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ΠΡΩΤΟΤΥΠΗ ΕΡΓΑΣΙΑ

Left ventricular geometry and function in hypertensive patients with left ventricular hypertrophy and mild valvular insufficiency (The LIFE Study)

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ABSTRACT

Background: Mild to moderate aortic and mitral regurgitation are frequently detected on routine echocardiograms in asymptomatic patients with hypertension but their prevalence and impact on LV geometry and function is unknown. **Purpose:** To assess the prevalence and impact of mild to moderate mitral and/or aortic insufficiency on left ventricular structure and function in patients with hypertension and left ventricular hypertrophy. **Methods and Results:** Patients with stage I-III hypertension and electrocardiographic evidence of left ventricular hypertrophy enrolled in the Losartan Intervention For Endpoint reduction (LIFE) study were evaluated. Of the 9,193 patients enrolled in LIFE, 960 participated in the echo substudy. As part of the baseline evaluation these patients underwent 2-dimensional, M-mode and Doppler echocardiography. Mitral or aortic insufficiency measures of left ventricular structure and function were assessed using standardized techniques. Of 939 patients with appropriate LV measurements and Doppler data for inclusion in the present analysis, 646 had no mitral or aortic regurgitation. A total of 242 patients had mild (1+) valvular regurgitation, including 146 with 1+ MR alone, 53 with 1+ AR alone and 45 with mild regurgitation of both valves. Fifty-one patients had moderate (2+ or 3+) valvular regurgitation, including 12 with moderate MR alone, 17 with moderate AR alone and 22 with moderate regurgitation of both valves. Compared to patients with no valvular insufficiency, those with mild or moderate insufficiency had larger left ventricular end diastolic diameter (5.25 vs 5.33 and 5.59 cm; p<.05 and 0.01 respectively),and higher left ventricular mass (232 vs 235 and 248 gr, P=NS and<.001). In analyses that adjusted for gender, patients with mild mitral and/or aortic regurgitation had larger LV internal dimensions (5.25 vs 5.33 cm, p<.05), higher LV mass indexed for either body surface area (122 vs 125 gr/m2, p<.05 or height$^{2.7}$ (55.4 vs 57.3, p<.05) and larger left atrial diameters. In similar analyses, patients with moderate regurgitation of one or both valves had larger LV chambers (5.25 vs 5.9 cm, p<.001), greater mean LV mass in absolute terms (232 vs 248 gr, p<.001), as well as after indexation for body surface area or height$^{2.7}$ and higher Doppler stroke volume. The patients with moderate valvular regurgitation also had a higher prevalence of LV hypertrophy, due to an increased prevalence of eccentric LV hypertrophy. There was no difference among groups defined by the presence and severity of valvular regurgitation in cardiac output, total peripheral resistance or pulse pressure/stroke volume, indicating that the observed inter-group differences in LV geometry

were not due to differences in the hemodynamic severity of hypertension. Patients with moderate valvular regurgitations had significantly higher circumferential end-systolic wall stress (CESS), a measure of myocardial afterload, and lower CESS/ESVI, a measure of LV chamber contractility when compared to patients without valvular regurgitation. Conclusions: This data indicates that hypertensive patients with mild to moderate mitral or aortic valvular insufficiency have significant structural and functional changes of the left ventricle that may affect prognosis.

INTRODUCTION

Left ventricular hypertrophy (LVH) is an adaptive processes that helps maintain cardiac performance in the setting of increased afterload; Although this process initially is beneficial, and desirable at more advanced stages LVH becomes detrimental and leads to increased ratesisk fofr cardiovascular eventscomplications. Thus, established LVH is known to be an independent predictor of stroke, myocardial infarction, other vascular complications, cardiac arrhhythmia, sudden death and heart failure[1-3].

