J Exp Clin Med 2011;3(3):112–115

Contents lists available at ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Hormone Therapy and Blood Pressure in Postmenopausal Women

Hiroyuki Sumino [1]*, Shuichi Ichikawa [2], Shu Kasama [2], Takashi Takahashi [3], Hisao Kumakura [2], Yoshiaki Takayama [2], Kazutomo Minami [2], Tsugiyasu Kanda [4], Masahiko Kurabayashi [5], Masami Murakami [1,6]

[1] Clinical Laboratory Center, Gunma University Hospital, Maebashi, Gunma, Japan
[2] Department of Cardiology, Cardiovascular Hospital of Central Japan, Shibukawa, Gunma, Japan
[3] Laboratory of Infectious Diseases, Graduate School of Infection Control Sciences, Kitasato University, Minato-ku, Tokyo, Japan
[4] Department of Community Medicine, Kanazawa Medical University Himi Municipal Hospital, Himi, Toyama, Japan
[5] Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan
[6] Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

ARTICLE INFO

Article history:
Received: Dec 3, 2010
Revised: Jan 31, 2011
Accepted: Feb 21, 2011

KEY WORDS:
angiotensinogen;
blood pressure;
estrogen;
postmenopausal women;
progesterone

Blood pressure increases in many women after menopause. Ovarian hormones, particularly estrogen, may be responsible, at least in part, for the lower blood pressure in premenopausal women. However, the mechanisms responsible for the increase in blood pressure in women after menopause are not yet fully known. In this article, we focused on estrogens and reviewed the effects of estrogen on the clinic blood pressure in women. Oral high-dose conjugated equine estrogen (CEE) administration and oral contraceptive use have been reported to increase the blood pressure in women. On the other hand, although oral common- and low-dose CEE administration had little effect on the blood pressure in younger postmenopausal women, oral common-dose CEE administration produced a slight increase of the blood pressure in older postmenopausal women with or without an established coronary heart disease. Transdermal 17β-estradiol had either no effect or produced a slight decrease in blood pressure in postmenopausal women. Raloxifene had no effect on blood pressure in postmenopausal women. In addition, concomitant administration of progestogens had little additional effect on the blood pressure in women receiving estrogen therapy. Oral high dose of CEE administration and oral contraceptive administration to post- and premenopausal women, respectively, and oral common-dose CEE administration to older postmenopausal women with or without established coronary heart disease should call for caution, particularly in individuals with uncontrolled hypertension. Further large, long-term, controlled, randomized studies are needed to confirm these findings.

1. Introduction

Before menopause, blood pressure is lower in women than that in age-matched men.[1,2] In both aging men and women, the systolic and diastolic blood pressures increase, although in later years, the diastolic blood pressure plateaus or even declines.[1,3] The first decade after menopause is accompanied by an increase of the blood pressure.[1,3] In the 7th decade of life, the prevalence of hypertension among women is higher than that in men.[1,3] Ovarian hormones, particularly estrogens, may be responsible, at least in part, for the lower blood pressure in premenopausal women and for the increase in blood pressure in postmenopausal women. However, the increase in blood pressure in postmenopausal women does not occur as soon as the ovary becomes senescent but, rather, over a number of years.[4] Although other factors, such as endothelial function, endothelin, oxidative stress, renin–angiotensin–aldosterone system (RAAS), obesity, and the sympathetic nervous system, may also contribute to the increased blood pressure in postmenopausal women,[5,6] the mechanisms responsible for the increased blood pressure in women after menopause are not yet fully understood. In this article, we focused on estrogens and reviewed the effects of estrogens on the clinic blood pressure in women (Table 1).

2. Estrogens and Blood Pressure

2.1. Oral conjugated equine estrogen

Data on the effects of oral conjugated equine estrogens (CEEs) on the clinic blood pressure are inconsistent and include reports of little effect on the blood pressure[7–19] as well as of blood pressure elevation.[20–23] Some studies demonstrated that oral high-dose

* Corresponding author. Clinical Laboratory Center, Gunma University Hospital, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan.
E-mail: H. Sumino <suminoh@med.gunma-u.ac.jp>

1878-3317/$ – see front matter
doi:10.1016/j.jecm.2011.04.005

Table 1 Effects of hormone therapy on blood pressure in postmenopausal women

Parameter	Oral CEE			Oral contraceptive	Transdermal E2	Oral raloxifene		Progesterone		
	High dose, 1.25 mg/d	Common dose, 0.625 mg/d	Low dose, 0.3125 mg/d			High dose, 120 mg/d	Common dose, 60 mg/d	MP	MPA	
								Cyclic	Continuous	Cyclic
Blood pressure	Increase	No change (younger) Increase (older)	No change	Increase (premenopausal women)	No change or decrease	No change	No change	No change	No change	No change

