Negative U-wave as a Predictor of Antihypertensive Treatment Effect on Regression of Echocardiographic Hypertrophy in Hypertensive Patients

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SUMMARY

To clarify the mechanism and the predictors of the reduction in left ventricular mass (LVM) induced by antihypertensive drugs, forty hypertensive patients were classified according to the presence of left ventricular hypertrophy (LVH) as defined by echocardiographic LVM findings (LVH group: 27 patients, non-LVH group: 13 patients) and according to the presence of negative U-waves (NU) (NU group: 10 patients, non-NU group: 30 patients). Negative U-waves appeared in the LVH group only (10 of 27 patients). The hemodynamic determinants were investigated as a mechanism of LVM reduction in 38 of these patients who were treated for 2 years with antihypertensive drugs. In the LVH group, thickness of interventricular septum (IVST), posterior wall thickness (PWT) and LVM increased significantly compared to the non-LVH group. In the NU group, the left ventricular end-diastolic dimension (LVDD) was significantly larger and the relative wall thickness was significantly smaller compared to the non-NU group in the LVH group, with no difference in LVM between the two groups. Negative U-waves disappeared in all cases after treatment.

Significant decreases in LVDD and LV wall thickness were observed in the NU group and significant decrease in LV wall thickness in the non-NU group. LVM index was reduced by 24.0% in the NU group and 9.5% in the non-NU group. The disappearance of negative U-waves was an independent predictor of the reduction of LVH. (*Jpn Heart J* 1999; 40: 31-44)

Key words: Antihypertensive drugs, Left ventricular mass, Left ventricular hypertrophy, Negative U-wave, Cardiac hemodynamics, Diastolic dysfunction.

HYPERTENSIVE patients with LVH have a higher incidence of coronary artery disease and cardiac death, and have a poorer prognosis than patients without LVH.¹⁻³⁾ LVH is diagnosed not only by electrocardiographic find-

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ings but also by echocardiographic findings, such as parameters of left ventricular wall thickness and left ventricular mass (LVM). It has been suggested that an increase in these parameters is important as a determinant factor in prognosis.³⁻⁵⁾ LVM is reduced by antihypertensive drugs, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, β -blockers, and diuretics.⁶⁾ It is known that the effect of diuretics is predominantly due to a reduction in the left ventricular diameter,⁷⁾ whereas the effect of other antihypertensive agents is due to a reduction in wall thickness. On the other hand, according to a recent long-term study⁸⁾ in which a significant reduction in LVM was observed after treatment with captopril, hydrochlorothiazide, or atenolol, but not after treatment with diltiazem, clonidine, or prazosin, antihypertensive drugs have effects on LVM independent of the magnitude of the reduction in blood pressure. It was reported that reduction of LVM with hydrochlorothiazide was associated with decreased LV wall thickness rather than decreased LV cavity.⁸⁾ It was suggested that the mechanism of LVM reduction due to diuretics was different from that of LVM reduction as described above. The authors have previously reported that the antihypertensive action in hypertensive patients differs according to the hemodynamics of the patient.⁹⁾ It was also considered that hypertensive patients with negative U-waves showed cardiac hemodynamic status characterized by an increase in cardiac output and LVDD. Therefore, this study was based on the hypothesis that differences in the mechanism of LVM reduction are due to differences in the hemodynamics of patients. The objectives of this study are 1) to clarify the presence of a group of hypertensive patients with increased LVM who have disparate hemodynamic status, and 2) to clarify the mechanism and the predictors of the reduction of LVM by antihypertensive drug treatment in this group. To clarify these objectives electrocardiographic and echocardiographic findings in hypertensives with normal and increased LVM were compared, and the reduction in LVM by antihypertensive drugs was investigated in patients treated with these drugs throughout the entire period of the study.

MATERIALS AND METHODS

Subjects: Forty previously untreated patients (26 males, 14 females) with essential hypertension ranging in age from 35 to 72 years (mean age: 58.7 ± 9.7 years) were included in the study. The subjects were initially examined as outpatients in the period from March 1994 to December 1996. Subjects who satisfied the following criteria were considered to have hypertension: systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 95 mmHg or both on at least two occasions at the outpatient clinic. The patients with a history of coronary heart disease and those with hypertrophic cardiomyopathy were

excluded from this study. Furthermore, no patient had a history of cerebrovascular accident, valvular heart disease, or congestive heart failure. Data were compared with those obtained in 20 normotensive subjects (11 males, 9 females) without cardiovascular disease ranging in age from 35 to 69 years (mean age: 56.7 ± 10.0 years).

