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Study of Regression of Left Ventricular Hypertrophy with Angiotensin Converting Enzyme Inhibitors in Patients of Hypertension

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ABSTRACT
Hypertension is a leading cause of morbidity and mortality globally, often associated with cardiovascular diseases (CVDs). Left ventricular hypertrophy (LVH) is a preclinical cardiac condition linked to hypertension. This study aimed to assess the effects of Enalapril, an ACE inhibitor, on left ventricular parameters and other related factors in hypertensive patients. The study included patients with hypertension and LVH, measuring various cardiovascular parameters before and after Enalapril treatment. Parameters assessed included left ventricular mass (LVM), left ventricular internal diameter (LVID), posterior wall thickness (PWT) and interventricular septal thickness (IVST). Additionally, age and gender distributions of hypertensive patients were analyzed. Enalapril treatment led to a significant reduction in LVM, PWT, IVST, systolic blood pressure and diastolic blood pressure. The study also found that hypertension was more prevalent in males and increased with age. ECG criteria for LVH demonstrated lower sensitivity compared to 2D echocardiography. Enalapril treatment resulted in favorable changes in left ventricular parameters and blood pressure, highlighting its effectiveness in managing hypertension and associated cardiac conditions. The study emphasizes the importance of ACE inhibitors in controlling hypertension and preventing cardiovascular complications.

INTRODUCTION

Left ventricular hypertrophy (LVH) is a major risk factor for cardiovascular events in hypertensive individuals, posing a higher risk for stroke, heart failure, coronary artery disease and sudden cardiac death. Epidemiological studies indicate LVH's strong association with severe cardiovascular events, marking it as a more significant risk factor than traditional cardiovascular risk factors, regardless of age, gender, or other risks[1]. Mitigating LVH is crucial for maintaining cardiac function and improving survival. Age is a key risk factor in LVH development and although LVH is linked to increased cardiovascular risk, it's often not considered a standard risk factor, possibly due to its perception as a subclinical condition[2].

LVH results from myocardial remodeling triggered by mechanical and neurohormonal activation, involving catecholamines, angiotensin II and endothelins. Genes related to left ventricle structure and those involved in cell signal transduction, hormonal regulation, growth factors, calcium balance, and blood pressure regulation contribute to LVH development[3]. Animal and human studies show that antihypertensive therapy can regress LVH, which in turn reduces cardiovascular risk. Timely detection of LVH is essential for accurate cardiovascular risk assessment, with electrocardiography (ECG) being a valuable, affordable, and widely available tool for LVH detection[4].

The primary methods for detecting LVH are ECG and 2D echocardiography. LVH, as an independent predictor of cardiovascular events, can be identified through ECG, which also provides insights into ventricular overload, ischemia, conduction abnormalities and arrhythmias. Among antihypertensive drugs, diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are most effective in reducing LVH[5]. Beta blockers are less effective compared to ACE inhibitors, possibly due to less afterload reduction[6]. ACE inhibitors reduce myocardial cytokines, growth factors, collagen formation, myocyte growth, and enhance nitric oxide release, reducing morbidity, ischemic events and mortality in heart failure patients, including those with hypertension. Enalapril, an ACE inhibitor, effectively targets angiotensin II, derived from angiotensin I and is a potent antihypertensive agent for both renovascular and essential hypertension[7]. It reduces arterial pressure by lowering total peripheral resistance without causing reflex cardiac effects and facilitates the regression of LVH in hypertensive individuals. The present study is a prospective interventional investigation conducted over six months with 60 patients to study regression of left ventricular hypertrophy with Angiotensin converting enzyme inhibitors in patients of hypertension.

MATERIALS AND METHODS

The present prospective interventional study was conducted over 18 months, from December 2016 to May 2018 at Malla Reddy Institute of Medical Sciences. The study included 60 hypertensive patients who were attending the outpatient department. Ethical approval was obtained from the Ethical and Scientific Committee of MRIMS, Hyderabad. Patients were duly informed about the drug's adverse effects and their rights.

