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Some Thoughts on the Vasculopathy of Women With Ischemic Heart Disease

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Considerable experimental and clinical data indicate that sex has an important influence on cardiovascular physiology and pathology. This report integrates selected literature with new data from the Women's Ischemia Syndrome Evaluation (WISE) on vascular findings in women with ischemic heart disease (IHD) and how these findings differ from those in men. A number of common vascular disease-related conditions are either unique to (e.g., hypertensive disorders of pregnancy, gestational diabetes, peripartum dissection, polycystic ovarian syndrome, etc.) or more frequent (e.g., migraine, coronary spasm, lupus, vasculitis, Raynaud's phenomenon, etc.) in women than men. Post-menopausal women more frequently have many traditional vascular disease risk conditions (e.g., hypertension, diabetes, obesity, inactivity, and so on), and these conditions cluster more frequently in them than men. Considerable evidence supports the notion that, with these requisite conditions, women develop a more severe or somewhat different form of vascular disease than men. Structurally, women's coronary vessels are smaller in size and appear to contain more diffuse atherosclerosis, their aortas are stiffer (fibrosis, remodeling, and so on), and their microvessels appear to be more frequently dysfunctional compared with men. Functionally, women's vessels frequently show impaired vasodilator responses. Limitations of existing data and higher risks in women with acute myocardial infarction, need for revascularization, or heart failure create uncertainty about management. A better understanding of these findings should provide direction for new algorithms to improve management of the vasculopathy underlying IHD in women. (J Am Coll Cardiol 2006;47:30S–5S) © 2006 by the American College of Cardiology Foundation

Considerable data indicate that sex has an important influence on cardiovascular (CV) physiology and pathology (1,2). The purpose of this report is to critically review selected clinical and experimental data, while integrating new findings from the Women's Ischemia Syndrome Evaluation (WISE), on vascular findings related to ischemic heart disease (IHD) in women and how these findings differ from those in men. The hypothesis is that women with IHD have evidence for a more severe or different form of vascular disease compared with men. These data should help to better define the vasculopathy underlying IHD as it occurs in women and suggest direction for new algorithms to improve detection and management at an early stage.

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VASCULAR DISEASE RISK CONDITIONS

Gender-related differences in clinical findings linked to vascular disease are best illustrated by risk conditions unique to women (Table 1). In the peripartum period, some examples include the hypertensive disorders of pregnancy (e.g., preeclampsia and eclampsia), proximal coronary artery and aortic root dissection, as well as gestational diabetes and delivering a thin baby. For example, the relatively common (~5% to 10% of term pregnancies) hypertensive disorders of pregnancy are associated with significant increase in IHD later in the mother's life (3,4). For the relatively rare coronary or aortic dissection, the IHD risk is obvious. But gestational diabetes, occurring in 2% to 9% of pregnancies, results in sustained glucose intolerance or diabetes in most cases and implications for vascular disease that are not as obvious (5,6). Mothers who once gave birth to thin babies are also at increased risk for IHD (7). It has been suggested that these mothers, like their children, have impaired vascular function, which was already present during the process of implantation interfering with placental function leading to low birth weight. Many of these conditions have been linked with oxidative stress, endothelial dysfunction, inflammation, insulin resistance, defective angiogenesis, and dyslipidemia (8–11). Perhaps these conditions explain, at least in part, some non-genetic factors in a family history of CV disease that play a role in the lifelong risk for IHD in women.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CAD = coronary artery disease
CV = cardiovascular
EPC = endothelial progenitor cell
IHD = ischemic heart disease
WISE = Women's Ischemia Syndrome Evaluation

Examples of risk conditions unique to women unrelated to the peripartum period but linked to hypertension, obesity, insulin resistance, and IHD include polycystic ovarian syndrome, hypoestrogenemia of central origin, and estrogen replacement, which are reviewed elsewhere in this supplement (12) (Table 1). Additionally, women have higher frequencies of vasculitis (e.g., Takayasu's arteritis, temporal arteritis, rheumatoid vasculitis, lupus vasculitis, polymyalgia rheumatica, etc.) compared with men.

