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HYSTERECTOMY IS ASSOCIATED WITH LARGE ARTERY STIFFENING IN ESTROGEN-DEFICIENT POSTMENOPAUSAL WOMEN

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Abstract

Objective—Hysterectomy, with or without oophorectomy is associated with increased cardiovascular disease (CVD) risk due, in part, to an adverse CVD risk factor profile. Large artery stiffening, a biomarker of vascular aging, increases the risk for CVD. We determined whether hysterectomy with or without bilateral oophorectomy (BLO) is associated with arterial stiffening in healthy postmenopausal women.

Methods—We conducted a cross-sectional study including estrogen-deficient postmenopausal women who had a hysterectomy with ovarian preservation (N= 24; 59±1 year, mean±SE) or with BLO (N=21; 58±2 year), and had no hysterectomy/no BLO (N=58; 58±1 year). Arterial stiffness (arterial compliance and beta stiffness index) was measured by ultrasonography of the carotid artery.

Results—Carotid artery compliance was lower in women with hysterectomy alone and in women with hysterectomy with BLO compared to women with no hysterectomy (0.66±0.03 and 0.71±0.06 versus 0.89±0.03 mm²/mmHg×10⁻¹, respectively, both P<0.05). There were no differences in traditional CVD risk factors (i.e., adiposity, blood pressure and fasted lipids and lipoproteins, glucose and insulin) between the groups. After adjustment for age, menopause duration, prior menopausal hormone therapy duration, parity, waist-to-hip ratio, systolic blood pressure and sex-hormone binding globulin, hysterectomy status remained a significant predictor of arterial compliance.

Conclusions—These results indicate that hysterectomy status (with or without BLO) is associated with greater arterial stiffening in estrogen-deficient postmenopausal women. The greater arterial stiffening with hysterectomy was not related to an adverse CVD risk profile. Large

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artery stiffening may be an important mechanism by which hysterectomy increases the risk of CVD in postmenopausal women.

Keywords

vascular function; aging; menopause

Introduction

Cardiovascular disease (CVD) is the leading cause of death for women in the United States ¹. The prevalence of CVD increases with advancing age in both women and men, with premenopausal women having a lower prevalence compared with age-matched men until around the time of the menopause transition, where thereafter, women have an equal or greater prevalence of CVD ¹. This female advantage has often been attributed to the protective effects of estrogen during the premenopausal years which is then lost when ovarian function declines with menopause. Indeed, premature menopause, including hysterectomy with ovarian preservation or with oophorectomy (bilateral or unilateral) has been reported to be a significant predictor of CVD^{2, 3}. The CVD risk associated with hysterectomy itself (with intact ovaries) has been attributed to early menopause related to premature ovarian failure from disruption of ovarian blood flow ^{2, 4}. The increased CVD risk with hysterectomy (regardless of oophorectomy status) has been attributed to an adverse CVD risk factor profile ³. However, a substudy of the Women's Health Initiative (WHI) placebo-controlled trial of conjugated equine estrogens demonstrated that hysterectomy (including bilateral or unilateral oophorectomy) without history of menopausal hormone therapy (HT) was associated with subclinical coronary artery disease independent of traditional CVD risk factors ⁵. Moreover, among women with bilateral oophorectomy (BLO), HT use within 5 years of surgery was associated with a lower prevalence of subclinical atherosclerosis ⁵. These findings are consistent with the idea that estrogen deficiency associated with hysterectomy is related to the development of CVD. Because hysterectomy is the second most common surgical procedure among women in the United States a full understanding of the mechanisms behind its link to increased CVD risk is of clinical importance ⁶.

Large artery stiffening, a biomarker of vascular aging, is a predictor of CV events ⁷. In most individuals vascular aging is a gradual process. However, in certain conditions, including menopause, the vascular aging process appears to be accelerated, particularly with estrogen deficiency. Indeed, artery stiffness is greater in postmenopausal women compared to age-matched premenopausal women and lower in postmenopausal women using HT compared to women not using HT ⁸⁻¹⁰. However, whether hysterectomy with or without BLO alters age-associated large artery stiffening in postmenopausal women is unclear. Accordingly, in the present study we determined whether hysterectomy with or without BLO was associated with large artery stiffening in estrogen-deficient postmenopausal women.

