Journal of Cardiology 23: 165–175, 1993

Is left ventricular systolic dysfunction in hypertensive patients with heart failure normalized by long-term antihypertensive therapy?

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Summary

The critical left ventricular (LV) mass when hypertensive heart failure appears, and whether LV dysfunction in hypertensives with heart failure is normalized by long-term antihypertensive therapy were investigated. LV dimension, LV mass, LV mass index, LV ejection time (LVET) and pre-ejection period (PEP) were measured in 27 normal subjects and 56 essential hypertensives, the latter divided into three groups: group I, without LV hypertrophy; group II, with LV hypertrophy; and group III, with hypertensive heart failure. LV mass and LV mass index were 135.0±23.8 g and 85.8±11.7 g/m^2, respectively, in normal controls, 133.0±30.8 g and 82.0±18.4 g/m^2 in group I, 222.3±38.0 g and

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Received for publication November 9, 1991; accepted October 21, 1992 (Ref. No. 37-129)

136.1±19.9 g/m² in group II, and 422.0±30.3 g and 235.7±19.6 g/m² in group III of essential hypertensives. The upper limits of LV mass and LV mass index in group II (mean+2SD) were about 300 g and 180 g/m², respectively. Significant shortening of LVET was observed only in group III, but PEP was prolonged with an increase in LV mass. LV diastolic dimension and PEP were not normalized by long-term antihypertensive therapy (mean: 16 months). These results indicate that the critical LV mass marking the transition from non-failing hypertrophied left ventricle to failing ventricle associated with essential hypertension is about 300 g, or LV mass index of 180 g/m², and that LV dilatation and depressed myocardial contractility in essential hypertensives with a past history of congestive heart failure were not normalized by chronic antihypertensive therapy.

Key words
Essential hypertension | Heart failure | Left ventricular mass | Irreversible myocardial damage

Introduction

Myocardial hypertrophy of the left ventricle associated with hypertension occurs as a pathophysiologic adaptation to the increased afterload[1]. Increased left ventricular wall thickness reduces wall stress and permits the heart to adapt to the pressure overload without succumbing to congestive heart failure. However, congestive heart failure inevitably results when the left ventricle cannot adequately sustain the afterload. Little is known about the critical values of the left ventricular mass and function which change from the compensated to the decompensated stage during the pathophysiologic response to the increased afterload[2,3]. In addition, no investigation has evaluated whether regression of the hypertrophied left ventricle and normalization of the left ventricular dysfunction in essential hypertensive patients with congestive heart failure are achieved by long-term antihypertensive therapy.

This study determined the left ventricular mass and the left ventricular function at the critical point when the heart of patients with essential hypertension enters the decompensated stage and evaluated whether regression of the hypertrophied left ventricle and normalization of left ventricular dysfunction in essential hypertensives with heart failure were achieved by long-term antihypertensive therapy.

Patients and methods

Subjects

The study included 56 essential hypertensive patients (38 men and 18 women) with clear echocardiograms selected from 68 consecutive essential hypertensive patients admitted to our clinic between January 1988 and March 1989, and selected patients with a history of heart failure due to high blood pressure admitted to our clinic in the last 8 years. Hypertension was defined as systolic blood pressure ≧160 mmHg and/or diastolic blood pressure ≧95 mmHg measured in the outpatient clinic[4]. The 56 patients were classified into 3 groups based on interventricular septal thickness (IVST) and left ventricular posterior wall thickness (PWT) determined by echocardiography and clinical symptoms. IVST and PWT were both less than 10 mm in group I patients (n=22), IVST and/or PWT were 10 mm or greater in group II patients (n=26). There was a history of hypertensive heart failure in group III patients (n=8). Patients with valvular heart disease, significant coronary artery stenosis, diabetes mellitus, or bundle branch block shown by electrocardiography were excluded from the study. Twenty-seven normotensive volunteers (17 men and 10 women) with no history of hypertension and no abnormalities detected by physical examination, electrocardiogram, chest radiogram and echocardiogram served as the control group.