Women also have somewhat different clinical findings that relate to pathophysiology of IHD than male counterparts. The woman with IHD often is older, has a greater risk factor burden, and more functional disability (12,13). Aging attenuates many estrogen-related potentially beneficial vascular responses (2) including endothelial progenitor cells (EPCs) (14) and coronary microvascular function in the WISE (15). Experimental models have linked sex hormones and other risk conditions (e.g., hypertension, diabetes, and so on) to IHD in women (2). Briefly, high estrogen levels before menopause and decreasing estrogen and progesterone levels after menopause are believed to influence IHD in women. Estrogen exerts effects via receptors abundant in vascular tissue to transduce signals regulating expression of many genes, and it also has nongenomic actions. Variations in plasma sex hormones and receptor genes, acting with endothelial and vascular smooth muscle factors, are potential links to the differences in vascular structure and function that contribute to both heterogeneity among women and gender differences in IHD.

Table 1. The Vasculopathy of Women With IHD: Risk Conditions Versus Men

Traditional risk conditions
Higher prevalence in postmenopausal women
More frequent clustering
When present, higher level (e.g., if hypertensive, higher BP, higher LDL, and so on)
Older age
More frequent vasculitis (e.g., lupus, temporal arteritis, Takayasu's, and so on)
Conditions unique to women
Peripartum
Hypertensive disorders of pregnancy
Gestational diabetes
Delivering a thin baby
Coronary or aortic root dissection
Polycystic ovarian syndrome
Hypoestrogenemia of hypothalamic origin
Hormone replacement therapy
Others

BP = blood pressure; IHD = ischemic heart disease; LDL = low-density lipoprotein.

ALTERATIONS IN VASCULAR STRUCTURE

Large artery structure appears different in women (Table 2), illustrated by the fact that their coronary arteries are smaller than men independent of body size (16). Changes in artery size (e.g., remodeling) occur in response to physiologic (e.g., exercise) or pathologic conditions (e.g., atherosclerosis, hypertension, and so on). Female vessels uniquely undergo remodeling during and after pregnancy. Traditionally, this has been considered physiologic remodeling, but, in the presence of peripartum conditions linked with IHD (e.g., coronary dissection, thin babies, gestational diabetes, and so on), this may not be the case. Recently, potentially pathologic gender-related differences in remodeling have been described in cardiac transplant recipients and transgender patients.

Female hearts transplanted to women show little change in coronary artery size over time, but, when transplanted to men, they show progressive coronary enlargement independent of body size and left ventricular hypertrophy (17). A link between arterial size and sex hormones is supported by studies of transsexuals where brachial artery size in genetic men taking estrogens is smaller compared with control men (18,19). Genetic women taking androgens have larger arteries than control women (20). Androgen-deprivation therapy in genetic men is associated with smaller artery size compared with control men (21). These findings imply that sex hormones have different effects on arterial remodeling with androgens causing enlargement (e.g., positive remodeling). Positive remodeling may be a marker of vascular injury (22–24), and perhaps such injury could explain the high event rate observed among women with nonobstructive coronary angiographic findings in the WISE (25). Also, larger brachial artery size was associated with more angiographic evidence of coronary artery disease (CAD) (26). Brachial artery size, readily measured noninvasively by ultrasound, may be helpful to identify women with early atherosclerosis.

Postmenopausal women more frequently have atherosclerosis risk conditions (e.g., hypertension, diabetes, metabolic syndrome, obesity, and so on) than men, and these conditions more frequently cluster in women. Adding the risk conditions unique to women noted previously would predict more atheroma burden in their smaller coronary arteries. Even with apparently "normal" coronary angiography, diffuse atherosclerosis may result in abnormal resistance limiting myocardial flow (27) with deleterious consequences for revascularization (28,29). Study of transplant donor hearts suggest coronary atherosclerosis without apparent flow limiting stenoses has a similar prevalence comparing men and women (30). These findings support the notion that severe coronary atherosclerosis may alter structure in many of these women without recognition by angiography.