CEE = conjugated equine estrogen; E2 = 17β-estradiol; MP = micronized progesterone; MPA = medroxyprogesterone acetate.

administration of CEE (1.25 mg/d), isolated from the urine of pregnant mares, increased the blood pressure.[23] A postmenopausal woman developed hypertension after high-dose CEE administration for 5 months; however, she became normotensive at 3 months after discontinuation of the therapy.[23] On the other hand, oral low-dose administration of CEE (0.3 mg/d) alone or CEE combined with oral medroxyprogesterone acetate (MPA) for 3 months to healthy postmenopausal women had no impact on the blood pressure.[8,19] Hepatic first-pass metabolism of orally administered CEE at a high dose induces the RAAS, resulting in overproduction of angiotensinogen, whereas oral low dose of CEE may show negligible hepatic first-pass effect and RAAS activation.

Several small clinical studies have reported the effects of oral common-dose administration of CEE (0.625 mg/d) on the blood pressure in relatively young (mean age less than 60 years) and relatively old (mean age greater than 60 years) postmenopausal women. Oral common-dose administration of CEE alone or CEE combined with MPA to normotensive and hypertensive younger postmenopausal women had no effect on the blood pressure.[8–19] Common-dose administration of CEE for 3 months had no effect on the blood pressure in normotensive[8] and hypertensive younger postmenopausal women who were not receiving antihypertensive drug treatment.[9] Common-dose administration of CEE with MPA for 3–24 months also had no effect on the blood pressure in normotensive and hypertensive younger postmenopausal women receiving antihypertensive drug treatment.[10–19] In addition, several large randomized clinical trials have investigated the effects of hormone therapy on blood pressure in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions Trial found no significant change of the blood pressure among 875 healthy young normotensive postmenopausal women randomized to receive oral common-dose CEE treatment alone, CEE in combination with MPA or micronized progesterone, or placebo for 3 years.[7] The Women's Health Initiative (WHI) reported a slight but significant increase of the systolic blood pressure by 1.5 mmHg, but not of the diastolic blood pressure, after a follow-up period of 2 years in 8506 healthy older postmenopausal women with intact uteri treated with a combination of CEE and MPA.[21] Another WHI trial of 5310 older postmenopausal women who had undergone hysterectomy demonstrated a slight but significant increase of the systolic blood pressure by 1.1 mmHg, but not of the diastolic blood pressure, after oral common-dose administration of CEE alone.[22] The Heart and Estrogen/Progestin Replacement Study also confirmed the slight systolic blood pressure–elevating effects of oral common-dose CEE plus MPA treatment in 1380 older postmenopausal women with established coronary heart disease.[20] In the Heart and Estrogen/Progestin Replacement Study and the WHI, common-dose administration of CEE alone or CEE in combination with MPA to older postmenopausal women with or without established coronary heart disease resulted in only minimal changes of the systolic blood pressure after several years of follow-up.

The mechanisms by which oral common-dose administration of CEE might increase the blood pressure in older postmenopausal women with or without established coronary heart disease, but not in younger postmenopausal women, still remain unclear. However, some possibilities are considered. Endothelial dysfunction could contribute to the increased blood pressure. Studies in older postmenopausal women with[24] or without[25] established coronary artery disease found no significant effect, whereas those of relatively young healthy postmenopausal women showed significant improvement of the endothelial function by oral common-dose CEE therapy.[26] Although oral common-dose administration of CEE promotes angiotensinogen production by means of hepatic first-pass metabolism in both younger and older postmenopausal women, such administration improves endothelial function only in younger postmenopausal women and not in older postmenopausal women with or without an established coronary heart disease. Thus, common-dose CEE treatment appears to have little effect on the blood pressure in younger postmenopausal women but appears to increase the blood pressure in older postmenopausal women with or without established coronary heart disease.

2.2. Transdermal 17β-estradiol

To date, the effects of transdermal estrogen on the clinic blood pressure have not been well studied. No effect of the administration of transdermal 17β-estradiol for 12 months was observed on the blood pressure in either normotensive or hypertensive postmenopausal women.[27–30] Transdermal 17β-estradiol treatment with MPA for 12 months or 24 months lowered the blood pressure in normotensive postmenopausal women.[16,18] Transdermal application of estrogens avoids hepatic first-pass and RAAS activation. Therefore, transdermal 17β-estradiol administration may have either no effect or produce a small decrease of the blood pressure in postmenopausal women. Larger clinical trials of transdermal estrogen with longer durations of follow-up would be needed to confirm these findings.

