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Hormone replacement therapy improves arterial stiffness in normotensive postmenopausal women

Sayaka Miura, Eiichi Tanaka, Akiko Mori, Mayumi Toya, Kazuhiro Takahashi, Kenji Nakahara, Masahide Ohmichi *, Hirohisa Kurachi

Department of Obstetrics and Gynecology, Yamagata University School of Medicine, 2-2-2, Iidanishi, Yamagata, Yamagata 990-9585, Japan

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Abstract

Objectives: Aortic stiffness, determined by the pulse wave velocity (PWV), is an independent marker of cardiovascular risk. PWV is mainly influenced by age-associated alterations of arterial wall structure and blood pressure (BP). To determine the impact of hormone replacement therapy (HRT) on arterial compliance in normotensive, postmenopausal women, we examined the effects of HRT on PWV. *Methods:* Fifty-six postmenopausal women aged 50–70 years were recruited into the present retrospective study from the patients visiting our menopause clinic. Twenty-seven women who were prescribed HRT (14 on estrogen alone and 13 on estrogen plus progestogen) for several months to 6 years and an age-matched group of 29 women not on HRT were studied (Study 1). Nine postmenopausal women were also studied before and at 4 weeks of the treatment of estrogen replacement therapy (ERT) (Study 2). Brachial to ankle PWV (baPWV), which is correlated with aortic PWV, was determined using an automatic device, BP-203PRE. *Results:* In Study 1, PWV was significantly correlated with age in both groups (controls: $r = 0.392$, $P = 0.035$; HRT group: $r = 0.471$, $P = 0.013$), and HRT significantly lowered the PWV value at all ages examined (Mean $\pm$ S.D. of baPWV in controls: 1382.2 ± 114.1; HRT: 1245.3 ± 124.8, $P = 0.0001$). In Study 2, baPWV decreased significantly after ERT ($P < 0.05$), without a significant change in systolic BP ($P = 0.851$). *Conclusions:* Estrogen appears to improve arterial compliance independently of BP within 4 weeks.

Keywords: PWV; Arterial stiffness; HRT

Abbreviations: PWV, pulse wave velocity; HRT, hormone replacement therapy; EAT, estrogen replacement therapy; baPWV, brachial to ankle pulse wave velocity; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol.

* Corresponding author. Tel.: +81-23-628-5393; fax: +81-23-628-5396.
E-mail address: masa@med.id.yamagata-u.ac.jp (M. Ohmichi).

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1. Introduction

It has been shown that an increase in the aortic stiffness, determined by the measurement of aortic pulse wave velocity (PWV), is an independent marker of cardiovascular risk in the hypertensive patients [1]. PWV depends on smooth muscle relaxation [2], endothelial function [3], and the arterial wall structure, and is mainly influenced by age-associated alterations of the arterial wall and blood pressure (BP) [4]. At the present time, the only effective therapy available to improve vascular wall stiffness is to reduce wall stress by lowering intravascular distending pressure by antihypertensive drugs [5]. Epidemiological evidence suggests that hormone replacement therapy (HRT) is effective in preventing coronary heart disease among postmenopausal women [6]. In postmenopausal women, it has been shown that HRT improves carotid-femoral PWV (cfPWV), but not femoral artery to the dorsalis pedis PWV (fdPWV)[7]. Recently, the development of a new device has made it much easier to estimate cfPWV by measurement of brachial to ankle PWV (baPWV), which correlates well with cfPWV[8]. To determine the impact of HRT on arterial compliance in normotensive, postmenopausal women, we examined the relationship between HRT and baPWV.

2. Subjects and methods

2.1. Study 1

Fifty-six postmenopausal women aged 50–70 years were recruited from the patients visiting our menopause clinic for a routine health check between October 2001 and January 2002. Patients of age below 50 years or premenopausal status, or with hypertension (systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg), diabetes (fasting glucose level > 110 mg/dl), or overt hyperlipidemia (total cholesterol level above 240 mg/dl and/or serum low-density lipoprotein cholesterol above 160 mg/dl, triglyceride level above 150 mg/dl, high-density lipoprotein cholesterol (HDL) level below 40 mg/dl, or use of lipid-lowering drug) were strictly excluded. All women had passed menopause, as confirmed by amenorrhea for at least 12 months and by serum FSH levels above 30 mlU/ml and serum estradiol levels below 10 pg/ml.