Mild to moderate aortic and mitral regurgitationinsufficiency are frequently detectedseen on routine echocardiogramsphy in asymptomatic hypertensive patients, with hypertension and/or LVH although their prevalences have is not been determinedknown. Studies in population-based samples of predominately normotensive adults have shown associations of mild-to-moderate mitral and aortic regurgitation with greater LV chamber size and mass[4-6]. HoweverFurthermo, re the impact ofit is not clear whether these mild to moderate valvular regurgitationleaks on LV geometry and function in hypertensive patients is unknownimpose additional hemodynamic burden on the left ventricle (LV).

Both mitral and aortic regurgitation can be the result of the process of geometric adaptation due to moderate/severe hypertension. Progressive valvular ibsufficiency can lead to volume expansion and structural changes of the LV eventually leading to decompensation. The process of LV remodeling in response to pressure overload affects both the structure and function of the valve apparatus. In the case of secondary MR, an increase in LV mass and volume leads to an increase in the size of the annulus, annular contraction during systole decreases, LA size increases, and malalignment of the papillary muscles develop, preventing effective leaflet coaptation in systole[3]. MR imposes a hemodynamic load on the LV leading to progressive eccentric hypertrophy and dilatation.

Controlled studies have identified an association between uncontrolled hypertension and mild aortic root enlargement[7]. Other studies have suggested an association between higher arterial pressure and greater severity of mitral regurgitation in patients with mitral valve prolapse[8,9]. Aortic regurgitation results from disease of either the aortic leaflets or the aortic root that distorts the leaflets and prevents their coaptation[4]. The most common cause of AR secondary to the cardiac geometric adaptations of pressure overload is annuloaortic ectasia, idiopathic aortic root dilatation associated with hypertension and aging. AR leads to progressive LV dilatation that produces a large total stroke volume, and this increase in stroke volume causes an increased pulse pressure which subsequently can lead to systolic HTN and increased afterload, further affecting LV function and structure.

The purpose of the ppresent study was therefore undertaken to assess the prevalences of mild to moderate forms of mitral or aortic regurgitation insufficiency in patients with hypertension and electrocardiographic LVH and to determine their early impact of these valvular lesions on LV structure and function.

PATIENTS AND METHODS

Subjects: P: Nine hundred and sixty patients with stage I-III hypertension enrolled in the Losartan Intervention For Endpoint reduction (LIFE) study[5,6] were evaluated. Of the 9,1934 patients enrolled in LIFE, >approximately 10%[5] participated in the echo substudy. As part of the baseline evaluation these patients underwent 2-two dimensional, M-mode and Doppler echocardiography. All patients gave written informed consent under protocols approved by iThe Institutional Review Boards at each of the participating institutions approved the study. Prior to enrollment, all patients had a screening electrocardiogram that showed LV hypertrophy by either sex-adjusted Cornell voltage (SV3 + RaVL with 6 mm gender adjustment in women) x duration criteria ≥2,440 mm x msec) or Sokolow-Lyon voltage (SV1criteria: SV1 + RV5 RV5-/RV66 >38 mm[5]). IThe composite electrocardiographic criterion used for LIFE recruitment was based on results of previous studies[7,8] and it was anticipating to have approximately 94-

96% specificity and 45-50% sensitivity. Pilot data suggested that anatomic LV hypertrophy would be present in about 18-22% of hypertensive patients free of inthe several exclusion criteria for specified in tthe LIFE study included (absence of severe LV dysfunction, heart failure or other conditions requiring therapy with angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or beta blockers, angina or myocardial infarction or stroke in the past 6 months or blood pressure that rose to >200 mmHg systolic or 115 mmHg diastolic during 2 weeks a run-in period of placebo treatment). Taken together, these estimates yielded projections that from 62 to 78% of LIFE patients would have anatomic LV hypertrophy detectable by echocardiography[9]. Normal values, 2.5th and 97.5th per-centiles were drawn from a large previously-studied population of 362 apparently normal adults from our laboratory using the same echocardiographic protocol for obtaining LV dimensions and systolic LV function and the same reading procedures as patients in the current study[10].