Measurement of the left ventricular mass

Left ventricular mass (LVM) was calculated by the method of Devereux and Reichek[5]. LVM index (LVMI) was defined as LVM divided by body surface area. The IVST was measured exactly by excluding the moderator band and accessory tendon attached to the left-sided interventricular septum[6]. After identification of the moderator band and the accessory tendon using two-dimensional echocardiography, the IVST and PWT were measured using M-mode echocardiography according to the recommendations of the American Society of Echocardiography[7].

Measurement of systolic time intervals

Systolic time intervals were measured from the simultaneous recording of an electrocardiogram, a phonocardiogram, and a carotid pulse tracing at a paper speed of 100 mm/sec. Systolic time intervals were measured as reported previously[8]: 1) left ventricular ejection time (LVET)=from the onset of the upstroke on carotid pulse tracing to dicrotic notch. The initial upstroke and the end of LVET were determined tangentially. To adjust LVET for heart rate, LVET was corrected (LVET index=LVETI) by the equation of Weissler et al[9]; 2) preejection period (PEP)=(Q-II)−LVET, where Q-II is electromechanical systole, defined as the interval from the beginning of QRS complex of the electrocardiogram to the beginning of the aortic component of the second heart sound. This study expressed these intervals as the mean of measurements from five consecutive beats.

Study protocols

Protocol I: The relationship between left ventricular mass and left ventricular function in patients with essential hypertension was investigated using echocardiographic and mechanocardiographic examinations. Medication was stopped for at least one week in groups I and II, while group III patients were examined at the out-patient clinic.

Protocol II: The left ventricular function of patients in group III was examined again after blood pressure was well controlled. To obtain adequate control of blood pressures, all patients participating in the protocol II study were treated with nifedipine (30 mg/day), methyldopa (250–500 mg/day) and furosemide (40–80 mg/day or 2 days). In addition, 3 patients received enalapril (5 mg). The mean follow-up period was 16±22 months. Informed consent was obtained from all subjects participating in the study.

Statistical analysis

All values are expressed as mean±SD. Statistical evaluation used analysis of variance, and subsequent comparisons between mean values for groups used Duncan's multiple range test.

Results

Table 1 shows the profiles of the control and patient groups. Mean blood pressures measured at the outpatient clinic were highest in group III, medium in group II and the lowest in group I.

Fig. 1 shows LVM and LVMI in the control and patient groups. There was no significant difference in LVM and LVMI between the control and group I, but LVM and LVMI increased with the development stage of hypertension. The upper limits of LVM and LVMI in group II (mean+2SD) were about 300 g and 180 g/m^2, respectively.

Fig. 2 shows LVETI and PEP in the control and patient groups. There were no significant differences in LVETI among the control and patient groups I and II, but a significant shortening of LVETI was observed in group III. PEP increased with an increase in LVM.

Fig. 3 shows there was a fairly high correlation between PEP and LVET. In addition, there was a turning point at a PEP of about 140 msec. LVET decreased linearly with prolonged PEP of more than 140 msec, but remained almost constant for PEP in the range of less than 140 msec.

Fig. 4 shows the changes in left ventricular diastolic and systolic dimensions, and in PEP before and after long-term antihypertensive therapy in group III patients. Systolic and diastolic blood pressures were decreased from 218±14 to 162±14 mmHg, and from 130±

Table 1. Patient characteristics and data from mechano-

	Age (yrs)	SBP/DBP (mmHg)	HR (beats/min)	LVET/LVETI (msec)
Normotensive controls	45±9	128±24 / 78±10	65±8	284±17 /393±11
Essential hypertensives				
Group I (n=22)	43±12	164±19*/ 95±11*	67±10	275±21 /386±16
Group II (n=26)	46±9	184±20*/107±16*	63±8	280±18 /383±14
Group III (n=8)	48±9	218±14*/130±14*	71±6#	229±20*/350±15*

Values are mean±SD. # $p<0.05$ (vs normotensive controls); * $p<0.01$ (vs normotensive controls).
SBP, DBP=systolic, diastolic blood pressure; HR=heart rate; LVET, LVETI=left ventricular ejection time, left ventricular ejection time index; PEP=pre-ejection period; LVDd=left ventricular end-diastolic.