Inclusion Criteria:

- Patients diagnosed with essential hypertension
- Hypertensive patients who have left ventricular hypertrophy

Exclusion Criteria:

- Hypertensive patients without left ventricular hypertrophy
- Individuals with congestive heart failure
- Patients with valvular heart disease
- Cases of cardiomyopathy
- Patients already on antihypertensive medication other than Angiotensin-converting enzyme inhibitors
- Hypertension due to secondary causes

Intervention: The intervention involved administering Enalapril (10 mg Tablet) once daily for six months. ECG and 2D Echocardiography were conducted before and after the 6-month period for each patient. The 2D Echocardiography was performed using a Philips Affinity 50 model machine, with the same machine used for follow-up to eliminate objective bias.

Data Collection: Patient consent was obtained. Selection was based on the inclusion and exclusion criteria. Data was gathered through patient history, clinical examination and relevant investigations. The 60 patients received Enalapril (10 mg Tablet) daily for six months. They were informed about potential drug side effects and encouraged to report any issues. Regular follow-ups ensured compliance.

Statistical Analysis: Data analysis was performed using the SPSS software package, incorporating frequency, percentage, mean, median, standard deviation and T-test.

RESULTS

The study's age distribution, detailed in Table 1, shows the majority of participants (40%) were in the 41-50 years age group. The mean age of subjects was 56.50 years, with a median of 58.00 years and a mode of 48.00 years. The age range spanned from 39-80

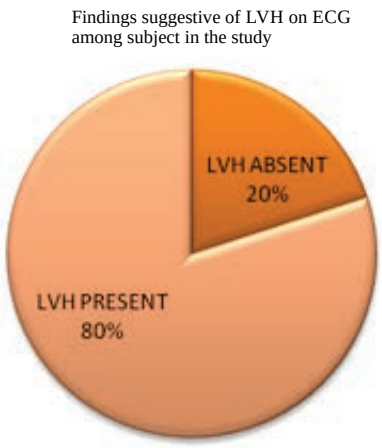

Fig. 1: Findings suggestive of lvh on ecg among subjects in the study

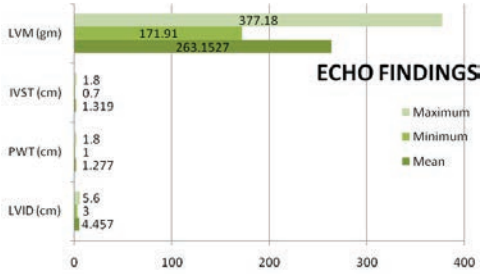

Fig. 2: Findings On Echo Among Subjects In The Study Before Intervention

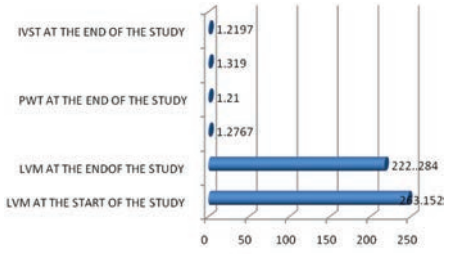

Fig. 3: Findings On Echo At The Start And End Of The Study

years, with the least represented group being those under 40 years (3.33%). The standard deviation of 10.91 years indicates a broad spread of ages among participants (Fig 2).

The findings from the study regarding Left Ventricular Hypertrophy (LVH) as detected by electrocardiogram (ECG) among participants are as follows out of the 60 subjects, LVH was absent in 12 cases (20%) and present in 48 cases (80%).

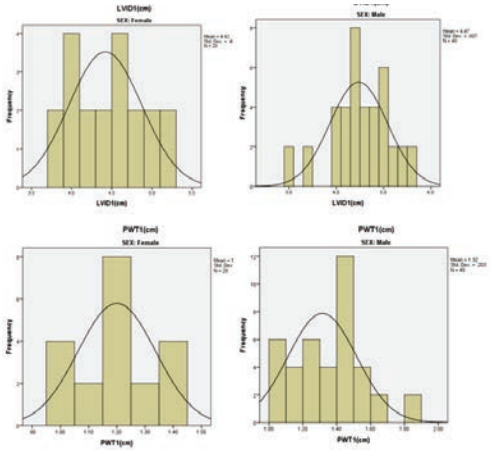

Fig. 4: Left Ventricular Internal Diameter And Posterior Wall Thickness At The Initiation Of The Study