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Structural changes in large arteries from aging and atherosclerosis increase arterial stiffness (31). In diabetic women, but not men, age-related stiffening of the aorta occurs (32). Alterations in large artery stiffness were observed in a sample of women from the WISE compared with age- and body mass index-matched control women (33). In other postmenopausal women with CAD, brachial pulse pressure, another measure of arterial stiffness, was associated with CAD progression, independent of risk factors or hormone replacement (34). In the WISE, pulse pressure was an independent predictor of CAD severity and clinical outcomes (35). Non-invasive measures of arterial stiffness may be useful to estimate the structural consequences of atherosclerosis in post-menopausal women and may provide insight into the effect of therapies on stiffness and adverse outcomes.

Microvascular structural damage secondary to aging, hypertension, diabetes, left ventricular hypertrophy, and other processes is also likely to be important in women. To this end, retinal microvascular abnormalities have been linked to past blood pressure (36), inflammation, and endothelial dysfunction (37). Such microvascular abnormalities predict IHD outcomes in women but not men (38). Thus, retinal microvascular structural alterations allow non-invasive investigation of systemic vascular pathology.

VASCULAR FUNCTION

Functional alterations as changes in vascular reactivity also suggest a more severe disease in women implicating both endothelium and smooth muscle (Table 2). Sex hormones exert effects on vascular reactivity via endothelium and also directly on smooth muscle (2). Various mechanisms are involved, ranging from gender-specific influences on nitric oxide synthase gene (39) to sex-hormone–related differences in L-type voltage-gated Ca^{2+}-activated K^{+} channels (2,40) and also include effects on vascular repair (41). Because women's vessels spend considerable time under widely varying hormonal influences (e.g., puberty, pregnancy, peripartum, and menopause), their vessels may be programmed for more severe functional alterations compared with men.

Table 2. The Vasculopathy of Women With IHD: Coronary Structure and Function Versus Men

Structural findings
Macrovessels and microvessels
Smaller size
Increased stiffness (fibrosis, remodeling, and so on)
More diffuse disease, erosion >rupture
Microemboli, rarefaction (drop out), disarray, and so on
Functional findings
Macro- and microvessels
Endothelial dysfunction
Smooth muscle dysfunction (Raynaud's, migraine, CAS)
Inflammation
Plasma markers
Vasculitis (Takayasu's, rheumatoid, SLE, CNSV, giant cell, and so on)

CAS = coronary artery spasm; CNSV = central nervous system vasculitis; IHD = ischemic heart disease; SLE = systemic lupus erythematosus.

Role of coronary endothelial dysfunction. More than half the women tested with acetylcholine in the WISE had coronary endothelial dysfunction, which independently predicted adverse outcomes (42). The risk conditions present in women, alone or in clusters, increase oxidative stress to injure endothelium of both large and small vessels in varying degrees (43,44). In large arteries of women presenting with chest discomfort, endothelial dysfunction is a marker for early atherosclerosis before structural changes to the vessel wall are appreciated by angiography (45). Vascular injury resulting in endothelial dysfunction has been linked to positive remodeling of large coronary arteries without flow-limiting lesions (22). Endothelial dysfunction of the microvasculature has the potential to limit myocardial perfusion (45,46).