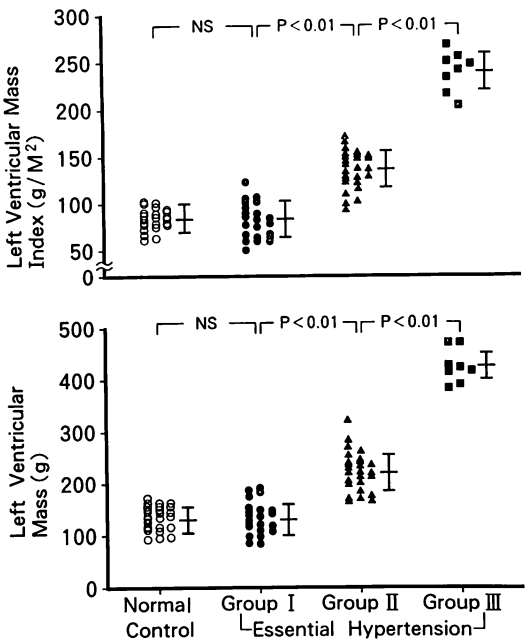

Fig. 1. Comparisons of left ventricular mass and left ventricular mass index in control and essential hypertension patient groups.

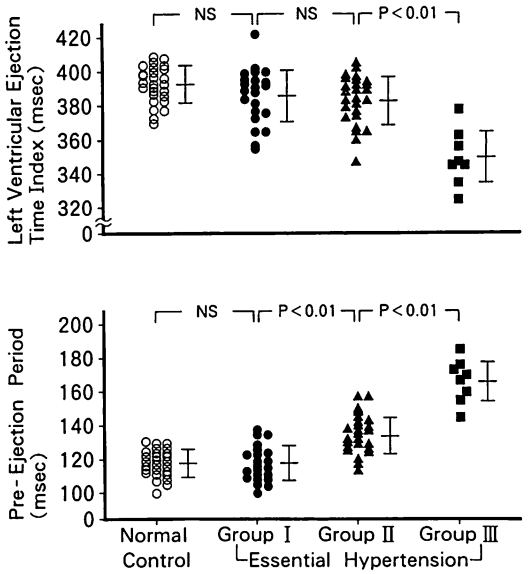

Fig. 2. Comparisons of left ventricular ejection time index and pre-ejection period in control and essential hypertension patient groups.

14 to 98±21 mmHg, respectively. Despite the significant decrease in blood pressures, no significant improvement in left end-diastolic and end-systolic dimensions and PEP was observed.

Fig. 5 shows the echocardiographic changes in a group III patient who was followed up for more than 9 years. At his first visit for assessment of exertion dyspnea, blood pressure was 248/128 mmHg and echocardiography showed marked dilatation and disturbed filling of the left ventricle (**Fig. 5A**). His blood pressure was controlled well, but marked dilatation of the left ventricle persisted (**Figs. 5B, C** and **D**). The LVM measured during admission decreased from about 400 to 300 g after antihypertensive therapy, but high values of LVM ranging between

cardiographic and echocardiographic analyses

PEP (msec)	LVDd (mm)	IVST (mm)	PWT (mm)	LVM (g)	LVMI (g/m²)
118±8	47.5±2.6	7.5±0.8	7.8±0.8	135.0±23.8	85.8±11.7
118±10	48.0±4.1	7.4±0.3	7.8±0.8	133.0±30.8	82.0±18.4
133±11*	47.3±4.0	10.3±1.4*	11.4±1.7*	222.3±38.0*	136.1±19.9*
166±12*	58.4±5.3*	11.9±2.0*	15.1±1.8*	422.0±30.3*	235.7±19.6*

dimension; IVST=interventricular septal thickness; PWT=left ventricular posterior wall thickness; LVM, LVMI=left ventricular mass, left ventricular mass index.

