Reviews

Hypertension in Women

Michel E. Safar and Harold Smulyan

Essential hypertension presents itself differently in men and women. Before the menopause, there are obvious hormonal differences between the sexes and it is now known that after the menopause, the arterial tree ages differently. At all ages, the shorter stature in women and the obligatory shorter arterial tree induce faster heart rates and earlier reflected arterial pulse waves. These factors operate to influence systolic blood pressure (BP), pulse pressure (PP), PP amplification, diastolic time, and diastolic BP. The circulatory effects of these variables in youth and with aging help to explain the time dependent and aging differences in cardiovascular risk between men and women. The development of left ventricular hypertrophy, isolated systolic hypertension, and the complications after acute myocardial infarction are also explicable in part by these gender-specific hemodynamic factors. Gender differences are also demonstrable in epidemiologic studies. Although an increased systolic BP is a cardiovascular risk in both sexes, a U-shaped curve describes the diastolic BP risk relationship in men but not in women. There is also a difference in the response to antihypertensive therapy, with a lesser benefit for women in heart disease prevention. These findings raise many remaining unanswered questions. Do some antihypertensive agents have gender-specific effects? Are the dose–response curves different for individual drugs or drugs in combination? Should therapeutic targets for systolic BP, diastolic BP, or PP differ between the sexes? Future answers to such questions would reduce the therapeutic trial and error now necessary for the selection of an individual patient’s antihypertensive regimen. Am J Hypertens 2004;17:82–87 © 2004 American Journal of Hypertension, Ltd.

Key Words: Hypertension, women, arterial distensibility, aging, antihypertensive therapy.

Differences between men and women in the pathophysiology, risks, and treatment of essential hypertension have been noted for many years. Messerli et al. who reported on disparate cardiovascular findings in the two sexes in 1987, also noted that clinical differences had been described as early as 1913 by Jane-way and later by Pickering in 1955. More recent reviews of the literature have kept the issue alive stressing the lack of information on the mechanisms for the gender differences between the young and the old and even hints that the results of antihypertensive therapy may also differ. If true, in the future unisex treatment may become outdated.

Some similarities between the sexes do exist. In both men and women the mechanisms of most hypertension remains unknown, and hypertension continues to be a strong determinant of cardiovascular disease in both sexes. Despite these similarities, there are a few primary causes of hypertension that occur only in women. These include eclampsia in pregnancy and the hypertension associated with the use of contraceptive agents. Women also differ from men in that their development of cardiovascular (CV) disease is delayed approximately 10 years. These observations have led to the speculation that, before the menopause, the female sex hormones offer risk protection unavailable to men. Unfortunately, postmenopausal hormone replacement has not proved to be an effective preventive measure. Nonetheless, the recently demonstrated relationships between estrogens and improved endothelial function suggest that hormonal changes may still be important in the mechanism of hypertension in women. In addition, there are at least two other hemodynamic, nonhormonal differences that may also account for the behavior of hypertension between the sexes—wave reflections and heart rate.

The purpose of this review is to expand on these nonhormonal, hemodynamic relationships in women as well as their associations with the age-delayed CV risks and their influence on the effectiveness of long-term drug treatment of hypertension.

Hemodynamic Characteristics of Hypertensive Women

At all ages in our previous study, women had a lower brachial systolic blood pressure (BP), diastolic BP, and mean BP than men, but they also had a lower brachial
pulse pressure (PP) below age 40 years and a higher PP over age 55 years (Fig. 1). Two important factors help to explain these findings—early wave reflections due to short stature and high heart rate.

First, the short stature in women, when compared to men, imposes a reduced length of the arterial tree now believed responsible for differences in ventriculovascular coupling. After ventricular ejection, the pressure wave propagates along the arterial tree at a given pulse wave velocity (PWV), which is governed by the wall stiffness of the conduit. The wave reaches relative obstructions at arterial branch points and the arterioles, where some of the pressure wave is reflected and returns toward the heart. At a normal PWV, the reflected wave reaches the central aorta in late systole or early diastole of the same beat (Fig. 2). The shorter the arterial tree, and the faster the incident and reflected waves travel, the more likely the reflected waves will return to the central aorta in early to mid systole where they amplify the peak systolic pressure. By failing to return in diastole, the reflected waves do not reinforce the diastolic pressure on which coronary flow is dependent.

