Gender Differences in the Regression of Electrocardiographic Left Ventricular Hypertrophy During Antihypertensive Therapy

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Despite a common underestimation of cardiovascular (CV) risk in women, CV disease represents the leading cause of death in Western countries in both sexes. It is now widely recognized that the pathophysiology and the clinical manifestations of CV diseases differ significantly between genders. After a period of relative “protection” from CV events in the premenopausal phase, the increase in CV risk associated with aging becomes steeper in females after menopause. The mechanisms underlying this phenomenon are not completely understood; changes in body composition, plasma glucose and lipid levels, and in blood pressure (BP) values may partially explain the observed increase in CV risk. A significant effect exerted by gender in cardiac adaptation to increased workload has been described, with women having a greater increase in the prevalence of left ventricular hypertrophy and of concentric geometry with progressive aging.

ECG, despite being introduced in clinical practice >100 years ago, still represents one of the most extensively used diagnostic tools in CV medicine and is a powerful index for the assessment of CV risk in hypertensive patients. Several studies have demonstrated the prognostic significance of left ventricular hypertrophy (LVH) detected by the ECG in hypertensive patients; in addition, strong evidence exists that favorable changes over time of ECG indices of LVH are associated with a better prognosis in different populations.

In this issue of Hypertension, Okin et al report the results of a posthoc analysis performed in 9193 hypertensive patients included in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study; during 4.8 years of antihypertensive treatment, women had significantly less reduction in both Cornell product and Sokolow-Lyon voltage than men. Gender differences in the reduction of LVH by both Cornell product and Sokolow-Lyon voltage were already apparent after 6 months and became progressively greater over the course of follow-up.

At the end of the study women were 32% less likely to have had greater than the median level of regression of Cornell product LVH and 15% less likely to have had regression of LVH by Sokolow-Lyon criteria. Furthermore, when LVH regression was defined as a reduction of Cornell product or Sokolow-Lyon voltage to below their partition values, significant gender differences were still observed.

The study by Okin et al for the first time clearly demonstrates lesser regression of ECG LVH in hypertensive females in comparison with males for similar BP decrease. Of note, the difference was highly significant, even taking into account possible confounders such as baseline ECG LVH levels, baseline and change in BP, treatment group, obesity, age, and other baseline gender differences. The findings of the study give further insights on the evolution of cardiac organ damage in women and are concordant with recent data from the population included in the LIFE echocardiographic substudy. In fact, in 863 patients, Gerdts et al observed a significantly higher prevalence of echo-LVH in hypertensive females in comparison with their male counterparts, both at baseline and during treatment. The observed parallelism between electrocardiographic and echocardiographic indices of LVH in the LIFE Study gives further consistency to the results, which appear representative of a true biological phenomenon.

The observed differences in LVH regression, together with the greater prevalence of LVH, might contribute to the explanation of the steeper increase in the risk of CV events with aging in hypertensive women. Previous studies have suggested that the presence of LVH may be associated with a greater increase in CV risk in females than in males. Interestingly, a recent posthoc analysis has shown that losartan-based treatment in LIFE resulted in fewer overall CV events, reduced total mortality, and less new-onset diabetes in women than in men. However, significantly more women required hospitalization for angina pectoris in the losartan group than in the atenolol group (hazard ratio: 1.70; 95% CI: 1.16 to 2.51; P=0.007). Caution is certainly needed in the interpretation of these findings, which are the result of a posthoc analysis. However, the lesser reduction of LVH in women could be a possible pathophysiologic mechanism underlying the increase in episodes of symptomatic myocardial ischemia. Although the relation between changes of ECG-LVH and incidence of CV events is consistent even after adjustment for gender, Okin et al had to assess directly whether this relation was in fact still maintained in the population of women examined in their study.

Another relevant aspect is represented by the fact that previous studies have clearly demonstrated that the prognostic information provided by ECG and that provided by echocardiography are, at least in part, independent each other and that, therefore, the 2 techniques may be complementary...
in CV risk assessment. The lack of decrease in both echo- and ECG LVH in a significant number of female patients might have a particularly adverse prognostic significance.

Some aspects of the study deserve further considerations. Differences in hemodynamic parameters might have influenced the reduction of LVH: women had slightly but significantly higher systolic BP values at baseline and tended to have lesser reductions in BP during treatment. However, these differences were small, and, furthermore, gender differences in LVH reduction persisted after adjusting for BP values in a multivariable model. It is, however, possible that the greater increase in central systolic BP in females with aging could have lead to an amplification of these differences at the level of the ascending aorta, thus significantly affecting LVH regression in women. Of note, pulse pressure amplification (upper limb pulse pressure/central pulse pressure), has been shown to be significantly lower in women as compared with men, and recent data suggest that this parameter may be a much better predictor of LVH regression during antihypertensive treatment than brachial BPs.

Some caution is needed in the interpretation of the results of the study by Okin et al. In fact, it must be kept in mind that these results were obtained in patients >55 years of age (and ≤80 years), with moderate-to-severe hypertension and with evidence of electrocardiographic LVH. The prevalence of electrocardiographic LVH in primary health care is low, ranging from 9% to 14% in women and from 15 to 19% in men. Therefore, caution is advisable in extrapolating the results observed in this highly selected, high-risk population to hypertensive patients who are encountered in everyday clinical practice. Further studies will better clarify whether the LIFE Study results can be extrapolated to hypertensive patients with a lower risk profile. In addition, the reason why women had less CV events despite less reduction of ECG-LVH and, in general, the relation between ECG changes during treatment and prognosis in women deserve further investigation. Nevertheless, these authors should be thanked, having added further information to the important topic of gender differences in the incidence of organ damage and CV disease.

Disclosures

None.

References

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