The patients were classified into two groups according to the presence of left ventricular hypertrophy (LVH) as defined by pre-drug echocardiographic LVM findings (27 patients in the LVH group and 13 patients in the non-LVH group) and according to the presence of negative U-waves in the electrocardiographic findings at the initial examination (10 patients in the NU group and 30 patients in the non-NU group).

Administration method: Of the 40 hypertensive patients given antihypertensive drugs during the above-mentioned period, 38 patients (25 males, 13 females) were retrospectively selected according to the following inclusion criteria in order to evaluate the reduction in LVM after long-term administration of antihypertensive drugs. The inclusion criteria were 1) patients who had been treated with pharmacologic antihypertensive therapy for 2 years, 2) patients with pre- and post-drug (2 years after treatment) echocardiographic and electrocardiographic data, 3) patients without complications of atrial fibrillation, or right or left bundle branch block. The remaining two patients were excluded for reason due to shortage of the duration of treatment. Calcium antagonists were used exclusively as the drug of first choice for treatment throughout the entire period of the study. Of the 38 patients given antihypertensive agents, 36 patients received calcium antagonists (benidipine, nicardipine, amlodipine, nifedipine and nisoldipine) as the drug of first choice for hypertensive treatment and the remaining two patients took β -blockers (bisoprolol and carvedilol) during initial therapy because of occurrence of ventricular premature beats. Of the 36 patients given calcium antagonists, 3 patients took the other antihypertensive drugs because of flushing and headache and 5 patients stopped calcium antagonists because of excessive lowering of blood pressure during the administration of a combination of calcium antagonists. Then 8 patients were treated with the other drugs. Finally calcium antagonists were used in 28 of these patients during the entire study. The target blood pressure during therapy was $< 140/90$ mmHg without adverse drug effects. If an adequate antihypertensive effect was not observed after the antihypertensive drug treatment, the dosage of these drugs was increased and an ACE inhibitor or a β -blocker was coadministered.

Of the 28 patients given calcium antagonists, monotherapy with calcium antagonists was used in 10. A combination therapy of calcium antagonists and β -blockers was used in 5 patients and calcium antagonists and ACE inhibitors in 13 patients. Of the 10 patients without calcium antagonists, monotherapy with ACE

inhibitors was used in 4 and with β -blockers in 2, and a combination therapy of β -blockers and ACE inhibitors was used in 4 patients.

Measurement: M-mode and two-dimensional echocardiograms were obtained using a Nippon Hewlett Packard SONOS 1000 with a 2.5 or 3.5 MHz transducer (Tokyo). The measurements of echocardiograms were performed with standard techniques by a physician who was unaware of the patient's clinical state. LVDD, IVST and PWT were measured by the conventional method as recommended by the American Society of Echocardiography (ASE).¹⁰ Left ventricular mass (LVM) was calculated by the correction of the ASE cube mass using the following formula:^{11,12}

$$\text{LVM(g)} = 0.80 \cdot 1.04 \cdot \{ [\text{internal dimension (cm)} + \text{septal thickness (cm)} + \text{posterior wall thickness (cm)}]^3 - [\text{internal dimension (cm)}]^3 \} + 0.60.$$

LVM index was calculated by dividing LVM by body surface area. Echocardiographic LVH was diagnosed when LVM index was greater than 110 g/m² in women and greater than 131 g/m² in men.¹³ Relative wall thickness was defined as IVST plus PWT divided by LVDD. The left ventricular end-diastolic volume, systolic volume, cardiac output and left ventricular ejection fraction were calculated by the disk summation method of ASE.

Mitral inflow velocities were recorded by standard pulsed-wave Doppler at the tips of the mitral valve. From the mitral inflow recordings, peak early (E) and atrial (A) velocities were measured and A/E ratio was calculated. Total peripheral resistance (TPR) was calculated as mean blood pressure $\times$ 80/cardiac output.

The QT and QTc intervals were automatically measured. The presence of an isoelectric line between the negative U-wave and the T wave was used as a criteria for identifying U waves in this study, as previously described by Lepeschkin.¹⁴

Methods: Resting electrocardiograms and echocardiograms were obtained from hypertensive patients and normotensive subjects, and hemodynamic parameters were compared between the two groups. In addition, the changes in hemodynamic parameters were compared between LVH and non-LVH groups and between NU and non-NU groups in hypertensive patients before and after 2 years of treatment.

Statistical analysis of data: All analyses were performed using SPSS software (version 7.5, SPSS inc.). All data are expressed as mean $\pm$ standard deviation and were assessed by Student's *t*-test. Differences in the incidence of negative U-waves and ST-T abnormalities were tested using the Chi-square test in hypertensive patients.