Second, a faster heart rate, known also to be related to arterial tree length, induces a shorter diastolic period, a more rapid fall off in diastolic pressure, a lower stroke volume, and a significantly lower aortic diastolic BP at all ages in women in comparison with men (Fig. 1). Other things being equal, the faster heart rate alone could account for the lower systolic BP in women. This is true especially in young women in whom the amplification of the primary systolic wave by reflections is less than in older women due to the younger, more compliant arterial tree and the slower PWV. Because in young women, the brachial systolic BP is much lower than in men and the diastolic BP less so, the PP is also lower than in men. Those factors in women that derive from body size remain throughout life, but are modified by arterial stiffening with aging in ways that differ from men.

With loss of estrogen at the menopause, there is no abrupt increase in BP, but there is elastin fragmentation and collagen accumulation in the arterial tree, with a substantial increase in the intrinsic rigidity of the arterial wall. This induces an increase in PWV, which occurs more rapidly with aging in women than in men, resulting in a more rapid increase over time in brachial and central systolic BP in women than in men. The greater increase in

FIG. 1. Effects of aging on systolic blood pressure (SBP), pulse pressure (PP), diastolic blood pressure (DBP), and pulse wave velocity (PWV). (Left A) SBP by gender (P < .001) and evolution by age (P < .001). (Left B) DBP by gender (P = .01) and evolution by age (P < .001). (Right A) PP by gender (P = NS), evolution by age (P < .001) and age–gender interaction (P = .02). (Right B) PWV by gender (P = NS) and evolution by age (P < .001). Pairwise comparisons made using a Bonferroni test. Reprinted from J Am Coll Cardiol, with permission from The American College of Cardiology Foundation.

FIG. 2. Effect of reflected waves on recorded pressure pulses in the central and peripheral arterial tree. (A) In youth; (B) in the elderly. Incident wave into the periphery (coarse dotted line); reflected wave from the periphery (fine dotted line); recorded wave (solid line).
systolic BP with aging in women reverses the lower PP found in young women, to a higher PP in older women than in older men (Fig. 1). Thus, at more than 50 years of age, an increased prevalence of isolated systolic hypertension is observed in women, probably due both to early wave reflections from a short arterial tree and increased aortic rigidity.

To summarize the hemodynamic changes in women, the low brachial and central diastolic BP and altered wave reflections are a consequence of short stature at any age, whereas the high brachial and central systolic BP and PP are mainly due to the postmenopausal development of central conduit artery stiffening superimposed on the shorter arterial tree. Thus, the hemodynamic patterns of aging differ in hypertensive men and women with a predominant resistive component in men and a predominant capacitive component in women.

PP Amplification and Diagnostic Difficulties in Hypertensive Women

In both men and women, mean BP remains nearly constant along the arterial tree, whereas PP increases markedly from central to peripheral arteries. This PP amplification is due to the propagation of the pressure wave within progressively narrower and stiffer vessels and the resulting summation of wave reflections. Thus, in young normal subjects, systolic BP increases by 12 to 14 mm Hg from the aorta to the brachial artery, whereas diastolic BP slightly decreases approximately 1.0 mm Hg. Therefore, in both men and women, central and brachial diastolic BP are nearly the same, whereas brachial systolic BP is markedly higher than that in the carotid artery or aorta (Fig. 2). Due to the differences in wave reflection and stroke volume, brachial systolic BP is higher in men than in women, whereas carotid systolic BP is almost identical. However, in both sexes, PP amplification is markedly influenced by two similar factors: heart rate and aging.

With faster heart rates and a reduced duration of the ejection fraction, there is a substantial increase in PP amplification in men and women. This has also been shown in studies using atrial pacing. Under baseline conditions, this hemodynamic change is most obvious in young women who have faster heart rates than young men, and a higher systolic BP (≥14 mm Hg) in the brachial artery than in central arteries. With anxiety-induced tachycardia in young women, increased brachial systolic BP may be an explanation for their “white coat hypertension.” Thus, as a consequence of tachycardia, brachial systolic BP may be elevated while carotid and aortic systolic BP remain normal. This suggests caution in the diagnosis of hypertension in young women—especially those with tachycardia.

With aging there is a tendency for brachial and aortic systolic BP to increase but aortic systolic BP increases more than brachial systolic BP, because the initially compliant aorta stiffens more than the initially stiff brachial artery. Thus, at more than 50 years of age, the two systolic BP levels become nearly equal (Fig. 2). This hemodynamic response to aging is observed both in men and women, but the effect on brachial PP is different because at all ages, diastolic BP is lower in women than in men. As mentioned, young women have a more compliant central arterial tree than young men, but with aging the aorta becomes stiffer in older women than in older men. This also helps to account for the smaller PP in young women and the larger PP in older women than in men of similar ages (Fig. 1). In the Framingham Study, a lower diastolic BP and higher PP for any given systolic BP were related to increased CV risk, but there was no analysis of gender differences.

