

Myocardial Ischemia in Women When Genetic Susceptibility Matters

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Abstract

Ischemic heart disease is the most common cause of death in both female and male genders. Though coronary artery disease is the most common determinant of ischemia in males, women present more often chest pain associated with normal epicardial coronary arteries. In females, coronary microvascular dysfunction plays a key role in developing symptoms and imbalance between delivery and request of coronary blood flow. Coronary ion channels play a major role in the regulation of coronary blood flow. According to the epidemiological, pathophysiological and clinical differences between male and female genders in ischemic heart diseases, it is legitimate to suspect the possible impact of gender on modulating the effect of cardiovascular risk factors. Whereas it is well known the role of estrogens in cardiovascular system, the role of genetics it has never been extensively addressed. Considering the high prevalence of coronary microvascular dysfunction in females and the regulatory function of coronary ion channels, we speculate that genetic differences in genes encoding the ion channels could be a major determinant of the difference in ischemic phenotypic expression among genders. Our previous study clearly shows that the single nucleotide polymorphism rs5215_GG of KCNJ11 gene encoding for coronary KATP channel is more prevalent in women and reduces the susceptibility to ischemic heart disease regardless the presence of other cardiovascular risk factors. This finding suggests a major role of genetics in the development of ischemic heart diseases and warrants further studies to evaluate the usefulness of genetic screening in clinical daily practice.

Keywords: Ischemic heart disease; Coronary artery disease; Coronary microvascular dysfunction; Ion channels; KATP; Gender; Females

Introduction

Ischemic heart disease (IHD) is defined as a myocardial ischemic condition in which cardiomyocytes receive a lower coronary blood flow (CBF) than they require [1,2]. Predominantly, IHD may represent the consequence of coronary artery disease (CAD) defined by the presence of coronary atherosclerotic plaques that reduce the CBF direct to myocardium, when they fill more than 50% of coronary lumen [2-7]. However, coronary microvascular dysfunction (CMD), defined by the presence of an impaired coronary vasomotor tone, may cause IHD also independently from the presence of CAD [2-7]. Among cardiovascular diseases (CVD), IHD is the most common cause of death for both female and male gender, but actual evidences reveal that the spectrum of IHD in women exceeds the standard knowledge [8]. From the epidemiological point of view, IHD affects females at a more advanced age and they have more comorbidities at the ischemic event presentation time than males [8]. This difference may be due to female hormone protection that may also explain the low incidence of cardiovascular (CV) events in pre-menopausal aged women [9]. In female gender more than male one, IHD underlies a wide and varied spectrum of pathophysiological mechanisms beyond the presence of coronary atherosclerotic lesions such as CMD, coronary vasospasm and coronary artery dissection [9,10]. Over 50% of symptomatic middle-aged women show predominantly CMD, characterized by a predominance of functional dysfunction over anatomical anomalies [8]. From clinical point of view, unconventional ischemic triggers and atypical symptoms including nausea, fatigue, dyspnea, abdominal pain and atypical thoracic pain characterize the IHD manifestation more frequently in females than males [10-14].

Literature Review

Role of gender on traditional risk factors for ischemic heart disease

It is well known that gender influences susceptibility to develop

IHD by modulating the effect of CV risk factors and this influence is so strong up to consider it as a CV risk factor [15-17].

Young women with low CV risk are affected by IHD less than males with the same CV risk, conversely post-menopausal women present higher profile risk and CV mortality than men of the same age and with the same risk factors [15-17]. This strongly suggests that the lack of estrogens strengthens the effect of CV risk factors more likely leading to endothelial dysfunction, loss of vascular compliance, alterations in myocardial flow and ischemia [8,18].

Arterial hypertension and diabetes mellitus (DM) seem to produce similar effects on CVD onset and progression between genders. Arterial hypertension is highly prevalent in females, especially in African population, over the age of 55 and represents a major cause of IHD, heart failure (HF) and stroke in a comparable way to males [15,19,20]. Moreover, the reduction of blood pressure values has the same impact on the reduction of IHD and stroke risk independently from gender [15,19,20]. The impact of DM in the determinism of IHD is comparable between the two genders and females with DM have double risk to be hospitalized for CVDs and to manifest their complications than women without DM [8,21].

Smoking is the leading and preventable risk factor for IHD and shows a dose-dependent association with the risk to provoke acute myocardial infarction (AMI) [15]. The impact of smoking is associated with greater risk of CVD and thromboembolic disease in females

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rather than males and the relative risk of developing these diseases is increased by the use of oral contraceptives [15,22].

