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# **Sex and Gender Aspects in Vascular Pathophysiology**

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## **Abstract**

Cardiovascular disease (CVD) is a leading cause of global mortality in men and women. The prevalence, pathophysiology, clinical manifestations and outcomes of CVD observed in these two populations is being increasingly recognized as distinct. In this editorial we provide an overview of mechanisms related to differences in vascular pathophysiology between men and women and explore the contributions of both sex and gender.

Cardiovascular disease (CVD) is a leading cause of global mortality in men and women[1]. The prevalence, pathophysiology, clinical manifestations and outcomes of CVD observed in these two populations is being increasingly recognized as distinct[2,3]. Although CVD comprises of many distinct diseases, they share similar risk and disease factors that may interact with sex and gender. Many forms of CVD including hypertension, stroke and ischaemic heart disease (IHD) are driven by vascular pathology such as endothelial dysfunction, vascular remodelling and atherosclerosis. In this article we will focus on the role of sex and gender in vascular diseases and particularly in IHD.

IHD remains overall more prevalent and occurs earlier in life in men than women and exemplifies the role of sex and gender in CVD [4]. Several studies have demonstrated a higher burden of comorbidities, rates of rehospitalization and potentially mortality following acute coronary syndrome (ACS) in women compared to men[5–7]. Concerningly, the annual incidence of hospitalization due to myocardial infarction has substantially increased in young women despite decreasing in men[8].

### **Genetic Associations**

Putative mechanisms underpinning these differences have highlighted the importance of sexual dimorphism. Transcriptomal sexual dimorphism may arise from differential allosomal gene expression. Examination of the role of the X chromosome has thus far been hindered due to the complexity of this allosome's genetics owing to X chromosome inactivation and gene dosage, which has resulted in its exclusion from genome-wide association studies[9]. In a recent analysis of X chromosome variants in ~100,000 people, of which 28.2% demonstrated coronary heart disease, no association with IHD was identified[10]. Conversely, in men with Y chromosome haplogroup I, which may modulate the inflammatory response, demonstrated a ~50% higher age-adjusted increase in

IHD compared with other Y chromosome lineages in the British Heart Foundation Family Heart Study[11]. Importantly, as dyslipidaemia significantly influences IHD risk, the Y chromosome *HindIII*(-) genotype also exhibits higher total cholesterol and low low-density lipoprotein cholesterol (LDL) levels, independent of testosterone levels in men[12].

### **Sex Hormones**

Women have a lower risk for developing IHD than age-matched men until the menopause, where thereafter they develop an accelerated phenotype resulting in a rapid rise in the prevalence and mortality related to IHD[13]. The cardioprotection evident prior to the onset of the menopause is anticipated to be related to oestrogen, a group of hormones comprised of 17  $\beta$  estradiol, estrone and estriol. Conversely, conflicting results from epidemiological and meta-analyses studies, and the lack of sufficiently powered randomized control trials has hindered our understanding of the role of testosterone, its deficiency and replacement, in the development of IHD [14].

Vascular smooth muscle cells (VSMCs) are a major structural and functional component of the vessel wall and express sex hormone receptors. They are integral to maintaining vascular structure, regulating vasotone and have been implicated in several pathophysiological processes such as the development of atherosclerosis and IHD[15]. A comprehensive review of complexity of sex hormone receptor expression, signalling and regulation of cardiovascular function in the context of sex differences is beyond the scope of this editorial[16]. Briefly, due to the high lipid solubility of estradiol, it can rise to sufficient concentrations in the VSMCs to initiate endothelium-independent mechanisms[17]. The vascular effects of oestrogen are mediated via the oestrogen receptors (ER $\alpha$ , ER $\beta$  and the G protein-coupled oestrogen receptor (GPER)). Numerous potentially beneficial effects have been attributed to the effect of oestrogen on vascular smooth muscle cells including the

activation of upregulation and activation of BK channels, inhibition and increases degradation of voltage gated calcium channels, and suppression of PKC and Rho kinase expression and function. These mechanisms lead to hyperpolarization of sarcolemma, which inhibits and calcium influx thereby promoting vasodilation. Furthermore, oestrogen exerts an inhibitory effect on the growth and proliferation of VSMCs, likely through the inhibition of MAPK transactivation, nuclear transcription and the expression of growth factors in an effect mediated via rapid non-nuclear ER $\alpha$  signalling promoting Akt and Erk dephosphorylation[18].

These features are clearly advantageous with respect to the development of atherosclerotic disease. However, data from postmenopausal women receiving hormone replacement therapy suggests that oestrogen therapy following periods of significant oestrogen deprivation, increased age, or in higher risk cardiovascular conditions ameliorates this benefit and potentially harms[19–21]. Similarly, transgender women appear to have a higher risk of stroke and potentially IHD, and are exposed to oestrogen in the context of relative hormonal deprivation[22]. This data suggests that oestrogen exposure in an at-risk phenotype may promote atherogenesis, however, mechanistic studies exploring this relationship are lacking.