2.3. Oral contraceptives

Use of oral contraceptives has been shown to be associated with hypertension. In 22 premenopausal women who developed hypertension while on oral contraceptive pills, the blood pressure levels returned to normal after discontinuation of the oral contraceptive (the blood pressure levels before, during, and after the discontinuation of oral contraceptive use were 125/76 mmHg, 183/110 mmHg, and 130/82 mmHg, respectively).[23] In a prospective cohort study of 68,297 healthy premenopausal nurses, current users of oral contraceptives had an increased risk of development of hypertension (relative risk = 1.8; 95% confidence interval = 1.5–2.3).[31] It is important to note that the estrogens used in contraceptive pills (e.g., ethinyl estradiol) are different from the natural estrogen, estradiol (e.g., 17β-estradiol). Unlike the natural estrogen, estradiol, the synthetic estrogen ethinyl estradiol increases the blood pressure,[32] suggesting that the effects of natural and synthetic estrogens differ markedly and may influence

the mechanisms involved in the regulation of blood pressure. For example, even though contraceptive estrogens are administered at lower doses (30–200 μg) than estrogens (0.625–2 mg) used for hormone therapy, contraceptive estrogens increase the blood pressure.[32] Oral contraceptives may induce hepatic synthesis of angiotensinogen more strongly than oral estrogens used for hormone therapy.

3. Selective Estrogen Receptor Modulators and Blood Pressure

Raloxifene, a benzothiophene derivative that binds to the estrogen receptor,[33] is a selective estrogen receptor modulator. Raloxifene has estrogen-agonist effects on the bones and lipid profile, and estrogen-antagonist effects on the breast and uterus.[34,35] Several small clinical studies have investigated the effects of oral common-dose administration of raloxifene (60 mg/d) on the clinic blood pressure in postmenopausal women. Common-dose administration of raloxifene for 6 months or 12 months had no effect on the blood pressure in either normotensive or hypertensive osteoporotic postmenopausal women under antihypertensive drug treatment,[36,37] which was associated with a lack of effect of oral raloxifene on the components of the RAAS.[36] In addition, a large randomized clinical trial investigating the effects of raloxifene on the clinic blood pressure in postmenopausal women found no significant effect of the drug on the blood pressure after 6 months among 390 healthy postmenopausal women randomized to common- or high-dose (120 mg/d) raloxifene treatment or placebo.[35] Although the mechanisms explaining the lack of effect of oral raloxifene on the components of the RAAS and blood pressure in postmenopausal women remain unclear, raloxifene administration appears to have no effect on the blood pressure in postmenopausal women.

4. Progesterone and Blood Pressure

In women with intact uteri receiving estrogen therapy, concomitant administration of either natural progesterone or a synthetic progestin is necessary to prevent endometrial hyperplasia and carcinoma. Natural progesterone, such as micronized progesterone, has no androgenic properties, whereas some synthetic progestins, such as MPA and norethisterone acetate, possess androgenic side effects, which raise the concern of potentially harmful effects on blood pressure regulation. Concomitant administration of MPA or norethisterone acetate has been shown to attenuate estrogen-induced increase in the production of nitric oxide[38] and prostacyclin[39] in endothelial cell cultures. However, the Postmenopausal Estrogen/Progestin Interventions Trial showed no significant change in blood pressure after 3 years in healthy normotensive postmenopausal women randomized to oral common-dose treatment with CEE alone, CEE in combination with cyclic or consecutive MPA or cyclic micronized progesterone, or placebo after 3 years.[7] Taken together, progestogens given in either cyclic or consecutive regimens of hormone therapy may have little additional effect on the blood pressure.

5. Conclusion

The literature on the effects of estrogens on the clinic blood pressure in women is confusing and inconsistent. Oral high-dose CEE treatment and oral contraceptive use increase the blood pressure in women. On the other hand, although oral common- and low-dose CEE treatment has little effect on the blood pressure in younger postmenopausal women, oral common-dose CEE treatment produces a small increase in blood pressure in older postmenopausal women with or without an established coronary heart disease. Transdermal 17β-estradiol has either no effect or produces a small decrease in blood pressure in postmenopausal women. Raloxifene has no effect on the blood pressure in postmenopausal women. In addition, concomitant administration of progestogens has little additional effect on the blood pressure in women receiving estrogen therapy. Oral high dose of CEE administration and oral contraceptive administration to post- and premenopausal women, respectively, and oral common-dose CEE administration to older postmenopausal women with or without an established coronary heart disease should call for caution, particularly in individuals with uncontrolled hypertension. Further large, long-term, controlled, randomized studies are needed to confirm these findings.

