Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: informahealthcare.com/journals/iblo20

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To cite this article: Julia Wong, Shirley Wong, Paul S. Handa & Carl E. Abbott (2005) Hormone replacement use, arterial distensibility, cardiac structure and circadian blood pressure profile in menopausal women, Blood Pressure, 14:1, 12-20, DOI: 10.1080/08037050510008797

To link to this article: https://doi.org/10.1080/08037050510008797

Blood Pressure. 2005; 14: 12–20

Taylor & Francis
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ORIGINAL ARTICLE

Hormone replacement use, arterial distensibility, cardiac structure and circadian blood pressure profile in menopausal women

JULIA WONG[1], SHIRLEY WONG[1], S. PAUL HANDA[2] & E. CARL ABBOTT[3]

From [1]School of Nursing, Dalhousie University, Halifax, Nova Scotia, Canada, [2]Department of Nephrology, Atlantic Health Sciences Corporation, Saint John, New Brunswick, Canada, and [3]Internal Medicine, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Abstract
Observational and interventional studies that evaluate the impact of hormone replacement therapy (HRT) on cardiovascular changes have produced inconsistent and inconclusive results. The present study sought to elucidate the influence of HRT on aortic distensibility, left ventricular mass (LVM) and 24-h blood pressure (BP) profile in 38 menopausal women who were either HRT users or non-users. The two groups were similar for age, ambulatory BP, aortic distensibility, cardiac mass, lipid profile and body mass index but differed in clinic diastolic BP (DBP). HRT non-dippers had significantly lower clinic and daytime DBP and a smaller nocturnal BP reduction than dippers. Daytime DBP was significantly and inversely related to duration of HRT use. The present study demonstrates that hormonal therapy after menopause lowers DBP, but shows no significant influence on aortic distensibility, cardiac mass or 24-h BP profile. HRT users who were dippers demonstrated a significantly greater nocturnal BP reduction. Long-term controlled trials are needed to better define the effects of estrogen and progestin on the aorta, the heart and 24-h BP profile in normotensive and hypertensive menopausal women.

Key Words: *24-h blood pressure, aortic distensibility, HRT, LVMI, menopause*

Introduction

Menopause is associated with several cardiovascular changes including elevated systolic blood pressure (SBP), increased left ventricular mass (LVM), arterial stiffness and reduced nocturnal blood pressure (BP). The observation that the later onset of coronary heart disease (CHD) in women compared with men has led to the speculation that this may be due to higher endogenous estrogen levels in premenopausal women than in men. Thus, replacing the estrogen lost at menopause appears to be attractive and plausible treatment for preventing many cardiovascular changes associated with menopause.

Systolic hypertension afflicts 50% of menopausal women and is an important risk factor for stroke and CHD. Treatment and control of high BP can reduce the morbidity and mortality from CHD and stroke (1,2). Epidemiological evidence suggests that hormone replacement therapy (HRT) is effective in preventing CHD among postmenopausal women (3). Estrogens have been found to exert vasoprotective effects as they reduce BP (4), influence the renin–angiotensin system, and may act as calcium-blocking agents (5,6).

The results of the first report from the Women's Health Initiative Study (7,8), a large randomized primary prevention trial, and the Heart and Estrogen/progestin Replacement Study (HERS) (9), a secondary prevention trial, raise questions against the putative cardioprotective effects of estrogen. In fact, results from the Women's Health Initiative Study (7) indicated an increase of 49% in stroke rates in women receiving estrogen and progestin, with most of the increase occurring in

Correspondence: Julia Wong, Ph.D., Dalhousie University, School of Nursing, 5869 University Avenue, Halifax, Nova Scotia, Canada B3H 3J5. Fax: (902) 494-3487. E-mail: Julia.Wong@Dal.Ca

(Received 27 July 2004; accepted 27 September 2004)