Methods

Participants

One hundred and three healthy postmenopausal women (46 to 80 years of age) who were estrogen-deficient (no use of HT for at least 6 months at study entry) were studied. Postmenopausal women did not have menses for at least 1 year and had follicle stimulating hormone (FSH) concentrations greater than 30 IU/liter. Forty-five women had a history of either hysterectomy with ovarian preservation (n=24) or hysterectomy with BLO (n=21) and 58 women did not have a hysterectomy or BLO. Age at menopause, postmenopause duration, prior HT use, age at menarche, and parity were obtained from the medical history

and physical exam. The number of years postmenopause was estimated from self-reported age at menopause in women who did not have a hysterectomy or who had a hysterectomy with ovarian preservation, and from self-reported surgery date in those who had a hysterectomy with BLO. Women were sedentary or recreationally active (no planned regular exercise >3 days/wk), normotensive, nonsmokers, not taking any cardiovascular or lipid-lowering medications, and free of overt chronic diseases as assessed by medical history, physical examination, standard blood chemistries and hematological evaluation. All women gave their written informed consent to participate. All procedures were reviewed and approved by the University of Colorado at Boulder Human Research Committee and the University of Colorado Denver Colorado Multiple Institutional Review Board.

Study Procedures

All measurements were performed at the University of Colorado at Boulder and the University of Colorado Denver Clinical Translational Research Centers (CTRC) following at least a 4-hour fast (12 hours for determination of metabolic parameters) and abstinence from caffeine.

Arterial Stiffness

Two common indices of arterial stiffness were measured: carotid artery compliance which is the change in cross-sectional area of a vessel per unit of pressure, and beta stiffness index which provides an index of arterial compliance adjusted for distending pressure. Arterial compliance and beta stiffness were determined using high resolution ultrasound imaging of the carotid artery as previously described^{9, 11}. Peripheral arterial blood pressure was measured with a semi-automated device (Dinamap, Johnson & Johnson) over the brachial artery¹¹. Carotid images were analyzed for arterial distention and intimal-medial thickness (IMT) using Vascular Analysis Tools v. 5.5. All images were coded by number, blinded to group assignment and analyzed by the same individual (KLM). Time points that corresponded with maximal systolic expansion of the carotid artery and basal (minimum) diastolic relaxation were selected. Because the near-wall IMT cannot be precisely measured on a consistent basis¹², diameter was measured as the distance between the vessel far-wall boundary, corresponding to the interface between the lumen and intima, and a near-wall boundary, corresponding to the interface between the media and adventitia. Note that this will tend to slightly overestimate the true absolute lumen diameter, as well as influence the corresponding calculated wall stresses (see below). IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface¹². Wall thickness was normalized for lumen size and was expressed as IMT/lumen diameter ratio. Because arterial remodeling (i.e., change in structural properties in response to atherogenic and/or hemodynamic factors within the artery) is thought to be an adaptive response aimed at maintaining arterial wall stresses within certain limits to possibly preserve arterial compliance, circumferential wall stress was calculated. Circumferential (tangential wall stress (dyn/cm²), the tension that acts perpendicular to the arterial wall, was calculated using $[(MBP \times D)/2]/IMT$, where MBP is mean blood pressure (dyn/cm²), D is diameter in centimeters, and IMT is expressed in centimeters^{13, 14}. The intra-observer within participant reliability for the measurement of carotid artery compliance was determined on 9 participants studied on two different days at least one week apart. The coefficient of variation for the two trials was $4 \pm 2\%$ for carotid artery compliance and $3 \pm 1\%$ for carotid IMT.

