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Blood pressure and protocols of postmenopausal HRT administration

Hypertension is a major risk factor for cardiovascular disease in men and women. Elevated systolic and diastolic blood pressures and, in women, elevated pulse pressure are independent risk factors associated with cardiovascular mortality. The prevalence of hypertension increases with age and it remains to be determined what impact, if any, menopause has on this phenomenon.

Some experiments performed in relevant animal models and several recent clinical studies have been analyzed below to update the data on blood pressure changes related to menopause and HRT.

Blood pressure effects of menopause

The prevalence of hypertension (HTA) increases markedly in women beyond the age of 50 years. HTA is one of the main cardiovascular risk factors which might explain the excess cardiovascular morbidity and mortality in postmenopausal women (in France, see data from INSERM 1994). HTA and overweight are the most prevalent risk factors for coronary heart disease in postmenopausal women (Mansur et al., 1996). However, the question whether blood pressure increases independently of age following menopause has not yet been conclusively answered. In fact, the blood-pressure changes associated with menopause are difficult to evaluate because menopause coincides with aging. An increase in body weight is also an important determinant of the increased blood pressure and prevalence of HTA in postmenopausal women. Several longitudinal and cross-sectional studies have addressed the alleged association between HTA and menopause. However their conclusions remain contradictory. The longitudinal surveys suggest that menopause itself is not associated with an increase in blood pressure and a greater incidence of HTA, whereas some cross-sectional studies have found a positive association. Staessen et al. (1989) suggested that the menopause itself is accompanied by a rise in systolic, diastolic and pulse pressures, independently of age, resulting in a higher prevalence of HTA in women who are postmenopausal compared with those in the premenopausal state. Their

observations suggest that ovarian failure and the ensuing estrogen deficiency may influence the age-related increase in blood pressure in women.

In addition, the menopause is associated with enhanced stress-induced cardiovascular responses and elevated diastolic ambulatory blood pressure during the workday (Owens et al., 1993). The heightened cardiovascular stress responses of postmenopausal women may play a critical role in determining the risk of subsequent cardiovascular morbidity and mortality. In climacteric and ovariectomized hypertensive women, Muneta et al. (1992) reported marked impairment of baroreflex, possibly through the central nervous system, associated with increased blood pressure response to mental stress. These abnormalities could be related to the deprivation of estrogen because they were improved by estrogen therapy during a month. Further clinical studies are needed to support the hypothesis that estrogens could be cardioprotective via their modulation of stress responses.

The menopause is also associated with modifications of some haemodynamic parameters. The steeper slope of systolic blood pressure on age following menopause and a decrease in arterial distensibility probably contribute to the increased pulse pressure observed in postmenopausal subjects. In women especially, the calculated pulsatile component index (correlated with pulse pressure) was positively correlated with death from coronary artery disease and could be a risk factor independent of the steady component in women older than 55 years (Darne et al., 1989). Systolic blood pressure and pulse pressure are influenced by the pattern of left ventricular ejection and aortic input impedance, principally via the distensibility of large arteries and the intensity and timing of arterial wave reflection. The relatively small body size of women and, after menopause, the decrease in arterial distensibility (increase in pulse wave velocity) result in a persisting increased effect of wave reflections in central arteries (London et al., 1995).

Blood pressure effects of HRT in animal studies

In some experimental models (spontaneously hypertensive rats and rats with deoxycorticosterone (DOC)-salt HTA), the development of HTA is sexually dimorphic. In these rat strains, the rate of increase in arterial blood pressure and the level to which it rises are greater in males than in females. In these rats, the gonadal steroid hormones can affect the course of HTA. In DOC-salt-hypertensive rats, ovariectomy exacerbated hypertension and these effects were reversed by chronically treating females with estradiol. The mechanisms by which estrogen attenuates the development of DOC-salt HTA remain to be identified. The effects of estrogen may result in part from modulation of the antidiuretic and pressor actions of vasopressin and, in part, from modulation of the sympathetic nervous system at the level of the central nervous system or the vasculature. Progesterone alone had no effect on the

development of DOC-salt HTA in ovariectomized rats. However, when given in combination with estradiol, progesterone transiently prevented the ameliorating effect of estradiol (Crofton and Share, 1997).

