# Reversal Of Left Ventricular Hypertrophy In Asiatic Hypertensives With Lisinopril

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**Summary:**

**LVH is considered to be a significant risk factor for coronary artery disease and sudden death. Angiotensin converting enzyme (ACE) inhibitors have been demonstrated to be effective for the regression of LVH when used in antihypertensive doses. The aim of this study was to determine the effect of Lisinopril on regression of left ventricular hypertrophy (LVH) in asiatic patients with hypertension. Thirtyeight patients of essential hypertension with echocardiographically proven LVH (LVMI > 24 gm/m² in males and > 122 gm/m² in females) were studied to evaluate the changes in LV mass and function after the administration of ACE inhibitor Lisinopril. LV mass was calculated from Penn. convention measurement using cube formula of Devereux. Throughout the trial period, the mean arterial pressure was well controlled, at week 0 it was 128.33±5.81 mmHg, at week 12 it was 106.21±6.10 mmHg and at week 24 it was 107.26±3.61 mmHg. All patients showed regression of LV mass. LVMI at week 0 was 160.23±29.99 gm/m², at week 12 it was 139.99±29.36 gm/m² (P=0.0001) and at week 24 it was 132.52±30.02 gm/m² (P=0.0001). The mean ejection fraction increased by 4.40% (P=0.0001). In conclusion LVH in hypertensive patients can be reversed by Lisinopril and that too without deterioration of LV function.**

## Introduction

LVH is an independent risk factor for coronary artery disease and sudden death. It does not depend solely on the level of blood pressure but may also be mediated by neurohormonal factors[1] including the activity of the renin angiotensin system and the sympathetic nervous system[2]. Despite the fact that as hypertension develops the unit wall tension declines, LVH is of major prognostic significance i patients with essential hypertension. The possibl mechanisms of increased cardiovascular mortalit and morbidity associated with LVH are: decreased left ventricular filling, decreased coronary reserv and impaired myocardial oxygenation, increased incidence of ventricular arrhythmias and decreased myocardial contractility[3].

Several animal and clinical studies have dem onstrated that reduction in blood pressure is no always associated with reversal of LVH.

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Meta-analysis of 109 treatment studies for regression of LVH shows that ACE inhibitors, Beta blockers and calcium channel antagonists all reduce LVH and that the effect is more prominent with ACE inhibitors[4] and this is probably due to their antiproliferative, antiadrenergic and vagal stimulating effects[5]. In this study, the effect of an ACE inhibitor, Lisinopril was studied in patients with essential hypertension for regression in the left ventricular hypertrophy with 24 weeks treatment.

## Patients and Methods

### Method

250 patients, newly diagnosed or pre-treated with sustained essential hypertension were evaluated for left ventricular hypertrophy by echocardiography. Out of these 40 patients, 12 males and 28 females, who met the inclusion criteria were included in the study, 38 patients completed the study and out of these 2 patients were lost to follow-up.

### Study Protocol

The study design was open and it was conducted in 3 phases.

Fig. I

### Inclusion Criteria

Newly diagnosed or pre-treated, males and females between 18 years to 70 years having mild to moderate hypertension with left ventricular hypertrophy as demonstrated on echo with or without following associated conditions:

i. Cardiac decompensation NYHA Class I, II, III.

ii. Diabetics.

iii. Hypercholesterolemic.

iv. Hyperurecaemic.

v. Impaired renal function with creatinine clearance of > 30 ml/mm.

### Phase 1: Selection Phase

During this phase patients were evaluated for left ventricular hypertrophy echocardiographically and for inclusion and exclusion criteria mentioned below by clinical and laboratory parameters (Complete blood pressure and ESR, Urine detail report, serum sodium, serum creatinine, random blood sugar and serum cholesterol).

### Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are given in figure 1 and 2.

### Phase 2: Wash out Period (Week 3 to Week 0).

Pre-treated patients full filling the inclusion criteria underwent step-wise dose reduction of antihypertensive drugs which were completely stopped 4 days prior to starting Lisinopril (Novatec). At the end of washout period echocardiography was performed for left ventricular hypertrophy.

