions of the heart[28]. In other words, when preload is decreased or afterload increased, the ejection phase indices are depressed even if the inotropic state of LV is constant. The present study demonstrated the failure of ejection phase indices in differentiating EHT subgroups. Ideally, when the contractile state is to be assessed, a load-independent index must be employed.

The end-systolic pressure—volume relation, E_{max}, which is generally used for estimating the length-tension relation, was considered as a sensitive measure for the assessment of the myocardial contractile state in human[21,30]. The utility of this relation has been developed by the finding that the peak systolic pressure can be substituted for the end-systolic pressure without significantly altering these properties[21,36]. In this study, the systolic blood pressure obtained with a cuff sphygmomanometer was utilized as a close approximation to the peak systolic LV pressure[36], as long as valvular heart diseases were not involved. Therefore, the peak systolic pressure—end-systolic volume relation, E'_{max}, which is easily obtained in clinical practice, was defined as an index of the myocardial contractile state[20,25]. In addition, the peak systolic pressure—end-systolic volume relation was well represented by a straight line, where the use of two systolic pressure—volume data points for the calculation of E'_{max} in this study (Fig. 2) was in accordance with Mehmel et al.[21].

Since the slope and the position of the end-systolic pressure—volume relation proved a reliable feature of the LV contractile state[2,41], a simultaneous application of the slope and its position as a new index of LV inotropic state would be a valuable indicator. The intercept of the end-systolic pressure—volume relation on the volume axis (theoretical value of end-systolic volume extrapolated to zero systolic pressure, V_0 in Fig. 2) has been considered as a possible additional index of LV contractility because it might reflect the maximum pumping capacity of LV and it should be independent of preload[9,18]. In this study, however, the V_0

value varied widely among patients (−16 to 46 ml). Therefore, instead of applying the negative V_0 value, E'_{max} was normalized by volume intercept at the peak systolic pressure=100 mmHg, i. e., E'_{max}/V_{100}, as a new index of the ventricular contractile state (Fig. 2).

Volume intercept V_{100} was selected as a parameter instead of V_0, firstly because the intercept of peak systolic pressure—end-systolic volume could cause disappearance of 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 subjects and thirdly because the end-systolic pressure—volume relation can be approximated by a linear line in the range of 50 to 150 mmHg[38]. In addition, the crossing point of each individual slope in the majority of EHT patients was not recognized above the level of 100 mmHg peak systolic pressure and a positive correlation between E'_{max} and E'_{max}/V_{100} in the EHT patients was observed in both NIF and ISDN interventions (Fig. 4).

To evaluate the LV performance in this study, E'_{max}/V_{100} was used as a sensitive index of contractility, because it did separate the three EHT subgroups significantly and clearly. This index provided a similar value in N and H1, indicating that in patients with uncomplicated essential hypertension the LV function was not involved. To prove the independence of this index on acute change in afterload and preload, NIF and ISDN were used, because these two agents have a different mode of actions on the circulatory system, producing a different effect on LV hemodynamics. NIF exhibited vascular smooth muscle relaxation by inhibiting the slow calcium channels and the movement of calcium ions across the cell membranes[44]; however, the mechanism by which ISDN produced a venodilatation is not yet clearly understood[22]. It has been reported that NIF decreases the tone of resistance vessels, leading to lower arterial BP[45], while ISDN dilates capacitance vessels, resulting in a decrease of venous return and thereby a BP reduction[22].

As NIF acts predominantly on the arteriolar system[44,45], the accelerated HR in the EHT subgroups and normotensive subjects observed in this study might be associated with sympathetic response reflected by the elevation of plasma cathecholamines[24]. However, unlike NIF, ISDN-induced venodilatation did not alter HR, even if it was found to increase catecholamine release in the EHT subgroups and normotensive subjects[26]. In this regard, these results are in accord with the previous investigation by Tarazi et al.[42] who reported that vasodilators which lower the blood pressure by a dilating effect on resistance vessels increase HR, but those that cause a dilatation of capacitance vessels do not elevate HR. This phenomenon may be explained by the release of right atrial wall stretch secondary to a reduction of venous return which might produced an inadequate stimulation on sinoatrial node, resulting a slowing to rates[4].

The difference in the degree of decrement of EDVI after NIF and ISDN confirmed that NIF acts predominantly on afterload reduction while ISDN on preload reduction. The findings of venodilatation and the consequent reduced preload by nitrate provided an explanation for the decline in stroke volume and cardiac output[22]. Under normal condition, cardiac output is limited by the rate of venous return, so that the heart serves as a "demand pump", with a pumping capability for exceeding the level of cardiac output required under normal circumstances[29]. In the present study, the increased in CI after ISDN in H3 (Table 5) was most likely the result of change in the LV end-systolic pressure—volume relationship. In H3, in whom the slope of the peak systolic pressure—end-systolic volume line was reduced, the decrement of EDVI after ISDN was smaller than that of ESVI and thereby cardiac output should be increased. The systolic phase indices like EF, mVcf and MNSER were found to be markedly increased in N and EHT subgroups both after NIF and ISDN. These findings confirmed that these indices were dependent on variations in both afterload and preload.