Blood Analyses

Fasted plasma concentrations of glucose, triglycerides, total- (Roche Diagnostic Systems, high-density-lipoprotein (HDL-C, Diagnostic Chemicals, Ltd, Oxford CT) cholesterol were determined using enzymatic/colorimetric methods, and low-density-lipoprotein cholesterol

(LDL-C) was determined using the Friedewald equation ¹⁵. Plasma or serum concentrations of estradiol and sex hormone-binding globulin (SHBG) were measured using conventional radioimmunoassay. The homeostasis model (fasting glucose $\times$ fasting insulin/22.5; HOMA) was used to calculate the insulin sensitivity index ¹⁶. All assays were performed by the University of Colorado Denver CTRC core laboratory. Intra- and interassay coefficients of variation were as follows: 1) glucose, 0.67% and 1.44% respectively; 2) insulin, 5.2% and 9.8%; 3) triglyceride, 0.82% and 2.18%; 4) total cholesterol, 0.85% and 1.54%; 5) HDL-C 0.5% and 1.12%; 6) estradiol, 4.3% and 8.2%; and 7) SHBG, 3.6% and 5.7%.

Body Composition and Maximal Oxygen Consumption

Total fat mass and fat-free mass were determined using dual energy x-ray absorptiometry (DPX-IQ, Lunar Corp.). Minimal waist and hip circumferences were measured according to previously published guidelines and waist to hip ratio (WHR) was calculated ¹⁷. In a subset of women (No hysterectomy = 52, Hysterectomy Alone = 15, Hysterectomy with BLO = 14), maximal oxygen consumption, a measure of maximal aerobic exercise capacity, was determined using an incremental treadmill exercise protocol as described previously ¹⁸.

Statistical Analysis

χ^2 tests were used to assess differences in categorical variables (e.g., ethnicity, prior HT use) between women who did not have a hysterectomy, hysterectomy alone and hysterectomy with BLO. One way ANOVA was used to assess group differences in continuous variables (i.e participant characteristics and hemodynamic/carotid artery structure) and arterial stiffness measurements. If significant differences were observed with ANOVA analysis, Scheffe *post hoc* analysis for multiple comparisons was performed to identify significant differences among the mean values. The skewness of postmenopause duration, estradiol, triglycerides and SHBG necessitated logarithmic transformation and mean data presented have been re-exponentiated with 95% confidence interval. Exploratory analyses were performed using Pearson product correlations to test for the presence of significant linear bivariate relations between variables of interest.

To determine whether hysterectomy status was independently related to arterial stiffness, linear regression was performed where carotid artery compliance or beta stiffness was entered as the dependent variable and Hysterectomy Alone and Hysterectomy with BLO were entered as independent variables, with No Hysterectomy being the reference group; model A. To ensure that any observed association between hysterectomy status and arterial stiffness was not confounded by age, menopause and HT duration, parity, cardiovascular risk factors or sex hormone concentrations, we used a multiple regression model that included all of these factors that were significantly correlated with arterial stiffness (model B). Although VO_{2max} was significantly associated with arterial compliance and beta stiffness it was excluded from model B due to limited sample size for this variable. SHBG was not a significant correlate of beta stiffness in the population as a whole, and was therefore not included in the regression model for beta stiffness. Multicollinearity was controlled for examining the correlations and associations between all independent variables included in the regression to detect a high level of association and by examining the tolerance and the Variance Inflation Factor. Data are presented as mean $\pm$ SE unless otherwise noted and alpha was set at 0.05. Data analysis was performed with SPSS software, version 19.0.

Results

Participant Characteristics (Table 1)

Ethnicity, race and past HT use were similar among groups. Time since menopause was longer and age at menopause was younger in women with hysterectomy with and without BLO compared to women with no hysterectomy (all $P < 0.01$, Table 1). Parity was greater and SHBG was lower in women with hysterectomy with ovarian preservation versus women with no hysterectomy ($P < 0.05$, Table 1). Duration of previous HT use was greater in women with hysterectomy and BLO compared to women with no hysterectomy ($P < 0.01$, Table 1). There were no group differences in body composition, blood pressure, estradiol, or fasted blood lipids, glucose and insulin concentrations.