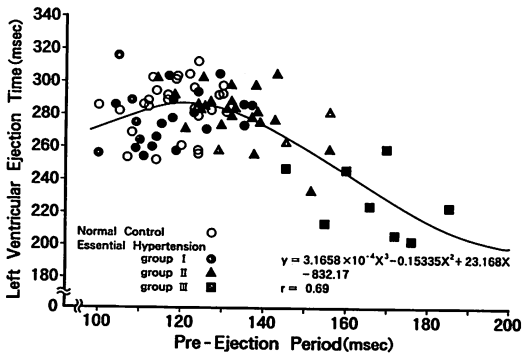

Fig. 3. Relationship between pre-ejection period and left ventricular ejection time in control and essential hypertension patient groups.

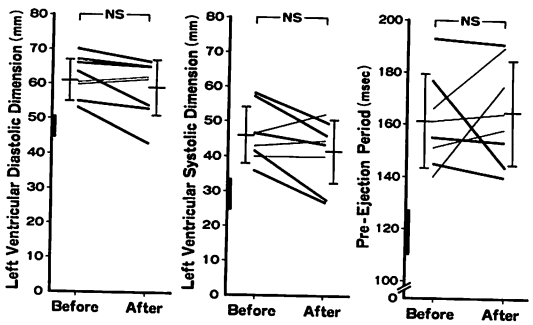

Fig. 4. Effect of antihypertensive therapy on left ventricular diastolic and systolic dimensions, and pre-ejection period in group III essential hypertensive patients.

Black bar in each column shows mean±SD in control group.

330 and 360 g persisted during the subsequent 9 years.

Fig. 6 shows the short axial thallium-201 myocardial scintigrams in a group II patient (**Fig. 6A**) and in a group III patient (**Fig. 6B**). The thallium-201 uptake was homogenous in the group II patient, but heterogenous in the group III patient.

Discussion

Our study shows that the critical indicators of myocardial mass marking the transition from the non-failing hypertrophied left ventricle to the failing left ventricle associated with essential hypertension are LVM of about 300 g and LVMI of 180 g/m². LVET, which reflects stroke volume, was markedly shortened after this point. In addition, depression of myocardial contractility was observed with the progression of myocardial hypertrophy. The study also showed that left ventricular dilatation and depressed myocardial contractility in essential hypertensives with a past history of congestive heart failure were not normalized by long-term antihypertensive therapy.

The progressive increase in left ventricular hypertrophy associated with chronic arterial hypertension ultimately results in congestive heart failure. Few reports have investigated the critical transition of heart weight from the non-failing hypertrophied left ventricle to the failing left