ISSN 0803-7051 print/ISSN 1651-1999 online
DOI: 10.1080/08037050510008797

non-fatal events. The risk of stroke appeared during the second year and persisted through the fifth year. The Nurses' Health Study (10) reported that the risk of stroke was statistically significantly increased among women taking 0.625 mg or more oral conjugated estrogen daily (relative risk 1.35 [CI 1.08–1.68] for 0.625 mg/day and 1.63 [CI 1.18–2.26] for $\geqslant$1.25 mg/day) and those taking estrogen plus progestin (relative risk 1.45 [CI 1.10–1.92]). Thus far, these trials have failed to show benefits of oral estrogens with respect to prevention of CHD. Observational and interventional studies that evaluate the impact of postmenopausal HRT on blood vessels, the heart and circadian BP profile have produced inconsistent and inconclusive results. Some studies showed that HRT significantly lowered arterial stiffness in normotensive postmenopausal women (11,12), while others found no changes in arterial distensibility, the reciprocal of arterial stiffness (13,14). Recent tests of the hypothesis that estrogen replacement therapy reduces CHD risk through prevention or reversal of structural changes in the heart have yielded contradictory results. HRT was associated with significant reduction (15,16), increase (17) or no change (18) in LVM. Conflicting evidence also exists with respect to effects of HRT on 24-h BP. Butkevich et al. (19) and Mercuro et al. (20) reported that HRT can restore the expected nocturnal BP reduction, whereas Mills and colleagues (21) found no significant effect on daytime or night-time BP in healthy non-smoking postmenopausal women. The present study sought to further elucidate the influence of HRT on aortic distensibility, LVM and the 24-h BP profile in normotensive and hypertensive menopausal women.

Materials and methods

Subjects

Twenty normotensive and eighteen hypertensive women (mean age 58.6 ± 1.0 years, age range 50–74 years) were recruited in the study through advertisements in local newspaper and hypertension clinic based at two university-affiliated hospitals. All women were menopausal; menopause was defined as natural (cessation of menses for at least 12 months) or surgical (hysterectomy with bilateral oophorectomy). Subjects were either HRT (estrogen therapy, with or without progesterone) users or non-users; hypertensive women were either currently receiving antihypertensive agents or not receiving these agents. The BP criteria used for defining hypertension were clinic cuff SBP $\geqslant$140 mmHg and a diastolic BP (DBP) $>$90 mmHg. Exclusion criteria for entry in the study were sleep disorder, diabetes mellitus, previous myocardial infarction, angina, congestive heart failure, valvular heart disease and stroke. The study protocol was in accordance with the ethical standards of the Helsinki declaration of 1983 and approved by the University Health Sciences Human Research Ethics Board. All subjects gave written informed consent.

Study protocol

Supine cuff BP (BP) was recorded by a clinic nurse using a mercury sphygmomanometer following a 5-min resting. Korotkoff phases 1 and 5 were taken as the SBP and DBP, respectively. Immediately after the cuff BP determination, all subjects underwent 24-h BP monitoring using a non-invasive automatic recorder (SpaceLabs Model 90207 Ambulatory Blood Pressure Monitor, Redmond, WA, USA). The monitor used the oscillometric method to measure BP and was preset at 30-min intervals during daytime (06.01 to 22.00 h) and at hourly intervals during night-time (22.01 to 06.00 h). Following the completion of 24-h BP monitoring, blood samples were drawn from the antecubital vein with subjects sitting for lipid profile analysis (total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein). Subjects were instructed to fast overnight and to refrain from cigarette smoking on the morning when plasma samples were taken. Ultrasonographic determination of the aortic dimensions and left ventricular measurements were made by M-mode echocardiogram (echo) and 12-lead electrocardiogram (ECG) in the echo laboratory.

The aortic diameter was recorded by M-mode echo 3 cm above the aortic valve according to the methods recommended by the American Society of Echocardiography. The measurement of aortic diameters has been described elsewhere (22). M-mode measurements of the left ventricle were obtained to estimate the LVM. An experienced echo technologist performed all echocardiograms under the supervision of a cardiologist experienced in echo. The records were coded and a cardiologist blinded to the data about the subjects independently made the measurements on five consecutive cardiac cycles. The aortic diameters in combination with BP measurements obtained during echo formed the basis for calculation of aortic distensibility (AOD) using the formula described by Stefandis et al. (23).

$$\text{AOD} = 2 \times (\Delta \text{ aortic diameter})/(\text{diastolic diameter}) \times (\Delta \text{ aortic pressure})$$

where Δ aortic diameter=systolic−diastolic diameter, and Δ aortic pressure=cuff SBP−cuff DBP (brachial artery pressure by sphygmomanometer obtained during echo). AOD is expressed in kPa.