Arterial Stiffness is Greater in Postmenopausal Women with a History of Hysterectomy

Carotid artery compliance was 25% lower in women with hysterectomy with ovarian preservation and 20% lower in women with hysterectomy with BLO compared to women with no hysterectomy (both $P < 0.05$, Figure 1). Qualitatively similar results were obtained when the data were expressed as beta stiffness index with the exception that there was no significant difference in beta stiffness index between women with a history of no hysterectomy compared to those with a hysterectomy with BLO ($P = 0.51$). There were no differences in carotid artery compliance ($P = 0.59$) or beta stiffness index ($P = 0.37$) between women with hysterectomy with ovarian preservation and those with hysterectomy with BLO.

Table 2 presents the peripheral hemodynamic and carotid artery structure. Carotid lumen diameter and interadventitial diameter were smaller in women with hysterectomy with BLO compared to women with no hysterectomy (both $P < 0.01$) but was not different between hysterectomy with ovarian preservation and no hysterectomy women. Carotid artery distention was lower in women with hysterectomy alone ($P < 0.01$) and tended to be lower in women with hysterectomy with BLO ($P = 0.08$) compared to women with no hysterectomy ($P < 0.01$). There were no differences in carotid diameter, interadventitial diameter and distention between women with hysterectomy alone compared to those with BLO. There also were no differences in IMT, IMT/diameter ratio, peripheral blood pressure or tangential wall stress between any of the groups (all $P > 0.70$).

In the overall population, carotid artery compliance was inversely related to age ($r = -0.45$), parity ($r = -0.37$), postmenopause duration ($r = -0.28$), WHR ($r = -0.27$), and seated systolic blood pressure ($r = -0.31$) and positively related to SHBG ($r = 0.25$) and VO_2max ($r = 0.26$) (all $P < 0.05$). Beta stiffness index showed the same general relations, but was not significantly correlated with SHBG. Among postmenopausal women with hysterectomy with and without bilateral oophorectomy, carotid artery compliance was inversely related to age ($r = -0.43$), postmenopause duration ($r = -0.30$), parity ($r = -0.41$), WHR ($r = -0.37$) and seated systolic ($r = -0.42$) and diastolic ($r = -0.34$) blood pressure, and positively related to SHBG ($r = 0.31$) (all $P < 0.05$). Beta stiffness index showed a positive correlation with age ($r = 0.46$), parity ($r = 0.30$) and seated systolic blood pressure ($r = 0.34$) (all $P < 0.05$).

Regression analysis confirmed the above results that hysterectomy status is a significant predictor of arterial stiffness. Initial crude analysis (model A) showed that hysterectomy alone ($\beta = -0.33$, $P = 0.001$) and hysterectomy with BLO ($\beta = -0.25$, $P = 0.01$) were significant predictors of arterial compliance. Hysterectomy alone was a significant predictor of beta stiffness index ($\beta = 0.29$, $P = 0.004$) but not hysterectomy with BLO ($\beta = 0.14$, $P = 0.15$). After adjustment for age, postmenopause duration, past HT duration, parity, WHR, systolic blood pressure and SHBG (model B) the results were qualitatively similar. In model B, in addition to hysterectomy alone ($\beta = -0.24$, $P = 0.02$) and hysterectomy with BLO ($\beta =$

-0.23, $P=0.03$), age ($\beta = -0.32$, $P=0.003$) was also a significant predictor of arterial compliance, and for beta stiffness index, only hysterectomy alone ($\beta = 0.25$, $P=0.02$) and age ($\beta = 0.31$, $P=0.009$) were significant predictors. Figure 2 demonstrates the decline in arterial compliance at a given age for women with hysterectomy with/without BLO and no hysterectomy.