Echocardiographic Measurements & Performance: Echocardiographic procedures for this study were based on procedures employed in previous studies[11,12] and have been described previously[6,9,13]. Color flow Doppler recordings from parasternal and apical windows were used to search for aortic and mitral regurgitation[16]. Aortic regurgitation (AR) was identified based on the extent of diastolic turbulent flow, indicated by a variance signal, in the LV, with mild (1+) AR identified by a jet occupying <20% of aortic annular diameter at its origin and extending less than half way to the tip of the anterior mitral leaflet; mild-moderate (2+) AR by jets filling 20-40% of annular diameter extending up to the tip of the anterior mitral leaflet; moderately severe (3+) AR by jets occupying 40-60% of anularannular diameter extending to or slightly beyond the tip of the anterior mitral leaflet; and severe (4+) AR by jets occupying >60% of annular diameter extending to the posterior wall of the left ventricle or more than ½ way to the LV apex[5,16]. For jets oriented perpendicular to the aortic anular plane, rather the crossing the valve's LV surface, priority was given to jet width criteria (ibid).

Mitral regurgitration (MR) was assessed by color Doppler using a modification of the method developed by Miyatake et al[17] with pulsed-wave Doppler. The severity of MR was graded on a four point scale on the basis of the farthest distance reached from the mitral orifice: ≤1.5 cm = mild (1+) MR, 1.5-3.0 cm=moderate (2+) MR, 3.0-4.5 cm= moderately severe (3+) MR and >4.5 cm = severe (4+) MR[6]. When centrally-oriented MR jets were unusually narrow, 2+ to 4+ MR grades were reduced by one grade MR grades and 1+ to 3+ MR grades were increased by one when unusually wide jets had disproportionate areas to their length or when eccentric jets hugged the left atrial wall[16].

Dick probably here is appropriate to add some details of the methods used to sample the AV/MV and the quantitaion methods for MA and AI.

Calculation of Derived Variables and Left Ventricular Hypertrophy: End-diastolic LV internal dimension and s (i.e. interventricular septal dimension, LV internal dimension anand posterior wall thicknesses) were used to calculate LV mass using a formula which has been shown to yield values closely related (r=0.90) to necropsy LV weight[14] and which had good inter-study reproducibility (RHO= 0.93) in a separate study[15]. Relative wall thickness was calculated as diastolic posterior wall thickness/ LV internal radiumens ion in diastole[16]. LV hypertrophy was considentifired present when LV mass index exceeded 116 g/m^2 in men orand 1044 g/m^2 in women[12]. Increased relative wall thickness was present when >0.43, which represents the 97.5th percentile in normal subjects[17]. LV geometry was defined using LV mass index and relative wall thickness as previously described[18].

Left Ventricular Systolic Performance: LV ejection fraction was calculated by Teichholz' formula[19]. Endocardial fractional shortening [%] was calculated from LV internal dimension in diastole and systole[20]. Values <0.27%, representing the 2.5th percentile in normal subjects[10,17], were considered indentifiedcative of depressed LV systolic chamber function. In individuals with increased relative wall thickness[21] or LV dilatation[22] endocardial shortening is not representative of that at the LV midwall where mean LV end-systolic wall stress is applied. Therefore o avoid misleading results obtained by relating endocardial fractional shortening to mean end-systolic stress across the LV wall, we used the relation between midwall shortening and midwall circumferential end-systolic stress measured at the level of the LV minor axis[21,23]. The location in the LV wall at end-systole of the surface between the inner and outer halves of the myocardium at end-diastole can be identified by the assuming the ratio of inner/outer myocardial shell volu-