2.2. Study 2

Nine postmenopausal women (including women with surgical menopause) aged 30–54 were recruited from our clinic between October 2001 and April 2002. Two women had passed menopause as confirmed by the same criteria as for Study 1. Seven women had surgical menopause and were followed for longer than 3 months. Exclusion criteria except for age were the same as for Study 1.

3. Protocol

3.1. Study 1

Twenty-seven women on HRT (14 on oral conjugated equine estrogen (CEE, Premarin® 0.625 mg) alone and 13 on estrogen plus medroxyprogesterone acetate (Provera® 2.5 mg)) and an age-matched group of 29 women not on HRT were studied. HRT was prescribed for several months to 6 years. All patients were given informed consent.

3.2. Study 2

Nine women were studied before and at 4 weeks of the treatment with CEE (0.625 mg) for estrogen replacement therapy (ERT). All patients were given informed consent.

4. Measurement of baPWV

BaPWV was determined using an automatic device, BP-203PRE (Cohn, Komaki, Japan), which allows pulse wave recording and automatic calculation of baPWV as previously described and validated. Pearson's correlation coefficients of intraobserver and interobserver reproducibility were $r = 0.98$ and 0.87, respectively [8]. Pressure

waveforms of the brachial and tibial arteries were recorded after 10 min of bed rest. At the same time, electrocardiogram monitoring was performed with electrodes placed on both wrists, and arrhythmia was evaluated. Heart sounds S1 and S2 were detected using a microphone set on the left edge of the sternum at the fourth intercostal space. The pressure waveforms obtained at two different sites were simultaneously recorded to determine the time interval between the initial rise in the brachial and tibial pressure waveforms.

5. Results

5.1. The effect of HRT on baPWV

We first compared the baPWV in the non-HRT and HRT groups. The characteristics of the subjects (Study 1) are given in Table 1. Overall, there were no significant differences in age, systolic or diastolic BP, total or HDL cholesterol, or BMI; the only significant difference observed was for LDL cholesterol ($P = 0.001$). In Fig. 1, baPWV was plotted against age in the two groups. In both groups, PWV was significantly correlated with age (controls: $r = 0.392$, $P = 0.035$; HRT group: $r = 0.471$, $P = 0.013$) and HRT significantly lowered the PWV value at all ages examined (mean $\pm$ S.D. of baPWV in controls: 1382.2 ± 114.1; HRT: 1245.3 ± 1248, $P = 0.0001$). Although HRT group contains ERT group, the PWV value was not different significantly between HRT and ERT groups (data not shown). Subjects with aortic PWV below 940 cm/s, which corresponds to baPWV 1400 cm/s, have been reported to show a lower risk for cardiovascular disease [9]. The ages of the subjects in whom baPWV reached this level (1400 cm/s) were 56.7 and 66.4 years in the control and HRT groups, respectively.

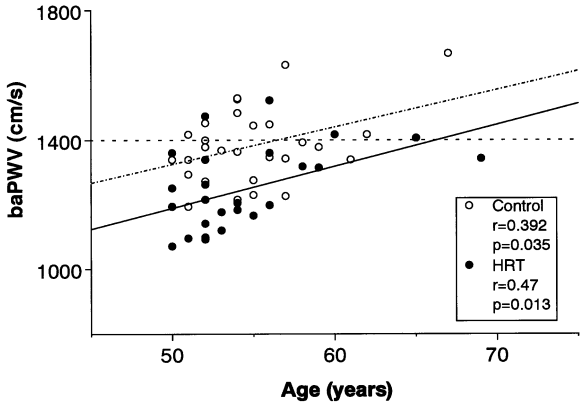

Fig. 1. Relationship of brachial to ankle PWV (baPWV) to age in women with and without HRT. BaPWV was plotted against age in the two groups in Study 1.