Discussion

The novel finding of this study is that healthy postmenopausal women with a history of a hysterectomy have stiffer large elastic arteries compared to postmenopausal women with no history of hysterectomy. The greater arterial stiffness is evident in both women with BLO and in those with ovarian preservation with hysterectomy. Additionally, the greater arterial stiffness in women with a history of hysterectomy does not appear to be associated with an adverse arterial remodeling nor is it related to an adverse CVD risk factor profile.

Hysterectomy with ovarian preservation and with BLO is associated with a greater degree of coronary atherosclerosis, calcified plaque, and increased CVD events^{2, 3, 5, 19}. The mechanisms underlying these associations have not been fully elucidated, although recent data from the WHI Observational Study attribute the increased CVD risk with hysterectomy to an adverse CVD risk factor profile³. However, our results demonstrating that women with hysterectomy with or without BLO have greater arterial stiffening (i.e., reduced arterial compliance) compared to age-matched women with no hysterectomy provides evidence for a possible biological effect of hysterectomy per se on arterial health. First, in contrast to previous observational studies^{2, 3, 5}, we only included women who were normotensive, non-smokers, non-diabetic and not taking cardiovascular or lipid lowering medications, thus, removing some potential influence of overt disease and medication status on the vascular wall. Second, there were no differences in carotid IMT, blood pressure, adiposity, blood lipid profile, glucose, insulin or maximal aerobic capacity between our groups indicating that women with hysterectomy with or without BLO did not have a worse CVD risk profile. Finally, hysterectomy status remained a significant predictor of carotid artery compliance after adjustment for CVD risk factors (i.e., WHR and blood pressure) that were correlated with arterial compliance. As such, our data indicate that the greater arterial stiffening observed in women with hysterectomy with or without BLO is not related to an adverse CVD risk profile but rather possibly to an independent biological effect of hysterectomy on the arterial wall. Because arterial stiffness, a biomarker of vascular aging, is an independent predictor of CVD and all-cause mortality⁷, our findings suggest that the increased CVD risk with hysterectomy may be mediated via an acceleration in vascular aging.

The mechanisms by which hysterectomy increases arterial stiffness in women are unclear. Women who have a history of hysterectomy have been reported to have greater parity which is associated with increased CVD risk^{20, 21}. Pregnancy is associated with insulin resistance, lipid abnormalities, inflammation, and impaired endothelial function^{21, 22}. As such, the increased CVD risk has been attributed to accumulated damage from these factors with successive pregnancies. In the present study, parity was higher in women with hysterectomy alone compared to women with no hysterectomy and was inversely correlated with carotid artery compliance. However, after adjusting for parity, hysterectomy remained a significant predictor of carotid artery compliance indicating that the greater arterial stiffness in women with hysterectomy was not related to the potential metabolic or inflammatory adverse effects associated with a greater number of pregnancies.

In the present study, serum SHBG concentrations were lower in postmenopausal women with a history of hysterectomy with ovarian preservation compared to women who did not have a hysterectomy. Low SHBG has been reported to be associated with increased

coronary atherosclerosis and CVD events²³. The link between low SHBG and CVD risk has been attributed to hyperandrogenism, as well as an adverse metabolic profile (i.e., elevated glucose, insulin, LDL cholesterol and central adiposity) and inflammation^{24, 25}. Consistent with this, in the present study, SHBG concentrations were strongly correlated with WHR ($r = -0.53$) and insulin ($r = -0.51$) within women with hysterectomy with or without oophorectomy. Moreover, SHBG was positively correlated with carotid artery compliance in the overall population and within women with hysterectomy but not in women with no hysterectomy, suggesting that low SHBG concentrations may be a mechanism contributing to the greater arterial stiffening in women with hysterectomy. However, including SHBG in the regression analyses did not eliminate the effect of hysterectomy on arterial stiffness in our population.

