Regression of left ventricular hypertrophy and cardiovascular risk changes in hypertensive patients

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Key words:
Echocardiography; Electrocardiography; Hypertension; Hypertrophy; Myocardial infarction; Stroke.

Hypertensive left ventricular hypertrophy (LVH) may be detected in about one third of people with hypertension. When an individual with elevated blood pressure develops LVH, the risk of adverse cardiovascular events in the ensuing years almost doubles even in the absence of symptoms. Because of this high added risk, hypertension and other modifiable risk factors should be managed aggressively with lifestyle measures and drugs. LVH can be considered a biological assay which reflects and integrates the long-term exposure not only to pressure overload, but also to several hemodynamic and non-hemodynamic factors which may promote progression and instabilization of atherosclerotic lesions and, ultimately, lead to adverse clinical events. LVH can partially or totally regress following antihypertensive treatment and lifestyle changes including losing excessive weight and decreasing salt intake. Angiotensin II antagonists and ACE-inhibitors seem to be the most effective drugs for reversing LVH. Evidence is accumulating that regression of LVH is associated with a significant reduction in the subsequent risk of cardiovascular disease. According to a recent meta-analysis, effective reversal of LVH is associated with a 59% lesser risk of subsequent adverse events as compared with the persistence or new development of LVH.

(Ital Heart J 2004; 5 (7): 505-510)

Received March 11, 2004; accepted March 30, 2004.

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The first experimental studies which dealt with regression of left ventricular hypertrophy (LVH) date back to about six decades ago when Patton et al.[1] showed that cardiac hypertrophy could be reversed by nephrectomy in spontaneously hypertensive rats. LVH regression in hypertensive humans was first noted during treatment with veratrum in patients with severe hypertension[2]. In the subsequent years, several clinical studies reported the occurrence of serial changes in the ECG indexes of LVH during antihypertensive treatment[3-5]. With the beginning of the echocardiographic era, it became apparent that serial changes in left ventricular dimensions and wall thickness could be accurately monitored. Fouad et al.[6] first showed in the early 1980s that treatment of hypertension could be accompanied by a reduction in left ventricular mass detected at echocardiography. However, despite the clear evidence of the adverse prognostic impact of LVH at ECG[7] and echocardiography[8-10], the prognostic benefits related to regression of LVH above and beyond the benefits related to the changes in blood pressure (BP) and other risk factors have not been fully appreciated until recently.

In general, the fact that only a few studies may achieve a power sufficient to detect the prognostic impact of serial changes of LVH either at ECG or echocardiography in hypertensive subjects is not surprising considering the generally low rate of major cardiovascular events in hypertension and the need to collect hundreds of readable tracings before and during treatment, even before the occurrence of a first cardiovascular event. A low drop-out rate in these studies is also mandatory in order to collect a sufficient number of person-years of follow-up and, hence, a sufficient number of incident events.

Regression detected with electrocardiography

In the Framingham Heart Study[11], the subjects with baseline LVH who showed an increase over time in the ECG voltages were twice as likely to suffer a cardiovascular event over the subsequent years as compared with those with a decrease in the voltages. This observation from Framingham was the first to substantiate the prog-

nostic value of serial changes of LVH, detected with ECG, in a general population sample including normotensive and hypertensive subjects. In a subset of high-risk individuals included in the Heart Outcomes Prevention Evaluation (HOPE) study[12], the composite endpoint of cardiovascular death, myocardial infarction and stroke occurred in 12% of patients without LVH at ECG or its regression during the follow-up, as compared to 16% among those who either developed or failed to reduce LVH (p = 0.006).

However, because traditional ECG is less sensitive than echocardiography for the detection of LVH[13-15], the evolution of cardiac structural changes from before to during treatment would continue to be missed by ECG in several patients. Of note, none of the available studies of the prognostic value of serial changes in the ECG indexes of LVH has been specifically conducted in hypertensive patients.