The diminished aortic distensibility with aging has been found to correlate with increasing follicle-stimulating hormone levels in women. This correlation is compatible with, but does not prove, a causal hormonal relationship. Associated genetic factors may also play a role in the development of age-related arterial stiffness. Telomeres shorten in everyone with aging but the telomeres of women are longer than those of men at all ages. In a French population of men and women, telomere length was significantly related to PP in men but not in women. This was also true of the relationships between telomere length and PWV, a surrogate for central aortic stiffness. Thus, telomere length, an index of biological aging, is more influential on arterial aging in men than in women. These relationships confirm gender differences but do not guarantee causality.

Epidemiologic Findings

The incidence of coronary and cerebrovascular events in women at all ages is substantially lower than in men but increases disproportionately in women after the menopause. The mechanisms underlying postmenopausal loss of cardioprotection are unclear but gender differences in diastolic BP and PP may contribute to these differences in the rapidly increasing CV risk in women. There is little information, however, to support a direct effect of heart rate on CV risk in women. Postmenopausal women in many normotensive and untreated hypertensive populations exhibit a greater increase in PP, due to both a greater increase in systolic BP and a greater decline in diastolic BP than do men over a similar age range. This may explain the greater incidence of isolated systolic hypertension in elderly women than in elderly men. Because PP predicts stroke, myocardial infarction, CV mortality, and all-cause mortality independent of other BP indices, gender differences in PP might be expected to confer gender-specific risk. The higher PP observed in older women is consistent with the greater age-related increase in left ventricular mass and the prevalence of left ventricular hypertrophy compared with age-matched men.
These data may further explain the greater age-related mortality and incidence of complications after myocardial infarction including angina, congestive heart failure, and reinfarction in elderly women compared to men.35–37

To further illustrate this issue, the role of CV mortality for different systolic BP levels has been recently studied in middle-aged men and women. The goal was to investigate whether diastolic BP in addition to systolic BP should be considered for better risk evaluation.38 Subjects (77,023 men; 48,480 women) aged 40 to 70 years with no major CV disease and no antihypertensive treatment were examined in Paris between 1972 and 1988. In both sexes, CV mortality increased with the systolic BP level. In men and women with normal systolic BP (≤140 mm Hg), diastolic BP did not influence CV mortality after adjustment for age and systolic BP. In men with systolic hypertension, a U-shaped curve related CV mortality and diastolic BP with the lowest mortality rates in the group whose diastolic BP ranged from 90 to 99 mm Hg. Age- and systolic BP-adjusted CV mortality was higher in men by 73% (P < .02) in the group with diastolic BP <90 mm Hg and by 65% (P < .001) in the group with diastolic BP ≥110 mm Hg. In contrast, in women with systolic hypertension, diastolic BP was positively and linearly correlated with CV mortality (Fig. 3). Therefore, in middle-aged subjects, classification of CV risk according to diastolic BP levels should take gender into account, when systolic BP levels are elevated. Men with systolic hypertension are at higher risk when their diastolic BP is “normal” (<90 mm Hg) than when their diastolic BP is mildly to moderately elevated.39 In women of the same age, however, systolic-diastolic hypertension represents a higher risk than isolated systolic hypertension. Finally, not only do young and middle-aged women have a lower CV risk than men of the same age, but the risk also differs according to the gender-related contribution of systolic BP and diastolic BP among those who are hypertensive.

**FIG. 3.** Cardiovascular mortality adjusted for diastolic blood pressure (DBP) in men and women. Calculations using a Cox proportional hazards regression for men (left) and women (right) with high systolic blood pressure (SBP) (≥150 mm Hg) according to DBP levels. For the same SBP level, there is a U-shaped relationship between DBP and cardiovascular mortality in men, with a linear relationship in women. *P < .02; **P < .001 v DBP 90 to 99 mm Hg; \( P < .01 \) (χ² trend test). Reprinted from *J Am Coll Cardiol,*39 with permission from The American College of Cardiology Foundation.