### Phase 3: Treatment Phase (Week 0 to Week 24)

Paitnets selected were started at day 1 of week 0 on Lisinopril 5mg to 10mg/day and the dose was adjusted so as to have the mean arterial pressure below 110 mmHg. Blood pressure, and physical examination was performed every 2 week. A 12 lead ECG, echocardiography and laboratory parameters mentioned above were performed at week 12 and week 24.

### Blood Pressure Measurement

Blood pressure was recorded in the seated position after 5 minutes of rest. At baseline a patient was classified as hypertensive if his diastolic blood pressure was > 90 mmHg. Blood pressure was measured at each visit, i.e. after every 2 weeks. Systolic blood pressure was recorded at phase-1 and diastolic blood pressure at phase-5. Mean arterial pressure was calculated as diastolic blood pressure plus one third of the difference between systolic and diastolic blood pressure.

Fig. II

**Exclusion Criteria**

1. Patient with diastolic pressure of 115 mmHg or more.
2. Patient with malignant or accelerated hypertension.
3. Secondary hypertension.
4. Pregnant or nursing mothers and women of potentially childbearing age who are not following a medically accepted method of contraception.
5. Any disease medication or other abnormal conditions which compromises the function of the GIT or liver that could result in altered absorption of Lisinopril significant hepatic impairment as indicated by ALT or bilirubin level of 20% above the normal laboratory range.
6. History of unstable angina or myocardial infarction during the last 3 months.
7. Patients with valvular heart disease.
8. Clinically significant abnormal values for any of the following laboratory tests; Hb, WBC, Platelet count, Serum K+ less than 3.2 mEq/L.
9. Patient receiving following drugs: Tricyclic antidepressants and MAO inhibitors, Lithium, Potassium-sparing diuretics and Nasal decongestants.

**Electrocardiography**

ECG was recorded at baseline and at week 12 and 24. ECG recordings were analyzed for the presence of LVH.

**Echocardiography**

M-Mode echocardiography was performed under 2D monitoring using ALOKA SSD 243 with sector scanner and a 3.5MHz transducer. The echocardiographic recordings were taken at 25 mm/sec. Left ventricular dimensions and interventricular septal and posterior wall thickness were taken at the tip of the mitral valve, an average of 3 readings were taken and all measurements were made by 2 blinded observers.

Left ventricular dimensions and posterior wall thickness were measured according to the recommendations of American Society of Echocardiography. However for the left ventricular mass the left ventricular dimensions were measured according to Penn. Convention. Left Ventricular Fractional shortening was calculated as EDD-ESD/EDD. (EDD=End Diastolic Diameter, ESD=End Systolic Diameter). Left ventricular mass was calculated by Devereux formula as:

$$LVM=1.04\ ([LLVID_P+PWT_P+IVST_P]^3 - [LVID_P]^3) - 13.6g.$$

**Statistical Analysis**

Statistical significance of difference between various measurements at week 0, 12 and 24 was compared by software package SP SS-5 utilizing students 2 tailed "t" test for p-value.

**Results**

A total of 38 patients completed this study 10 (26.3%) were male and 28 (73.7%) were female patients. The mean age of these patients was 49.70 years (Table-1).

**TABLE 1**

**Number and Age of Patients**

| | No. | Mean Age | Std Dev. |
|---|---|---|---|
| Male | 10 (26.3%) | 48.30 | 5.56 |
| Female | 28 (73.7%) | 50.21 | 5.03 |
| Total | 38 | 49.70 | 5.10 |

Systolic, diastolic and mean arterial pressures at week 0, 12 and 24 are given in table 2. The mean arterial pressure at week 0 was 128.33±5.81 mmHg, while at week 12 and 24 it was well controlled, i.e. 106.21±6.10 and 107.26±3.61 mmHg respectively.

