

## Sex Differences: Potential Impact in Vascular Physiopathology or Ischemic Heart Disease

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### ABSTRACT

*Pathophysiological mechanisms for development and progression of ischemic heart disease, which is essentially an age-related condition, may differ between men and women. Age-related changes in cardiac and vascular anatomy and physiopathology combined with traditional risk factors affect the likelihood of developing heart disease. Sex specific features of cardiac and vascular remodeling with age are associated with a higher prevalence of ischemic heart disease in women post-menopause. Cardiac symptoms such as chest pain/discomfort are often less in women, which generally results in less aggressive clinical treatment compared to men. Incidentally, treatment guidelines for acute myocardial infarction have for the most part, been established from studies with a large male cohort. Sex differences relating to effects of ischemia on overall cardiovascular function could contribute to worse clinical outcomes for females. Treatment options for women also arise because they generally present with multiple co-morbidities. The present review focuses on recent findings for sex differences in pathogenesis of ischemic heart disease, vascular function as well as potential use of cardio protection strategies.*

### Keywords

Heart disease, Vascular function, Sex differences, Acute myocardial infarction, Ischemic conditioning.

### Introduction

Biological sex differences affect progression of cardiovascular disease. In men and women microvascular disease, epicardial atherosclerosis and endothelial dysfunction stimulate vessel remodeling leading to myocardial ischemia [1,2]. While men appear to be more susceptible to typical clinical vascular changes, women generally are at greater risk for atypical vascular disease [3]. Interestingly, women with ischemic heart disease (IHD) often present with no angiographic evidence of obstructive coronary artery disease (CAD) [4-7]. Whereas «female protection» against development of cardiovascular disease has been widely researched, numerous questions remain as to why, once CAD is manifest, clinical outcomes in women are worse [8].

Multiple comorbidities display sex differences with regard to

onset, frequency, morbidity and mortality [9,10]. Sex-specific relationships for cardio metabolic diseases, including obesity and diabetes, remain largely unexplored. However, recent findings suggest that differences in disease sequelae occur in both men and women with underlying cardio metabolic disease [11]. In patients with chronic kidney disease symptoms may be more pervasive in females because of greater clinical use of diuretics particularly in older females [12]. Both sex and age are important modifiers of gene expression in the mammalian heart [13,14]. Heart size differs between males and females in relation to age, which contributes to variations in overall cardiac function. In men greater absolute values for left ventricle (LV) mass, wall thickness and cavity dimensions are reported [15,16]; however, relative wall thickness of the heart is not different [17]. For women an increase in LV wall thickness [18] and concentric remodeling [19,20] is observed and is often accompanied by marked LV diastolic dysfunction [21]. Systolic torsion and circumferential LV shortening also appears to be greater in women [22] and is probably related to greater pulsatile load and differential gene expression of extracellular matrix

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components [23-25]. While cardiac performance is dependent on cardiac work the pressure buffering properties of elastic arteries also plays an important role. As such, a compliant arterial system (i.e. from conductance arteries to the microvasculature) is required for optimal cardiovascular performance. Differences in micro vessel function between sexes is an important area of study since modulations in oxygen exchange at the cellular level in the heart is a risk factor for progression of IHD.

Ischemic heart disease involves an imbalance between myocardial oxygen supply and demand [26] and is caused by obstructive or non-obstructive atherosclerotic CAD, or myocardial ischemia (produced by micro vessel or endothelial dysfunction, vasomotor abnormalities, etc.) [27]. Patterns of cardiac remodeling caused by adverse cardiovascular events, vary between sexes during ageing. The debate over menopause versus biological ageing and their contribution to age-related cardiovascular risk is important and ongoing. Common cardiovascular risk factors (i.e. LDL cholesterol, apo-lipoprotein B, etc.) in women change in relation to age but not with menopause [28]. Data from the Framingham study suggest that cardiovascular risk status affects age at menopause but not vice-versa. As such, risk factor levels change during menopause likely because of a combination of chronologic ageing and menopausal transition. Significant correlations between post-menopausal status, average age of menopause or clinical outcomes were not evident from a meta-analysis [29]. Intrinsic non-hormonal factors that happen during a complete lifespan may also be more important than changes that occur during midlife [16,30,31] but overall, risk factor monitoring need to be prioritized for women [32,33].

For this review, we searched basic science and clinical papers using MEDLINE, PubMed and Google Scholar with the search terms: sex differences, vascular function, myocardial infarction, cell death and ischemic conditioning. Herein, we review the current literature describing sex-specific differences and its impact on pathogenesis of acute myocardial infarction, vascular function, cellular protection strategies and outcomes. We paid particular attention to biological sex (not gender domain), but understand that while mechanisms between gender identity and cardiovascular disease risk may be important they have not been clearly established [34].