To test whether the disappearance of negative U-waves was independently associated with a reduction of LVM, univariate and then multivariate analyses

(logistic regression with stepwise selection of predictive variables), with change in LVM (%) as the dependent variable, mean blood pressure, QRS amplitude (SV1 + RV5), negative U-waves, electrical axis, IVST, PWT, cardiac output, and total peripheral resistance before treatment as a covariate, were performed in 27 patients with LVH. Differences were considered significant at $p < 0.05$.

RESULTS

Characteristics of electrocardiographic and echocardiographic findings in hypertensive patients: Blood pressure, SV1 + RV5 amplitude, the extent of left axis deviation, QTc interval, IVST, PWT, LVDD, left ventricular end-systolic dimension (LVSD), LVM, LVM index, relative wall thickness, and A/E ratio were significantly increased in the LVH group compared to the normotensive group, as shown in Table I. In addition, TPR was also significantly higher in

Table I. Comparison of Electrocardiographic and Echocardiographic Findings between Normotensive and Hypertensive Groups with LVH and non-LVH

	Normotensive group	Hypertensive group	
		LVH	non-LVH
Number of patients	20	27	13
Males/females	11/9	16/11	10/3
Age (yr)	56.7 ± 10.0	61.0 ± 7.7	53.8 ± 11.7 [#]
Systolic blood pressure (mmHg)	127.6 ± 11.1	170.7 ± 15.1***	169.4 ± 11.2 ^{§§§}
Diastolic blood pressure (mmHg)	81.2 ± 3.7	101.5 ± 9.8***	102.7 ± 7.7 ^{§§§}
Mean blood pressure (mmHg)	96.2 ± 5.3	124.4 ± 9.5***	125.0 ± 7.9 ^{§§§}
Heart rate (beats/min)	68.6 ± 10.4	70.9 ± 14.3	63.1 ± 7.8
SV1 + RV5 (mm)	27.0 ± 4.9	39.7 ± 14.4***	34.1 ± 8.5 ^{§§}
Negative U-wave (cases/%)	0	10(37)	0 [@]
ST-T abnormality (case/%)	0	8(30)	0 [@]
Electrical axis (°)	48.0 ± 20.1	7.3 ± 27.2***	24.7 ± 18.1 ^{§§#}
QT (msec)	385.5 ± 25.2	399.6 ± 36.3	404.6 ± 22.6 [§]
QTc	407.7 ± 19.0	432.8 ± 36.6**	422.0 ± 27.6
Thickness of interventricular septum (mm)	9.0 ± 0.9	13.3 ± 2.8***	11.4 ± 1.8 ^{§§§#}
Posterior wall thickness (mm)	8.9 ± 0.9	11.5 ± 1.4***	10.5 ± 1.3 ^{§§§#}
Left ventricular end-diastolic dimension (mm)	45.9 ± 3.3	49.3 ± 5.8*	47.0 ± 5.4
Left ventricular end-systolic dimension (mm)	27.6 ± 3.4	30.7 ± 7.0***	28.2 ± 5.3 ^{###}
Left ventricular mass (g)	141.8 ± 30.6	250.8 ± 58.6***	183.8 ± 21.9 ^{§§§###}
Left ventricular mass index (g/m ²)	87.1 ± 13.8	147.1 ± 10.7***	105.3 ± 11.4 ^{§§§###}
Relative wall thickness (%)	0.40 ± 0.01	0.50 ± 0.12***	0.48 ± 0.12 [§]
Left ventricular ejection fraction (%)	71.6 ± 4.6	68.3 ± 10.7	73.6 ± 6.0
A/E ratio	1.06 ± 0.08	1.45 ± 0.33***	1.29 ± 0.41
Cardiac output (L/min)	4.9 ± 0.5	5.5 ± 1.4	5.1 ± 1.1
Total peripheral resistance (dynes · sec · cm ⁻⁵)	1569.0 ± 146.4	1922.7 ± 490.9**	2075.4 ± 509.6 ^{§§§}

LVH = left ventricular hypertrophy, mean ± SD.

LVH; ≥ 131 g/m² in men and ≥ 110 g/m² in women. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (normotensive vs LVH), [§] $p < 0.05$, ^{§§} $p < 0.01$, ^{§§§} $p < 0.001$ (normotensive vs non-LVH), [#] $p < 0.05$, ^{##} $p < 0.01$, ^{###} $p < 0.001$ (LVH vs non-LVH), [@] $p < 0.05$ (Chi-square test).

the LVH group compared to the normotensive group.