Regression detected with echocardiography

The explosive growth of quantitative echocardiography allowed the execution of follow-up studies in more and more cohorts of hypertensive patients, with the opportunity of serial and accurate assessments of cardiac structural changes over time. Thus, a link was noted in some studies between regression of LVH detected by echocardiography and a reduction of major cardiovascular events in essential hypertension[16-20].

In a multicenter study from Russia[16], 304 hypertensive men with echocardiographic LVH were followed for an average of 4 years and, over this period, the left ventricular mass decreased by approximately 30 g in those without new cardiovascular events, while it increased by 0.3 g in those with new events. In a first study from Italy[17], a group of hypertensive subjects underwent echocardiographic assessment of the left ventricle before therapy and after an average of 10 years of follow-up. Cardiovascular events were more frequent among the subjects without regression of LVH than among those with a persistently normal left ventricular mass. Of particular note, the event rate did not differ between the subset with regression of LVH and that with a persistently normal left ventricular mass. This study was the first to demonstrate an association between serial changes in left ventricular mass and the risk of cardiovascular disease, despite the limitation that some of the events actually occurred before the follow-up echocardiographic study. Consequently, this study could not completely establish the predictive value of serial changes in left ventricular mass in patients still free of cardiovascular disease at the time of follow-up study. Such an observation was possible in a study from our group[18], in which patients with essential hypertension underwent echocardiography and 24-hour non-invasive ambulatory BP monitoring before therapy and during follow-up, before developing cardiovascular events. In the subset with LVH at the baseline visit (26% of all patients), the cardiovascular event rate was 1.58 per 100 person-years among those who achieved regression of LVH, vs 6.27 events per 100 person-years among those who did not (p = 0.002). The lower cardiovascular risk in the patients with regression of LVH compared to those without regression remained significant in a multivariate analysis after adjustment for several confounding variables including the changes in 24-hour ambulatory BP. A representative tracing of one of these patients, who also showed a notable improvement of his hypertensive retinopathy, is reported in figure 1.

In a similar study from France[19], the incidence of cardiovascular events was 4.8% in the hypertensive subset without LVH both before and during treatment, 9.6% in that with regression of LVH and 15% in that without regression of LVH. Similar data have been recently reported in a study by Koren et al.[20].

Quite recently, we completed a meta-analysis[21] of four of the aforementioned studies[17-20] which were quite small in size, but similar in their design and experimental procedures. Specifically, we compared the outcome of two pre-defined groups of subjects characterized by: a) persistence or new development of LVH vs regression of LVH; b) regression of LVH vs a persistently normal left ventricular mass.

An additional study[16] was excluded from analysis because the report did not allow precise identification of the three pre-specified groups with a persistently normal left ventricular mass, regression of LVH and persistence or new development of LVH. Overall, the four eligible studies included 1064 hypertensive subjects (41% women) aged 45-51 and 106 cardiovascular events. The echocardiographic study was carried out before beginning treatment and after 3-10 years of follow-up. Compared to subjects with lack of regression or new development of LVH, those who achieved regression of LVH showed a 59% lesser risk of subsequent cardiovascular disease (95% confidence intervals 22-79, p = 0.007). The lesser risk of events associated with regression of LVH was consistent across the individual studies. Compared to subjects with regression of LVH, those with a persistently normal left ventricular mass showed a similar risk of subsequent events (odds ratio 0.64, 95% confidence intervals 0.31-1.30, p = 0.21). However, since the risk of events was 36% lower among the subjects who never experienced LVH compared to those with regression and since the confidence intervals were wide (Fig. 2)[21], our study could not provide conclusive evidence that regression of LVH reduces the risk of subsequent events to the same level as that of subjects who never presented with this condition.