### Sex Hormones

Male and female sex hormones affect regulation of vascular function; however, their actions are not uniform between sexes. Expression or abundance of sex hormone receptors in vascular smooth muscle differs between males and females causing important variations in vascular function [35]. Receptors for various sex hormones (estrogen, progesterone, testosterone) are readily found in vascular endothelium and smooth muscle [36,37]. Interactions of sex hormones with nuclear/cytosolic receptors triggers numerous genomic effects mediated by activation of signalling pathways that can stimulate or inhibit cell growth and proliferation [38]. Estrogen or testosterone effects on vasoregulation (i.e. tone, elasticity, etc.) affect progression of cardiovascular disease; however, the overall effects of testosterone – generally believed to negatively affect

the heart - on cardiac physiology are less studied therefore in a review we concentrate specifically on estrogen effects. Estrogen receptors are localized in myocardium, vascular endothelium, smooth muscle and adventitial cells [39]. Estrogen-mediated gene transcription involves direct binding to receptors within the nucleus [40]. Inhibition of estrogen receptor activity adversely affects both structural and functional remodeling in females, which has the potential to worsen cardiac dysfunction. Post-menopausal estrogen replacement therapy appears to reduce the incidence of adverse coronary events and associated mortality [41].

In females, estrogen: 1- modulates vascular tone via endothelin (ET-1) [42] and multiple nitric oxide (NO)-dependent [43] and independent [44] pathways and 2- affects vessel reactivity by stimulating NO release from endothelium [45]. Biological effects of ET-1 occur via activation of ETA or ETB receptor subtypes the ratio of which, and location, varies depending on the vascular bed (arteries > arterioles) [46]. Bolus intravenous ET-1 produces a biphasic response with an initial decrease (via NO and prostacyclin synthesis in ETB-stimulated endothelium [47,48]) followed by a long-term increase (mediated by ETA receptor subtypes in smooth muscle [49]) in vascular resistance. Findings from our laboratory reported that coronary resistance vessels in males are more sensitive to ET-1 [50]; these findings have been corroborated in mesenteric arteries from rats with spontaneous hypertension [51]. Age and phase of the menstrual cycle also play an important role in endothelial function [52]. DuPont and coworkers recently reported that vascular aging phenotypes, mediated by sexually dimorphic molecular mechanisms, occur later in females [53]. Modulation of vascular responses to ET-1 depends on age, sex and vessel type. For example, vessel responses to ET-1 are lower in aorta of females and resistance arterioles in males [51,54] but are greater in larger male coronary vessels [55]. Responses to endogenous ET-1 is therefore an important determinant for regulation of organ perfusion [56]. Furthermore, myogenic responses are known to be modified by local changes in NO production when estrogen levels are modified [44,45,57,58].

Endothelial dysfunction causes an increase in peripheral resistance consequent to greater release of ET-1 or by reduced synthesis of vascular relaxation factors. Higher circulating plasma ET-1 levels correlate with heart failure and IHD [59]. Production of NO in premenopausal women is greater than in men [60]. Thus, the balance between NO and ET-1 production (regulated through autocrine feedback mechanisms [61-63]) is critical for vasoregulation [64]; for example, reduced production of NO attenuates sensitivity of vascular smooth muscle to the effects of vasoconstrictor compounds [65,66]. In female rats subject to acute myocardial ischemia, treatment with estrogen has shown variable results [67]; however, blockade of estrogen receptors worsens ischemic injury [68,69].

Administration of estrogen to males, to induce post-ischemic protection, was inconclusive [70,71]. Treatment with sex hormones has been reported to restore endothelial function [72]. In ovariectomized rabbits, treated with either 17 $\beta$ -estradiol

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or DHEA (dehydroepiandrosterone), we reported significant improvement of myocardial perfusion [73]. Positive treatment effects were attributed to normalization (particularly at the level of the microvasculature where oxygen exchange at the cellular level is crucial) of the oxygen supply-demand equilibrium due to a shift in coronary pressure-flow parameters.

### **Vascular Physiopathology**

Arteries are classified as being elastic or muscular and comprise distinct layers each with a different cellular composition (endothelial, smooth muscle, etc.) to ensure maximum functionality [74]. Vessel wall biology and vessel size differs between men and women but cellular or molecular mechanisms responsible have not been established. Sex hormones such as estrogen or other sex-specific factors that control vessel tone and size are potential candidates [75-77]. Vascular endothelium is involved in regulation of arterial tone, platelet function and inflammatory cell interactions, coagulation and vessel growth [78] via the synthesis/release of a plethora of vasoactive compounds [79]. Patterns of vascular remodeling over time also differ between the sexes [16] and are caused by a host of risk factors [80]. In women with CAD, arterial wall thickness is greater [81] and abnormal endothelial and non-endothelium dependent vessel function is common [6,82,83] thereby increasing the risk for adverse short-term outcomes [79,84,85].