5.2. Comparison of baPWV before and after HRT

Both baPWV and systolic BP were compared before and after HRT for 4 weeks. The character-

Table 1
Characteristics of the study population in Study I

	Control ($n = 29$)	HRT ($n = 27$)
Age (years)	56.8 ± 4.2	54.4 ± 4.5
SBP (mmHg)	122.8 ± 8.0	124.4 ± 12.6
Diastolic BP (mmHg)	75.1 ± 7.8	76.0 ± 6.7
Mean arterial pressure (mmHg)	96.2 ± 7.3	94.3 ± 8.5
Heart rate (beats/min)	69.7 ± 8.7	63.5 ± 5.6 *
Total cholesterol (mg/dl)	213.0 ± 34.7	207.0 ± 22.1
LDL cholesterol (mg/dl)	128.3 ± 39.3	107.9 ± 19.4 *
HDL cholesterol (mg/dl)	70.6 ± 13.6	76.3 ± 11.7
BMI (kg/m^2)	23.8 ± 2.8	22.1 ± 3.1
PWV (cm/s))	1382.2 ± 114.1	1245.3 ± 124.8 **

* $P = 0.001$.
** $P = 0.0001$.

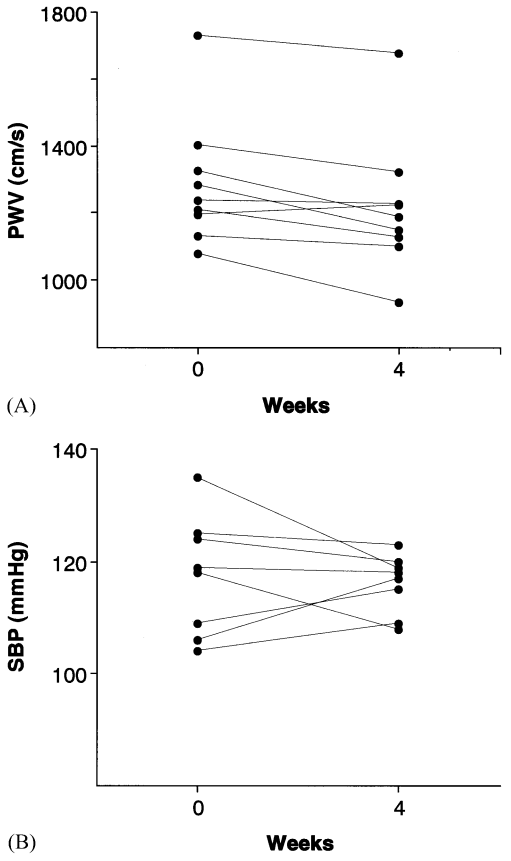

Fig. 2. Comparison of PWV and systolic BP (SBP) before and after ERT for 4 weeks. PWV and SBP were plotted before and after ERT for 4 weeks in Study 2.

istics at baseline of these subjects (Study 2) are given in Table 2. Fig. 2A shows baPWV at baseline and after 4 weeks of ERT. No further decrease was observed after 4 weeks of ERT (data not shown). BaPWV decreased significantly after the medication ($P < 0.05$), but Fig. 2B shows that there was no significant change in systolic BP ($P = 0.851$).

6. Discussion

Many epidemiological and basic studies had reported that estrogen has the significant function in the vasculature of preventing the primary development of cardiovascular disease in women [10,11]. However, the results of the first report from the Women's Health Initiative's (WHI) [12], a large randomized primary prevention trial, and the Heart and Estrogen/progestin Replacement Study (HERS) [13], a secondary prevention trial seem to raise questions against the cardioprotective effect of estrogen. Although subjects of WHI are healthy women, the wide age distribution (50–79 years), high incidence of obesity (mean BMI = 28.5), and late start of HRT do not correspond to the traditional use of HRT. Thus, the studied population presented numerous risks of diseases related to aging, in particular cardiovascular disease. On the other hand, the results of the Estrogen in the Prevention of Atherosclerosis Trial, a randomized, double-blind, placebo-controlled trial, showed that unopposed ERT with 17β-estradiol reduces progression of intima-media thickness (IMT) in healthy postmenopausal women without preexisting cardiovascular disease [14], suggesting a vascular protective effect by estrogen.