Dyslipidemia represent a major CV risk factor for both the genders. Although females under 50 years have more favorable lipid profiles than males, cholesterol levels steeply increase in post-menopausal period, while in male's lipid profile tends to remain stable over time [15,23].

Psychological stress has an impact in the onset and prognosis of IHD as well as other CVD and seems to play a more significant role in women [15,24,25] (Table 1). For example, the INTERHEART study demonstrated that the concomitant exposure to several psychosocial risk factors, such as depression or stress at home or work, was significantly associated with acute myocardial infarction [26]. Additionally, Takotsubo cardiomyopathy typically occurs in the setting of postmenopausal females affected by mental or physical stress, in absence of obstructive CAD [27-30].

Role of ion channels on the regulation of coronary blood flow

Coronary tree satisfies myocardium energetic requests through a continuous modulation of CBF [2-4,31,32]. It is possible by means several regulation mechanisms which act in different manners along coronary tree modifying coronary artery resistances [2,4,31].

Shear stress related vasomotion and neuro humoral regulation are the main CBF regulatory mechanisms acted at the epicardial compartment while metabolic and myogenic mechanisms play a critical role at the distal compartment of coronary circulation [2,4,31].

Coronary ion channels represent the final effectors of the CBF regulation mechanisms, and they regulate both the tone of smooth muscle cells and the endothelial function [2-4,31,32]. Several ion channels are expressed in coronary circulation [2-4,31,32].

Sodium voltage gated channels (Nav) stimulate cell depolarization and they are the main effectors of endothelial dependent vasodilation which acts via nitric oxide (NO) production [2,4,31]. There are four types of potassium channels: Calcium-dependent potassium channels (KCa), voltage-dependent potassium channels (Kv), triphosphate adenosine-sensitive potassium channels (KATP), and inward-rectifier potassium (Kir) channels [2,4,31]. According with their opening, K⁺ goes out from the cell determining its hyperpolarization while if they are closed, K⁺ remain inside the cell contributing to its depolarization [2-4,31,32] (Figure 1). KCa are distinguished on the base of conductance in big (BKCa), mainly expressed on smooth muscle cells, intermediate (IKCa) and small (SKCa) mainly expressed on endothelial cells [2,4,31,33,34]. Kv is the final effector of endothelial dependent and independent vasodilation and it is a target of hydrogen peroxide (H₂O₂) and other reactive oxygen species (ROS) [2-4,31,32].

Coronary KATP is predominantly involved in the metabolic modulation of vascular tone and it is made up of two subunits, the Kir subunit and sulphonylurea-binding subunit (SUR) [2-4,31,32]. The two main subunit combination of coronary KATP channel are Kir6.2/SUR2A and Kir6.1/SUR2B [2-4] (Figure 2).

Voltage gated calcium channels (Cav) contribute to CBF regulation via intracellular Ca⁺⁺ levels regulation [2-4,31,32].

Gender differences in pathophysiology of ischemic heart disease

Pathophysiological mechanisms underlying IHD in females are complex and still unexplained. Estrogens have a protective role

against IHD in premenopausal women, because they improve vascular function and vasodilation stimulating NO production [15,35]. Furthermore, estrogens are involved in re-endothelialization and mobilizing endothelial progenitor cells (EPC) [15,36]. Fertile females have higher levels of EPC than males, while there is no difference between post-menopausal females and same aged men [15,37] (Figure 3). Moreover, intracoronary infusion of estradiol improves CBF reserve in women but not in men [15,38]. More studies are needed to verify if a specific timing of starting of hormone therapy may reduce the risk of CAD [15,39]. Conversely, the role of androgens in the susceptibility of developing CVD is less clear. Recently, Zhao et al. reported that among post-menopausal women a higher testosterone/estradiol ratio was associated with an elevated risk for incident CVD, IHD and HF events [40]. Moreover, higher levels of testosterone were associated with increased CV events. These results pointed out a possible detrimental effect of endogenous androgens due to vasoconstriction, increased platelet aggregation through up-regulation of thromboxane, accumulation of visceral fat, dyslipidemia and increased levels of cardiometabolic risk factors [41,42]. In this view, androgen deficiency seems to have a protective role against CVD.

Both obstructive and non-obstructive CAD, which are more common after menopausal onset, seem to have peculiar characteristics in women and this observation is presumably related to the exposure of CV and metabolic systems to estrogens [15].