The LVM was derived from measurements obtained from M-mode echo examination with the subjects in a partial left decubitus position. LVM was determined by the conventional method developed by Devereux & Reichek (24). The following formula was used for calculation of the LVM:

$$\text{LVM (g)} = \left[(\text{LVIDd} + 2\text{LVPWTd})^3 - (\text{LVIDd})^3\right] \times 1.05$$

where LVIDd is the left ventricular internal end-diastolic diameter and LVPWTd is the left ventricular posterior wall end-diastolic thickness.

Subjects were classified as dippers and non-dippers according to their BP circadian variation. Pierdomenico et al.'s (25) definition was used to classify subjects as dippers and non-dippers. A non-dipping pattern was defined as a difference in the mean daytime and night-time BP $<10\%$, while a difference of $>10\%$ and $<20\%$ in mean daytime and night-time BP was considered as a dipping pattern. Some patients who were non-dippers for SBP and dippers for DBP, and others who were dippers for SBP and non-dippers for DBP, were classified according to SBP changes because nocturnal decrease in SBP has been shown to confer a reduced cardiovascular risk (26).

Statistical analysis

Sample size was calculated based on the formula $n=\{(za+zb)\text{SD}\}2$, where D is the detectable D2, difference of means, and SD is the standard deviation. Minimum and maximum values of D and the corresponding SD are obtained from previous work (27,28). We estimated that we needed to enroll 142 subjects, 71 subjects in each of HRT user and non-user groups to achieve 80% statistical power with 0.05 level of significance.

In view of the small number of subjects enrolled in the study coupled with uneven number of subjects in HRT user and non-user groups, non-parametric statistics were used to analysis the data. Results are presented as the median and quartiles. To test for differences in median values between HRT users and non-users, and dippers and non-dippers, non-parametric one-way analysis of variance statistics were used. The proportions of dippers and HRT users were compared with the use of χ^2. The relationship of HRT to aortic distensibility, cardiac mass and ambulatory BP was analyzed by linear regression analysis in which other factors affecting AOD, LVM and 24-h BP were used as confounders. These included age, 24-h SBP and 24-h heart rate. The data were processed using the software packages SAS/STAT (SAS Institute, Cary, NC, USA). Values of $p<0.05$ were considered statistically significant.

Results

Baseline characteristics of HRT users and non-users

In the entire cohort of study subjects, there was an even division in the proportion of HRT users and non-users (50% users vs 50% non-users). The two groups did not differ significantly in age, ambulatory BP, aortic distensibility, LVM, lipid profile, time since menopause and the proportion of hypertension. The clinic DBP was lower in HRT users than in non-users. The baseline clinical characteristics of HRT users and non-users are summarized in Table I. Subgroup comparison of clinical characteristics between hypertensive HRT users and non-users showed that clinic DBP was significantly lower in hypertensive HRT users than that of hypertensive women not receiving HRT (Table II).

Ambulatory BP and HRT

Two subjects were unable to complete the 24-h BP monitoring; therefore, analyses of ambulatory BP were based on 36 subjects. In view of the small number of hypertensive subjects receiving HRT (10 HRT users and seven HRT non-users), we grouped normotensive (median BP 118/73.2 mmHg, interquartile range 27/14.7 mmHg) and hypertensive (median BP 124.7/77.1 mmHg, interquartile range 18.7/11.4 mmHg) HRT users in our analysis of the clinical characteristics of HRT-dippers and non-dippers. Results showed that 55.6% exhibited dipping circadian pattern while 44.4% did not. Non-dippers had significantly lower daytime DBP than dippers. They also demonstrated a significantly smaller nocturnal BP reduction than dippers (Table III).

Relationship of HRT to aortic distensibility, cardiac mass and 24-h BP

HRT did not correlate significantly with AOD, LVM and 24-h BP except for daytime DBP, which was found to associate significantly and inversely with duration of HRT use in the entire cohort of subjects, controlling for daytime heart rate (Fig. 1).

Table I. Clinical characteristics of HRT users and non-users in total group.