The parameters, except in age, heart rate, QTc interval, LVDD, LVSD, LV ejection fraction, cardiac output and A/E ratio were significantly increased in the non-LVH group compared to the normotensive group. The mean age of the non-LVH group was significantly lower than that in the LVH group. The incidence of negative U-waves and ST-T abnormalities was significantly higher in the LVH group compared to that in the non-LVH group, (37% vs 0%, 30% vs 0%, $p < 0.05$ in both cases). The QRS axis significantly revealed left axis deviation in the LVH group compared to the non-LVH group. As for echocardiographic findings, IVST, PWT, LVSD, LVM, and LVM index were significantly greater in the LVH group compared to the non-LVH group.

Table II shows a comparison of the electrocardiographic and echocardiographic findings between normotensive and hypertensive groups with NU and non-NU in LVH patients. Blood pressure, heart rate, SV1 + RV5 amplitude, the extent of left axis deviation, IVST, PWT, LVDD, LVSD, LVM,

Table II. Comparison of Electrocardiographic and Echocardiographic Findings between Normotensive and Hypertensive Groups with NU and non-NU in LVH Patients

	Normotensive group	LVH group	
		NU	non-NU
Number of patients	20	10	17
Males/females	11/9	5/5	11/6
Age (yr)	56.7 ± 10.0	58.4 ± 5.3	62.5 ± 8.5
Systolic blood pressure (mmHg)	127.6 ± 11.1	170.4 ± 10.7***	170.9 ± 15.2 ^{§§§}
Diastolic blood pressure (mmHg)	81.2 ± 3.7	106.0 ± 11.2***	98.6 ± 8.0 ^{§§§}
Mean blood pressure (mmHg)	96.2 ± 5.3	127.5 ± 12.8***	34.1 ± 6.8 ^{§§§}
Heart rate (beats/min)	68.6 ± 10.4	78.5 ± 14.0*	66.4 ± 12.8 [#]
SV1 + RV5(mm)	27.0 ± 4.9	42.8 ± 11.5***	37.8 ± 15.8 ^{§§}
ST-T abnormality (case/%)	0	6(60)	2(12) [@]
Electrical axis (°)	48.0 ± 20.1	9.1 ± 26.4***	6.2 ± 28.3 ^{§§§}
QT (msec)	385.5 ± 25.2	378.0 ± 28.2	404.7 ± 32.9 [#]
QTc	407.7 ± 19.0	424.9 ± 27.9	426.5 ± 37.4
Thickness of interventricular septum (mm)	9.0 ± 0.9	12.0 ± 2.7***	13.9 ± 2.7 ^{§§§}
Posterior wall thickness (mm)	8.9 ± 0.9	11.0 ± 1.3***	11.8 ± 1.4 ^{§§§}
Left ventricular end-diastolic dimension (mm)	45.9 ± 3.3	53.7 ± 4.7***	46.7 ± 4.8 ^{##}
Left ventricular end-systolic dimension (mm)	27.6 ± 3.4	30.9 ± 10.9**	28.8 ± 6.7
Left ventricular mass (g)	141.8 ± 30.6	250.8 ± 65.5***	251.1 ± 56.2 ^{§§§}
Left ventricular mass index (g/m ²)	87.1 ± 13.8	146.0 ± 21.4***	147.7 ± 20.9 ^{§§}
Relative wall thickness (%)	0.40 ± 0.01	0.40 ± 0.09	0.56 ± 0.10 ^{§§§###}
Left ventricular ejection fraction (%)	71.6 ± 4.6	65.6 ± 12.3	69.9 ± 9.8
A/E ratio	1.06 ± 0.08	1.40 ± 0.41*	14.7 ± 0.28 ^{§§§}
Cardiac output (L/min)	4.9 ± 0.5	6.9 ± 1.2***	4.7 ± 0.8 ^{###}
Total peripheral resistance (dynes · sec · cm ⁻⁵)	1569.0 ± 146.4	1534.5 ± 322.0	2151.0 ± 428.6 ^{§§§###}

LVH = left ventricular hypertrophy, NU = negative U wave, mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (normotensive vs NU), § $p < 0.05$, §§ $p < 0.01$, §§§ $p < 0.001$ (normotensive vs non-NU), # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ (NU vs non-NU), @ $p < 0.05$ (Chi-square test).

LVM index, and A/E ratio were significantly greater in the NU group compared to the normotensive group. In addition, cardiac output also significantly increased in the NU group compared to the normotensive group but no significant difference in TPR between the two groups was observed. In the non-NU group, on the other hand, the relative wall thickness and TPR, which showed no significant difference in the NU group, significantly increased compared to the normotensive group. However, no significant differences in heart rate, LVDD, LVSD or cardiac output were observed between the non-NU and normotensive groups.