Of course, the results of our meta-analysis should be interpreted in the context of its limitations. No information can be drawn on the prognostic impact of regression of LVH over a longer time interval than that examined in the reviewed studies. A further limitation, inherent to all meta-analyses, is the potential publica-

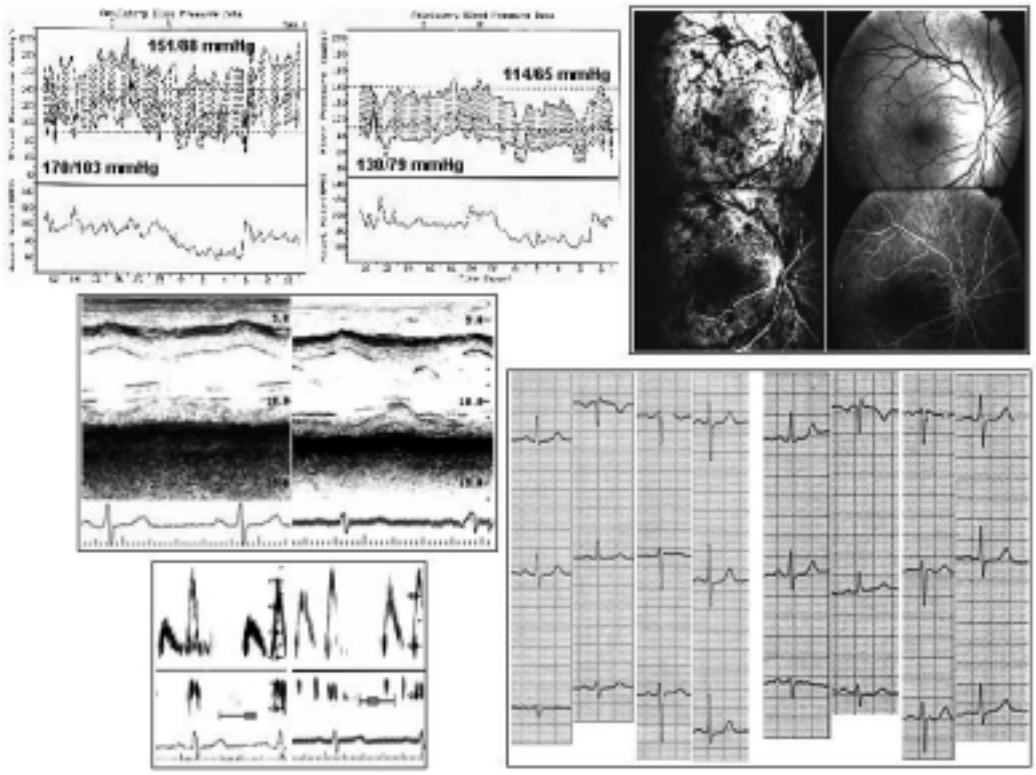

Figure 1. *Tracings of a patient before and during antihypertensive treatment.*

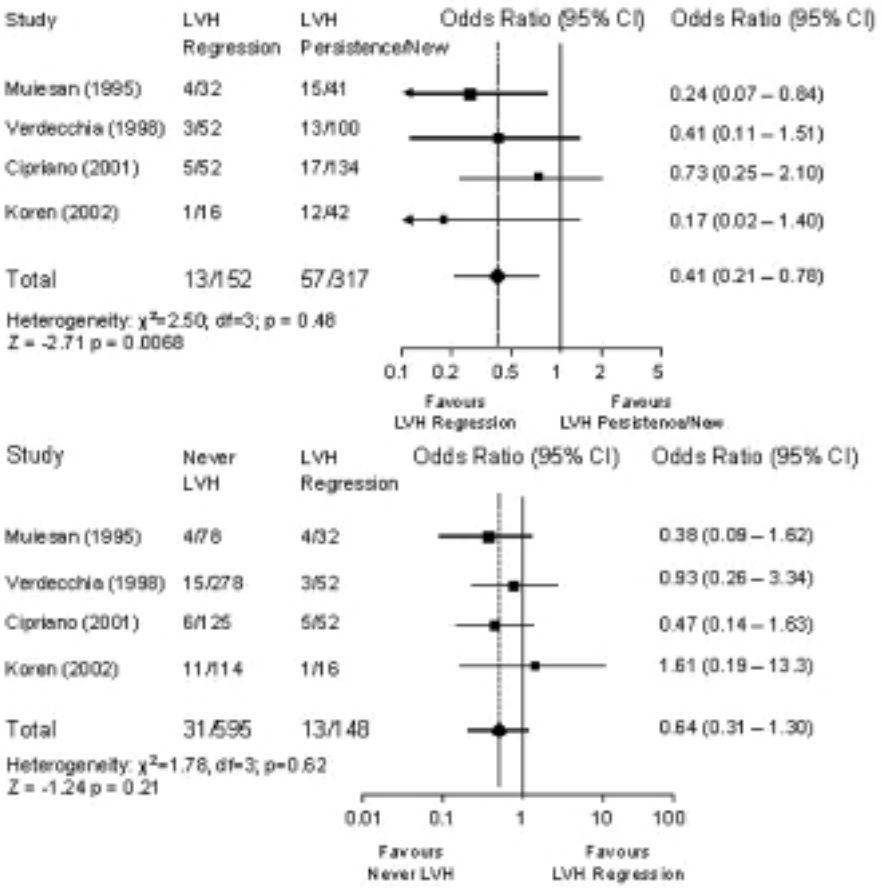

Figure 2. *Meta-analysis of studies which addressed the prognostic value of serial changes in left ventricular mass in patients with essential hypertension. CI = confidence intervals; LVH = left ventricular hypertrophy. From Verdecchia et al.[21], with permission.*

tion bias. Studies which demonstrated an association between changes in LVH and outcome may have more chance to be published than negative studies. Another limitation to meta-analyses is the lack of multivariate assessment in the overall sample. It is uncertain to what extent the prognostic benefit of LVH regression may be accounted for by serial changes in other covariates, although changes in BP and other cardiovascular risk factors have been considered in the multivariate analyses of individual studies[17-20]. Furthermore, the baseline and follow-up echocardiographic tracings were read in the individual centers, not in a single independent laboratory, thereby introducing another potential error. Finally, the timing of follow-up visits and treatments were not standardized.

Because of these limitations, the results of our overview need to be confirmed in large trials. Preliminary data from the Losartan Intervention for Endpoint Reduction (LIFE) study[22], not yet available *in extenso*, seem to go in the same direction by showing that the composite endpoint of cardiovascular death, non-fatal myocardial infarction and stroke decreases with a reduction in left ventricular mass independently of treatment, BP changes and other determinants of risk.