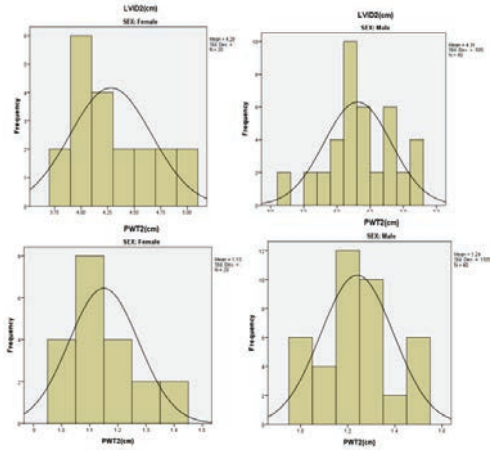

Fig. 5: Left Ventricular Internal Diameter and Posterior Wall Thickness at the End of the Study

This indicates a high prevalence of LVH among the study's hypertensive patients, with the majority exhibiting evidence of LVH on their ECG readings. Fig.1 and 2 shows before intervention, echocardiographic findings in the study showed the following average values Left Ventricular Internal Diameter (LVID) was 4.457 cm, Posterior Wall Thickness (PWT) 1.2767 cm, Interventricular Septal Thickness (IVST) 1.319 cm and Left Ventricular Mass (LVM) 263.1527 grams. The median and mode values for these measurements were slightly varied, with a standard deviation indicating a moderate range of variability among subjects. The minimum and maximum values ranged from 3 cm to 5.6 cm for LVID, 1 cm to 1.8 cm for PWT, 0.7 cm to 1.8 cm for IVST and 171.91 grams to 377.18 grams for LVM. After the intervention, echocardiographic findings showed a reduction in cardiac dimensions and mass among subjects. The

Table 1: Demographical distribution of the subjects

Age	Frequency	Percentage
<40 years	2 cases	3.33
41-50 years	24 cases	40.00
51-60 years	10 cases	16.67
61-70 years	18 cases	30.00
71-80 years	6 cases	10.00
Gender		
Female	20	33.3
Male	40	66.7
Total	60	100

Table 2: Findings on echo among the subjects in the study after intervention

Echo findings	LVID 2(cm)	PWT2 (cm)	IVST2 (cm)	LVM2 (gm)
Mean	4.3 (cm)	1.21 (cm)	1.2196 (cm)	222.884 (gm)
Median	4.2 (cm)	1.2 (cm)	1.2(cm)	213.375 (gm)
Mode	4 (cm)	1.2 (cm)	1.3 (cm)	200.33 (gm)
Std. Deviation	0.4610 (cm)	0.1504 (cm)	0.166 (cm)	49.357 (gm)
Minimum	3 .2 (cm)	1 (cm)	0.7 (cm)	144.48 (gm)
Maximum	5.2 (cm)	1.5 (cm)	1.6(cm)	333.7 (gm)

Table 3: Interventricular septal thickness and left ventricular mass at the initiation of the study

Interventricular septal wall thickness	Male	Female
Mean	1.3635	1.2300
Median	1.4000	1.2000
Std. deviation	0.22761	0.11286
Minimum	0.70	1.10
Maximum	1.80	1.40
Left ventricular mass	Male	Female
Mean	276.9985	235.4610
Median	280.9650	211.5300
Std. deviation	69.13248	65.19228
Minimum	171.91	172.57
Maximum	377.18	349.93

Table 4: Interventricular septal thickness and left ventricular mass at the end of the study (LVM2)

Interventricular septal thickness	Male	Female
Mean	1.2550	1.1490
Median	1.3000	1.1000
Std. Deviation	0.17679	0.12401
Minimum	0.70	1.00
Maximum	1.60	1.40
Left Ventricular Mass	Male	Female
Mean	232.1330	204.3870
Median	230.8000	191.1550
Std. Deviation	46.41874	52.19424
Minimum	144.92	144.48
Maximum	333.70	310.13

Table 5: Comparison of left ventricular mass, posterior wall thickness, and interventricular septal thickness at the beginning and the end of the study after the use of enalapril.