A comparison of the results of the NU and non-NU groups shows that heart rate and the incidence of ST-T abnormalities significantly increased in the NU group compared to the non-NU group. Of the 8 patients with ST-T abnormalities, 6 patients had ST-segment depression in V5 and/or V6 (≥ 0.05 mV) in the NU group and 2 patients marked ST-segment depression (≥ 0.1 mV) with T wave flattening or inversion in V5 and V6 in the non-NU group. LVDD was significantly greater in the NU group than in the non-NU group, and relative wall thickness was significantly thicker in the non-NU group than in the NU group. While cardiac output significantly increased in the NU group compared to the non-NU group, TPR was significantly higher in the non-NU group compared to the NU group.

Effect of antihypertensive drugs on hypertensive patients: Table III shows the electrocardiographic and echocardiographic findings before and after antihypertensive drug treatment. Systolic, diastolic, and mean blood pressures all significantly decreased after treatment. Negative U-waves appeared in 10 (26%) out of 38 patients before treatment but disappeared in all cases after treatment ($p < 0.05$) while ST-T abnormalities did not significantly disappear after treatment. SV1 + RV5 amplitude significantly decreased and electrical axis significantly increased (toward the right axis) after treatment. As for echocardiographic findings, IVST, PWT, LVM, and LVM index significantly decreased after treatment. The overall effect of LVM index was a reduction of 13.7%. In addition, TPR was also significantly reduced after treatment.

Patients treated with antihypertensive drugs were classified into LVH and non-LVH groups, and the results of the groups were compared. In the LVH group, not only did systolic, diastolic, and mean blood pressures significantly decrease, but SV1 + RV5 amplitude also significantly decreased. Furthermore, negative U-waves which appeared in the LVH group disappeared in all cases after treatment. In the non-LVH group, on the other hand, only blood pressure, LVM, LVM index and TPR significantly decreased after treatment. LVM index was reduced by 14.8% in the LVH group and 10.5% in the non-LVH group.

Table IV shows a comparison of electrocardiographic and echocardiographic findings in LVH groups with NU and non-NU before and

Table III. Comparison of Electrocardiographic and Echocardiographic Findings in Hypertensive Patients Treated with Antihypertensive Drugs for Two Years

	Total		LVH group		non-LVH group	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Number of patients	38		27		11	
Males/females	25/13		16/11		9/2	
Age (yr)	58.7 ± 9.8		61.1 ± 7.7		52.9 ± 12.4 [#]	
Systolic blood pressure (mmHg)	170.3 ± 14.0	132.3 ± 6.8***	170.7 ± 15.1	130.5 ± 7.7***	171.8 ± 13.5	135.6 ± 5.0***
Diastolic blood pressure (mmHg)	101.9 ± 9.6	83.5 ± 10.8***	101.5 ± 9.8	83.4 ± 12.2***	102.5 ± 8.2	83.6 ± 7.9***
Mean blood pressure (mmHg)	124.6 ± 9.3	99.7 ± 5.5***	124.4 ± 9.5	98.3 ± 5.6***	125.6 ± 8.2	102.3 ± 3.5***
Heart rate (beats/min)	69.2 ± 13.3	68.5 ± 11.5	70.9 ± 14.3	67.7 ± 11.7	64.3 ± 19.6	70.2 ± 11.3
SV1 + RV5 (mm)	38.8 ± 13.6	36.3 ± 13.1*	39.7 ± 14.4	36.4 ± 13.4	35.3 ± 9.1	36.2 ± 12.8
Negative U-wave (cases/%)	10(26)	0@	10(37)	0@	0	0
ST-T abnormality (cases/%)	8(21)	7(18)	8(30)	7(26)	0(0)	0(0)
Electrical axis (°)	10.8 ± 27.2	25.1 ± 29.1*	7.3 ± 27.2	22.4 ± 29.4*	19.4 ± 26.5	31.8 ± 28.7
QT (msec)	397.6 ± 31.0	402.6 ± 34.3	399.6 ± 36.3	405.8 ± 35.5	405.4 ± 24.6	392.3 ± 25.3
QTc	423.9 ± 32.2	427.6 ± 36.5	432.8 ± 36.6	428.9 ± 41.7	419.1 ± 29.2	424.2 ± 20.0
Thickness of interventricular septum (mm)	12.7 ± 2.6	11.5 ± 2.2***	13.3 ± 2.8	11.8 ± 2.2***	11.3 ± 2.0	10.8 ± 2.1
Posterior wall thickness (mm)	10.6 ± 2.6	9.4 ± 1.4***	11.5 ± 1.4	10.4 ± 1.7***	10.6 ± 1.9	10.1 ± 1.1
Left ventricular end-diastolic dimension (mm)	48.7 ± 5.7	48.5 ± 4.0	49.3 ± 5.8	48.6 ± 4.0	45.9 ± 5.2	44.8 ± 5.3
Left ventricular end-systolic dimension (mm)	29.9 ± 6.7	29.0 ± 3.9	30.7 ± 7.0	29.9 ± 3.9	27.9 ± 5.1	27.1 ± 3.4
Left ventricular mass (g)	224.7 ± 59.2	195.1 ± 54.5***	250.8 ± 58.6	209.0 ± 70.5***	178.2 ± 23.1	160.7 ± 27.2*
Left ventricular mass index (g/m ²)	134.9 ± 30.1	116.1 ± 30.4***	147.1 ± 10.7	125.0 ± 30.5***	104.2 ± 13.9	93.9 ± 15.6*
ΔLVMI (g/m ²)				18.5 ± 22.4	21.6 ± 23.3	11.0 ± 18.7
ΔLVMI (%)				13.7 ± 15.3	14.8 ± 15.3	10.5 ± 14.8
Relative wall thickness (%)	0.49 ± 0.15	0.47 ± 0.13	0.50 ± 0.12	0.46 ± 0.14	0.48 ± 0.13	0.49 ± 0.11
Left ventricular ejection fraction (%)	69.8 ± 9.9	68.7 ± 6.8	68.3 ± 10.7	68.3 ± 7.3	73.0 ± 6.7	69.9 ± 5.5
A/E ratio	1.38 ± 0.34	1.29 ± 0.29	1.45 ± 0.33	1.30 ± 0.30	1.29 ± 0.37	1.27 ± 0.29
Cardiac output (L/min)	5.3 ± 1.9	4.5 ± 1.2***	5.5 ± 1.4	4.5 ± 1.3***	5.0 ± 1.22	4.5 ± 1.1
Total peripheral resistance (dynes·sec cm ⁻⁵)	1986.0 ± 509.2	1833.7 ± 444.9**	1922.7 ± 490.9	1846.0 ± 467.3*	2119.8 ± 541.2	1804.0 ± 415.7***