mes remains constant through the cardiac cycle[24]. Midwall shortening is calculated as [(LV internal dimension in diastole + ½(interventricular septum in diastole + posterior wall thickness in diastole))3 – (LV internal dimension in systole + ½ (interventricular septum in systole + posterior wall thickness in systole)]/ (LV internal dimension in diastole + ½ (interventricular septum in diastole + posterior wall thickness in diastole)). Midwall shortening <14%, the 2.5th percentile of values in the normal subjects[10,17], identified depressed LV midwall shortening. End-systolic stress, as the primary measure of myocardial afterload, was estimated at the midwall from M-mode tracings, using a cylindrical model described by Gaasch et al.[23,25]. End-systolic stress[21] of 174 kdynes/cm^2 corresponds to the 97.5th percentile in normals[10]; accordingly, higher values identified increased myocardial afterload. Stress-corrected endocardial fractional shortening and midwall shortening are derived from as observed/ predicted shortening. Stress-corrected fractional shortening <94% and stress-corrected midwall shortening <83% correspond to 2.5th percentiles of normal values[10] and were considered indicative of low LV chamber and myocardial function.

LV diastolic function

LV diastolic filling was evaluated by classifying patients' mitral valve flow pattern according to the ratio of E and A-wave velocities of flow between the mitral tips and in the mitral annulus, the deceleration time of early diastolic transmitral blood flow and the isovolumic relaxation time (IVRT). Age-appropriate normal limits (5th or 95th percentiles) in individuals 60 years or older who are free of hypertension, diabetes, obesity, clinical evident coronary heart disease and heart failure are IVRT >105 msec and mitral annulus E/A-ratio <0.6[23,35]. Deceleration time <150 msec was regarded as short[36,37] and over 250 msec was considered prolonged[38-40]. Abnormal diastolic filling patterns were classified by a modification of the approach of Appleton et al.[36]: abnormal relaxation was identified by prolonged IVRT (>105 msec) and deceleration time (>250 msec) as well as reduced mitral annulus E/A ratio (<0.6), restrictive pattern was identified by short or normal IVRT (<105 msec), reduced deceleration time (<150 msec) and E/A-ratio >1.5, "pseudonormal" pattern was recognized by the combination of prolonged IVRT (>105 msec) with normal deceleration time and E/A-ratio and LV filling was considered normal when IVRT was <105 msec, deceleration time between 150 to 250 msec and E/A ratio between 0.6 and 1.5.

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Statistics: SPSS 11.0 software ver. 11.0.1 (SPSS, Inc. Chicago, IL) was used for statistical analyses. Results are mean ± standard deviation or frequencies expressed as percentages. Differences in continuous variables between two groups were assessed by Student's t-test; comparison among multiple groups was performed by ANOVA with the Sheffé post-hoc test. Univariate relations between variables were assessed as partial correlations, adjusting for the known impact of gender on LV function. Independent correlates of continuous LV measures of LV systolic performance were identifiidentified by multiple logistinearc regression analysis using an enter procedure with assessment of collinearity diagnostics. A 2-tailed p-value <0.05 was considered statistically significant.

RESULTS

Patient Clinical Characteristics

As previously reported[15], Demographics and baseline characteristics of the entire LIFE population have been reported the elsewhere. Of 960 patients in the LIFE echocardiography sub study closely resembled the entire LIFE study population with regard to baseline blood pressure, heart rate, body build and prevalences of cardiovascular conditions and diabetes, but included higher proportions of male and African-American patients, Of 939 patients with necessary LV measurements and Doppler data for inclusion in the present analysis, 646 had no mitral or aortic regurgitation. A total of 242 patients had mild (1+) valvular regurgitation, including 146 with 1+ MR alone, 53 with 1+ AR alone and 45 with mild regurgitation of both valves. Fifty-one patients had moderate (2+ or 3+) valvular regurgitation, including 12 with moderate MR alone, 17 with moderate AR alone and 22 with moderate regurgitation of both valves. 828 qualified for the present analysis. Of the 264 patients with mild to moderate AR or MR, 228 patients had insignificant AR &/or MR(+1 Grade). Baseline clinical characteristics were similar in the two study groups are given depicted in table 1.