In normotensive animals, local and systemic administration of estradiol-17β appears to induce no change in blood pressure, possibly as a result of compensatory mechanisms. In non pregnant, ovariectomized ewes (n=5), estradiol-17β (3 mg) was introduced into both uterine arteries, followed 120 min later by systemic estradiol-17β (1 mg/kg) (Magness and Rosenfeld, 1989). Haemodynamic parameters, plasma renin activity from arterial blood, mean arterial pressure at the lower abdominal artery, uterine blood flow and cardiac output were measured. The local administration of estradiol-17β resulted in a progressive rise in uterine blood flow that began between 30 and 60 min and achieved maximum values by 90 to 120 min. Uterine vascular resistance decreased significantly between 30 and 60 min and remained decreased throughout the rest of the study. Systemic parameters were unchanged. Mean arterial pressure was unchanged throughout the study. Cardiac output increased gradually after systemic estradiol-17β, reflecting an increase in heart rate. There was a significant fall (20 ± 3.1 %) in systemic vascular resistance. Plasma renin activity and angiotensin II were unchanged by local estradiol-17β. However, systemic estrogen caused significant increases in both parameters. These results suggest that the acute haemodynamic effects of systemic estradiol-17β are systemic vasodilation which could induce reflex-mediated tachycardia and an increase in cardiac output with no change in blood pressure. Further studies are needed to determine the effects of estrogen on the heart, central nervous system and renin-angiotensin system in experimental and clinical studies.

These data (and some others) suggest that estrogen could play an important role in modulating blood pressure and the pathogenesis of HTA in different animal species. The clinical effects of postmenopausal estrogen replacement therapy on blood pressure remain, however, unclear (review Schwartz et al., 1995).

Blood pressure effect of HRT in normotensive women

In normotensive women, four studies (three randomized or placebo-controlled and one non-randomized, prospective) were selected to analyze the effect of HRT on blood pressure.

In the study by Hassager et al. (1987) (table 14.I), a two-year placebo-controlled study, spontaneously postmenopausal women (110) aged 45-54 years were allocated to four treatment groups: the first two groups received blindly either a cyclic oral combination of estrogen (estradiol valerate, 2 mg) and cyproterone acetate or oral placebo; the other two

Table 14.I : Effects of HRT on blood presure in normotensive women

Authors	N	Age (years±SD)	HRT	Duration	Whole group		Individual data	
					SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Hassager et al. (1987)	110	45-54	- E2V (2mg, p.o) + CPA - E2P (0.6mg) + MP	2 years 2 years	no change no change	no change no change	no change no change	no change no change
Prough et al. (1987)	26	42-66	- CE (0.625mg, p.o, daily) + MPA (2.5mg, daily)	9 months	no change	no change	not reported	not reported
			- CE (0.625 mg, p.o, days 1-25) + MPA (10mg, days 16-25)	9 months	no change	no change	not reported	not reported
Saure et al. (1996)	310	50.8 ± 5	- E2 (1.5 mg, p.o) + DG (0.15mg)	12×28 days	no change	no change	not reported	not reported
		50.5 ± 4.8	- E2 (2mg+1mg p.o) + NETA (1mg)		no change	no change	not reported	not reported
Akkad et al. (1997)	90	30-59	- E2 (50 mg, patch)	6 months	reduction night : –4.2	reduction day : –4 night : –4.4	increase day :+6.5, n=14 night : +5, n=16	increase day : +7.3, n=6 night : +4.2, n=12
			- E (600 mg E2, 270 mg estriol, 1.4 mg E1, p.o)	6 months	no change	no change	increase day : + 6, n=17 night : + 8, n=26	increase day : + 4.4, n=20 night : + 7, n=16