Group	LVM at the start of the study	LVM at the end of the study	
Mean	263.1527	222.402	p-value equals 0.0372
SD	70.12678	49.357	t = 2.1194
SEM	14.1405	6.327	df = 78
	PWT at the beginning of the study	PWT at the end of the study	
Mean	1.2767	1.21	p-value equals 0.0354
SD	0.1904	0.1504	t = 2.1284
SEM	0.0246	0.0194	df = 118
Standard error of difference = 0.031			
	IVST at the beginning of the study	IVST at the end of the study	
Mean	1.319	1.2197	p-value equals 0.0045
SD	0.2059	0.1678	t = 2.8973
SEM	0.0266	0.0217	df = 118

Standard error of difference = 0.034

average Left Ventricular Internal Diameter (LVID) decreased to 4.3 cm, Posterior Wall Thickness (PWT) to 1.21 cm, Interventricular Septal Thickness (IVST) to 1.2196 cm and Left Ventricular Mass (LVM) to 222.884 grams. Median values echoed this reduction trend. The mode values indicated 4 cm for LVID, 1.2 cm for both PWT and IVST and 200.33 grams for LVM. The standard deviation was lower post-intervention, signifying less variability. The minimum and maximum values ranged from 3.2 cm to 5.2 cm for LVID, 1 cm to 1.5 cm for PWT, 0.7 cm to 1.6 cm for IVST and 144.48 grams to 333.7 grams for LVM, indicating an overall decrease in cardiac measurements (Fig. 3 and 4).

The study demonstrated a decrease in key cardiac measurements from the beginning to the end of the study period. The Left Ventricular Mass (LVM), initially

measured at 263.152 grams at the start of the study, decreased to 222.284 grams by the end of the study. Similarly, there was a reduction in the Posterior Wall Thickness (PWT) from 1.2767 cm at the beginning to 1.21 cm at the end. Interventricular Septal Thickness (IVST) also showed a decline, starting at 1.319 cm and reducing to 1.2197 cm by the study's conclusion. These changes indicate a positive effect of the intervention on cardiac structure, specifically in reducing left ventricular hypertrophy (Fig 5).

At the initiation of the study, Left Ventricular Internal Diameter (LVID1) measurements showed males had a higher average LVID1 (4.475 cm) compared to females (4.420 cm), with both genders having a median of 4.450 cm. Males displayed greater variability in LVID1, with a standard deviation of 0.6067 cm versus 0.4538 cm in females, and a wider range from 3.0 cm to 5.6 cm, compared to 3.8 cm to 5.1 cm in females.

At the study's beginning, Interventricular Septal Wall Thickness was higher in males (mean: 1.3635 cm) than in females (mean: 1.2300 cm), with males also showing greater variability (standard deviation 0.22761 cm vs. 0.11286 cm in females). The range for males was 0.70 cm to 1.80 cm, while for females, it was 1.10 cm to 1.40 cm. Regarding Left Ventricular Mass, males had a higher mean (276.9985 grams) compared to females (235.4610 grams), with males again exhibiting greater variability (standard deviation: 69.13248 grams vs. 65.19228 grams in females). The range for males was 171.91 grams to 377.18 grams, and for females, it was 172.57 grams to 349.93 grams (Tables 1-5).

At the end of the study, Left Ventricular Internal Diameter (LVID1) measurements were slightly higher in males (mean: 4.310 cm) than in females (mean: 4.280 cm), with medians of 4.250 cm for males and 4.150 cm for females. Variability was observed, with a standard deviation of 0.5053 cm for males and 0.3833 cm for females. Measurement ranges were 3.2 cm to 5.2 cm for males and 3.8 cm to 5.0 cm for females. Similarly, Left Ventricular Posterior Wall Thickness (PWT) measurements indicated higher values in males (mean: 1.240 cm) compared to females (mean: 1.150 cm) at the end of the study, with medians of 1.200 cm for males and 1.100 cm for females. Variability was present, with a standard deviation of 0.1549 cm for males and 0.1235 cm for females. Measurement ranges were 1.0 cm to 1.5 cm for males and 1.0 cm to 1.4 cm for females.

At the end of the study, Interventricular Septal Thickness: Males had a mean of 1.2550 cm with a range from 0.70 cm to 1.60 cm. Females had a mean of 1.1490 cm with a range from 1.00 cm to 1.40 cm. Left Ventricular Mass: Males had a higher mean Left Ventricular Mass (LVM2) of 232.1330 grams with a range from 144.92 grams to 333.70 grams. Females had a mean of 204.3870 grams with a range from 144.48 grams to 310.13 grams. Both groups displayed variability in these measurements.