LVH = left ventricular hypertrophy; LVMI = left ventricular mass index, mean ± SD. LVH; ≥131 g/m² in men and ≥110 g/m² in women. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 (before vs after treatment), [#]*p* < 0.05 (LVH vs non-LVH), @*p* < 0.05 (Chi-square test).

Table IV. Comparison of Electrocardiographic and Echocardiographic Findings in LVH Groups with NU and non-NU before and after the Treatment of Antihypertensive Drugs for Two Years

	NU group		non-NU group	
	Before treatment	After treatment	Before treatment	After treatment
Number of patients	10		17	
Males/females	5: 5		11: 6	
Age (y)	58.4 ± 5.3		62.6 ± 8.5	
Systolic blood pressure (mmHg)	170.4 ± 18.7	130.2 ± 7.6***	170.9 ± 15.2	130.7 ± 7.9***
Diastolic blood pressure (mmHg)	106.0 ± 11.2	83.8 ± 12.8***	98.6 ± 8.0	83.2 ± 12.5***
Mean blood pressure (mmHg)	127.5 ± 12.8	97.1 ± 7.5***	134.1 ± 6.8	97.1 ± 7.5***
Heart rate (beats/min)	78.5 ± 14.0	70.7 ± 8.9	66.4 ± 12.8	66.0 ± 13.0
SV1 + RV5 (mm)	42.8 ± 11.5	38.2 ± 12.9	37.8 ± 15.8	35.2 ± 14.0*
Negative U-wave (cases/%)	10(100)	0(0)@	0(0)	0(0)
ST-T abnormality (cases/%)	6(60)	5(50)	2(12)	2(12)
Electrical axis (°)	9.1 ± 26.4	28.0 ± 20.3*	6.2 ± 28.3	19.1 ± 31.4
QT (msec)	378.0 ± 28.2	391.0 ± 21.8	404.7 ± 32.9	415.9 ± 41.2
QTc	424.9 ± 27.9	422.2 ± 41.2	426.5 ± 37.4	432.9 ± 42.7
Thickness of interventricular septum (mm)	12.0 ± 2.7	10.4 ± 2.2**	13.9 ± 2.7	12.6 ± 3.6*
Posterior wall thickness (mm)	11.0 ± 1.3	9.8 ± 1.8*	11.8 ± 1.4	10.7 ± 0.8*
Left ventricular end-diastolic dimension (mm)	53.7 ± 4.7	49.9 ± 4.5***	46.7 ± 4.8	47.5 ± 4.8
Left ventricular end-systolic dimension (mm)	30.9 ± 10.9	33.9 ± 6.5	28.8 ± 6.7	29.4 ± 8.6
Left ventricular mass (g)	250.8 ± 65.5	190.7 ± 66.6***	251.1 ± 56.2	219.8 ± 49.4**
Left ventricular mass index (g/m ²)	146.0 ± 21.4	110.7 ± 25.6***	147.7 ± 20.9	133.7 ± 30.5**
ΔLVMI (g/m ²)		35.2 ± 28.6		13.8 ± 17.8§
LVMI reduction (%)		24.0 ± 19.8		9.5 ± 13.8§
Relative wall thickness (%)	0.40 ± 0.09	0.41 ± 0.05	0.56 ± 0.10	0.50 ± 0.07
Left ventricular ejection fraction (%)	65.6 ± 12.3	69.7 ± 10.2	69.9 ± 9.8	67.4 ± 5.1
A/E ratio	1.40 ± 0.41	1.26 ± 0.28	1.47 ± 0.28	1.32 ± 0.31
Cardiac output (L/min)	6.9 ± 1.2	5.2 ± 1.1**	4.7 ± 0.8	4.2 ± 0.9*
Total peripheral resistance (dynes·sec·cm ⁻⁵)	1534.5 ± 322.0	1504.5 ± 370.7	2151.0 ± 428.6	1976.5 ± 446.9***