Table 14.II : Effects of HRT on blood pressure in hypertensive women

Authors	N	Age (years±SD)	HRT	Duration	Whole group		Individual data	
					SBP (mmHg)	DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
Lip et al. (1995)	75	47.7±6.2 to 51.2±4.8	Oral E+P (n=38) E alone (n=28) E2 patches (n=7) Subcutaneous implants (n=2)	14 months	No change	No change	Increase ≥ 5 mmHg n=29	Increase ≥ 5 mmHg n=25
Zarifis et al. (1995)	287	53.7±7.5	« Class effect » Discontinuation of HRT	6 months	No change	No change	Decrease ≥ 5 mmHg n=8	Decrease ≥ 5 mmHg n=8

groups received blindly either percutaneous estradiol (Oestrogel® cream, 0.6 mg estradiol-17β) or placebo cream and were supplemented with micronized progesterone (Utrogestan® capsules, 100 mg) during the second year. There was no change in systolic and diastolic blood pressure in either hormone treatment group, whereas diastolic blood pressure tended to increase (the correlation between diastolic blood pressure and time was significant) in both placebo groups. None of the subjects developed hypertension over the 2-year period. The serum levels of both estrogens (estrone and estradiol) in the percutaneous group and the serum level of estrone in the oral group continued to rise during the first 6 months of treatment, suggesting that clinical studies on blood pressure and the cardiovascular effects of HRT should be performed only after 6 months of therapy. Plasma renin substrate remained unchanged with percutaneous estradiol but increased during oral treatment with estradiol at 12 months, after which it remained increased and unchanged. There was no correlation between plasma substrate and blood pressure. None of the measured variables (estrone, estradiol, renin substrate, diastolic and systolic blood pressure) appeared to be influenced by the addition of progesterone in women treated with percutaneous estradiol.

In a pilot study (Prough et al., 1987), 26 women aged 42 to 66 years (all patients had been amenorrheic for at least 1 year) were randomized in two parallel groups : group I was given conjugated equine estrogen (Premarin®, 0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily and group II received conjugated equine estrogen (0.625 mg) daily during days 1 through 25 of each cycle and medroxyprogesterone acetate (10 mg) during days 16 to 25 (table 14.I). Continuous estrogen/progestin therapy and cyclic estrogen/progestin therapy were equally effective in relieving symptoms of atrophic vaginitis and hot flashes ; serum total cholesterol, HDL and LDL cholesterol and triglyceride levels were not significantly altered from baseline in either group. Throughout the treatment period (9 months), blood pressures (systolic and diastolic) were not significantly altered by either method of HRT. Individual responses were not shown.

In a randomized, double-blind, multicentre study (Saure et al., 1996), the clinical effects of two sequential estrogen-progestin combinations containing either desorgestrel or norethisterone acetate (NETA) were compared in 310 climateric (peri-/postmenopausal) women with estrogen deficiency syndrome (table 14.I). Women (aged 50 ± 5 years) were randomly allocated to oral sequential treatment with either the estradiol-desorgestrel combination (1.5 mg estradiol for 24 days with 0.15 mg desorgestrel for the last 12 days followed by 1 placebo tablet for 4 days) or with the estradiol-NETA combination (Trisequens®, 2mg estradiol for 22 days with 1 mg NETA for the last 10 days followed by 1 mg estradiol for 6 days). Treatments were administered double-blind for 12 cycles of 28 days. Both regimens effectively alleviated menopausal complaints and did not induce hyperplasia of the endometrium. No major alterations in mean blood pressure or body weight occurred during

treatment. The difference in systolic and diastolic blood pressures within the groups and between the groups were not statistically significant, except for a decrease in diastolic pressure (–1.7 mmHg) in the estradiol-NETA group at the 6th cycle. No individual data were available.

In a nonrandomized, prospective study (Akkad et al., 1997), 90 normotensive oophorectomized women aged 30-59 years were allocated to transdermal treatment (patch delivering 50 mg estradiol daily, n=40) or oral estrogen (600 μg micronized estradiol, 270 μg estriol, 1.4 mg estrone, n=50) (table 14.I). All the women underwent ambulatory blood pressure measurements at entry and after 3 and 6 months of treatment. Oral treatment significantly reduced nighttime systolic and diastolic blood pressures after 3 months of treatment, but did not alter blood pressure after 6 months of treatment. Transdermal estrogen replacement therapy was associated with a significant reduction in mean nighttime ambulatory systolic and diastolic blood pressure as well as in daytime ambulatory diastolic blood pressure, after 6 months of treatment. Another important finding emerged from this ambulatory blood pressure study. Although the mean ambulatory blood pressure of the group as a whole remained unchanged during oral treatment and was reduced in the transdermal group, there was a considerable proportion (more than one-third and up to one-half) of women in both treatment groups whose blood pressure increased significantly (blood pressures rose by a mean of 4.5 to 8 mm Hg). The proportions of women whose blood pressure rose were similar in the two groups. The significance of this blood pressure elevation for long-term health is unclear.

