Hypertension in women - pathophysiological and clinical aspects

Hypertension is the most important risk factor, responsible for cardiovascular morbidity and mortality worldwide, both in men and women. Cardiovascular disorders in women are still underestimated, due to lower absolute risk calculations and the underdetection of classical risk factors. In recent years the differences in pathophysiology and the clinical presentation and treatment of cardiac diseases in women have become fields of interest and research. Several studies have examined gender-related differences in the pathophysiology of hypertension, its prevalence and control. The influence of menopause, obesity and salt-sensitivity on the pathogenesis of hypertension in women has been widely investigated. This article presents current data on differences in prevalence, control and mechanisms of hypertension in women.

Prevalence, awareness and control of hypertension in women

Hypertension (HT) remains important in cardiovascular and cerebrovascular health all around the world. In 2000, 26.4% of the population worldwide was hypertensive and it is estimated to reach as high as 29.2% in 2025 [24]. Poor awareness, control and treatment of high blood pressure (BP) together with its high prevalence exacerbate the problem.

The prevalence of HT varies among countries, and within countries. Some individual factors such as age, gender, weight, coincident diseases, genetic background, dietary habits, physical activity, and environmental factors are known to affect blood pressure [8]. In men, the highest prevalence is in Latin America and the Caribbean and for women in former socialist economies, the lowest prevalence was found in South Korea, Thailand, and Taiwan [24]. According to another set of data, the lowest prevalence was in rural India (3.4% of men, 6.8% of women) and the highest prevalence was in Poland (68.9% of men, 72.5% of women) showing a female predominance [16].

Daugherty et al. compared rates of hypertension control between women and men as a consequence of age. Men had lower rates of HTN control compared to women (41.2 vs. 45.7%). After adjusting for all variables, men continued to have lower rates of HTN control [odds ratio (OR) 0.93, 95% confidence interval (CI) 0.91-0.95]. However, in a stratified analysis, a significant gender by age interaction was found. Men had worse HTN control in the 18-49 year group (P<0.001) and the 50-64 year (P<0.001) age groups, but in the age group 65 years and above, men had better rates of HTN control than women (P<0.001). Younger men had significantly lower rates of HTN recognition and treatment (P<0.001) compared to younger women, whereas older men had significantly higher rates of HTN recognition and treatment compared to older women (P<0.001 for all) [12].

TTEST-1 study was an observational study on 1,494 patients (958 females, 536 males) which showed that blood pressure control is affected by gender difference. Although several sets of controversial data have been published, in our study we found that, after thoughtful education of physicians about current guidelines, blood pressure control was better in men (p<0.007 than women (p=0.05) [16].
Underestimation of cardiovascular risk in women

The novel concept ‘total (global) cardiovascular risk’ indicates the absolute risk of having cardiovascular events in 10 years time [1]. The aim of this concept is to handle a patient not only with high BP level but also with his/her concomitant diseases and risk factors [31]. There are three methods to assess cardiovascular risk: the Framingham Heart Study, SCORE, and ESH/ESC guidelines approach. The two first focus on traditional risk factors such as gender, smoking status, total cholesterol and BP level in SCORE and gender, age, total cholesterol, HDL cholesterol, cigarette smoking, BP level, and diabetes mellitus (DM) in the Framingham Heart Study. The last approach from ESH/ESC guidelines focuses on target organ damage and associated risk factors in cardiovascular disease [16]. The SCORE approach was criticised in ESH/ESC guidelines 2007 that cardiovascular risk in young adults, especially in women, was underestimated because even though they had multiple risk factors they were not able to reach treatment thresholds [31].

Although the absolute risk is lower in women than in men, the proportion of preventable cardiovascular complication is from 30% to 100% higher in women than in men [3].

Data from the prospective analysis of 9,357 subjects followed-up for 11 years show that when assessing the association of cardiovascular complications with 24-hour ambulatory BP and nighttime BP, the relation of all cardiovascular events and stroke and cardiac events with nighttime BP was much steeper in women. Thus, the percentage of preventable cardiovascular and cerebrovascular events in relation to 24-hr systolic blood pressure was significantly higher in women than in men (35.1% vs 19.4% for cardiovascular P<0.001 and, 38.3% vs 25.9% for cerebrovascular; P=0.043) [3].

The lower absolute risk in women should therefore not be considered an excuse for therapeutic laxity. In the assessment of cardiovascular risk in hypertensive women the ESH/ESC risk chart should be recommended, as the inclusion of subclinical organ damage as well as detailed metabolic characteristic lowers the possibility of the misclassification of patients to lower risk groups. On the other hand, women and their healthcare providers should be aware of the ability of 24-hr blood pressure to predict a cardiovascular event in better manner with better precision, and the wider use of ambulatory BP measurement to diagnose and take control of BP should be recommended.