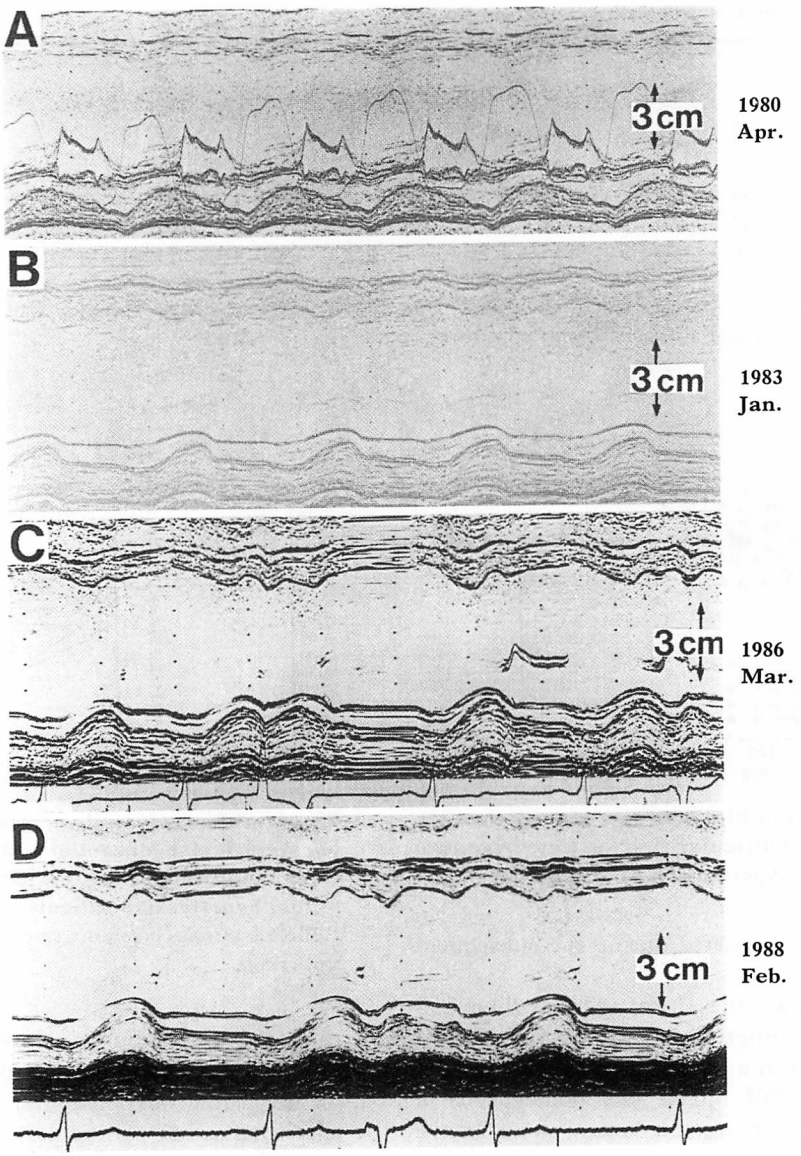

Fig. 5. Serial echocardiographic changes in a group III patient.

A is an echocardiogram recorded at his first visit for the treatment of exertion dyspnea. The blood pressure was 248/128 mmHg. B, C and D are echocardiograms recorded under well-controlled blood pressures.

ventricle. Linzbach found in autopsy cases that the critical weight of the left ventricle was approximately 200 g, which corresponded to a total cardiac weight of about 500 g[2]. Astorri et al in their autopsy study found that about 330 g for the left ventricle (or 250 g for the left ventricular free wall) was the critical weight[3]. The latter data are almost identical with the values in our