References

1. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;**25**:305–13.
2. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res* 2002;**53**:688–708.
3. Landahl S, Bengtsson C, Sigurdsson J, Svanborg A, Svardsudd S. Age-related changes in blood pressure. *Hypertension* 1986;**8**:1044–9.
4. August P, Oparil S. Hypertension in women. *J Clin Endocrinol Metab* 1999;**84**:1862–6.
5. Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. *Hypertension* 2004;**43**:918–23.
6. Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Hypertens Rep* 2006;**8**:368–76.
7. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;**273**:199–208.
8. Wakatsuki A, Ikenoue N, Shinohara K, Watanabe K, Fukaya T. Effect of lower dosage of oral conjugated equine estrogen on inflammatory markers and endothelial function in healthy postmenopausal women. *Arterioscler Thromb Vasc Biol* 2004;**24**:571–6.
9. Higashi Y, Sanada M, Sasaki S, Nakagawa K, Goto C, Matsuura H, Ohama K, et al. Effect of estrogen replacement therapy on endothelial function in peripheral resistance arteries in normotensive and hypertensive postmenopausal women. *Hypertension* 2001;**37**:651–7.
10. Sumino H, Ichikawa S, Kanda T, Sakamaki T, Nakamura T, Sato K, Kobayashi I, et al. Hormone replacement therapy in postmenopausal women with essential hypertension increases circulating plasma levels of bradykinin. *Am J Hypertens* 1999;**12**:1044–7.
11. Umeda M, Ichikawa S, Kanda T, Sumino H, Kobayashi I. Hormone replacement therapy increases plasma level of angiotensin II in postmenopausal hypertensive women. *Am J Hypertens* 2001;**14**:206–11.
12. Nogawa N, Sumino H, Ichikawa S, Kumakura H, Takayama Y, Nakamura T, Kanda T, et al. Effect of long-term hormone replacement therapy on angiotensin-converting enzyme activity and bradykinin in postmenopausal women with essential hypertension and normotensive postmenopausal women. *Menopause* 2001;**8**:210–5.
13. Miya Y, Sumino H, Ichikawa S, Nakamura T, Kanda T, Kumakura H, Takayama Y, et al. Effects of hormone replacement therapy on left ventricular hypertrophy and growth-promoting factors in hypertensive postmenopausal women. *Hypertens Res* 2002;**25**:153–9.
14. Sumino H, Ichikawa S, Ohyama Y, Nakamura T, Kanda T, Sakamoto H, Sakamaki T, et al. Effects of hormone replacement therapy on serum angiotensin-converting enzyme activity and plasma bradykinin in postmenopausal women according to angiotensin-converting enzyme-genotype. *Hypertens Res* 2003;**26**:53–8.
15. Sumino H, Ichikawa S, Kumakura H, Takayama Y, Kanda T, Sakamaki T, Kurabayashi M. Effects of hormone replacement therapy on office and ambulatory blood pressure in Japanese hypertensive postmenopausal women. *Hypertens Res* 2003;**26**:369–76.
16. Ichikawa J, Sumino H, Ichikawa S, Makoto O. Different effects of transdermal and oral hormone replacement therapy on the renin-angiotensin system, plasma bradykinin level, and blood pressure of normotensive postmenopausal women. *Am J Hypertens* 2006;**19**:744–9.
17. Sumino H, Ichikawa S, Kasama S, Takahashi T, Kumakura H, Takayama Y, Kanda T, et al. Different effects of oral conjugated estrogen and transdermal estradiol on arterial stiffness and vascular inflammatory markers in postmenopausal women. *Atherosclerosis* 2006;**189**:436–42.
18. Ichikawa A, Sumino H, Ogawa T, Ichikawa S, Nitta K. Effects of long-term transdermal hormone replacement therapy on the renin-angiotensin-aldosterone system, plasma bradykinin levels and blood pressure in normotensive postmenopausal women. *Geriatr Gerontol Int* 2008;**8**:259–64.