	HRT user (n=19)	HRT non-users (n=19)
Parameter	Median (Min., Q1, Q3, Max)	Median (Min, Q1, Q3, Max)
Age (years)	58 (50, 54, 60, 68)	58 (50, 52, 67, 74)
BMI (kg/m^2)	30 (19.1, 25.2, 33.2, 41.0)	29.2 (22.5, 24.4, 33.0, 49.49)
Clinic SBP (mmHg)	119.3 (100.7, 111.3, 132, 160)	126 (105.3, 116.7, 144.6, 176.0)
Clinic DBP (mmHg)	76.7 (58.7, 70, 79.3, 93.3)	79.3 (68, 72.7, 83.3, 100)*
Clinic PP (mmHg)	46.6 (26, 38, 55.3, 80)	50 (32.6, 36.7, 63.3, 90.7)
24 h ABPM (mmHg)		
24-h SBP	126 (106, 120, 132, 140)	124.7 $\pm$ 3.1
24-h DBP	75 (58, 67, 81, 85)	73 (59, 66, 80, 86)
24-h PP	51.5 (40, 47, 56, 70)	49 (35, 42, 56, 86)
Daytime SBP	127.7 (107.9, 122.7, 136.9, 140)	127.8 (105.8, 119.5, 143.7, 149.8)
Daytime DBP	75.9 (66.9, 69.3, 80.7, 91.3)	77.4 (59.9, 70.4, 83.7, 88.9)
Night-time SBP	112.8 (98.4, 110.3, 117.8, 150)	115.4 (88.3, 100.6, 128.1, 138.7)
Night-time DBP	65.1 (53.7, 62.9, 74.4, 86.1)	68.5 $\pm$ 2.0
Nocturnal BP reduction (mmHg)		
SBP	10 (−11, 4.7, 21, 29.1)	16.6 (−10.4, 10.4, 21.7, 26.4)
DBP	9.6 (−17.5, 4.2, 14.3, 28.4)	12.4 (0.5, 8, 16.6, 22.5)
24-h HR (beats/min)	73.5 (60, 68, 76, 94)	72 (56, 66, 78, 90)
AOD (10^{-3}/kPa)	21 (0, 5.8, 29.6, 44.8)	19.4 (0, 7.8, 30.6, 59.2)
LVM (g)	116.5 (65.1, 103.4, 135.2, 164.7)	123.4 (90.3, 97.8, 157.5, 173.9)
Lipid profile		
Cholesterol (mmol/l)	5.3 (3.24, 4.76, 6, 6.99)	6.02 (3.52, 4.63, 6.2, 7.36)
Triglyceride (mmol/l)	1.34 (0.47, 0.95, 1.67, 2.89)	1.18 (0.58, 0.85, 1.47, 2.65)
HDLc (mmol/l)	1.47 (0.97, 1.21, 1.77, 3)	1.64 (0.73, 1.28, 1.75, 1.94)
LDLc (mmol/l)	3.29 (1.51, 2.45, 4.09, 4.65)	3.99 (0.42, 2.56, 4.34, 5.23)
Hypertension (%)	61.1	38.9
Time since menopause (years)	8 (3, 5, 14, 24)	9 (1, 3, 17, 26)

Results are expressed in median and quartiles. *$p<0.05$ vs HRT non-users. Min, minimum; Q1, first quartile, Q3, third quartile, Max, maximum; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AOD, aortic distensibility; LVM, left ventricular mass; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