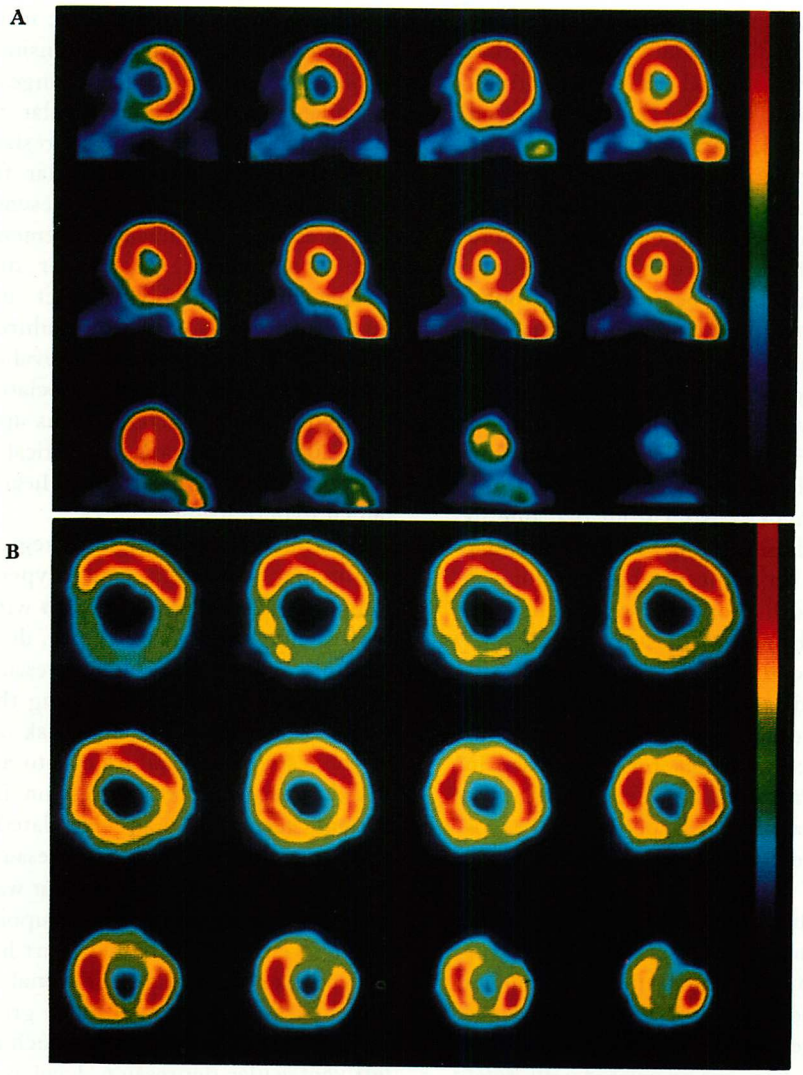

Fig. 6. Short axial thallium-201 myocardial scintigrams.
A: a group II patient, B: a group III patient.

study. Beyond this critical weight, cellular hyperplasia becomes evident with an increase in ventricular weight[2,3].

The intrinsic contractility of hypertrophied myocardium is still controversial. Hypertensive patients with left ventricular hypertrophy demonstrate cardiac function which is normal or above normal[10-17], so left ventricular hypertrophy appears to be a process of physiological adjustment, or an adaptation of the heart to physiologic stress. However, systolic and/or diastolic abnormalities in cardiac function associated with hypertension are also reported[18-21]. Several reasons for this discrepancy can be considered. A major reason is a difference in the severity of myocardial hypertrophy. In mild or borderline arterial hypertension, most hypertensive patients showed normal systolic function

and normal or moderately increased left ventricular contractility. Our data indicated that PEP in group I with normal LVM was normal, while PEP in groups II and III with increased LVM was prolonged. Variations in the indicators of left ventricular dysfunction or the phase of the cardiac cycle are also responsible. Systolic time intervals in hypertensive disease are a more sensitive indicator of left ventricular dysfunction in the presence of myocardial hypertrophy than echocardiographic measurements[20,21]. Ejection phase indicators are usually less sensitive for detecting left ventricular dysfunction due to arterial hypertension than indicators of isovolumic phase[22-25]. Finally it is very important to distinguish left ventricular hypertrophy due to essential hypertension from that due to hypertrophic cardiomyopathy. Left ventricular systolic function in hypertrophic cardiomyopathy is usually normal or super-normal despite the marked impairment of diastolic function[26]. Since PEP is a good index of myocardial contractility, our study showed that left ventricular hypertrophy associated with hypertension was almost always accompanied by a decrease in myocardial contractility. However, whether a decrease in contractility of hypertrophied myocyte occurs due to hypertension remains to be determined.