Table 1. Characteristic of Patients with No, Mild or Moderate and without Aortic and/or Mitral Regurgitation/AR

	No Regurgitation (n=646)	Mild (1+) Aortic and/or Mitral Regurgitation (n=242)	Moderate (2-3+) Aortic and/or Mitral Regurgitation (n=51)
Age	65,9±6,9	67,1±6,9	67,8±6,90
Women (N, %)	250 (38,7)	110 (45,5)*	30 (58,8)*
Systolic blood pressure (mmHg)	173±15	174±14	176±13
Diastolic blood pressure (mmHg)	99±9	97±9	97±120,003
Pulse pressure (mmHg)	75±15	77±15	79±17NS
Heart rate (min-1)	68±12	67±11	65±9
Body mass index (kg/m2)	27,6±4,4	27,1±4,5	26,6±5,3
Weight (kg)	79,5±14,0	77,3±14,6	73,5±13,7
Serum creatinine (mmol/l)	90±23	90±21	92±23
Serum cholesterol (mmol/l)	6,0±1,1	5,9±1,1	5,9±1,3
Urine albumin/creatinine (mg/mmol)	78±310	69±180	35±52
Myocardial infarction (%)	4,6	6,6	11,8
Angina (%)	7,9	11,2	11,8
Peripheral vascular disease (%)	8,0	8,3	5,9
Preripheral vascular disease (%)	4,8	6,2	5,9

Statistical significance versus patients without regurgitation: *=p<0,05, **=p<0,01

Table 1 needs to be expanded to include more baseline characteristics of all 960 patients Patients with mild and especially with moderate valvular regurgitation were more likely to be women than the patients without valvular regurgitation.

Body weight, body mass index and diastolic blood pressure and BMI tended to be lowerwere significantly lower and pulse pressure to be higher in patients with MR/AR (table 1). However these differences did not attain statistical significance in analyses that adjusted for gender[5], p<0.002, p< 0.037 respectively). Patients with MR/AR also had significantly lower diastolic pressure and higher pulse pressure (p<0.003, p<0.043 respectively). Heart rate was modestly but significantly lower and the prevalence of prior myocardial infarction higher in patients with moderate aortic and/or mitral regurgitation.

LV Geometry and Hemodynamics;

Table 2 presents the comparison of LV geometric and hemodynamic characteristics of patients with no valvular regurgitation and those with mild or moderate valvular regurgitation. In analyses that adjusted for gender, patients with mild mitral and/ or aortic regurgitation had larger LV internal dimensions, higher LV mass indexed for either body surface area or height$^{2.7}$ and larger left atrial diameters. In similar analyses, patients with moderate regurgitation of one or both valves had larger LV chambers, greater mean LV mass in absolute terms as well as after indexation for body surface area or height$^{2.7}$ and higher Doppler stroke volume. The patients with moderate valvular regurgitation also had a higher prevalence of LV hypertrophy, due to an increased prevalence of eccentric LV hypertrophy. Hs to those with insignificant AR and/or MR as indicated by the +1 grading assignment. There was a significant increase in LV diastolic diameter and a significant increase in LV mass in absolute numbers and when indexed by BSA or by height$^{2.7}$; however, there was no significant difference in the RWT among groups. There was no difference among groups defined by the presence and severity of valvular regurgitation in cardiac output, total peripheral resistance or pulse pressure/stroke volume, indicating that the observed inter-group differences in LV geometry were not due to differences in the hemodynamic severity of These findings are consistent with the pattern of eccentric hypertensionrophy.

LV Functional Characteristics

Measures of LV systolic and diastolic function are depicted in Table 3 depicts LV functional and hemodynamic parameters. In analyses that adjusted for gender, Patients with moderate insignificant valvular regurgitations had a significantly lower endocardial fractional shortening, an index of systolic function; a higher circumferential end-systolic wall stress (CESS), a measure of myocardial

Table 2. Left Ventricular Geometry and Hemodynamics in Hypertensive Patients with No, Mild or Moderate Aortic and/or Mitral Regurgitation