Discussion

The beneficial effects of HRT on BP in postmenopausal women have received considerable attention, yet studies investigating the impact of HRT on BP in normotensive and hypertensive menopausal women have produced inconsistent results (20,29–31). The present results show a mildly significant lower clinic DBP observed in menopausal women using HRT compared with non-users (2.6 mmHg in total group and 4.6 mmHg in hypertensive subgroup). This finding is corroborated by the regression analysis result, which showed a significant and inverse relationship between daytime DBP and duration of HRT use in the entire study group. Our observation of a decrease in clinic DBP is consistent with Scuteri et al.'s finding (4) that postmenopausal women who used oral estrogen showed a slightly significant lower clinic DBP than those who did not use estrogen. DBP is influenced primarily by the peripheral vascular resistance, which represents the tone of small arteries. It is generally recognized that arterial hypertension impairs endothelium-dependent vasodilatation (32). The reduction in DBP may reflect augmented vasodilatation by hormone, possibly mediated by endothelium-dependent responsiveness. Majmudar and colleagues (33) reported that postmenopausal women showed reduced vascular nitric oxide activity but was restored to premenopausal vascular nitric oxide activity after 2 weeks of estrogen replacement therapy. Although we did not evaluate the vascular nitric oxide activity of the HRT users, the possibility of higher nitric oxide levels in HRT users cannot be dismissed. On the other hand, subject selection bias could account for the significant difference in DBP between users and non-users. Matthews et al. (34) and Egeland et al. (35) found that HRT users had lower coronary risk factors (higher levels of high-density lipoprotein cholesterol and lower BP, weight and insulin) prior to its use. This pre-existing favorable CV risk profile could explain lower DBP among HRT users.

Our finding of lower clinic DBP in hypertensive HRT users compared with non-users agrees with that of Dallongeville et al. (36), who reported a slight

Table II. Clinical characteristics of hypertensive HRT users and non-users.

	HRT users (n=11)	HRT non-users (n=7)
Parameter	Median (Min, Q1, Q3, Max)	Median (Min, Q1, Q3, Max)
Age (years)	58 (50, 56, 64, 68)	58 (50, 51, 66, 67)
BMI (kg/m^2)	31.9 (19.1, 25.2, 36.5, 41)	30.6 (22.9, 26.2, 34.8, 49.9)
Clinic SBP (mmHg)	124.7 (109.3, 115.3, 134, 160)	129.3 (113.3, 122.7, 170, 176.6)
Clinic DBP (mmHg)	78.7 (58.7, 70, 80.7, 93.3)	83.3 (78, 79.3, 95.3, 100)*
Clinic PP (mmHg)	46.6 (36.7, 38.7, 53.3, 80)	50 (35.3, 35.4, 76, 90.7)
24 h ABPM (mmHg)		
24-h SBP	123.5 (116, 121, 131, 137)	132 (102, 107, 141, 141)
24-h DBP	74.5 (58, 67, 81, 85)	73 (64, 68, 83, 86)
24-h PP	54 (41, 48, 56, 62)	54 (36, 42, 56, 73)
Daytime SBP	126.8 (119.8, 122.7, 135.2, 140.8)	122.2 (110.6, 113.1, 145.9, 149.8)
Daytime DBP	77.1 (66.9, 69.3, 80.7, 86.4)	77.7 (68.4, 75.6, 88.6, 88.9)
Night-time SBP	122.6 (100, 111.2, 117.8, 137.7)	121.9 (94.3, 97.9, 132.6, 134.6)
Night-time DBP	67.1 (53.7, 63.2, 74.4, 76)	61.1 (56, 57.7, 75.8, 83.2)
Nocturnal BP reduction (mmHg)		
SBP	12.7 (−1, 4.9, 21, 25.9)	18.8 (−10.4, −4.2, 21.7, 24)
DBP	11.7 (−7, 4.2, 14.3, 21.6)	13.1 (5.4, 9.9, 17.2, 17.9)
24-h HR (beats/min)	75 (61, 69, 78, 94)	67 (64, 65, 72, 83)
AOD (10^{-3}/kPa)	11.7 (0, 4.3, 29.5, 57.7)	10.8 (−5.2, 0, 30.7, 32.6)
LVM (g)	112 (76.9, 103.4, 154.5, 164.7)	151.3 (95.4, 97.8, 164.3, 173.9)
Lipid profile		
Cholesterol (mmol/l)	5.32 (3.24, 4.76, 5.68, 6.72)	6.02 (4.12, 4.63.6.2, 7.4)
Triglyceride (mmol/l)	1.21 (0.47, 0.68, 2, 2.89)	1.04 (0.67, 0.85, 1.47, 1.98)
HDLc (mmol/l)	1.31 (1.03, 1.13, 1.60, 3)	1.71 (1.55, 1.61, 1.83, 1.91)
LDLc (mmol/l)	3.06 (1.57, 2.45, 4.49, 4.65)	3.39 (1.82, 2.3, 4.61, 5.23)
Time since menopause (years)	10 (4, 5, 17, 24)	9 (1, 1, 15, 26)