Table 2
Characteristics of the study population at baseline in Study 2 ($n = 9$)

Age (years)	46.2 ± 7.1
SBP (mmHg)	116.6 ± 10.3
Diastolic BP (mmHg)	71.0 ± 3.5
Mean arterial pressure (mmHg)	96.9 ± 15.4
Heart rate (beats/min)	67.2 ± 10.6
Total cholesterol (mg/dl)	195.9 ± 18.7
LDL cholesterol (mg/dl)	109.6 ± 20.2
HDL cholesterol (mg/dl)	68.1 ± 15.5
BMI (kg/m^2)	22.1 ± 1.55

In this study, we used an automatic waveform analyzer to measure baPWV to compare the arterial stiffness between normotensive women who were receiving and not receiving HRT. We also compared baPWV in subjects before and after ERT. BaPWV was significantly lower in the HRT group compared with the controls (Fig. 1), suggesting a vascular protective effect by estrogen on the large artery. This favorable effect occurred within 4 weeks (Fig. 2A), and therefore it seems to be largely independent of estrogen's effects on lipid metabolism, and dependent on direct action on the arterial wall. Moreover, there was no difference in BP between the two groups (Table 1) and in subjects before and after ERT (Fig. 2B); therefore,

estrogen is likely to improve arterial compliance independently of BR. Although to date no agents that affect arterial compliance independently of BP, serum lipid, and serum glucose status have been reported, we have clearly shown that estrogen has an impact on the arterial structure.

Recently, several non-invasive methods have been developed to assess the arterial compliance, but most are complex, time consuming, and need a specifically qualified operator. To evaluate the arterial compliance in the outpatient, the use of simple and reproducible methods is needed. The automatic device used in this study may be suitable for this purpose. It was reported that the non-invasive baPWV showed a good correlation with the aortic PWV obtained by invasive recording [8], indicating the validity of the non-invasive baPWV measurement. Moreover, the method that we used to measure baPWV does not require any specialized technique, and the examiner has only to wrap cuffs on the brachium and ankle. After these simple preparations, baPWV is automatically measured. The simplicity of this method makes it suitable for screening large populations.

IMT, another parameter that can be used to assess the atherosclerotic process in the carotid artery, also shows a protective effect by estrogen, but more than 2 years of HRT use is necessary to detect this effect of estrogen [15]. Flow mediated dilatation (FMD), an established procedure to evaluate endothelial function, also reflects estrogen's effect [16], but it is not affected by arterial structure (elastic fibers or collagen). Ovariectomy influences FMD as rapidly as within 1 week [17]. Recent studies suggest that nitric oxide (NO) is relevant to the arterial compliance, and inhibition of NO synthesis increases aortic stiffness [18]. Since estrogen activates endothelial NO synthase and leads to vasodilatation [19], estrogen may reduce arterial stiffness through a beneficial effect on endothelial function. Since HRT influenced the arterial stiffness within 4 weeks as determined by baPWV in this study, baPWV may be able to detect not only endothelial dysfunction but also an early alteration of arterial structure. However, further studies will be necessary to examine the association of baPWV with both structural vascular change as determined by IMT and functional vascular alteration as determined by FMD.

PWV was significantly correlated with age, and HRT significantly lowered the PWV value at all ages examined (Fig. 1). Thus, an interaction between estrogen's favorable effect and aging was detected. However, both the mechanism by which estrogen affects PWV and estrogen's long-term effects on vascular stiffness are still unclear and further investigations will be necessary to clarify them.

In conclusion, PWV measurement offers a simple, reproducible and non-invasive means to evaluate arterial stiffness and seems useful for assessing estrogen's direct effects on the vasculature in vivo.

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