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 Bartter 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-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 loss and blood pressure reduction.

References

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