Equally, testosterone mediates a multitude of potentially protective or harmful vascular effects such nitric oxide release, calcium mobilisation, apoptosis, senescence and reactive oxygen species (ROS) generation[23]. Consequently, the action of this sex hormone, and fundamental male characteristic, in relation to vascular pathophysiology merits further research and consideration.

### **Sex Factors and Vascular Health**

Ultimately, interplay between genetics and sex hormones promotes significant downstream physiological differences between men and women that in turn infer differential vascular risk.

Anatomically, these variations result in women developing smaller epicardial coronary arteries and higher baseline myocardial blood flow, thereby promoting increased endothelial shear stress and modulating endothelial function, atherogenesis and IHD[24]. Furthermore, the composition of plaque differs between men and women presenting with ACS. Despite presenting with a higher comorbid burden, women demonstrate less extensive coronary artery disease, plaque rupture, necrotic core and coronary calcium[25]. This is particularly important in conditions such as diabetes, where there is an increasing appreciation of the acceleration in risk for coronary artery disease in women with any form of diabetes. Indeed, diabetes erases any protective female advantage in regard to IHD[26,27].

### **Beyond Biological Sex: Gender Aspects of Vascular Pathophysiology**

Differences between men and women, however, should not be reduced to purely biological inherent traits. The integration of social determinants of cardiovascular disease, and importantly the mechanisms by which they occur, is imperative to understanding of these sex and gender variances[28]. Gender reflects the behavior elicited by men and women in response to sociocultural values and roles[29]. Gender therefore is a function of gender roles, identity, relations and societal institutions and expectations. Such effects were clearly apparent in the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study where women with acute myocardial infarction demonstrated lower socioeconomic status, high levels of psychosocial stressors, and lower quality of life at the time of the ischaemic event[30]. Moreover, in the Gender and Sex determinants of cardiovascular disease: from bench to beyond-Premature Acute Coronary Syndrome (GENESIS-PRAXY) Study feminine roles and personality traits, including anxiety, were associated with higher rates of recurrent ACS and major adverse cardiac events (MACE) compared with masculine characteristics and importantly this relationship was independent of sex[31]. Consequently, these

relationships are not limited to the sex of an individual and the degree to which a person exhibits masculine and feminine characteristics can vary significantly within and between sexes[32].

The mechanisms by which gender influences vascular risk is unclear, however, there is emerging evidence of the role of the stress caused by the socioeconomic restrictions imposed by gender.

Sustained mental stress and depression are now established as non-traditional risk factors in the development of IHD[33,34]. Moreover, following acute myocardial infarction, baseline elevations in stress levels are associated with significantly worse recovery in angina-specific and overall quality of life[35]. Although the effect of baseline stress on recovery did not vary between men and women, this trait was more prevalent in women who in turn demonstrated worse outcomes. This relationship holds true at a population level, where women are twice as likely to develop depression during their lifetime[36].

Young women who have experienced a myocardial infarction demonstrate a similar increase in ischaemia induced by conventional exercise or pharmacological-induced stress, however, have a two fold increase in mental stress-induced myocardial ischaemia compared to men of a similar age[37]. This phenomenon is associated with microvascular dysfunction and peripheral vasoconstriction in women but not men, suggesting that feminine stressors may induce ischaemia through sympathetically mediated effects on the microcirculation[38].

The high emotional stress associated with feminine gender may result in sympathetic activation and promote inflammation resulting in abnormal cardiac perfusion. The amygdala is a key neural component in stress and emotional responses[39]. Increased resting metabolic amygdala activity, as determined by 18F-fluorodeoxyglucose PET/CT, predicts major MACE independently of established cardiovascular risk factors[40]. This was associated with increased haemopoietic activity and arterial inflammation thereby suggesting a significant role of a neural–haemopoietic–arterial axis. Moreover,

higher amygdalar activation is associated with decreased left ventricular ejection fraction and fixed perfusion defects in women and not men[41].

### **Perspectives**

The inherent biological effects of sex and the external societal influences of gender, and the pathophysiological processes they elicit in IHD, but also in other vascular clinical conditions, are undoubtedly difficult to untangle[42]. Nevertheless, significant progress has been made in our appreciation of the integral and complementary relationship of sex and gender in the development of vascular disease. If we are to understand the mechanism by these fundamental concepts modulate vascular health and disease, we must ensure their robust incorporation into clinical research and practice.

### **Author Contribution**

All authors contributed to the writing and overall concept of this manuscript

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### **Competing interests**

The authors declare that there are not competing interests associated with this manuscript.

## **Abbreviations**

ACS, acute coronary syndrome; CVD, cardiovascular disease; ER $\alpha/\beta$ , oestrogen receptor  $\alpha/\beta$ ; GENESIS-PRAXY, gender and sex determinants of cardiovascular disease: from bench to beyond-premature acute coronary syndrome study; GPER, G protein-coupled oestrogen receptor; IHD, ischaemic heart disease; LDL, low-density lipoprotein; MACE, major adverse cardiac events; MAPK, mitogen-activated protein kinase; PKC, Protein kinase C; ROS, reactive oxygen species; VIRGO, Variation in recovery: role of gender on outcomes of young AMI patients; VSMC, Vascular smooth muscle cells

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