Normal endothelial repair processes may be adequate for this injury, but over time, repair processes may become inadequate for many reasons (e.g., loss of estrogen, overwhelming oxidative stress as associated with metabolic syndrome, hypertension, obesity, aging, and so on). Recent evidence indicates that bone-marrow–derived EPCs are important in vascular repair, and estrogen increases circulating EPCs by antiapoptotic effects (41). Circulating EPCs become depleted in individuals with multiple risk conditions and aging (41). Considering the density of risk conditions among women presenting with suspected IHD in the WISE, a reasonable hypothesis would be that such women are more vulnerable to continuing injury leading to more atherosclerosis than those without high densities of risk factor conditions. Some female unique conditions (e.g., pregnancy-associated hypertension or metabolic disorders, and so on) are also associated with endothelial dysfunction and make such women more vulnerable to develop IHD. Finally, because clinical manifestations of IHD in women present 10 or more years later in life than men, this occurs at time when aging likely has powerful effects on supply and quality of EPCs. Thus women, at this later stage of life, would be less capable of vascular repair, which could contribute to poor outcomes compared with men whose coronary vessels were preconditioned at an age when they were more capable of vascular repair.

Role of vascular smooth muscle dysfunction. Manifestations suggesting alterations of vascular smooth muscle function are more frequent in women than men (e.g., coronary artery spasm, Raynaud's phenomenon, and migraine), and both coronary spasm and migraine have been linked with IHD. Impaired smooth muscle relaxation has also been suggested as a marker for atherosclerosis (47). Coronary flow reserve attenuation, as observed in many of the WISE women with intracoronary adenosine (15,48–50), suggests impaired microvascular smooth muscle relaxation. Positron emission tomographic scanning results in a WISE subgroup without epicardial CAD suggest that the distribution of this microvascular defect is heterogenous

(51), and P31 cardiac magnetic spectroscopy results document high-energy phosphate depletion as seen with ischemia (52). Hypertension, diabetes, obesity, and other conditions found more frequently in postmenopausal women than men are associated with microvascular dysfunction. But atherosclerosis risk conditions account for <20% of the variability in coronary flow reserve, indicating that other factors, as yet to be identified, influence microvascular function (15).

Previous studies have also documented gender-related differences in skin flow responses to provocative maneuvers (43) and in endothelial nitric oxide production in skin microvasculature (44). Estrogen improves endothelial function, but menopause is associated with abnormal endothelial function in coronary microvessels. Estrogens, but not progestogens, antagonize the effect of menopause (53). So women are primed to have microvascular dysfunction, which has been suggested as a cause for ischemia without flow-limiting epicardial stenoses. Also, microvascular spasm may cause ischemia, and most of these patients are women (54–56). Recently, it has been suggested that endothelial-independent microvascular dysfunction to adenosine is an independent predictor of adverse outcomes in angina patients (57). These examples indicate that microvascular dysfunction has the potential to evoke angina-like symptoms and cardiac ischemia and is linked with adverse outcomes.

Relative roles of endothelial versus smooth muscle dysfunction and large vessels versus microvessels. Considerable evidence implicates the coronary microcirculation, along with large vessel atheroma, to explain findings in IHD (58). This includes wide variability in effort tolerance over time (a frequent finding in women), large scatter between stenosis severity and flow reserve (59), reduced flow responses to stress in regions perfused by non-stenotic vessels (60), variability in outcome after successful percutaneous intervention (61), the 25% of women with acute coronary syndrome (ACS) who have no flow-limiting stenosis (62), the predictive value of brain natriuretic peptide and C-reactive protein for adverse outcomes in women with ACS (63), and pathologic findings of plaque erosion with microvascular embolization in women dying with ACS (64).

In summary, considerable evidence indicates that the large and small coronary vessels of women with IHD may be more diseased compared to men (Tables 1 and 2). Under these circumstances, the consequences of a given ischemic episode would be expected to be altered in an unfavorable manner. In such women, an area of ischemic injury may not be limited because usual vasorelaxation required for collateral function is abnormal. This theory could help explain why women tolerate ACS poorly compared with men and why subsequent heart failure, for example, is not only more frequent but also more lethal in women than men. The foregoing should help the reader place the vascular findings from the WISE and other studies into a meaningful clinical perspective (Tables 1 and 2).

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