Protection against vascular disease has been in part, attributed to levels of sex hormones. The relation between endogenous estrogen and cardiovascular disease is documented [86] and studies investigating potential associations between circulating sex steroids, sex hormone interactions and development of CAD have provided variable findings [3,87]. Progression of heart failure in females is reportedly ovarian hormone dependent [40]. A recent review suggested that sex-related differences in regulation of the renin-angiotensin-aldosterone system by estrogen might be beneficial [88]. Mechanisms responsible for protection are not easy to evaluate but have previously been discussed [25].

### **Potential Consequences of Vascular Dysfunction**

Ageing and prevalence of cardiovascular risk factors contribute to progressive ventricular and arterial stiffening and ultimately contribute to pathogenesis of heart failure. Of interest is that ventricular-arterial stiffening appears to be exacerbated in women, moreso in older women [89].

**Arterial stiffness:** Vascular ageing differs between sexes and affects overt cardiovascular disease risk. Molecular mechanisms that contribute to different manifestations of cardiovascular system ageing remain poorly understood [53,90,91]. Changes in vessel function due to ageing include endothelial dysfunction, which lead to arterial stiffness and ischemic heart disease; these contribute to increases in systolic blood pressure and pulse pressure [92]. Arterial stiffness is an emerging marker for adverse cardiovascular events [89]. In pre-menopausal women (compared to men of similar age) autonomic tone and baroreceptor responses are lower but overall vascular function is preserved [93,94]; however,

progression of age-related arterial dysfunction occurs more rapidly in post- menopausal women [95]. In addition, subclinical alterations in arterial structure progress differently between the sexes. For example, risk factors such as carotid intima-media thickening, arterial calcification and atherosclerosis are more prevalent in younger men (compared to women of similar age) but with advancing age levels are analogous [96,97]. Atherosclerotic plaque characteristics (i.e. thin fibrous cap, lipid rich or necrotic core, etc.) also differ substantially between the sexes rendering men more susceptible to negative consequences of cardiovascular disease [98].

Pressure buffering properties of elastic arteries are essential for optimization of cardiac work as they allow for greater transfer of blood from the heart to the periphery while at the same time regulating undue fluctuations in pressure [89]. Aortic pulse wave analysis is generally used to evaluate arterial stiffness (in pre-clinical and clinical studies) [90]. When arterial stiffness is heightened the reflected wave travels faster and returns to the heart near systole resulting in higher systolic afterload and reduced diastolic coronary perfusion pressure [99]. Sex differences contribute to variations in development of arterial stiffness and higher pulse pressure, which are considered to be an important risk factor for development of cardiovascular disease [100]. The possibility that variations in morphometric (i.e. size, shape) and vessel anatomy between sexes may be responsible has been advanced [101,102] but this has not been clearly established at a mechanistic level [90]. Increased wall stress, left ventricular diastolic dysfunction and reduced ventricular- arterial coupling affects arterial stiffness more so in women [102-106]. Ventricular-arterial stiffening increases volume sensitivity whereby small changes in volume significantly augment systolic and pulse pressures.

Stability and compliance of the arterial wall requires a balance between extracellular matrix proteins such as elastin and collagen. Disruptions of this balance, which leads to arterial stiffening are exacerbated in the presence of cardiovascular risk factors [107]. Potential mechanisms of arterial stiffness include 1- alterations to extracellular matrix (i.e. augmented collagen deposition, increased elastin breakdown, etc.), 2- alterations to vascular smooth muscle cytoskeleton and 3- altered integrin and extracellular matrix interactions [108-110]. Various studies have described a role for vascular oxidative stress and increased production of oxygen radicals along with activation of angiotensin receptor mediated intracellular signalling. Unfortunately, most preclinical studies on age-related pathogenesis of arterial stiffness are limited to male subjects. Further studies to elucidate potential sex differences at the mechanistic level are essential; this might also be important for development and modification of treatment stratagems for women [111-113].

**Ischemic heart disease:** Ischemic heart disease continues to claim a disproportionate number of lives worldwide compared to other diseases. The incidence of acute myocardial infarction is significantly lower in pre-menopausal women (compared to age-matched men). As a result, clinical treatment for women with

acute myocardial infarction is often less aggressive which might help to explain the higher mortality risk [114-116] and worse clinical outcome (compared to age-matched men) following acute myocardial infarction. Sex is independently associated with a higher risk of mortality [117,118] but its influence on prognosis in patients with IHD remains largely unexplored.