Mechanisms of the prognostic benefit

Serial changes in left ventricular mass in treated hypertensive subjects might reflect the long-term level of activity of several hemodynamic and non-hemodynamic factors which may be active on progression and instabilization of atherosclerotic lesions. Thus, the favorable prognostic impact of LVH regression might reflect a lesser progression of atherosclerosis because of a variety of mechanisms not limited to BP control, whereas the lack of regression of LVH might be a marker of a more advanced progression of atherosclerosis. Numerous experimental and clinical studies support this line of thinking. The left ventricular mass and intima-media thickness are associated with BP in hypertensive subjects[23,24]. Insulin and insulin growth factors may simultaneously induce LVH[25-27] and intima-media lesions[28-30]. Angiotensin II activates intracellular reactions leading both to LVH[31-33] and progression of atherosclerotic lesions[34] and AT_1-receptor activation has an important role in the pathogenesis of atherosclerosis[35,36]. Endothelin stimulates both vascular cell migration and growth[37,38] and cardiac hypertrophy[39]. In clinical studies, HDL cholesterol showed an inverse association, independent of BP, with left ventricular mass[40,41]. Furthermore, plasma viscosity has been associated with both LVH[42] and an increased intima-media thickness[43] in hypertensive subjects. Finally, the association between LVH and stroke, apparently independent of office[44-46] and ambulatory[47] BP levels, strengthens the potential role of left ventricular mass as an integrated marker of atherosclerosis.