In normotensive women, the overall effect of HRT is to lower or not to change blood pressure. However, there are some unexplained discrepancies between these four studies. In the first study, none of the women developed HTA, whereas in the ambulatory study, individuable responses were variable and blood pressure increased in more than one-third of the women. These data were obtained in the context of a non randomized and uncontrolled study and these results, although very interesting, must be confirmed in appropriately designed trials. In the other studies the individual data were not available.

Blood pressure effect of HRT in hypertensive women

The effects of HRT in hypertensive postmenopausal women have been less extensively investigated, with only four studies (one retrospective, one small (n=12 women) and two open prospective studies) addressing this issue in the literature and to date, no controlled studies (Lip et al., 1995). The two open prospective studies are presented here.

In a prospective open study (Lip et al., 1994, table 14.II), in 75 hypertensive women (50.4 ± 5.6 years), there was no significant difference in mean

systolic or diastolic blood pressures following the introduction of HRT over a median follow-up of 14 months despite a progressive increase in mean body weight. Patients were diagnosed as postmenopausal on the basis of surgical or natural menopause and were diagnosed as hypertensive by WHO criteria. Thirty-eight patients received combined oral estrogen and progesterone therapy, 28 received estrogen only, 7 had estradiol patches and 2 had subcutaneous estrogen implants. Patients received antihypertensive therapy before HRT and adjustments made to the number of drugs required to maintain satisfactory blood pressure control during follow-up were noted. There was no significant difference in the average number of antihypertensive drugs at the end of the follow-up period for individual patients. There was no significant difference in mean systolic or diastolic blood pressures following the introduction of HRT (« class effect ») when compared with the pressures obtained before HRT. As in the normotensive women, individuable responses were variable and blood pressure (systolic and/or diastolic) went up by ≥ 5 mmHg in more than one-third of the patients, even with antihypertensive treatment, and in 5 women this rise in blood pressure led to the discontinuation of HRT. In view of the unsubstantiated rise in blood pressure reported in this study, confusion still exists with respect to prescribing HRT to postmenopausal women who also have HTA. Only large, prospective, randomized, placebo-controlled studies could specify the long-term effects on blood pressure of the different HRT regimens in hypertensive women.

In a prospective open study (Zarifis et al., 1995, table 14.II) the effect of discontinuing HRT was studied in hypertensive postmenopausal women. The patients had received HRT (« class effect ») for at least 1 year. The HRT was discontinued because of uncontrolled hypertension. Monthly follow-up following discontinuation of HRT lasted a maximum of 6 months. Twenty-eight hypertensive women (53.7 ± 7.5 years) were studied : 16 had surgical menopause and all the others had natural menopause. The average number of antihypertensive medications per patient was 1.7 before discontinuation of HRT and 1.9 after 6 months follow-up (no significant change). There were no significant differences in the mean systolic and diastolic blood pressure following discontinuation of HRT. However, when individual patients were studied, 8 had a rise in both systolic and diastolic blood pressure and 8 had a fall (≥ 5 mm Hg). These data are difficult to analyze but suggest that after discontinuation of HRT there was no change in blood pressure in the whole group of hypertensive postmenopausal women, over a 6 month follow-up period. The authors suggest that the rise in blood pressure in 8 women might have been due to a combination of increased stress due to stopping HRT and possibly the loss of any effect of HRT in suppressing any rise in blood pressure. In addition, this study could not exclude the possibility that HRT has a pressor effect in more than 30 % of women, since discontinuation of HRT resulted in a fall in blood pressure in 8 women.

