Estrogen and Different Aspects of Vascular Disease in Women and Men

Carl J. Pepine, Wilmer W. Nichols, Daniel F. Pauly

Considerable evidence indicates that sex hormones have an important influence on cardiovascular physiology and pathology. Recent work suggests that a mechanism based on estrogen receptor-alpha (ESR1) contributes to a range of structural and functional responses that relate to vascular disease. Most of this work focuses on ESR1 activity within the endothelium and yields variable findings due, at least in part, to differences in the vascular bed or species studied, as well as other experimental conditions such as age, estrogen status, degree of preconstriction, etc. But many findings in conduit arteries (eg, increased wall stiffness, spasm, etc) and microvessels (eg, reduced coronary flow reserve, hot flashes, etc) implicate smooth muscle cells (SMCs) in gender differences in vascular disease. These cells are directly responsible for extracellular matrix production and assure the integrity of the artery wall. They may be decreased, apoptotic, or dysfunctional in terms of synthesis and repair of extracellular matrix, which is destroyed in vulnerable plaque by macrophages.

In this issue of Circulation Research Montague and colleagues report that activation of ESR1 decreases human aorta SMC differentiation (Figure). Importantly, they found that SMCs of men, compared with women, had reduced ESR1 expression associated with increased differentiation markers. Their work suggests that ESR1 activation switches SMC to a form that may promote plaque vulnerability. Could markers. Their work suggests that ESR1 activation switches ESR1 expression associated with increased differentiation markers. Their work suggests that ESR1 activation switches SMC to a form that may promote plaque vulnerability. Could different activation states of ESR1 be responsible for shifting the functional characteristics of SMCs toward a phenotype that explains some complexities of gender-related differences in vascular disease?

Differences in Vascular Disease Between Women and Men

Risk conditions and clinical findings indicate that the pathophysiology underlying ischemic vascular disease differs between women and men. A number of conditions are unique to women (eg, early age at menopause, hypertensive disorders of pregnancy, gestational diabetes, peripartum aortic or coronary dissection, polycystic ovarian syndrome, hypothalamic hypoestrogenemia, etc). Other factors linked with vascular disease or dysfunction are much more frequent in women than men (eg, migraine, coronary spasm, vasculitis, Raynaud phenomenon, etc). On this background, postmenopausal women more frequently have many traditional vascular disease risk conditions (eg, diabetes, obesity, hypertension, inactivity, etc) which occur and cluster more frequently in women than men. In addition to this greater burden of risk factors, the woman with vascular disease often is older and has more functional disability than her male counterpart. Women have poor clinical outcomes compared with men with acute coronary syndromes, chronic coronary syndromes, coronary revascularization, and heart failure that cannot be explained by simply adjusting for age. So other factors must contribute to the increased severity of vascular disease in women compared with men.

Clinical Characteristics and Links With Sex Hormones

Although, ischemic vascular disease is the most frequent cause of death for women, its prevalence in women compared with men does not increase markedly until after menopause when major changes in sex hormones occur. During menopause estrogen levels are about one-tenth premenopause levels and the predominant source, estradiol, changes to estrone produced by conversion of androgens in adipose tissue. Age-dependent aromatase expression in SMCs provides a mechanism for local production of estrogens from androgens. Aging attenuates many estrogen-related potentially beneficial responses. Yet, we have observed that central-induced endogenous estrogen deficiency in younger women is associated with a >7-fold increase in risk of coronary obstruction. One interpretation is the widely varying estrogen/androgen balance occurring throughout a woman’s life contributes to differences in vascular disease compared with men. This includes high levels of estrogen premenopause and decreasing estrogen and progesterone levels postmenopause, along with changing hormone balance during pregnancy, peripartum, and oral contraceptive or replacement therapy. Such varying estrogen/androgen balance interacts with the female unique and traditional risk conditions, as well as diet (eg, phytoestrogens, etc), physical activity, psychosocial characteristics, etc, to modulate differences in vascular disease.

Estrogen exerts effects via 2 receptors abundant in vascular tissue to transduce signals regulating expression of many genes, and it also has nongenomic effects. Considerable evidence implicates the ESR1 in vascular structure and function. Attempts to link estrogen receptor-alpha gene (ESR1) variation with adverse outcomes yield mixed re-
Vascular SMC

ESR1
Genomic and Non-Genomic Effects
Inhibition of Contraction and Proliferation/Migration

High

ESR1 Expression

Greater Differentiation
Decreased ESR1 Expression
(siRNA)

Increased ESR1 Expression
(lentivirus)

Less Differentiation

Monopause

SMC

Greater Differentiation

Incorporate ESR1 activation on SMC function advance our understanding of vascular disease.31 Positive remodeling as a marker for plaque vulnerable to rupture or erosion could be linked with the high event rate observed among women with normal or non-obstructive coronary angiographic findings.32–34 The findings of Montague et al of differential effects of ESR1 activation on SMC function advance our understanding the role of estrogen in regulation of vascular physiology and pathology. These findings should shed light on the complexities of gender-related vascular disease.

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Disclosures

None.

References


Estrogen and Sex/Gender-Related Differences in Blood Vessels

Women have smaller and stiffer conduit arteries than men even when adjusted for height, weight, and arterial pressure,23,24 contributing to earlier return of reflected arterial pulse waves, widened pulse pressure, and adverse effects on myocardial oxygen supply and demand. We found brachial pulse pressure to be the best independent predictor of cardiovascular adverse outcomes among blood pressure measures,25 suggesting that elastic properties of conduit arteries are important in the vasculopathy of women.

Changes in artery size (eg, remodeling) may occur in response to physiologic (eg, pregnancy, exercise, etc) or pathologic (eg, atherosclerosis, hypertension, etc) stimuli. Insight into potentially pathologic gender-related differences in remodeling comes from cardiac transplant recipients and transgender patients. Female hearts transplanted to females show little change in coronary size over time.26 But female hearts transplanted to males show progressive coronary enlargement, independent of body size and left ventricular hypertrophy, that persist over time. Links between sex hormones and differences in arterial size are strengthened by studies of transsexuals where brachial artery size in genetic males taking estrogens is smaller compared with control males.27,28 Genetic females taking androgens have larger arteries than control females.29 Androgen-deprivation therapy in genetic males is associated with smaller brachial artery size compared with control males.30 These findings support the notion that sex hormone balance has different, and under certain circumstances opposite, effects on conduit artery remodeling with an androgen state causing positive remodeling compared with an estrogen state. Positive remodeling is not invariably a compensating response and is also a marker of vascular disease.31 Positive remodeling as a marker for plaque vulnerable to rupture or erosion could be linked with the high event rate observed among women with normal or non-obstructive coronary angiographic findings.32–34 The findings of Montague et al of differential effects of ESR1 activation on SMC function advance our understanding the role of estrogen in regulation of vascular physiology and pathology. These findings should shed light on the complexities of gender-related vascular disease.


27. Key Words: estrogen receptor-alpha (ESR1) ■ estrogen receptor-alpha genotype (ESR1) ■ gender-related vascular disease ■ women and vascular disease ■ men and vascular disease ■ vascular structure and function.
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