The effect of NIF on IVRT (Fig. 5A) seems to be related by a direct effect of this agent on the myocardium by altering calcium content or transport in the hypertrophied myocadium[16]. Additionally, NIF may ameliorate the impaired LV late diastolic filling, as estimated by the prolongation of PR-AC interval, in patients with EHT. This effect mainly resulted from the shortening of the AC interval of mitral

leaflet which was probably caused, in part, by reduction of LV afterload secondary to peripheral arterial dilatation. On the other hand, after ISDN administration a significant prolongation of IVRT was observed in all the subgroups and normal subjects (Fig. 5B). This prolongation can be interpreted as a larger decrease in venous return, since a larger decrement of EDVI represents a greater reduction of venous return. Since HR showed almost no changes after ISDN, the PR interval should be expected to be always constant after intervention; thereby the prolongation of the PR-AC interval consequently represents the shortening of the AC interval which may be caused by the decrease in venous return. The overall changes in systolic and diastolic indices observed in this study both after NIF and ISDN were clearly explained by the different sites of action of these two agents.

Possible criticisms on the methods used in the present study may include the following. First, the systolic cuff blood pressure was used to estimate the peak LV pressure, because only noninvasive measurements were used in this study. Studies in humans[36] have shown that the peak systolic blood pressure obtained with a cuff sphygmomanometer has a close correlation with a peak LV pressure. Since the peak systolic pressure may be used instead of the end-systolic pressure to calculate the slope of peak systolic pressure—end-systolic volume relation[20,21], the E'_{max} value in this study would not substantially differ from the value of E_{max}, although the value tended to shift toward a steeper slope[36]. Second, it is assumed that the LV contractile state remained constant at different levels of loading conditions during pharmacologic interventions. Although the agents used to induce pressure changes, NIF and ISDN, have no direct cardiac inotropic effect *in vivo*[5,45], the probability that sympathetic activation after vasodilators alters LV contractility cannot be dismissed. In animal studies[33], when sustained aortic constriction was abruptly released, acute sympathetic reflex influenced contractility was shown to be insignificant. Other observations[11] also provided an additional evidence that sympathetic nerve reflex did not play a significant role in the inotropic alteration of the normal heart. In the present study, since the accelerated sympathetic response as

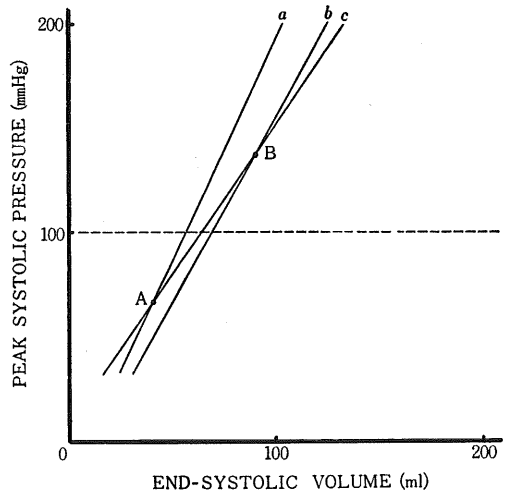

Fig. 6. Diagrammatic representation of the individual slope lines (*a*, *b* and *c*) of peak systolic pressure—end-systolic volume relation. When the lines, *a* and *c*, crossed at point (A) under 100 mmHg, the order between E'_{max}/V_{100} (*a*) and E'_{max}/V_{100} (*c*) were not changed compared with the order between E'_{max} (*a*) and E'_{max} (*c*). On the other hand, when the lines, *b* and *c*, crossed at point (B) above 100 mmHg, the order between E'_{max}/V_{100} (*b*) and E'_{max}/V_{100} (*c*) might be inverted compared with the order between E'_{max} (*b*) and E'_{max} (*c*).

reflected by compensatory elevation of plasma catecholamines after NIF[24] or after ISDN[26] administration was noted, this effect would be expected to increase the value of E'_{max} and E'_{max}/V_{100} that can mask the presence of depressed myocardial contractile force. Conversely, E'_{max} and E'_{max}/V_{100} observed in the present study could explicitly separate the degree of LV function in variable states of hypertensive LVH. Therefore, any sympathetic effect would not affect the validity of the conclusions. Third, if the slopes of the peak systolic pressure—end-systolic volume relation crossed under the level of 100 mmHg peak systolic pressure, the order of E'_{max}/V_{100} did not change the order of corresponding E'_{max}. However, if the slope crossed above the level of 100 mmHg, the order of E'_{max}/V_{100} might invert the order of corresponding E'_{max} (Fig. 6).

In conclusion, these data suggest that in hypertensive hypertrophy induced by pressure overload the LV contractile state is depressed and undergoes more impairment when ST-T

changes accompanied LVH. A modified index of contractility, E'_{max}/V_{100}, did separate significantly and clearly the LV function of the uncomplicated EHT subgroup (H1) from that of EHT with LVH (H2), and the LV function of H2 from that of LVH combined with ST-T changes (H3). Therefore, E'_{max}/V_{100} may be a useful index in evaluating the LV performance more reliably than the typical ejection phase indices or IVRT or PR-AC interval. By pharmacological interventions which exert actions on different sites, acute changes in afterload and preload do not substantially affect this index; thus supporting its use in the assessment of LV contractile state. Clinically, the application of UCG and ECG as a simple and readily available approach is valuable in evaluating the cardiac performance in patients with EHT. Moreover, it is reasonable to classify EHT patients, in whom the hypertensive cardiac failure has not yet occurred, into three subgroups as a means of assessing the LV function.

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