Antihypertensive Therapy and Therapeutic Trials in Hypertensive Women

From a historic perspective, it is noteworthy that the first therapeutic trial in hypertensive subjects was conducted exclusively in men, all selected from the US veterans population after the second World War.40 Subsequent therapeutic trials were performed in mixed populations of men and women, with the major entry criterion being an elevated diastolic BP, independent of age or gender. The first meta-analysis of the various therapeutic trials of hypertension indicated that a diastolic BP reduction of 5.7 mm Hg was associated with an approximate 40% reduction of strokes and an 8% reduction of coronary heart disease.31 This value of 5.7 mm Hg is very close to the differences in diastolic BP observed when large populations of untreated men and women are compared. In fact, the first demonstrated reduction of cardiovascular risk in women induced by the drug treatment of hypertension was noted in the Hypertension Detection and Follow-up Program6,42 and in the three major trials in isolated systolic hypertension.24 Here, CV morbidity and mortality were investigated in populations of elderly subjects with isolated systolic hypertension, the majority of whom were women. But, in this meta-analysis, the absolute benefit of therapy was greater in men.

In 1997, Gueffier et al43 compared the effects of antihypertensive drug treatment in 20,802 women and 19,975 men taken from a meta-analysis of seven previous therapeutic trials. From these trials, five were performed in elderly hypertensive subjects (mainly subjects with isolated systolic hypertension) and two trials in younger subjects with mild-to-moderate hypertension (mainly subjects with systolic–diastolic hypertension). Thus, the inclusion of subjects at entry was based on either systolic BP or on diastolic BP, or both. The odds ratios for benefit in any category of CV event did not differ significantly between men and women (Table 1). In absolute terms, the benefit in women was seen primarily for strokes, whereas in men, treatment prevented as many coronary events as strokes. They discussed the absolute risk reduction attributable to treatment that depended mainly on untreated risk, but this parameter was difficult to separate by gender in a meta-analysis of such a heterogeneous groups of subjects. Another report has also indicated that antihypertensive medications did not appear to be as effective in women as in men.44

There is much left to do to identify possible gender-specific differences in therapy. As previously described, the development of high systolic and PPs with aging is not the same in the two sexes, leading to the suspicion that the response to specific therapeutic agents may also differ. This has been recently confirmed by the observation that the absolute benefits of angiotensin-converting enzyme inhibitors differ in men and women.45 Many early trials used a defined reduction of the elevated diastolic BP as an
end point of therapeutic success. But in retrospect, this experimental design did not address the issue of an elevated systolic BP or PP, now recognized as major predictors of CV risk. The diastolic BP end point strategy also offered little help to the clinician treating the increasing numbers of elderly with isolated systolic hypertension, in whom the diastolic BP was already normal or low. Clinicians have had to determine, using educated trial and error, the most effective dose of each drug, alone or in combination, in each individual patient. Because it is known that there is no strict parallelism in the relative reduction of systolic BP and diastolic BP (and hence PP) for each antihypertensive agent and even less predictive value for gender differences, drug and dose choices must now be individualized. There is, however, growing interest in systolic BP and diastolic BP responses to single drugs in increasing doses (dose–response curves) as well as to drugs in combination.46,47 Future studies, which could identify such gender-specific dose responses, would find clinical utility in the selection of antihypertensive drugs and their doses.

**Conclusions**

Hypertensive men and women differ not only endocrinologically, but also in terms of their stature and the way in which the arterial tree ages. These factors influence hemodynamic settings, control of heart rate, PP, and cardiovascular risk. The direct comparison of men and women of the same age and mean BP has never been studied prospectively in a large population for the reduction of CV risk. Therefore, whether the drug treatment of hypertension in women is identical or different from that in men appears likely, but remains to be clearly identified.

**References**

6. Hypertension Detection and Follow-Up Program Cooperative Group: Five-year findings of the hypertension detection and follow-up program II. Mortality by race, sex and age. JAMA 1979;242:2572–2577.

**Table 1.** Estimate treatment effect by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Mortality</th>
<th>Cardiovascular-Related Death</th>
<th>Main Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>0.91 (0.81–1.01)</td>
<td>0.86 (0.74–1.01)</td>
<td>0.74 (0.66–0.83)</td>
</tr>
<tr>
<td>P</td>
<td>.094</td>
<td>.068</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>0.88 (0.80–0.97)</td>
<td>0.80 (0.70–0.91)</td>
<td>0.78 (0.71–0.86)</td>
</tr>
<tr>
<td>P</td>
<td>.013</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Reprinted with permission from the *Annals of Internal Medicine.*