A randomized controlled study was performed in 32 postmenopausal non insulin-dependent diabetic patients who were either untreated (n=16) or received percutaneous estradiol-17β (Oestrogel®, 1.5 mg/day estradiol) and natural progesterone for 6 months (Mosnier-Pudar et al., 1991). In both groups, half the women were hypertensive and received antihypertensive treatment before the inclusion in the study. Systolic and diastolic blood pressures were monitored by an automatic device (Dynamap). No significant inter or intra-individual variation in systolic or diastolic blood pressure was observed in either group. No significant difference was noted between the two groups, in terms of body weight, plasma renin substrate, plasma levels of total cholesterol, HDL, LDL-cholesterol, triglycerides, apolipoproteins A1 and B, fructosamine and glycosylated hemoglobin A1c.

There are no data on the effects of HRT on pulse pressure in normotensive or hypertensive women.

Critical analysis

The effect of HRT on blood pressure remains controversial. Studies involving estrogen and blood pressure have produced equivocal results, some showing slight decreases in blood pressure and others showing no change. The most prominent data from these studies are the fact that some normotensive or hypertensive women experience an « idiosyncratic » estrogen-induced hypertensive response. Further studies are needed to confirm these data (obtained only in two prospective studies) and to establish the basis of this phenomenom. One proposed mechanism is that estrogens could interact with the renin-angiotensin system. Oral estrogens were reported to cause changes in several liver-derived proteins like angiotensinogen. The natural estradiol exerts reduced hepatic activity after parenteral compared to oral administration in women and in a rat model (Krattenmacher et al., 1994). Recently, evidence was obtained of genetic linkage between the angiotensinogen gene (AGT) and hypertension, of an association of AGT molecular variants with the disease and of significant differences in plasma concentrations of angiotensinogen among hypertensive subjects with different AGT genotypes (Jeunemaitre et al., 1992). As no correlation was found in some studies between plasma concentrations of angiotensinogen and blood pressure, an analytical approach with a genetic linkage study, the identification of molecular variants of AGT followed by a comparison of their frequencies in estrogen-induced hypertensive cases and controls, and an analysis of variance of plasma angiotensinogen concentration in these hypertensive women as a function of AGT genotypes would help to understand this idiosyncratic response. Some data, obtained on a very small number of patients treated with various oral contraceptive preparations or ethinyl estradiol, suggest that oral estrogens could also induce the synthesis of an electrophoretically immunologically dis-

tinct form of renin substrate, high molecular weight renin substrate, which is significantly increased in women who have estrogen-induced hypertension (review Schwartz et al., 1995). Further studies are needed to confirm these data. On the other hand, after six months of treatment, oral HRT (estradiol valerate, 2 mg and norethisterone, 0.7 mg daily) was shown to reduce, by 20 % on average, angiotensin-converting-enzyme (ACE) activity in healthy postmenopausal women (Proudler et al., 1995). However, this controlled study did not assess the independent contributions of estrogen and progestagen to the changes in ACE activity. In addition, some questions remain on whether this HRT regimen reduced serum ACE to a similar extent in all ACE genotypes. An HRT-dependent reduction in ACE activity might affect vascular function and blood pressure through changes in angiotensin II and kinin concentrations. These data were not, however, confirmed in an open randomized trial performed in healthy postmenopausal women who were randomly assigned to receive either oral estradiol valerate (2 mg/day) or percutaneous estradiol (1.5 mg/day), both combined with micronised progesterone (200 mg/day) or no hormonal treatment. In these conditions, after 6 months of treatment, there was no significant difference in the mean change in ACE activity between the groups. Plasma ACE was not correlated with hormone concentrations (Scarabin et al., 1996). The influence of progestogens and ACE genotype should be further considered. As pulse pressure was shown to be an independent cardiovascular risk factor, the effects of HRT on pulse pressure should be investigated in normotensive and hypertensive women.

To conclude, The prevalence of hypertension increases in postmenopausal women associated with modifications of some haemodynamic parameters. In normotensive and hypertensive women, the overall effect of HRT is to lower or not to change blood pressure. However in two studies (one in normotensive and one in hypertensive women) blood pressure increased in more than one-third of women. These results must be confirmed in appropriate designed trials. Since few studies have been performed in hypertensive women, the presence of HTA seems to be a relative contraindication to using HRT.

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