The exact mechanism causing the decrease in myocardial contractility in hypertensive patients with myocardial hypertrophy remains unknown. A reasonable hypothesis proposes an imbalance between the oxygen supply and the demand due to a variety of mechanisms associated with myocardial hypertrophy[27]. A marked limitation of the coronary reserve in hypertrophied left ventricle[28-30], increase in oxygen consumption associated with the increase in left ventricular mass[27], impairment of O_2-diffusion capacity due to an increase in the diffusion distance between capillary and myocardial cell[31], and reduction of protein synthesis and decrease in myosin-ATPase activity in the hypertrophied myocardium[32,33] may contribute to a decrease in myocardial contractility in hypertensive patients. In addition to these myocardial factors, reactive changes of the cardiac interstitium associated with sustained hypertension also appear to be related to the cardiac changes[34]. Increase in collagen volume, perivascular fibrosis, and medial thickening of coronary resistance vessels probably impair left ventricular function and oxygen availability. In the presence of severe and prolonged cardiac involvement associated with hypertension, ventricular and coronary mechanisms invariably interact and result in myocyte necrosis and heart failure. Thallium-201 SPECT is very useful to evaluate the condition of the left ventricle associated with arterial hypertension. Heterogenous uptake of thallium-201 may indicate the critical state or the end stage of the hypertrophied heart due to sustained hypertension.

Lack of regression or little regression of left ventricular dilatation and hypertrophy was found in essential hypertensives with a past history of congestive heart failure, despite the satisfactory reduction in blood pressure. This is a very serious problem, indicating that these patients are constantly at high risk of recurrence of congestive heart failure due to an increase in blood pressure. Poor regression in group III patients seems to be largely related to left ventricular dilatation. Blood pressure elevation leads to increased left ventricular wall stress, but the extent markedly depends upon the size of the left ventricle. A dilated heart has a high initial wall stress, and an additional equal rise in blood pressure leads to a much greater increase in wall stress. Consequently, much more marked left ventricular depression develops in a dilated heart than in a non-dilated hypertrophied heart. Likewise, at a comparable pressure load, myocardial oxygen consumption also increases much more markedly in a dilated heart than in a non-dilated heart. This indicates that normalization of left ventricular pressure overload must be achieved. However, maintenance of the cerebral and renal blood flows makes control of the blood pressure at a normal level in group III type essential hypertensive patients very difficult, and poses a great dilemma in the treatment of this hypertensive group. Early diagnosis

and treatment of essential hypertension are the best approach to effective prevention and management of the cardiac complications of hypertension.

要　約

高血圧性心不全を合併した高血圧症患者の収縮期心機能障害は長期の降圧療法により正常化するか?

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本研究の目的は，1) 高血圧に伴う心肥大が代償性から非代償性に至る限界時の左室心筋重量を推定すること，および 2) 心不全を合併した高血圧症患者の収縮期心機能障害が長期の降圧療法により正常化するか否かを明らかにすることである．M モード心エコー図法により左室心筋重量，左室心筋重量係数を，また頸動脈波，心音図，心電図の同時記録により左室駆出時間 (LVET)，および駆出前時間 (PEP) を 27 例の健常対照群と 56 例の本態性高血圧症患者で計測した．本態性高血圧症患者は心肥大を認めない 22 例 (I 群)，心肥大を有する 26 例 (II 群)，および心不全の既往を有する 8 例 (III 群) に分類した．

健常対照群，本態性高血圧症患者 I 群，II 群および III 群の左室心筋重量と左室心筋重量係数は，それぞれ 135.0±23.8 g と 85.8±11.7 g/m², 133.0±30.8 g と 82.0±18.4 g/m², 222.3±38.0 g と 136.1±19.9 g/m² および 422.0±30.3 g と 235.7±19.6 g/m² であった．II 群の左室心筋重量と左室心筋重量係数の上限 (mean+2SD) はそれぞれ約 300 g と 180 g/m² であった．PEP は左室心筋重量の増加とともに延長したが，LVET の短縮は III 群においてのみ認められた．III 群のみ健常対照群に比し有意の左室拡張末期径の増加を認めた．平均 16 ヵ月の降圧治療にかかわらず，III 群の左心機能障害は正常化しなかった．

これらの結果から，高血圧に伴う代償性心肥大から非代償性心肥大に至る限界の左室心筋重量は約 300 g，左室心筋重量係数で 180 g/m² と推定された．また，非代償状態に陥った高血圧性肥大心の収縮力の低下は著しく，長期の降圧療法でも左心機能は正常化せず左心機能障害は不可逆的と考えられた．

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