19. Sanada M, Higashi Y, Nakagawa K, Tsuda M, Kodama I, Kimura M, Chayama K, et al. A comparison of low-dose and standard-dose oral estrogen on forearm endothelial function in early postmenopausal women. *J Clin Endocrinol Metab* 2003;**88**:1303–9.
20. Nair GV, Chaput LA, Vittinghoff E, Herrington DM. Pulse pressure and cardiovascular events in postmenopausal women with coronary heart disease. *Chest* 2005;**127**:1498–506.
21. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**:321–33.
22. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;**291**:1701–12.
23. Crane MG, Harris JJ, Winsor III W. Hypertension, oral contraceptive agents, and conjugated estrogens. *Ann Intern Med* 1971;**74**:13–21.
24. Yeboah J, Reboussin DM, Waters D, Kowalchuk G, Herrington DM. Effects of estrogen replacement with and without medroxyprogesterone acetate on brachial flow-mediated vasodilator responses in postmenopausal women with coronary artery disease. *Am Heart J* 2007;**153**:439–44.
25. Herrington DM, Espeland MA, Crouse III JR, Robertson J, Riley WA, McBurnie MA, Burke GL. Estrogen replacement and brachial artery flow-mediated vasodilation in older women. *Arterioscler Thromb Vasc Biol* 2001;**21**:1955–61.
26. de Kleijn MJ, Wilmink HW, Bots ML, Bak AA, van der Schouw YT, Planellas J, Engelen S, et al. Hormone replacement therapy and endothelial function. Results of randomized control trial in healthy postmenopausal women. *Atherosclerosis* 2001;**159**:357–65.
27. Sumino H, Ichikawa S, Ohyama Y, Takahashi T, Saito Y, Nakamura T, Kanda T, et al. Effect of transdermal hormone replacement therapy on the monocyte chemoattractant protein-1 concentrations and other vascular inflammatory markers and on endothelial function in postmenopausal women. *Am J Cardiol* 2005;**96**:148–53.
28. Sumino H, Ichikawa S, Kasama S, Kumakura H, Takayama Y, Sakamaki T, Kurabayashi M. Effect of transdermal hormone replacement therapy on carotid artery wall thickness and levels of vascular inflammatory markers in postmenopausal women. *Hypertens Res* 2005;**28**:579–84.
29. Beljic T, Babic D, Marinkovic J, Prelevic GM. The effect of hormone replacement therapy on diastolic left ventricular function in hypertensive and normotensive postmenopausal women. *Maturitas* 1998;**29**:229–38.
30. Lip GYH, Beevers M, Churchill D, Beevers DG. Hormone replacement therapy and blood pressure in hypertensive women. *J Hum Hypertens* 1994;**8**:491–4.
31. Chasan-Taber L, Wilett WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G, Colditz GA, et al. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation* 1996;**94**:483–9.
32. Woods JW. Oral contraceptives and hypertension. *Hypertension* 1988;**11**:II11–5.
33. Kauffman RF, Bryant HU. Selective estrogen receptor modulators. *Drug News Perspect* 1995;**8**:531–9.
34. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial: Multiple Outcome of Raloxifene Evaluation. *JAMA* 1999;**281**:2189–97.
35. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, Shah AS, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. *JAMA* 1998;**279**:1445–51.
36. Sumino H, Ichikawa S, Kasama S, Takahashi T, Kumakura H, Takayama Y, Kanda T, et al. Effects of raloxifene on the renin-angiotensin-aldosterone system and blood pressure in hypertensive and normotensive osteoporotic postmenopausal women. *Geriatr Gerontol Int* 2010;**10**:70–7.
37. Sumino H, Ichikawa S, Kasama S, Takahashi T, Sakamoto H, Koizumi A, Kanai H, et al. Effects of raloxifene on brachial arterial endothelial function, carotid wall thickness, and arterial stiffness in osteoporotic postmenopausal women. *Int Heart J* 2010;**51**:60–7.
38. Oishi A, Ohmichi M, Takahashi K, Takahashi T, Mori-Abe A, Kawagoe J, Otsu R, et al. Medroxyprogesterone acetate attenuates estrogen-induced nitric production in human umbilical vein endothelial cells. *Biochem Biophys Res Commun* 2004;**324**:193–8.
39. Mikkola T, Viinikka L, Ylikorkala O. Administration of transdermal estrogen without progestin increases the capacity of plasma and serum to stimulate prostacyclin production in human vascular endothelial cells. *Fertil Steril* 2000;**73**:72–4.