In women, the age-associated increase in arterial stiffness appears to be augmented around the menopause transition, presumably related to estrogen deficiency⁸⁻¹⁰. As such, premature menopause and the resulting estrogen deficiency may be a potential mechanism for the apparent acceleration in large artery stiffening with hysterectomy. Estrogen has been shown to influence factors that contribute to arterial stiffness including the structural composition within the arterial wall (i.e., increased elastin and decreased collagen and IMT) and the contractile state of vascular smooth muscle cells (i.e., increased nitric oxide bioavailability)^{14, 26, 27}. In the WHI Coronary Artery Calcium substudy, women who had any oophorectomy and no prior HT use had higher odds of subclinical atherosclerosis compared to women who had any oophorectomy and were prior HT users⁵. Additionally, among women with BLO, HT use within 5 years of oophorectomy was associated with a lower prevalence of subclinical atherosclerosis⁵. Similarly, in the Nurse's Health Study BLO before age 50 years was associated with an increased risk of all-cause mortality, CHD and stroke in those women who had never used HT²⁸. In the present study, women with hysterectomy with or without BLO had used HT longer than women with no hysterectomy. However, when past HT duration was controlled for in the regression model, hysterectomy remained a significant predictor of carotid artery compliance. This finding may be explained by the fact that there was no difference in the time since past HT use between the groups, and thus, the overall duration of estrogen deficiency was similar. Alternatively, it is possible that we were unable to detect the protective effect of past HT initiated within 5 years of menopause on arterial stiffness because of our small sample size and/or our inability to quantify timing of HT initiation with the onset of menopause.

We found that the influence of hysterectomy on arterial stiffening was similar between women with BLO and those with ovarian preservation, consistent with observational studies reporting an increased risk for CVD in women with hysterectomy alone^{2, 3}. Women with hysterectomy with ovarian preservation have been reported to have higher FSH concentrations and an earlier menopause (45 ± 4 year) compared to women with no hysterectomy (50 ± 4 year)^{4, 29}. The earlier menopause has been attributed to premature ovarian failure related to a disruption in ovarian blood flow with hysterectomy². Furthermore, women with a hysterectomy with ovarian preservation are less likely to be treated with HT than women who have BLO, and thus, are more likely to have an untreated relative estrogen deficiency⁵.

Considerations and Experimental Limitations

Even though carotid artery compliance was significantly reduced in women with hysterectomy regardless of oophorectomy status, this was not the case for beta stiffness index which was only significantly elevated in women with hysterectomy with ovarian preservation. Thus, a potential limitation to the study could be the small sample sizes in the hysterectomy groups compared to the no hysterectomy group. Beta stiffness index adjusts arterial compliance for distending pressures which were similar among the groups. Thus, it

is possible that if we had larger sample sizes in these groups that hysterectomy with BLO would have been associated with a greater beta stiffness index. Additionally, because carotid artery diameter was smaller in women with hysterectomy with BLO it is possible that their reduced carotid artery compliance was related to an adverse arterial remodeling. Arterial remodeling (i.e., alterations in artery structural characteristics in response to atherogenic and/or hemodynamic forces), is thought to be an adaptive response in order to maintain circumferential wall and shear stresses within the artery to possibly preserve compliance. Arterial remodeling is typically characterized by increases in IMT and diameter (outward remodeling), although it has been observed in the early stages of atherosclerosis that coronary arteries enlarge in relation to plaque area to preserve lumen until plaque area occupies 40% of vessel area³⁴. However, in the present study, the smaller carotid diameter in the hysterectomy with BLO women corresponded with a smaller carotid IMT and not a larger IMT. Moreover, there was no difference among the groups in IMT/lumen ratio or circumferential (tangential) wall stress, nor was IMT or wall stress correlated with measures of arterial stiffness. Thus, based on the available data that we have to assess arterial remodeling, it does not appear that the reduced arterial compliance in the women with hysterectomy with/without BLO is associated with a particular pattern of adaptive remodeling. These data are consistent with our previous studies demonstrating no differences in carotid IMT between age-matched sedentary and endurance-trained older adults despite the endurance-trained older adults having a significantly greater carotid artery compliance^{9, 11, 32}. Additionally, arterial stiffness has been reported to be similar between middle-aged adults with greater IMT compared to those with smaller IMT³⁵. One potential explanation for this phenomenon is likely due to the fact that the participants in the present study were healthy (normotensive, non-diabetic, no signs or symptoms of overt CVD).