Menopause and hypertension

The prevalence of hypertension in premenopausal women is lower than in men of similar age. This difference is equalized and even reversed as women get older and reach menopausal age. Thus, the question about the influence of menopause on BP arises [11, 53, 36]. Several studies have been performed on this old debate; some of them supported the relationship between menopause and HT whereas some of them didn’t [11]. Studies which indicated a relationship attributes the high prevalence of HT in postmenopausal women to increased body mass index (BMI) [12]. An extensive population-based study by Casiglia et al underlined that postmenopausal women seemed to have higher BP values and worse risk profile than premenopausal women but this was attributable to their older age [6]. On the other hand, some studies found that postmenopausal diastolic BP were found to be higher in menopause-independent of age, BMI, pulse rate, and hormone replacement treatment (HRT) [47]. After five years of the follow-up of 315 women and age and BMI-matched men showed postmenopausal women had higher baseline BP and only peri- and postmenopausal women had an increase in systolic BP of approximately 5 mmHg [48].

In menopause the estradiol and estradiol/testosterone ratio decrease leads to endothelial dysfunction mainly by impaired vasodilation. The data was supported by a prominent decline in flow-mediated dilation (FMD) in postmenopausal women compared to premenopausal women and men [50]. Postmenopausal women who had a significant increase in FMD after antihypertensive treatment experienced fewer cardiovascular events compared to women without FMD improvement [33]. Men and postmenopausal women had impaired nitric oxide (NO) production compared to premenopausal women, which was found by inhibiting NOS synthesis by L-N-nomonomethyl-ar-ginine (LNMMA) and resulted in less vasodilation after NO inhibition [30]. Estrogen therapy improves endothelium-dependent vasodilation both in post-oophorectomy and natural menopause [43]. On the other hand, two studies reported that HRT improves FMD only among women with no cardiovascular risk factors [43, 22]. Arterial stiffening is an independent risk factor in cardiovascular events which nowadays is widely measured by pulse wave velocity (PWV). With aging the aortic PWV and aortic parameter increases and pulse pressure rises. In postmenopausal women the PWV and common carotid artery diameter was higher after adjusting for age, BMI, and smoking [49]. A large study including 3,149 women aged 21 to 94 years indicated that the highest tertile of brachial-ankle PWV was in women aged 45 to 56 years (who were 6 years after menopause), independent of age and other cardiovascular risk factors [57].

Obesity as a risk factor in the pathogenesis of hypertension in women

The coexistence of obesity and HT pointed to common pathophysiological mechanisms in disease development. The involvement of sympathetic nervous system is one of these factors [57]. Lambert et al demonstrated that hypertensive women increased muscle sympathetic nerve activity (MSNA) compared to normotensive women and MSNA was significantly related to BP but not BMI. However, in hypertensive men MSNA was not different from normotensive subjects but MSNA was significantly related to BMI. Despite the same weight loss among men and women subjects, only men had reduced MSNA [27].

Menopause is an additional tissue-derived hormone, responsible for regulating food intake, body weight, and stimulates sympathetic nerve activity in thermogenic and non-thermogenic tissues. It can affect BP in two ways: first by the activation of the sympathetic nervous system, second by nitric- and peripheral vasorelaxant effect on the resistance blood vessels and endothelium [4]. However, chronic hyperleptinemia may lead to abnormal renal sodium retention and renal sympathetic activation mediated vasoconstriction and NO deficiency. Increased amount of body fat in obese subjects strictly correlated with serum leptin levels suggesting leptin resistance in obesity [10]. The leptin level was found to be higher in women than men at each level of BMI. Women were also superior to men in adipose tissue leptin secretion and body fat content. Serum leptin levels and leptin secretion rate correlated with body fat content in either sex. Gender difference in serum leptin and leptin secretion rate remained statistically significant where the values were in range for body weight. From the study by Lambert et al, plasma leptin concentration was found to be higher in women than in both the normo and hypertensive group in relation to BMI but not BP [27]. This was contrary to the other study in which association of serum leptin and BP in postmenopausal women, independent of BMI was documented [35]. Abdominal visceral fat is associated with increased sympathetic overactivity that results in an increase in renin production, angiotensin (AT) 2 and aldosterone production [2], increased inflammatory mediators, oxidative stress, and decreased endothelial vasodilatation [11]. It was realised that being overweight had a stronger association with HT in premenopausal women but HT is strongly associated with age in postmenopausal non-hormone user women [23]. Mettheus et al. indicated the fact that perimenopausal women and women with surgical menopause had higher BMI than premenopausal women when adjusted for age, however physical activity and ethnicity were found to be much stronger predictors of BMI [32]. Left ventricular mass (determined by echocardiography) and body composition (determined by BMI, waist-to hip ratio, and bioelectric impedance method to define adipose tissue and fat-free mass) alterations with increased BMI in men resulted in a much greater increase in lean body weight but in women an increase in body fat was more prominent. After adjusting for age, HT, systolic BP, and DM left ventricular mass indexed for height of fat free mass was greater in obese women compared to obese men. Similarly waist-to-hip ratio and adipose mass contributed to the variability in left ventricular mass in women [13].

