LEARNING THE ROPES: ASPECTS ON MALE VS. FEMALE SEX IN HYPERTENSION

Organ damage and pathophysiology

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Pathophysiology

Chronic hypertension leads to structural and functional changes in the heart and arteries.¹ The prevalence of hypertension-mediated organ damage increases with the severity and duration of hypertension. However, the development of organ damage in essential hypertension is influenced by a number of factors beyond the degree of pressure overload, including sex, ethnicity, sympathetic nervous activity, the renin-angiotensin-aldosterone system and co-morbidities (Figure 1).² Presence of co-morbidities like obesity and type 2 diabetes mellitus are associated with higher risk of hypertension-mediated organ damage resulting from profound metabolic changes, including disturbed sodium and water handling, paracrine effects of visceral fat tissue, cardiovascular inflammation, and secretion of vascular growth factors.² Hypertension is also in itself an inflammatory state.³ Experimental research has demonstrated that hypertensive stimuli like angiotensin II and high salt intake activate T-cells that become pro-inflammatory and infiltrate the heart, arterial adventitia and periadventitial fat, brain and kidney.³ These T-cells produce cytokines and interleukins that modulate hypertension and end-organ damage in a sex-specific manner.⁴ However, the role of these factors in pathogenesis of organ damage in hypertension needs to be tested in clinical studies.

Cardiac organ damage - more than LVH

Cardiac organ damage is common in hypertension, and may be identified by non-invasive cardiac imaging methods including electrocardiography, echocardiography, cardiac magnetic resonance imaging

and cardiac computed tomography of which the former two are particularly recommended for widespread use.¹

Use of echocardiography may optimize cardiovascular risk assessment and management in many hypertensive patients.¹ Left ventricular (LV) hypertrophy (LVH) is considered the hallmark of hypertensive heart disease and found in 30% of subjects even in mild hypertension, and in up to 90% of subjects with severe hypertension by echocardiography. The prevalence of LVH varies with ethnicity and disproportionately affects black individuals.⁵ LVH is also more prevalent and less modifiable by treatment in women than men.⁶ LVH profoundly influences prognosis in hypertension, and presence of LVH is associated with nearly a tripled risk of cardiovascular events in hypertensive subjects.⁷ LVH also offsets sex-differences in cardiovascular risk, so that women and men have the same risk when LVH is present in hypertension. Several clinical trials have documented that antihypertensive treatment reduces the prevalence of LVH in up to 70% of subjects, particularly by the use of angiotensin II receptor blockers or angiotensin converting enzyme inhibitors. In contrast, studies from clinical practice have demonstrated that LVH regression occurred in a minority, around 14% of subjects. In the Campania Salute Network project, new-onset LVH was detected in 21% of patients during 16 years of follow-up.⁸ Women and obese patients were less likely to achieve LV regression, pointing to the multifactorial pathophysiology of hypertensive organ damage.

Beyond LVH, a number of other measures of cardiac organ damage have been well documented as prognosticators in hypertension, including LV systolic

and diastolic dysfunction and left atrial (LA) dilatation. Thus, hypertensive heart disease should no longer be perceived as synonymous with LVH, but rather as an entity including different types of hypertension-mediated cardiac structural and functional changes that are all associated with high risk for clinical cardiovascular disease. Most hypertensive patients with LVH have normal LV systolic function when measured by ejection fraction (EF) at rest. Reduced EF is more commonly found in men than women, and in patients with reduced renal function or concomitant coronary artery disease. However, reduced LV myocardial function is often found in hypertension despite normal EF when assessed by more sensitive measures such as global longitudinal strain or midwall shortening. Presence of reduced systolic or diastolic LV function is associated with reduced prognosis in hypertension.^{1,2} It is well demonstrated that women have higher indices of LV systolic function than men both in normotension and in hypertension. Thus, sex-specific cut-off values for identification of cardiac organ damage including LVH and LV systolic dysfunction are recommended by current guidelines.¹

LA dilatation may reflect chronically reduced LV diastolic function or atrial cardiomyopathy. In hypertension, LA dilatation is more common in women than in men, and predisposes to atrial fibrillation, heart failure and ischemic stroke. In the community based Tromsø Study, uncontrolled systolic blood pressure was associated with a 2-fold increased risk of atrial fibrillation in women, but only a 50% increased risk in men.⁹ In middle-aged obese subjects, the majority has a dilated LA. The LA is a thin-walled structure, and antihypertensive treatment does not effectively reduce LA size, pointing to the importance of preventing rather than treating cardiac organ damage.

Arterial damage

Increased arterial wall thickness and stiffness may antecede the onset of hypertension, but is also a common type of organ damage in chronic arterial hypertension. The mechanisms of arterial stiffening

involve alteration of extracellular matrix in the arterial wall, smooth muscle cell hypertrophy and endothelial dysfunction that may be linked to aging, sex, obesity, glucose metabolism and genetic factors as well as hypertension. Arterial compliance is physiologically lower in women, while arterial elasticity is higher during the reproductive age, reflecting vascular effects of progesterone and estrogen. Sex differences in arterial inflammation, oxidative stress and major blood pressure regulators also contribute to the observed differences in the arterial function. Arterial stiffness may be assessed by pulse pressure measurement, echocardiography, vascular ultrasound or arterial applanation tonometry.¹ Several clinical studies in hypertension and population-based cohorts have demonstrated that higher arterial stiffness reflected by pulse pressure/stroke volume index or carotid-femoral pulse wave velocity (cf-PWV) predicts increased cardiovascular morbidity and mortality.¹ Women have higher arterial stiffness than men when assessed by pulse pressure/stroke volume index, but lower when assessed by cf-PWV. There is an urgent need for better standardization of diagnosis of increased arterial stiffness in clinical practice, including sex-specific cut-off values for identification. In the Framingham Heart study, increased cf-PWV was found in 60% of controlled and 90% of uncontrolled treated hypertensive subjects, based upon sex-specific mean values for cf-PWV in their cohort.¹⁰ These findings point to the superiority of prevention rather than treatment of arterial organ damage in hypertension.

Conclusion

In conclusion, hypertension-mediated organ damage in the heart and arteries is multifactorial and results from sex-specific interplay between hemodynamic factors, cardiovascular risk factors, co-morbidities and immune activation. Early diagnosis and management of hypertension and other cardiovascular risk factors in the individual subject may prevent development or slow progression of organ damage. Increased understanding of role of the immune system in development of organ damage in clinical hypertension is spoken for.

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Figure 1. Factors impacting development of hypertension-mediated organ damage in the heart and arteries