We recognize that because our study was cross-sectional we cannot prove causality and thus, our findings must be interpreted with caution. We relied on self-report measures of menopause, hysterectomy, HT use and duration of HT use, and thus, it is possible that this information and the classification of groups were inaccurate. We also cannot rule out other constitutional or genetic factors that could be influencing arterial stiffening in women with hysterectomy with or without bilateral oophorectomy. For example, low socioeconomic status and physical activity levels are associated with hysterectomy and increased CVD risk^{20, 30}. Thus, it is possible that women with surgical menopause had lower socioeconomic status and physical activity levels. To the extent possible we eliminated constitutional factors by matching the menopausal groups for age, CVD risk factors and aerobic capacity (VO_{2max}) and adjusted our analysis for parity and past HT use. Although VO_{2max} may not be representative of total daily physical activity it does reflect overall aerobic fitness and has been shown by numerous studies to provide a strong, independent graded inverse association with CVD and all-cause mortality in healthy and unhealthy populations³¹. Moreover, we and others have previously shown that maximal aerobic capacity is correlated with arterial stiffness in healthy older adults^{9, 11, 32, 33}. Additionally, we only studied healthy non-smoking, normotensive, sedentary postmenopausal women without evidence of overt chronic diseases, our findings can only be generalized to this population of women.

Clinical Significance

Hysterectomy is the second most common surgical procedure in women in the United States behind cesarean section with ~600,000 women undergoing hysterectomies a year⁶. As such, understanding the physiological changes that accompany gynecological surgical procedures is important when evaluating current standard of care and future health risk analysis. CVD is a public health concern in women³⁶, and the results of the present study provide new insight into the possible pathophysiological role of hysterectomy with or without bilateral

oophorectomy on CVD risk in healthy women. Specifically, our findings demonstrate that healthy women with hysterectomy have accelerated vascular aging compared to women with natural menopause independent of CVD risk factors. Vascular aging is a major risk factor for the development of CVD, and accelerated or early vascular aging may manifest into early CVD events³⁷. Because hormonal dysregulation may contribute to the initiation and progression of CVD^{38, 39}, a better understanding is needed of the effects of hysterectomy, premature menopause and the onset of hypoestrogenemia on the mechanisms initiating vascular aging.

Conclusions

In conclusion, our results demonstrate that women with a history of hysterectomy (regardless of oophorectomy status) is associated with greater arterial stiffening when compared with women of the same age without a history of hysterectomy. The greater arterial stiffening with hysterectomy was not related to an adverse CVD risk profile. Large artery stiffening may be an important mechanism by which hysterectomy increases the risk of CVD in postmenopausal women.

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Figure 1.

Baseline carotid artery compliance (top) and beta stiffness index (bottom) in postmenopausal women with no hysterectomy (open bar; n=58), hysterectomy alone (grey bar; n=24) and hysterectomy with bilateral oophorectomy (black bar; n=21). * $P < 0.05$ vs no hysterectomy.

Figure 2.

Carotid artery compliance in postmenopausal women with no hysterectomy (open circles), hysterectomy alone (closed triangles upside down) and hysterectomy with bilateral oophorectomy (gray triangles). Regression lines represent relation between age and carotid artery compliance in each group.