Results are expressed as median and quartiles. *$p<0.05$ vs non-dippers. Min, minimum; Q1, first quartile, Q3, third quartile, Max, maximum; ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AOD, aortic distensibility; LVM, left ventricular mass; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

beneficial effect of HRT on high BP in women on opposed or unopposed postmenopausal estrogen therapy but disagrees with the results of Lip et al. (37) and Czarnecka et al. (38). Both of these studies found no significant difference in BP in women receiving antihypertensive treatment together with HRT. The lower clinic DBP in hypertensive HRT users could not be explained by the effect of age since no significant difference was found between the users and non-users. The significant lower DBP among hypertensive women receiving HRT could be related to the divergent effects of antihypertensive drug use on BP. Vasoactive drugs that reduce smooth muscle tone in large arteries actively increase compliance, thus reducing SBP (39). In contrast, antihypertensive agents that decrease the sympathetic activity lower DBP by reducing the vascular resistance.

A growing body of evidence indicates that menopause influences circadian BP pattern and that HRT is beneficial in postmenopausal women with respect to improvement of menopausal symptoms. The issue of circadian BP profile in postmenopausal women receiving HRT has not yet been clearly elucidated. Mercuro and colleagues (20) reported that 17 β-estradiol significantly decreased 24-h SBP and DBP of menopausal hypertensive women and restored the expected reduction in BP during night-time in the non-dipper group. Sequentially combined HRT delivered by oral and transdermal routes was found to cause significant falls in daytime 24-h BP of normotensive postmenopausal women after 2 months of treatment (40). Our data showed that HRT non-dippers had significantly lower daytime DBP and a much smaller nocturnal reduction in BP than HRT dippers. This finding suggests that HRT exerts disparate effects on the blood vessels of dippers and non-dippers. A blunted or absent nocturnal fall of ambulatory BP has been found to be associated with higher future cardiovascular morbid events among women with ambulatory hypertension (41,42). Mercuro et al. (20) stated that persistent pressure overload expressed by a blunted nocturnal reduction in BP, might be the possible mechanism of increased cardiovascular risk after menopause. However, caution must be exercised in

Table III. Clinical characteristics of postmenopausal dippers and non-dippers receiving HRT.

	Dipper (n=8)	Non-dipper (n=8)
Parameter	Median (Min, Q1, Q3, Max)	Median (Min, Q1, Q3, Max)
Age (years)	56.5 (50, 54, 58, 67)	58.5 (54, 55, 62, 68)
BMI (kg/m2)	27.9 (19.1, 24.9, 36.6, 41)	30.9 (23.7, 26.0, 33.2, 36.5)
Clinic SBP (mmHg)	117 (103.3, 116, 129.4, 160)	118.3 (100.7, 106, 130, 136.7)
Clinic DBP (mmHg)	77.4 (66.7, 68.7, 20.4, 88)	73.4 (58.7, 68, 79, 93.3)
Cuff PP (mmHg)	43.3 (36.6, 37.4, 51.4, 80)	44 (26, 34.7, 54, 62)
24 h ABPM (mmHg)		
24-h SBP	124.5 (116, 121, 131, 137)	123 (106, 118.5, 135, 140)
24-h DBP	76 (67, 74.5, 81, 84)	68 (58, 66, 73.5, 85)
24-h PP	48 (41, 42, 54.5, 62)	55 (40, 49, 61.5, 70)
Daytime SBP	131.7 (125.9, 127.1, 137, 140.8)	121.9 (107.9, 120.2, 131.4, 139)
Daytime DBP	82 (75.3, 78.5, 85.8, 91.3)	69.5 (66.9, 68.2, 74.6, 76)*
Night-time SBP	111.3 (100, 106.5, 114.5, 137)	117.8 (98.4, 111.3, 129.6, 150)
Night-time DBP	65.8 (53.7, 63.5, 73.4, 75.8)	63.4 (54.1, 61, 71.9, 79)
Nocturnal BP reduction (mmHg)		
SBP	21.2 (3.1, 15.4, 25.4, 29.1)	0.7**
DBP	14.3 (4.2, 11.7, 19.9, 28.4)	5.0*
24-h HR (beats/min)	75 (68, 71, 77, 83)	70.5 (60, 63, 76, 94)
AOD (10^{-3}/kPa)	24.7 (0, 6.9, 34.9, 57.7)	18.1 (0, 4.1, 35.6, 50.2)
LVM (g)	111.6 (76.9, 101.3, 149.8, 164.7)	119.3 (65.2, 108.2, 125.5, 135.2)
Lipid profile		
Cholesterol (mmol/l)	5.21 (4.49, 4.79, 5.74, 6.72)	5.61 (3.82, 4.91, 6.24, 6.99)
Triglyceride (mmol/l)	1.50 (0.47, 0.68, 2.38, 2.89)	1.36 (0.86, 1.25, 1.5, 2.34)
HDLc (mmol/l)	1.31 (1.03, 1.06, 2.03, 3)	1.47 (0.97, 1.17, 1.69, 1.83)
LDLc (mmol/l)	3.14 (1.54, 2.36, 4.49, 4.65)	3.45 (2.25, 2.72, 4.31, 4.55)
HRT use (years)	5 (2, 2, 6, 6)	6 (3, 4.5, 14.5, 20)
Time since menopause (years)	8 ± 3.2	9.5 (3, 5, 20, 24)