	No Regurgitation (n=646)	Mild Aortic and/or Mitral Regurgitation (n=242)	Moderate (2-3+) Aortic and/or Mitral Regurgitation (n=51)
Septal thickness (cm)	1.16±0.14	1.15±0.18	1.15±0.16
LV internal dimension (cm)	5.25±0.55	5.33±0.60*	5.59±0.65***
Posterior wall thickness (cm)	1.07±0.12	1.06±0.15	1.06±0.11
LV mass (g)	232±53	235±63	248±59***
LV mass/body surface area (g/m^2)	122±24	125±29*	136±27***
LV mass/height2.7 (g/m2.7)	55.4±11.6	57.3±15.1*	61.9±13.7***
LV hypertrophy (%)	69	71	86*
Relative wall thickness (%)	0.41±0.06	0.41±0.08	0.39±0.06**
Concentric remodeling (%)	11.5	9.1	5.9
Eccentric hypertrophy (%)	43.8	49.4	66.7*
Concentric hypertrophy (%)	24.9	22.0	19.6
Left atrial diameter (cm)	3.9±0.6	4.0±0.6*	4.0±0.6
Doppler stroke volume (ml)	77±17	79±17	84±19***
Cardiac output (ml/min)	5189±1297	520±1255	5418±1184
Cardiac index (ml/min/m2)	2741±668	2798±686	2980±579
Total Peripheral Resistance ($Dynes*sec*cm^{-5}$)	1987±548	1982±608	1893±439
Pulse pressure/stroke volume (mmHg/ml)	1.05±0.34	1.06±0.34	1.01±0.38
Pulse pressure/stroke index ($mmHg/ml/m^{1.83}$)	1.99±0.60	1.95±0.58	1.80±0.57

Abbreviation: LV: Left ventricular.
Statistical significance versus patients without regurgitation, adjusted for gender: *=p<0.05, **=p<0.01, ***=p<0.005

Table 3. Left Ventricular Function in Hypertensive Patients with No, Mild or Moderate r-Aortic and/or Mitral Regurgitation

	NoRegurgitation (n=646)	Mild (1+) Mitral and/or R/Aortic Regurgitation (n=242)	Moderate (2+-3+) Mitral and/or Aortic Regurgitation (N=51)
Fractional shortening (%)	33±6	33±62	33±6
Midwall shortening (%)	15.4±2.1	15.5±2.3	15.7±2.1
CESS (kdynes/cm)	181±46	186±559	203±54***
CESS/ESVI	6.85±1.52	6.72±1.55	6.35±1.67**
Stress-corrected midwall shortening (%)	96.3±12.5	97.8±14.2*	100.9±12.8
Isovolumic relaxation time (msec)	115±24	114±24	121±22
Mitral valve E/A ratio	0.86±0.38	0.86±0.36	0.90±0.39
Mitral valve deceleration time (msec)	218±68	208±60	223±63

Abbreviation: CESS: Circumferential end-systolic stress, ESVI: End Systolic Volume Index
Statistical significance versus group with no regurgitation: *=p<0.05, ***=p<0.005.

afterload; and lower a decreased CESS/ESVI, a measure of LV chamber contractility when compared to patients without valvular regurgitations. Trends toward longer isovolumic relaxation time and deceleration time of early diastolic transmitral flow, indices of impaired early diastolic LV relaxation, did not attain statistical significance.

DISCUSSION

This study, for the first time, provides information on the impact of prognostic implications of mild and moderate MR and/or/AR in patients with LVH and mild to moderate HTN by evaluating echocardiographic indices of LV structure and fun-

ction in the patients participating in with insignificant AR/MR of the LIFE echocardiography substudy. In accord with data from national hospital discharge surveys ( ), valvular regurgitation was positively associated with female gender. After adjustment for the effect of gender, Levy et al, showed that an increase in LV mass predicts a higher incidence of clinical events, including death, attributable to cardiovasculthe present ar disease[1]. Our study showed that patients with mild, and especially with moderate insignificant AR and&/or MR, had larger LV cavity dimensions and greater LV mass than the patients without no valvular regurgitations. Of particular importance in addition, the insignificant regurgitation patients with moderate AR and/ or MR had a higher prevalence of LV hypertrophy, due to an increased frequency of eccentric LV hypertrophy, compared to similarly hypertensive patients. population had a lower weight and BMI, adding more significance to the findings of increased LV mass by absolute numbers and indexed for BMI. These findings extend to the high-risk population of hypertensive patients with LV hypertrophy the observation that mitral and/or aortic regurgitation was associated with greater LV size and hypertrophy previously reported in population-based samples of predominately normotensive adults ( ).

