Sex Differences in the Cardiac Effects of Early-Onset Hypertension

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Hypertension remains the single largest modifiable contributor to risk for heart failure with preserved ejection fraction (HFpEF).[1] The female versus male predominance of HFpEF remains incompletely understood but may be related to sex differences in the cardiac response to chronic hypertension. Efforts to explore this possibility have been challenging, largely due to fact that HFpEF typically presents in older age, and older women compared with older men tend to carry a greater burden of certain comorbid chronic disease traits (eg, obesity, chronic kidney disease) that can also impact various aspects of cardiac structure and function. Therefore, to minimize potential confounding by comorbid disease, we investigated sex differences in the extent to which subclinical cardiac disease is evident by midlife among people whose chronic hypertension began in early life (ie, hypertension starting at age <35 years).

We studied N=2683 participants (mean age 50±4 years, 57% women) of the CARDIA (Coronary Artery Risk Development in Young Adults) cohort,[2] who attended up to 8 serial examinations between 1985 and 2011, leading up to and including echocardiography at study cycle 8 (2010–2011) and did not have any key covariate data missing at attended exams. Blood pressure measurements at each exam were collected and calibrated using standardized methods, as previously described.[2] We categorized participants according to the onset age at which hypertension criteria were met (blood pressure ≥140/90 mm Hg or use of antihypertensive medication): <35 years, 35 to 44 years, ≥45 years, or no hypertension.[2] Echocardiographic left ventricular (LV) hypertrophy was defined as increased LV mass index >115 g/m^2 in males and >95 g/m^2 in females[2]; left ventricle diastolic dysfunction (DD) was defined as a ratio between peak velocity flow in early and late diastole of >2.0 or <0.8.[2] Using multivariable logistic regression models (adjusting for age, sex, body mass index, total serum cholesterol, high-density cholesterol, smoking status, use of antihypertensive medication, and diabetes mellitus), we related hypertension onset age group with presence versus absence of LV trait (LV hypertrophy or DD, prevalent in 16.6% and 9.0% overall). We observed that men with early-onset hypertension (starting at age <35 years) were much more likely to have LV hypertrophy (odds ratio, 3.88; 95% CI, 1.78–8.45) but not DD, when compared with men without hypertension (Figure). Conversely, women with early-onset hypertension were much more likely to have DD (odds ratio, 3.36; 95% CI, 1.42–7.93) but not LV hypertrophy, when compared to women without hypertension.

In older-aged cohorts, age-related concentric remodeling without elevation in LV mass (ie, overt hypertrophy) is seen more commonly in women than men.[3] Intriguingly, murine models have not only recapitulated these findings but also suggest that the female heart develops higher LV filling pressure in response to afterload resistance, especially when wall stress is higher than in males but also even when wall stress is similar.[4] The current analysis expands from prior observational and experimental reports and highlights a pronounced divergence between women and men in the cardiac effects that emerge in the setting of a chronic afterload stress that begins well before the menopausal transition in women. In particular, we observed a prominent association of early-onset hypertension with LV DD (but not hypertrophy) in women, which stands in contrast to a prominent association of early-onset hypertension with increase in LV mass (but not DD) in men. These results suggest that whereas the men tend to exhibit a cardiac remodeling response to hypertension stress that could serve to delay impaired function, women tend to exhibit a more limited cardiac remodeling response that renders susceptibility to dysfunction, particularly DD, which is a known precursor to HFpEF. This sexual dimorphism could be related to the more prominent increases in arterial stiffness seen in aging women than aging men[5] and, in turn, coupling of vascular-ventricular remodeling processes that may drive HFpEF pathophysiology. Further research is needed to validate and determine the mechanisms underlying our findings, as well as the extent to which they contribute to the consistently observed female predominance of incident HFpEF in later life.

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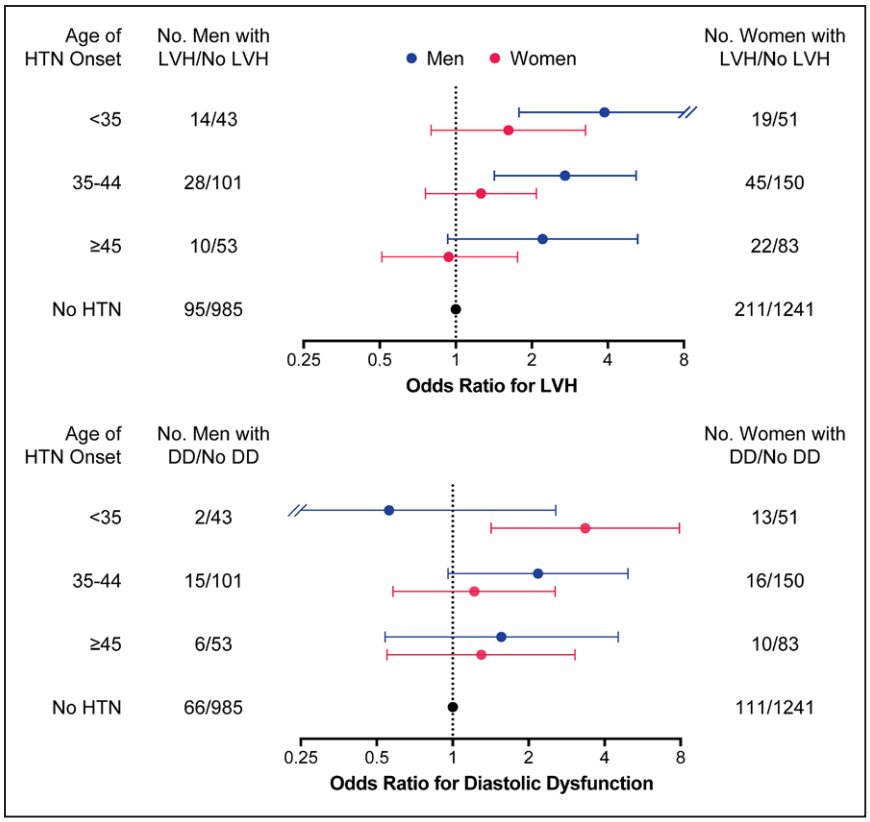

Figure. Early-onset hypertension and cardiac effects by sex. Although there was an overall trend observed for greater prevalence of left ventricular hypertrophy (LVH) and diastolic dysfunction (DD) among individuals with earlier compared to later onset hypertension, the findings were more specific for greater LVH in men and greater DD for women with early-onset hypertension. HTN indicates hypertension.

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Disclosures

None.

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