TABLE 2

| | Systolic mmHg | Diastolic mmHg | Map. mmHg |
|---|---|---|---|
| Week 0 | 164.34±16.31 | 109.21±4.07 | 128.33±5.81 |
| Week 12 | 144.47±14.81 | 88.68±4.09 | 106.21±6.10 |
| Week 24 | 142.63±9.09 | 88.95±3.07 | 107.26±3.61 |

Echocardiographic measurements at week 0 and 12 given in table 3 shows a significant reduction in the thickness of interventricular septum (IVS) and left ventricular posterior wall (LVPW) at week 12 (P=0.0001). The left ventricular internal dimensions, ejection fraction (EF) and fractional shortening (FS) did not show any significant change. The LV mass was 259.02±47.27 grams at week 0 and 226.27±46.11 grams at week 12 , showing a mean reduction of 32.75 (12.64%) grams. This reduction is significant statistically (P=0.0001). Similarly LV mass index also regressed significantly, i.e. by 20.24 gm/m² (from 160.23±29.99 gm/m² to 139.99±29.36 gm/m²) (P=0.0001).

While analysis of echocardiographic measurements between week 12 and 24 (table 4) shows a further decrease in the thickness of IVS and LVPW, but the LV dimensions did not change significantly. However LV function improved significantly showing an increase in ejection fraction by 5.23% (P=0.0001) and fractional shortening by 3.87% (P=0.002). The LV mass and LV mass index also showed further reduction during this period, i.e. 11.39 gm/m² and 7.47 gm/m² respectively. However this regression was less marked as compared to that observed during the first 12 weeks of study.

Table-5 shows the overall change in echocardiographic measurements of these patients, i.e. between week 0 and week 24. The overall decrease in thickness of IVS and LVPW was 0.17cm and 0.16 cm respectively, while there was no significant change in LV dimensions. LV mass index reduced by 44.14 (17.04%) grams during this period (P=0.0001) and LV mass index reduced by 27.71 gm/m² (17.29%) (P=0.0001). The ejection fraction increased by 4.40% (7.35%) (P=0.0001) and fractional shortening by 3.33% (7.31%) (P=0.022).

### Labs Parameters

CBC and ESR, urine routine examination urea, creatinine, serum electrolytes, random blood glucose and serum cholesterol were done at week 0, 12 and 24 and there was no change in their values between these weeks.

### Discussion

Left ventricular hypertrophy (LVH) is a structured adaptation of the heart to sustained hypertension severing to normalize the increased wall stress. Recent clinical studies have indicated that LVH is a powerful independent risk factor cardiovascular morbidity and mortality[7,8] particular for acute myocardial infarction, cardiac failure, arrhythmias and sudden death[9]. Ghali JK et al having shown the relative risk of death from any cause in patients with LVH compared with patients without LVH was 2.14 times more among those with coronary artery disease and 4.14 among those without coronary artery disease. They concluded that LVH is an important prognostic marker in patients with or without coronary artery disease[10]. Pringle SD et al have reported that symptomatic and silent myocardial ischemia is common in hypertensive patients with LVH, even in the absence of epicardial coronary artery disease[11]. Echocardiographically determined left ventricular mass is actually considered to be the most powerful risk indicator for cardiovascular disease and yields prognostic information beyond that provided by other cardiovascular risk factors.

Initial hemodynamic benefits of left ventricular hypertrophy are increased ventricular working capacity, normalization of systolic wall stress and maintenance of stroke volume, however, with chronic dilation the beneficial effects reaches a pleatue, coronary reserve declines, myocardial contractility is reduced and stroke volume decreases.

Pathologically there is hypertrophy of the cardiac muscles along with interstitial fibrosis which is due to synthesis and degradation of collagen by

TABLE 3

Echocardiographic Measurement at Week 0 and Week 12 (cm)±SD

| | Week 0 | Week 12 | Difference (%) | P. Value |
|---|---|---|---|---|
| IVS | 1.43±0.18 | 1.32±0.16 | 0.11% | 0.0001 |
| LVPW | 1.31±0.14 | 1.21±0.13 | 0.10% | 0.0001 |
| LVIDS | 3.24±0.45 | 3.25±0.45 | -0.01% | 0.737 |
| LVIDD | 4.43±0.45 | 4.40±0.51 | 0.03% | 0.276 |
| LVM* | 259.02±49.27 | 226.27±46.11 | 32.75% | 0.0001 |
| LVIM** | 160.23±29.99 | 139.99±29.36 | 20.24% | 0.0001 |
| EF | 59.87±10.66 | 59.04±8.44 | 0.83% | 0.387 |
| FF | 45.58±9.53 | 45.04±7.56 | 0.54% | 0.558 |

*Value in gram
**gram/meter sq.

interstitial fibrosis. It is suggested that chronic elevation of circulating aldosterone is associated with myocardial fibrosis. The combined involvement of myocyte, interstitium and intramyocardial vasculature leads to increased risk of ischemic heart disease, congestive cardiac failure and sudden death in patients with left ventricular hypertrophy.