In addition, the group with moderate insignificant valvular regurgitations also had higher LV myocardial afterload, as measured by circumferential end-systolic stress, and lower LV chamber contractility, as manifested by a lower end-systolic stress/end systolic volume index ratio, compared to equally hypertensive patients without valvular regurgitation. Previous studies have identified increased L V indexes of LV systolic function (EFS and cESS/ ESVI) and a significantly higher index of myocardial afterload and lower LV chamber contractility as predictors of, cESS. It is well known and evident that both systolic dysfunction and increased myocardial afterload are strongly associated with the development and progression of congethe development and progression of congesstive heart failure, ventricular arrhythmias and sudden death.

The presentis study documents a significant and hitherto largely unappreciated interaction between the adverse effects of hypertension and of concomitant valvular regurgitation on LV geometry and function. Patients with mild, and to an even greater extent moderate, mitral and/or aortic regurgitation had greater LV enlargement, hypertrophy, afterload and chamber dysfunction, all of which are known to be associated with an adverse prognosis. Taken together with studies documenting the strong predictive value of LV hypertrophy for cardiovascular events and all-cause mortality in hypertensive patients, these findings suggest that hypertensive patients with moderate or even mild concomitant valvular regurgitation are a group of patients at especially high cardiovascular risk. Further research is needed to verify this, and to determine whether changes in the severity of valvular regurgitation during antihypertensive treatment influenchas e the rates of subsequent cardiovascular events and of death. xposed a subgroup of hypertensive patients with LVH predisposed to increased cardiovascular morbidity and mortality and possibly could have therapeutic and management implications. Several studies (Keren, Seneviratine, Reske) have shown that the attenuation of progressive ventricular remodeling, primarily LVH, with ACE-I prevents the development of secondary MR/AR and reduces its magnitude once present[26-28]. LVH, a target-organ response to chronic pressure or volume overload, is associated with increased cardiovascular morbidity and mortality in patients with HTN as mentioned previously. Although the mechanisms by which LVH develops are incompletely understood, the effector hormone of the rennin angiotensin-system, angiotensin II, plays an important role. The RAS is an important modulator of cardiac function under normal and pathological conditions. Through AT1 receptors, AngII maintains systemic vascular resistance and blood volume expansion and contributes to long term growth and mitosis, thereby playing a significant role in the development of LVH. It is true that all antihypertensives, if used long enough can reduce LV mass by virtue of afterload reduction (Frolich); however, several studies have shown that ACE-I appear more potent than CCB, Beta Blockers and diuretics in the reduction of LV mass[29,30].

In addition, there have been more promising results in the realm of LV mass reduction with the use of ARBs, inhibiting the effects of AngII specifically at the AT1 receptor while leaving the AT2 receptor unopposed[31]. Interestingly, stimulation of the AT2 receptors opposes the hypertrophic and cell proliferative effects mediated by AT1 stimulation. Our subset of patients with insignificant valvular insufficiencies in the setting of LVH may benefit from long term treatment with an ARB, se-

condary to its inhibition of the both the trophic effects and pressure overload caused by stimulation of AngII production.

We provide evidence that in the future, insignificant valvular regurgitations (+1) may not be ignored in patients with LVH. Follow up data from the LIFE study will not only provide additional prognostic information and help define future therapeutic options for insignificant valvular regurgitations, but also possibly provide another reason for the beneficial effects of ACErennin angiotensin blockers inhibition on cardiovascular morbidity and mortality independent of BP reduction.

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