TABLE 1
Participant Characteristics

Variable	No Hysterectomy	Hysterectomy Alone	Hysterectomy with Bilateral Oophorectomy
n	58	24	21
Age, yr	57±1	59±1	58±2
Age at Menopause, yr	51±1	43±2 ^a	45±1 ^a
Menopause duration, yr ^c	5.34 (4.38-6.52)	10.77 ^a (6.86-16.92)	10.83 ^a (7.97-14.72)
Past HT Use, % yes (n)	67 (39)	67 (16)	91 (19)
Past HT duration, yr	2.46±0.4	4.0±1.2	6.7±1.2 ^a
Time since last HT use, yr	3.6±0.5	4.4±1.1	2.9±0.6
Age at menarche, yr	12.6±0.2	12.9±0.3	12.7±0.2
Parity, number of children	1.5±0.2	2.5±0.3b	2.2±0.4
Body Mass, kg	72.3±2.1	71.9±2.8	67.1±2.8
BMI, kg/m ²	26.9±0.7	27.6±1.0	25.5±1.2
Body Fat, %	40.2±1.0	49.9±1.4	38.3±1.9
Waist Circumference, cm	84.2±1.8	85.3±2.4	81.5±2.6
WHR	0.80±0.01	0.82±0.02	0.79±0.02
VO _{2max} , mL/kg/min ^d	24.5±0.7	23.7±0.9	23.6±1.4
Systolic BP, mmHg	118±2	118±3	118±3
Diastolic BP, mmHg	70±1	70±2	72±2
Resting Heart Rate, bpm	66±1	67±2	68±2
Estradiol, pmol/L ^c	94 (82-108)	94 (76-117)	71 (57-87)
SHBG, nmol/L ^c	141 (117-170)	92b (70-121)	101 (72-143)
Total Cholesterol, mmol/L	5.3±0.1	5.5±0.2	5.3±0.3
LDL Cholesterol, mmol/L	3.3±0.1	3.4±0.2	3.4±0.2
HDL Cholesterol, mmol/L	1.5±0.1	1.5±0.1	1.6±0.1
Triglycerides, mmol/L ^c	1.12 (0.99-1.27)	1.08 (0.87-1.33)	1.09 (0.89-1.34)
Glucose, mmol/L	5.0±0.1	4.9±0.1	4.9±0.1
Insulin, pmol/L	50.1±5.8	62.1±7.9	52.1±6.5
HOMA Index	1.6±0.2	1.8±0.2	1.6±0.2

^a p<0.01

^b p 0.05 vs No Hysterectomy

^c Skewed values, re-exponentiated to geometric mean and 95% confidence interval

^d Reduced sample size (No hysterectomy = 52, Hysterectomy Alone = 15, Hysterectomy with Bilateral Oophorectomy = 14). HT = Hormone Therapy, WHR = waist to hip ratio, BP = blood pressure, SHBG = sex hormone-binding globulin, LDL = low density lipoprotein, HDL = high density lipoprotein. Data are presented as mean±SE unless otherwise indicated.

TABLE 2
Peripheral Hemodynamics and Carotid Artery Structure

Variable	No Hysterectomy	Hysterectomy Alone	Hysterectomy with Bilateral Oophorectomy
n	58	24	21
Supine Brachial SBP, mmHg	116±2	119±2	117±3
Supine Brachial DBP, mmHg	68±1	69±1	70±1
Mean Arterial BP, mmHg	86±1	87±2	87±2
Pulse Pressure, mm Hg	46±1	48±2	48±2
Carotid Diameter, mm	6.59±0.07	6.35±0.11	6.15±0.12 ^a
Carotid Distension, mm	0.39±0.01	0.31±0.02a	0.33±0.02
Carotid IMT, mm	0.668±0.017	0.673±0.026	0.647±0.027
Carotid IMT/Diameter	0.102±0.002	0.106±0.004	0.105±0.004
Carotid Interadventitial Diameter, mm	7.26±0.08	7.05±0.12	6.80±0.13 ^a
Tangential Wall Stress, 10 ⁵ dyne/cm ²	5.8±0.1	5.6±0.2	5.7±0.2

^aP 0.01 vs No hysterectomy. Data are presented as mean±SE. SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, IMT = intimal-media thickness.