Meta analysis of 109 treatment studies showed that ACE inhibitors, B-Blockers and Ca antagonists all reduces left ventricular mass by reversing wall hypertrophy and that the effect is most prominent with ACE Inhibitors[4]. In addition to the well known antihypertensive effect of ACE Inhibition the discovery of new properties such as antiproliferative effects, antiadrenergic effect and vagal stimulating effects have contributed to the usefulness of this class of agents in the prevention and treatment of Cardiovascular disease.

We conducted this open study to analyze the effects of Lisinopril (Novatec) on regression of LVH in Asians. Our results show a significant reduction in left ventricular mass and left ventricular mass Index with 24 weeks treatment of Lisin-

TABLE 4

Echocardiographic Measurement at Week 12 and Week 24 (cm)±SD

| | Week 12 | Week 24 | Difference (%) | P. Value |
|---|---|---|---|---|
| IVS | 1.32±0.16 | 1.26±0.15 | 0.06% | 0.0001 |
| LVPW | 1.21±0.13 | 1.15±0.16 | 0.05% | 0.001 |
| LVIDS | 3.25±0.45 | 3.18±0.40 | 0.07% | 0.088 |
| LVIDD | 4.40±0.51 | 4.47±0.45 | 0.04% | 0.064 |
| LVM* | 226.27±46.11 | 214.88±47.63 | 11.39% | 0.031 |
| LVIM** | 139.99±29.36 | 132.52±30.02 | 7.47% | 0.029 |
| EF | 59.04±8.44 | 64.27±6.37 | -5.23% | 0.0001 |
| FF | 45.04±7.56 | 48.91±7.50 | -3.87% | 0.002 |

*Value in gram
**gram/meter sq.

**TABLE 5**

**Echocardiographic Measurement at Week 0 and Week 24 (cm)±SD**

| | Week 0 | Week 24 | Difference (%) | P. Value |
|---|---|---|---|---|
| IVS | 1.43±0.18 | 1.26±0.15 | 0.17% | 0.0001 |
| LVPW | 1.31±0.14 | 1.15±0.16 | 0.16% | 0.0001 |
| LVIDS | 3.24±0.45 | 3.18±0.40 | 0.06% | 0.181 |
| LVIDD | 4.43±0.45 | 4.47±0.45 | -0.04% | 0.347 |
| LVM* | 259.02±49.27 | 214.88±47.63 | 44.14% | 0.0001 |
| LVIM** | 160.23±29.99 | 132.52±30.02 | 27.71% | 0.0001 |
| EF | 59.87±10.66 | 64.27±6.37 | 4.40% | 0.0001 |
| FS | 45.58±9.53 | 48.91±7.50 | 3.33% | 0.022 |

*Value in gram
**gram/meter sq.

opril, however the reduction in LVMI is more prominent during the first 12 weeks, i.e. from 160 gm/m² at week 0 to 139 gm/m² at week 12 (12.6%), this may be due to the fact that the reduction of Mean Arterial Pressure was more during this period (Table 2), i.e., from 128 to 106 mmHg. While the reduction in LVMI between 12 to 24 weeks though is statistically significant is not very much, i.e. LVMI has reduced from 139 gm/m² at 12 week to 132 gm/m² (5.34%) at week 24, this may be due to the reason that the MAP remained almost constant between week 12 and week 24, i.e. 106 mmHg and 107 mmHg respectively.

This study also shows that left ventricular function was improved significantly during the study period. Ejection fraction and fractional shortening show an overall improvement of 4.40% (P=0.0001) and 3.33% (P=0.022) respectively. Other investigators have shown that Left ventricular function was maintained or was improved with LV mass regression[12-14]. This improvement was seen during the last 12 weeks of study where the regression in LV mass was less marked, giving an impression that Lisinopril initially helps in regression of LV mass and then improves the left ventricular function. However, other studies are required to prove this hypothesis.

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