LVH = left ventricular hypertrophy; NU = negative U wave; LVMI = left ventricular mass index; mean ± SD. **p* < 0.05, ***p* < 0.01, ****p* < 0.001 (before vs after treatment), §*p* < 0.05 (NU vs non-NU group), @*p* < 0.05 (Chi-square test).

Table V. Results of Univariate and Multivariate Analyses for Predictors of a Reduction of LVM

Variables selected	Beta-coefficient	<i>t</i> Value	<i>p</i> Value
Univariate analysis			
Mean blood pressure	0.185	0.943	0.354
QRS amplitude	0.038	0.189	0.852
Negative U-wave	0.479	2.729	0.011
Electrical axis	0.017	0.085	0.933
IVST	-0.248	-1.280	0.212
PWT	0.100	0.504	0.619
Cardiac output	0.449	2.515	0.019
Total peripheral resistance	-0.318	-1.676	0.096
Multivariate analysis [#]			
Negative U-wave	0.479	2.729	0.011
Cardiac output	0.247	1.108	0.279
Total peripheral resistance	-0.029	-0.128	0.899

LVM = left ventricular mass; IVST = thickness of interventricular septum; PWT = posterior wall thickness.

[#] Three variables ($p < 0.1$) were selected from all of the variables for univariate analysis.

after treatment. In the NU group, blood pressure significantly decreased after treatment. PWT, LVDD, LVM, LVM index and cardiac output significantly decreased after treatment. Negative U-waves disappeared in all cases after treatment while ST-T abnormalities disappeared in only one of six patients. Electrical axis significantly shifted to the right after treatment, but SV1 + RV5 amplitude did not significantly decrease after treatment. In the non-NU group, on the other hand, the blood pressure, SV1 + RV5 amplitude, IVST, PWT, LVM, LVM index, cardiac output and TPR were significantly reduced after treatment. LVM index was reduced by 24.0% in the NU group and 9.5% in the non-NU group. A significant difference was seen in LVM index reduction between the NU and non-NU groups.

As shown in Table V, the relation between negative U-waves and a reduction of LVM induced by long-term antihypertensive treatment was explored by use of multivariate analysis. The disappearance of negative U-waves was an independent predictor of treatment effects on the reduction of LVH.

DISCUSSION

Differences in cardiac hemodynamic parameters in patients with increased LVM: Echocardiographic LVH was attributable to increases in IVST, PWT, and LVDD. The increase in the A/E ratio indicated a decrease in left ventricular diastolic function. Interestingly, the negative U-waves appeared in the LVH group only.

In our previous investigation of the relationship between the appearance of negative U-waves in hypertensives and cardiac hemodynamic status, we reported

that while the NU hypertensive group is characterized by high cardiac output, the non-NU group is characterized by increased vascular resistance.⁹⁾ Therefore, in order to clarify the cardiac hemodynamics in the LVH group, the objective of the present study, the LVH group was classified into NU and non-NU groups, and the cardiac hemodynamic status of the two groups was compared. In comparison to the non-NU group, it was found that heart rate, LVDD, and cardiac output significantly increased in the NU group, whereas an increase in relative wall thickness and TPR was observed in the non-NU group. These findings coincided with our previously reported results⁹⁾ and similar results were also obtained for some patients in the LVH group in the present study. This result suggests that the hemodynamics of hypertensives with LVH is not uniform and that their cardiac hemodynamic status is different. Therefore, we investigated whether the increase in LVM, an echocardiographic index of LVH, is related to left ventricular dimension and/or wall thickness.