Results are expressed in median and quartiles *$p<0.05$ vs non-dippers. **$p<0.01$ vs non-dippers. ABPM, ambulatory blood pressure monitoring; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AOD, aortic distensibility; LVM, left ventricular mass index; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol.

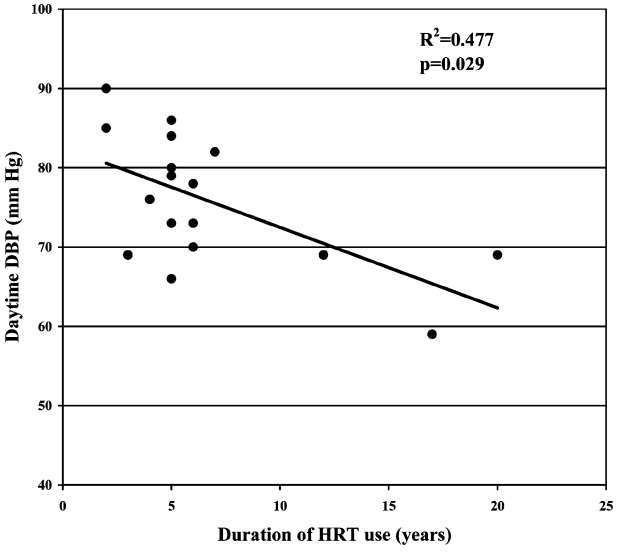

Figure 1. Relationship of daytime diastolic blood pressure (DBP) with duration of hormone replacement therapy (HRT) use in total group.

interpreting the nocturnal BP fall since we have no data on the subjects' BP values prior to HRT use. This lack of information precludes us from assessing the actual effects of HRT on BP.

The finding of no significant difference in AOD between HRT users and non-users in the present study is consistent with two prior studies of the effect of HRT on vascular properties. McGrath et al. (43) found no differences in carotid arterial distensibility between HRT and non-HRT groups. This finding was supported by Westendorp et al. (13) who observed no significant differences in change in arterial distensibility of the common carotid artery between perimenopausal women using hormone (17β-estradiol and17βE_2-D, or conjugated equine estrogens and norgestrel) and women using placebo after 6 and 24 months. Gorgulu and colleagues (14) demonstrated significant improvement in strain and beta index (measures of arterial stiffness), but no change in aortic distensibility adjusting for heart rate after 12 weeks of hormone therapy. On the other hand, other studies demonstrated favorable effects of estrogen on vascular properties (4,11,12). The

difference between our finding and those studies could be the different endpoints used. Studies have used systemic arterial compliance (SAC)(43), local carotid artery distensibility (44) and PWV (4) to evaluate the impact of hormone therapy on the viscoelastic properties of the arterial tree; all of these measures probably reflect essentially different arterial properties. SAC provides an overall estimation of the impedance of the arterial tree, but no direct measurements of the elastic properties of the aortic wall (23). PWV represents the integrated effect of the entire arterial segment investigated, regardless of the unknown tortuosity and tapering, both of which affect it (45). In the present study, we estimated AOD from echo measurements of aortic diameter at systole and diastole, and aortic pressure was estimated by brachial cuff BP taken at the time when echo measurements were made. This method allows us to estimate the elastic properties of the ascending aorta from its direct measurements.