Regression of LVH may be achieved through a reduction in myocyte volume and amount of interstitium. Studies of regression of severe LVH in patients undergoing aortic valve replacement showed an initial and rapid reduction in the myocyte volume, followed by a more prolonged phase (months or years) of progressive reduction in the interstitial fibrosis[48]. In patients with hypertension, ethical reasons preclude execution of serial assessments of myocyte cell mass and myocardial fibrosis through biopsies. However, in a study in hypertensive humans which included serial myocardial biopsies, lisinopril decreased the left ventricular mass through a reduction of myocardial fibrosis without important effects on BP and myocyte mass, whereas hydrochlorothiazide reduced the left ventricular mass through a reduction in BP and myocyte mass[49]. In general, serial changes in left ventricular mass are correlated with changes in BP[50] and the association appears to be closer with the changes in the 24-hour ambulatory BP[51].

Clinical implications

Regression of LVH in treated hypertensive subjects should be considered as a favorable prognostic marker that reflects a reduced risk of subsequent cardiovascular disease. In contrast, the patients with persistence, or lack of regression, of LVH over time, should be considered at elevated cardiovascular risk even in the presence of a normal achieved BP[18]. An aggressive therapeutic management directed at achieving a BP reduction over a 24-hour period and a strict control of concomitant modifiable risk factors seem mandatory in these high-risk patients.

Almost all available antihypertensive drugs are effective in inducing BP lowering and regression of LVH. In a recent meta-analysis of 80 randomized double-blind controlled studies which involved more than 4000 patients[52], the left ventricular mass index decreased by 13% with angiotensin II receptor antagonists, by 11% with calcium antagonists, by 10% with ACE-inhibitors, by 8% with diuretics, and by 6% with beta-blockers. Angiotensin II receptor antagonists, calcium antagonists, and ACE-inhibitors were significantly more effective than beta-blockers[52]. However, an effective and sustained BP lowering remains mandatory to achieve regression of LVH[18].

Future directions

More studies are needed to clarify the relative merits of ECG and echocardiography for cardiovascular risk stratification in hypertensive subjects. Surprisingly, despite being a clinically important issue, there are only a few studies which compared the prognostic value of these two techniques in such patients. Cost-ef-

fective analyses are also needed. As a result, many clinicians are still uncertain about whether echocardiography provides information that is really additional to that provided by ECG and traditional risk factors in uncomplicated hypertensive subjects. Such uncertainty is reflected by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[53] which included ECG, but not echocardiography, among the routine laboratory tests that are recommended before initiating therapy.

It is reasonable to suggest that low-risk hypertensive subjects may particularly benefit from an echocardiographic assessment of the left ventricular structure. In a large cohort of low-risk hypertensive subjects defined by the absence of diabetes, ECG LVH and proteinuria, with creatinine levels < 106.08 mmol/l (1.2 mg/dl) and no more than two additional risk factors, the odds ratio for major cardiovascular events over a follow-up period up to 13 years was 1.70 (95% confidence intervals 1.23-2.36) for each 11 $g/m^{2.7}$ increment in left ventricular mass independently of confounding variables ($p < 0.01$)[54]. Thus, echocardiographic examination might be particularly indicated in subjects in whom, on the basis of the guidelines, no immediate pharmacological treatment is required. In these subjects, an increased left ventricular mass at echocardiography would define a worse risk class and the need for immediate antihypertensive treatment. In contrast, the echocardiographic information might be less relevant for decision-making in patients already assigned to a high risk score, for whom aggressive treatment has already been scheduled[55]. It is reasonable to propose that subjects with clear evidence of an increased left ventricular mass should undergo at least one further echocardiographic study during follow-up in order to evaluate whether the LVH has regressed or not.

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