Interestingly, Nicholls et al. demonstrated that women with obstructive CAD have a lower atheroma volume than men, despite the presence of more CV risk factors in women [15,43]. Moreover, a high calcium score in the coronary arteries is more common in men. Existing evidence reveals consistent difference in plaque morphology and composition between the two genders [8,44]. Plaque erosion is more common in younger women, while plaque rupture is more common in men and in older women [8,18]. In young women, the erosion of plaque beneath an incompletely damaged endothelium, differs from the characteristic inflammatory processes that usually cause degradation of the extracellular matrix and thinning of the fibrous cap of atherosclerotic plaque, leading to plaque rupture and thrombus formation [10]. This may explain the higher mortality rates after myocardial infarction in younger women, but not older women, compared with men [8,45]. Furthermore, among patients without obstructive CAD, women have a lower atheroma burden compared with men, even at early stage [15,46].

CMD is actually considered as a major pathophysiological mechanism for IHD in females in the absence of significant coronary obstruction [15,47]. Sex-specific differences in microvascular blood flow appear very early in life. Stark et al. demonstrated that male infants have higher baseline flow on skin microcirculation than females [15,48]. In some animal experiments, females and males had different superoxide concentration and vascular permeability [15,49]. Huxley et al. demonstrated that blood levels of endothelin-1 (ET-1) are different between males and females as endothelin receptors distribution [50]. Moreover, coronary alpha- adrenergic tone is downregulated by female sex hormones while it increases significantly in post-menopausal period [50,51]. Wong et al. reported a gender difference function of coronary Transient receptor potential channel (TRP) between males and females [52]. Indeed, they demonstrated that TRPV4 may play a role in NO-mediated vasodilation of only female pig isolated coronary arteries while TRPC3 may mediate vasodilation induced by NO and endothelium derived hyperpolarizing factor (EDHF) in only male pig isolated coronary arteries [52]. Aziz et al. demonstrated that females