The results of the present study revealed that increases in IVST and PWT are more important than an increase in LVDD as a determinant of increased LVM in the LVH group. However, it was suggested that in some LVH cases in the NU group, an increase in LVDD was more important than IVST and PWT as a determinant of increased LVM. It was suggested that this hemodynamic status is compatible with that of eccentric LVH as described by Ganau.¹⁵⁾ It has previously been reported that 93% of cases with negative U-waves are associated with cardiac disease.¹⁶⁾ However, despite several subsequent reports regarding the importance of the clinical significance of negative U-waves,¹⁶⁻¹⁹⁾ the genesis of U-waves is still not understood.^{14,20)} It is known that negative U-waves also appear transiently in hypertensives in association with a rapid increase in blood pressure.²¹⁾ Regression of LVH has been emphasized in recent years as an important goal of antihypertensive therapy but, in an evaluation of the effect of antihypertensive drugs, it is important to take into account the lack of uniformity in the cardiac hemodynamic status of LVH.

Effects of hypertensive drugs on reduction of LVM: LVH is associated with a greater risk of myocardial infarction, stroke, sudden death, and death of any case.^{4,5)} Furthermore, regression of LVH has been shown to be associated with an improvement of cardiac function, an increase in coronary reserve, and a reduction of cardiovascular events.²²⁻²⁴⁾

The regression effect of calcium antagonists against LVM is weaker than that of ACE inhibitors, and the reduction in LVM as a whole was 11.9%.⁶⁾ In the present study the overall effect of LVM was a reduction of 14.8% (24% for the NU group, and 9.5% for the non-NU group). Therefore, it can be argued that the LVH regression rates were significantly higher in the NU group than in the non-NU group after hypertensive drug treatment.

On the other hand, an analysis of the LVM reduction mechanism of anti-hypertensive drugs in terms of hemodynamic status found that, while decreases in LVDD and LV wall thickness were important in the NU group, a decrease in LV wall thickness was important in the non-NU group for LVM reduction. The disappearance of negative U-waves was not secondary to the regression in LVH, but a direct effect on the reduction of LVH. It was also noted in the NU group that SV1 + RV5 amplitude did not significantly decrease after treatment, while electrical axis significantly shifted to the right axis after treatment. On the other hand, SV1 + RV5 amplitude significantly decreased after treatment, but electrical axis did not significantly shift to the right after treatment in the non-NU group. It was suggested that the reduction in LVM in the NU group might be mainly due to a decrease in LV dimension. According to a meta-analysis by Dahlof,⁶⁾ the regression in LVH after treatment with calcium antagonists is not due to a decrease in LV volume but to a decrease in wall thickness, and only diuretics reduce LVH by a decrease in LV volume. Gottdiener *et al.*,⁸⁾ on the other hand, reported that the regression in LVM after treatment with diuretics was due to a decrease in LV wall thickness. These findings suggest that the hemodynamics of hypertensive patients and responses to antihypertensive drugs vary with the presence of negative U-waves. Thus, the different effect of cardiac hemodynamic status of hypertensives should be taken into account in an evaluation of the antihypertensive effect and LVM reduction caused by antihypertensive drugs.

Role of negative U-waves in patients with hypertensive heart disease:

Some reports have suggested the possibility that negative U-waves occurred in diastolic dysfunction of left ventricular wall via a mechanical stretch during increased afterload.^{9,16,25-27)} In the present study, blood pressure before treatment was similarly elevated in NU and non-NU groups in hypertensive patients. This finding indicates that high blood pressure is an important but not a crucial factor in appearance of negative U-waves in hypertensive patients. We found no consistent change in pattern of ST-T changes associated with the change in U wave polarity after treatment. Therefore, it appears that the mechanism of negative U-waves related to diastolic events may indicate the ischemic manifestations of hypertensive heart disease.

Study limitation: Since the present study was retrospective, it was not possible to determine the relationship between neurohumoral factors and renin-angiotensin system in LVH patients in the NU group. In addition, the present study mainly examined the concomitant effect on LVM of antihypertensive drugs. In the future, the relationship between the diversity of hemodynamics in hypertensives with LVH and the effect of single-drug therapy using various antihypertensive drugs needs to be clarified in a prospective study.

Conclusion: The cardiac hemodynamic status of hypertensive patients with LVH is not uniform. It was suggested that in some LVH cases in the NU group, an increase in LVDD was more important than IVST and PWT as a determinant of increased LVM. The disappearance of negative U-waves was an independent predictor of the reduction of LVH.

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