Estrogens, Salt, Blood Pressure, and Cardiovascular Disease in Women
How Do We Interpret the Data?

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Until recently cardiovascular disease in women has been a largely neglected and poorly understood issue, in part related to the misconception of a lower incidence among females compared with males, underrepresentation of females in clinical trials and observational studies until recently, and nontraditional presentation of symptoms in many females. Women have been typically viewed as largely protected from cardiovascular disease until menopause, and thereafter a rise in prevalence has been recognized, presumably related to hormonal decline.

Hormonal replacement therapy (HRT) has been viewed as a useful prophylactic approach to ward off such events after menopause as well as to minimize menopausal symptoms. However, recent studies have yielded conflicting results regarding the protective effects of estrogen administration in preventing myocardial infarction and stroke. Indeed, the results of the Women’s Health Initiative have been interpreted as showing a neutral effect of estrogen administration in women in the 50 to 59 age decile and an adverse cardiovascular effect in older subjects. Whereas different pharmacological regimens may have been used in these replacement trials, the impact of these regimens on known risk factors for cardiovascular disease, such as blood pressure, lipoprotein profiles, insulin sensitivity, endothelin, C-reactive proteins, and other vasoactive substances, has not been carefully investigated.

The relationship between estrogen and progesterone administration in the form of oral contraceptives and blood pressure, a major risk factor for stroke and cardiovascular disease, has been recognized for 4 decades. Population studies have documented a small but significant rise in systolic blood pressure in women receiving oral contraceptives in the 1970s, but only a small proportion of such women demonstrated a rise into the hypertensive range. Whereas epidemiologists remind us repeatedly that a small upward shift in blood pressure for an entire population can have dramatic effects on cardiovascular outcome, clinical concern has been focused on the minority of women developing hypertension with these agents. The prevalence of hypertension declined with the reduction in dose of estrogen in contraceptive preparations that occurred in the 1980s and thereafter. This has been counterbalanced by the increased use of HRT in postmenopausal women. The age-related increase in blood pressure, particularly systolic pressure, that is notable after age 50 occurs in both men and women, as does the increased prevalence of hypertension. The slope of this relationship may be even steeper in women than in men. Salt-sensitivity of blood pressure, as defined by conventionally accepted methods, has also been shown to increase with age. Some, but not all, studies have suggested a gender difference in salt-sensitivity of blood pressure. It is reasonable to attribute such age-related changes in blood pressure and salt sensitivity, at least in part, to the dramatic hormonal alterations that occur with menopause and to consider the benefits of HRT. Thus the report by Schulman and colleagues in the current issue of Hypertension is of particular interest.

These investigators performed a novel salt-sensitivity test in 40 middle-aged women undergoing hysterectomy-oophorectomy for non-neoplastic processes before surgery and 4 months later. They observed a greater rise in blood pressure following an acute intravenous saline infusion in those defined as salt-sensitive with a similar fall in blood pressure following administration of intravenous furosemide. The number of women demonstrating salt-sensitivity with this technique increased significantly 4 months after surgery. Unfortunately, the investigators did not compare the results of their novel protocol with other salt-sensitivity protocols to confirm the validity of the technique. The authors argue that their protocol may have actually underestimated the actual frequency of salt-sensitivity. Nonetheless, it would be reassuring to know that this approach is congruent with others used for the same purpose.

Studies have confirmed that the responses of other acute protocols for the definition of sodium sensitivity are correlated with the blood pressure response to dietary manipulations of sodium intake. Whereas the technique used in the study of Schulman and colleagues involves rapid sodium loading by administration of intravenous saline, the sodium and volume depletion induced by intravenous administration of 40 mg of furosemide during a 3-hour period may not necessarily equate to a 24-hour period of low sodium intake and volume depletion with oral furosemide. Intravenous furosemide may have effects that are different from those of orally administered drug.

There are several apparent differences that emerge between the results with this technique and previous reports using...
other methods. Whether these differences relate to the methods used or the population studied is not clear. The original study by Barter and colleagues noted no differences in blood pressure following a high-salt diet in comparison to baseline measures; rather it was the response to the low-salt diet that defined salt-sensitivity and resistance. Similarly, the method used by our group and many others involving rapid volume expansion with a 2-L intravenous infusion followed the next day by a low-salt diet and 3 doses of oral furosemide separated salt-sensitive and resistant subjects on the basis of the magnitude of decrease in blood pressure with sodium and volume depletion rather than a rise with salt loading, which was not observed. Moreover, virtually all investigators who have examined this issue report an exaggerated natriuresis in salt-sensitive subjects in comparison with non-salt-sensitive or salt-resistant individuals. Yet the “salt-sensitive” subjects of Schulman’s study had lower urinary salt excretion in response to intravenous furosemide despite greater weight loss and blood pressure reduction.

Another consistent observation has been a suppressed or sluggish response of the renin–angiotensin system to the low-salt diet or volume depletion maneuver. Because estrogen therapy increases angiotensinogen (renin substrate), thereby increasing renin activity (ie, angiotensin generation), one would anticipate lower renin levels and thus greater salt-sensitivity as manifest by a greater fall in blood pressure with sodium and volume depletion following oophorectomy. Unfortunately, renin levels were not reported in the present study. Curiously, the urinary sodium excretion data presented suggests that the subjects were ingesting 30% to 50% more sodium than the nominal 120 mmol/d at baseline. Beyond these methodological issues, what are the broader implications of these findings in a small group of 45 to 52 year-old women undergoing surgical menopause?

The study by Schulman and colleagues suggests that surgical menopause is rapidly followed by dramatic changes not only in the acute blood pressure responses to an intravenous salt load but also to a variety of alterations that have been described as components of the metabolic syndrome and have been linked to an increased risk of cardiovascular events. The authors quite appropriately focused on blood pressure, a measure influenced by a multitude of factors. Similarly, the etiology of hypertension as a major risk factor for cardiovascular and renal disease is also heterogeneous and multifactorial. Most investigators confirm that many hypertensive subjects are salt-sensitive, but the etiology of this phenomenon is also multifactorial. In some hypertensive subjects, salt-sensitivity can be clearly linked to abnormal and autonomous hyperproduction of aldosterone (primary aldosteronism) whereas in others, relative aldosterone excess within the normal range has been proposed. For many salt-sensitive subjects an inability to stimulate renin release in response to a decrease in blood pressure or reduction in perceived extracellular fluid volume appears to be involved. This may be because of renal parenchymal disease, age-related decrease in adrenergic responsiveness, reduced nephron mass, alterations in angiotensin II receptor activity, or other renal factors.

Perhaps the cohort studied by Schulman and colleagues permits the addition of yet another etiology, the sudden withdrawal of ovarian hormones in middle-aged women. It will be of great interest to observe whether these changes can be reversed by estrogen administration and to understand further the mechanisms that may be involved. However, evaluation of that possibility will not be an easy task. As previously noted, blood pressure responses to estrogen administration are dose-dependent, as evidenced by the historic observations with oral contraceptives as well as by the observations that whereas menopausal symptoms can be largely ameliorated by administration of conjugated equine estrogen in doses of 0.3 mg daily, larger doses are associated with higher prevalence of hypertension and a lack of cardiovascular disease benefit as demonstrated by the Women’s Health Initiative. Moreover, the route of administration of estrogen may also have very different effects on vasoactive substances as was observed when oral and transdermal estrogen administration were compared in postmenopausal women. In summary, new observations raise new questions and the joy of discovery continues.

References

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