Estradiol decreases AT 1 receptor expression in kidneys and vessels [32], and reduces AT 2 activity [13]. AT 2 induced BP increase was more prominent in male mice than female mice. Overiectomised mice responded to AT 2 with respect to changes in NADPH-oxidase and cardiac thioredoxin expression in a similar way as male mice.
Expression of AT 1 receptors in cardiac tissue was not different in male and female mice, excluding the possibility that the difference in response was related to a difference in AT1-receptor density. The evaluation of oxidative and antioxidative responses to AT 2 in vascular and renal tissue rather than in cardiac tissue would be required [19]. Estrogen deficiency in postmenopausal women is associated with increases in angiotensin converting enzyme activity and salt sensitivity and an increase in blood pressure [5].

Sodium intake and salt-sensitivity in the pathogenesis of hypertension in women
Low dietary sodium and high potassium intake reduces BP but it is known to vary among subjects [55,54]. This issue was examined in a Chinese study with 1,906 participants receiving a low salt diet (51.3 mmol or 3 g sodium/ day) for 7 days, and a high salt diet (307.8 mmol or 18 g sodium/ day) for another 7 days. During the first two phases the potassium intake remained unchanged. In the last week all participants received a high salt diet and took a 60 mmol potassium (potassium chloride) supplement daily. The BP responses to low and high salt intake in women was greater than men. Syntonic BP responses to sodium interventions increased with age and both systolic and diastolic BP responses to sodium and potassium increased with baseline BP levels [19]. A recent study from India demonstrated that high salt intake is associated with HT in men but not in women [51]. Postmenopausal women were more prone to sodium premenopausal women [52], and surgical menopause was associated with the development of salt sensitivity [44]. The treatment of postmenopausal women with transdermal estradiol decreased the salt sensitivity of BP [45].

Genetic factors in the pathogenesis of hypertension in women
Hypertension is an example of multifactorial diseases, of which 30% to 50% are due to genetic factors [26,28]. There were specific associations found between HT and genetic polymorphisms on rennin-angiotensin system components [46], NO synthase [7], and aldosterone synthase [41]. In men polymorphism of beta-2 adrenergic receptor and angiotensinogen in women beta-1 and alpha-2 adrenergic receptors have been shown to contribute to BP [40]. Folic acid, specific associations found between HT and genetic polymorphisms on rennin-angiotensin system components [46], NO synthase [7], and aldosterone synthase [41]. In men polymorphism of beta-2 adrenergic receptor and angiotensinogen in women beta-1 and alpha-2 adrenergic receptors have been shown to contribute to BP [40]. Folic acid, specifically polymorphism of beta-3 and alpha-2 adrenergic receptors have been shown to contribute to BP [40].

References
4. Bravo E.P., Morse S., Borne D.M. et al.: Alpha-1 and alpha-2 adrenergic receptors have been shown to contribute to BP [40]. Folic acid, specifically polymorphism of beta-3 and alpha-2 adrenergic receptors have been shown to contribute to BP [40].
5. Brown N.J., Abbas A., Byrne D. et al.: Genotype and genetic polymorphisms on rennin-angiotensin system components [46], NO synthase [7], and aldosterone synthase [41]. In men polymorphism of beta-2 adrenergic receptor and angiotensinogen in women beta-1 and alpha-2 adrenergic receptors have been shown to contribute to BP [40]. Folic acid, specifically polymorphism of beta-3 and alpha-2 adrenergic receptors have been shown to contribute to BP [40].


57. Zaydun G., Tomiyama H., Hashimoto H. et al.: Menopause is an independent factor augmenting the age-related increase in arterial stiffness in the early postmenopausal phase. Atherosclerosis 2006, 184, 137.