The study conducted a comparative analysis of cardiac parameters before and after the use of Enalapril. The results revealed significant improvements in various aspects of cardiac health. Firstly, Left Ventricular Mass (LVM) showed a notable reduction, with the mean LVM decreasing from 263.1527 to 222.402. This reduction was statistically significant, as indicated by a p-value of 0.0372. Similarly, Posterior Wall Thickness (PWT) exhibited positive changes. The mean PWT decreased from 1.2767 to 1.21, with a significant p-value of 0.0354. Furthermore, Interventricular Septal Thickness (IVST) also demonstrated substantial improvement. The mean IVST decreased from 1.319-1.2197, with a highly significant p-value of 0.0045.

DISCUSSIONS

Hypertension is a prevalent condition in India and worldwide, contributing significantly to morbidity and mortality. Cardiovascular disease (CVD) accounts for a substantial portion of global deaths, with around 30% attributed to CVD annually. Approximately half of these CVD-related deaths are linked to hypertension, a condition strongly associated with overall cardiovascular risk. Prolonged hypertension can lead to left ventricular hypertrophy (LVH), a preclinical cardiac condition that may eventually result in life-threatening complications[1].

LVH is a strong predictor of major cardiovascular events, with its echocardiographic prevalence varying from 20% to over 70% based on criteria and study populations. Detecting LVH through physical examination alone can be challenging. While electrocardiograms (ECG) using voltage criteria and QRS duration can identify LVH with high specificity, they lack sensitivity. In contrast, echocardiography, being eight times more sensitive, is the reference method for LVH detection[8]. Left ventricular mass (LVM) or left ventricular mass index (LVMI) is used to define LVH, with an LVMI greater than 125 g m^{-2} indicating LVH.

Research, including the Framingham Heart Study, demonstrates that LVH is reversible and responsive to blood pressure reduction through antihypertensive therapy. Increased usage of ACE inhibitors, which inhibit the angiotensin-converting enzyme (ACE), has contributed to a decline in high blood pressure prevalence and a concurrent reduction in LVH and cardiovascular disease mortality[9]. ACE inhibitors play a crucial role in managing comorbid conditions associated with hypertension, such as diabetes, and in alleviating LVH, retinopathy and nephropathy due to hypertension. However, sporadic cases of

life-threatening hyperkalemia in patients with normal renal function on ACE inhibitors have been reported. In terms of age distribution, hypertension is prevalent among individuals aged 40-50 years, followed by those aged 61-70 years. These findings align with studies by several studies[10], which also reported higher hypertension prevalence in older age groups.

Regarding gender distribution, the majority of hypertension cases in the study were males, consistent with findings from earlier studies[11,12]. However, gender-based differences in hypertension prevalence may result from factors like physical activity and undiagnosed heart disease in men. ECG changes showed that 80% of patients had LVH indications, while 2D echocardiography had higher specificity for detecting LVH compared to ECG. This aligns with the conclusion that ECG is specific but less sensitive for detecting LVH, with echocardiography being the preferred method[13].

The study observed that systolic blood pressure decreased from an initial mean of 159.33 mm Hg, with similar trends seen in studies by Pitt *et al*.[14]. Diastolic blood pressure also decreased from an initial mean of 99.0 mm Hg, consistent with findings in other studies. The left ventricular mass (LVM) mean was higher in males than females, a gender difference that remains constant during adulthood. Several studies reported similar trends in LVM reduction with ACE inhibitors[3].

Left ventricular internal diameter (LVID) showed a mean reduction from 4.457 cm to 4.3 cm after Enalapril treatment. Posterior wall thickness (PWT) reduced significantly from 1.277 cm to 1.21 cm after Enalapril treatment, aligning with observations in Batlouni *et al*.[15] study Interventricular septal thickness (IVST) also decreased significantly from 1.319 cm to 1.21 cm after Enalapril treatment, consistent with findings in Cuocolo study.

In summary, the study highlights the positive effects of Enalapril in reducing left ventricular mass, posterior wall thickness and interventricular septal thickness, leading to improved cardiac health in hypertensive patients. These findings are consistent with previous research and emphasize the importance of ACE inhibitors in managing hypertension and associated cardiovascular conditions.

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