Acute myocardial ischemia (classified on the basis of electrocardiographic presentation) influences regional ST-segment profiles [119,120]; for instance, ST-segment elevation myocardial infarction (STEMI) is characterized by a  $\geq 2$  mm ST segment elevation and prominent T waves) while non-ST-segment elevation myocardial infarction (NSTEMI) consists of ST-segment depression with T wave inversion. STEMI is life threatening and time sensitive and requires rapid intervention to alleviate symptoms. European Society of Cardiology Guidelines for management of STEMI advise that females comprise a distinct subset and therefore require particular attention with regard to diagnosis and treatment [121]. A greater risk for net adverse clinical events has been reported in females with STEMI; however, these patients are often older and present with more comorbidities (i.e. hypertension, diabetes, chronic kidney disease, vascular disease, etc.) [122]. Thus, it is not clear that differences are real; they could be related to other factors including symptom-to-door or door-to-balloon times that are generally longer in women [123-125]. A recent study from China, reported that long-term outcomes in female patients with STEMI were worse (compared to short-term data) [126]. Reasons for poorer outcomes in females with STEMI are multifactorial and include psychological stressors, intrinsic variations in angiogenesis, physiopathology of ischemic heart disease and sex hormone deficiency [126,127]. Finally, a prospective observational cohort study of females with STEMI from Sweden reported that sex was independently associated with reduced eGFR, a strong independent risk factor for short as well as long-term mortality.

**Animal studies with acute myocardial infarction:** In situ experimental findings from diverse animal species regarding effects of sex and myocardial infarction in relation to sex are equivocal [128-130] with some studies reporting reduced susceptibility to ischemic injury in females [128,131,132]. Indeed, post-ischemic incidence of cardiac arrhythmias, ventricular contractile dysfunction and necrosis are all reportedly mitigated in studies comparing females versus males [133-135].

Acute cellular injury caused by arterial obstruction stimulates release of a host of inflammatory mediators that participate in the development of organ dysfunction and post-ischemic remodeling. In both animal and human studies, production of pro-inflammatory cytokines varies between the sexes in response to cellular injury [136,137]. For example, post-ischemic activation of myocardial p38 MAPK (mitogen-activated protein kinase) differs in females and results in significantly decreased cytokine production [135]. Thus, subtle biochemical differences between sexes could affect ischemia-induced alterations at the cellular level. These differences in cardio protection might be related to release of other humoral

factors that are known to activate intracellular signalling pathways.

### Potential cardio protective strategies

Activation of endogenous cellular protection mechanisms post-injury have been under intense scrutiny since Murry et al published their paper on reduction of ischemic injury by preconditioning [138]. Exercise training (potential candidate for preconditioning) also has infarct-sparing effects; however, protection is variable between sexes [131,139-141]. For ischemic preconditioning, application of multiple, brief cycles of non-lethal ischemia followed by restoration of blood flow to the same vascular bed prior to a prolonged ischemic event significantly delays progression of cell death [138,142,143]. Conditioning-mediated protection, reported in all species studied including humans, may also be influenced by sex. In animal studies that compared the level of protection by ischemic conditioning between males and females infarct size was reduced less in the female heart [144-146]; however, recent findings suggest that sex may not be a determinant for conditioning mediated protection [147]. Multiple pathways that lead to reduced cellular injury may involve sex hormones. For instance, in mice, subject to global ischemia preceded by ischemic preconditioning, post-ischemic contractile function was only improved in older animals. However, this was not observed for males suggesting that both age and sex could be critical determinants of ischemic conditioning-mediated cytoprotection [132]. In clinical studies of remote conditioning, no differences between sexes with regard to biomarker release or infarct size have been reported to date [148-151].

### Conclusions

Activation of specific physiological mechanisms or intracellular signalling pathways that are involved in the pathogenesis of cellular injury in relation to sex have not been established. Regulation of blood perfusion, within the microvasculature, probably differs between the sexes and may contribute to early limitation, and later worsening of myocardial function with ageing. Improved understanding of these differences could be important for clinical diagnosis and treatment of women with vascular or ischemic heart disease. While female hearts are initially believed to be more resistant to ischemia-reperfusion injury compared to males, current data show that protection is age-dependent. Further studies need to address risk factors to understand how they may be responsible for increased morbidity and mortality particularly in older women. New clinical stratagems that tailor to the needs of women with acute myocardial infarction and its consequences are also required.

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