Studies of effects of estrogen and HRT on cardiac structure have yielded inconsistent and inconclusive results. Our finding of a statistically non-significant difference in LVM between menopausal HRT users and non-users agrees with that reported by Kangro et al. (46), Snabes et al. (18), Kessel et al. (47) and Gorgulu et al. (14), but disagrees with other studies that showed a significant reduction in LV mass with HRT in postmenopausal women (15,16,48). A likely explanation for no difference in LVM may be related to a lack of difference in AOD between these groups. Previous studies (49,50) have shown that aortic stiffness is significantly and independently associated with LVM, even after adjusting for mean arterial pressure. Consistent with Cuspidi et al.'s report (51), we found no difference in LVM between HRT users with and without a normal fall in BP during night-time. This lack of significant difference in cardiac mass may not be related to the non-dipping phenomenon *per se*, but to a greater BP level over 24 h (52). It has been reported that 24-h overall BP variability is one of the most important hemodynamic variables involved in the pathogenesis of left ventricular hypertrophy (53).

Limitations of the study

A methodological limitation is the antihypertensive treatment used by our study subjects; it is not known whether antihypertensive treatment may alter the benefits of HRT. Furthermore, various antihypertensive agents have different effects on vascular elasticity. Antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, nitrates and low-dose diuretics have a favorable vasoprotective effect on conduit vessels in elderly patients (54,55). In contrast, beta-blockers as monotherapy have been shown to increase conduit vessel stiffness and the magnitude of the reflected wave (56,57). Given that we had no data on the type, dose and duration of antihypertensive agents used, we were unable to control for the effects of these agents on the aortic distensibility and cardiac mass in our analysis.

Issues that could affect results of our study include the type, dose and route of administration of hormone treatment used. Menopausal women in our study received estrogen, with or without progesterone, which could be administered orally, transdermally or vaginally. Previous studies have clearly demonstrated the differential effect of estrogen and progestin on cardiovascular changes. While estrogen produces vasoprotective effects, progestin antagonizes them. O'Connell (58) stated that in addition to having different concentration, oral estrogens undergo a significant first-pass liver metabolism, which results in reduced bioavailability and a hormonal profile different from that of transdermal estrogen.

Another limitation of this study is that it was not designed as a double-blind, randomized, placebo-based study. The classification of subjects into dippers and non-dippers according to one single 24-h recording may not be appropriate. Manning et al. (59) found a different short-term variability in circadian BP according to dipping status at baseline, being significantly greater in patients classified at first ambulatory BP monitoring as non-dippers than in dippers. In addition, the number of subjects included in the study was small. Therefore, we cannot exclude the possibility of a selection bias in the results. Moreover, the small sample size seriously limits the statistical power to detect significant differences in AOD, LVM and 24-h BP profile between HRT users and non-users.

Conclusions

The present study demonstrates that hormonal therapy after menopause lowers DBP, but no significant influence on aortic distensibility, cardiac mass or 24-h BP profile. HRT users who were dippers demonstrated a significantly greater nocturnal BP reduction. A selection bias in the study population and the lack of longitudinal observations do not allow us to make categorical conclusions about beneficial effects of HRT use in menopausal women. A larger double-blind, randomized, placebo-based study is needed to better define the effects of estrogen and progestin on the aorta, the

heart and 24-h BP profile in normotensive as well as hypertensive postmenopausal women.

Acknowledgements

This work was supported by a grant-in-aid from the Medical Research Fund of New Brunswick, Canada. We thank the Department of Biochemistry at the Queen Elizabeth II Health Sciences, Halifax, Nova Scotia and the Atlantic Health Sciences Corporation, Saint John, New Brunswick for the plasma lipid measurements. Cardiologists at the Queen Elizabeth II Health Sciences and Atlantic Health Sciences Corporation provided expert technical advice for the ultrasound measurements.

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