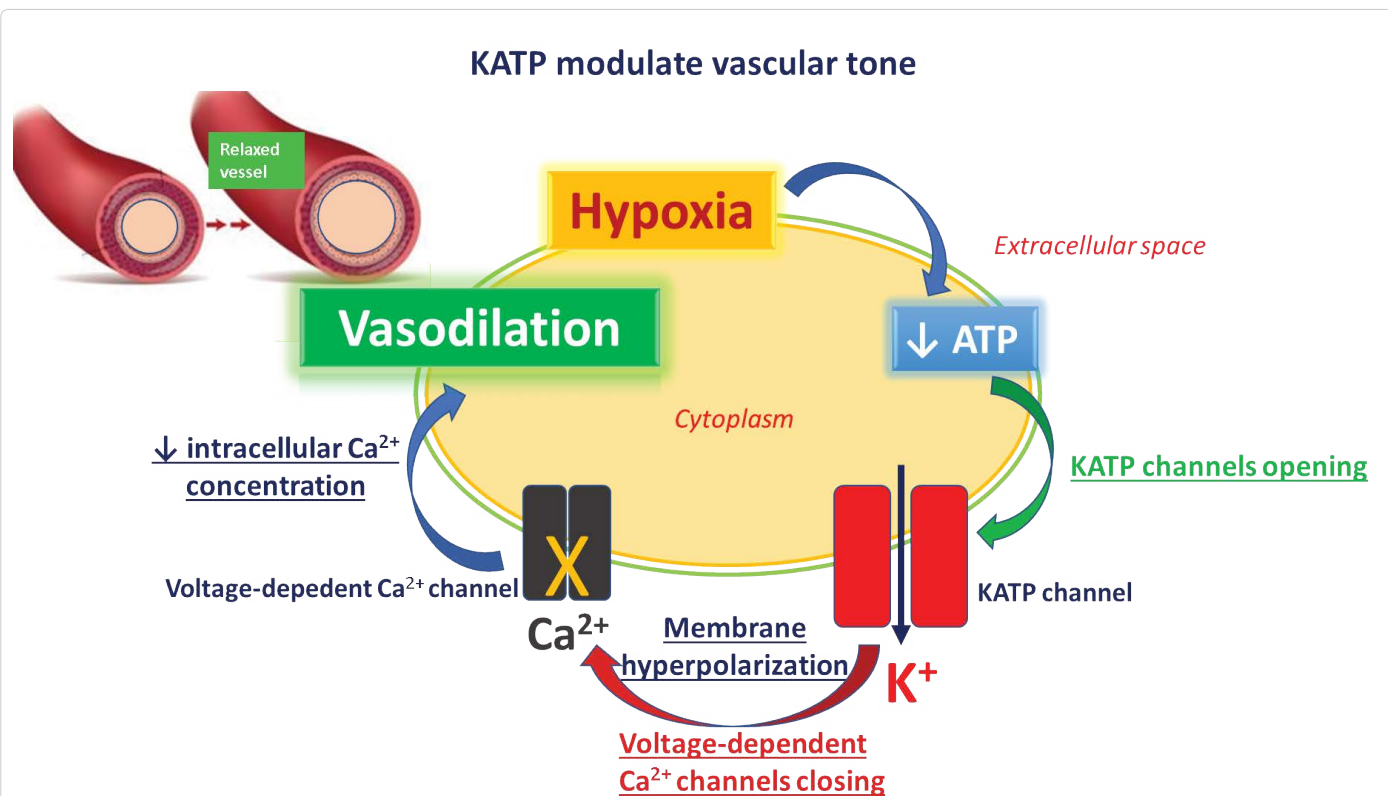


Figure 1: Physiological role of coronary KATP; myocardial work and hypoxia are associated with ATP consumption that is a stimulus for endothelial and smooth muscle cells KATP opening. The consequent K⁺ efflux determines cell hyperpolarization, voltage dependent Ca²⁺ channels inhibition and vasodilation.

Structure of KATP and its subunits

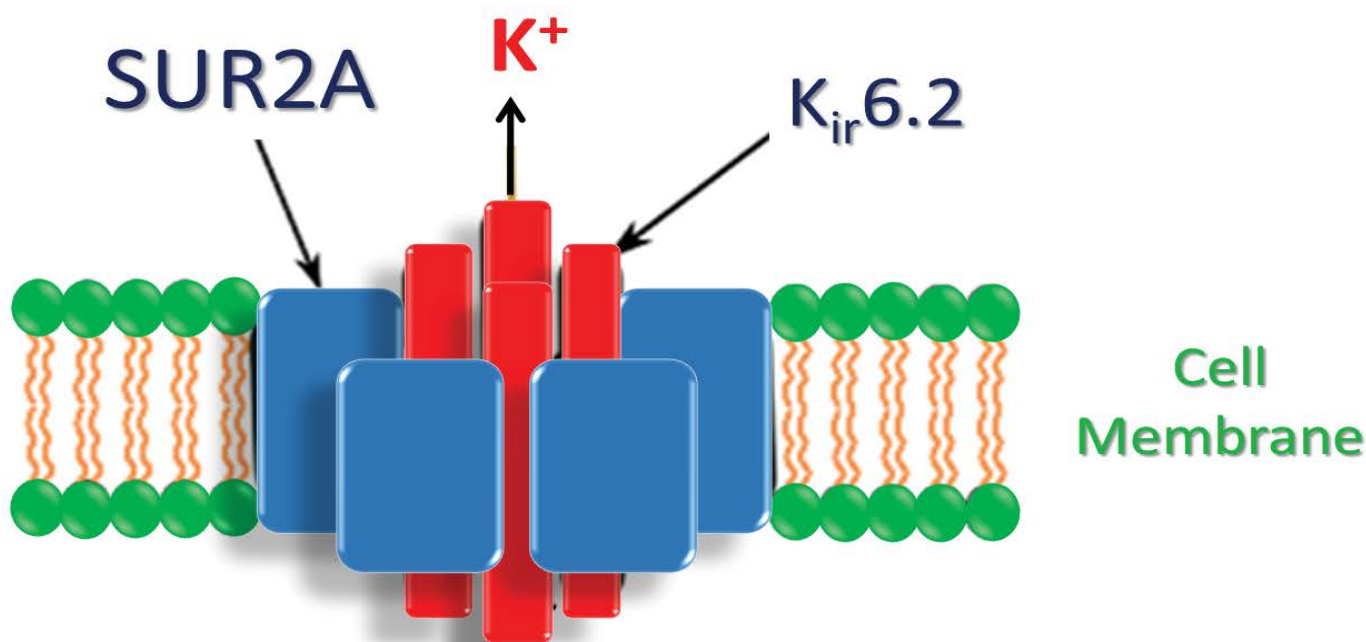
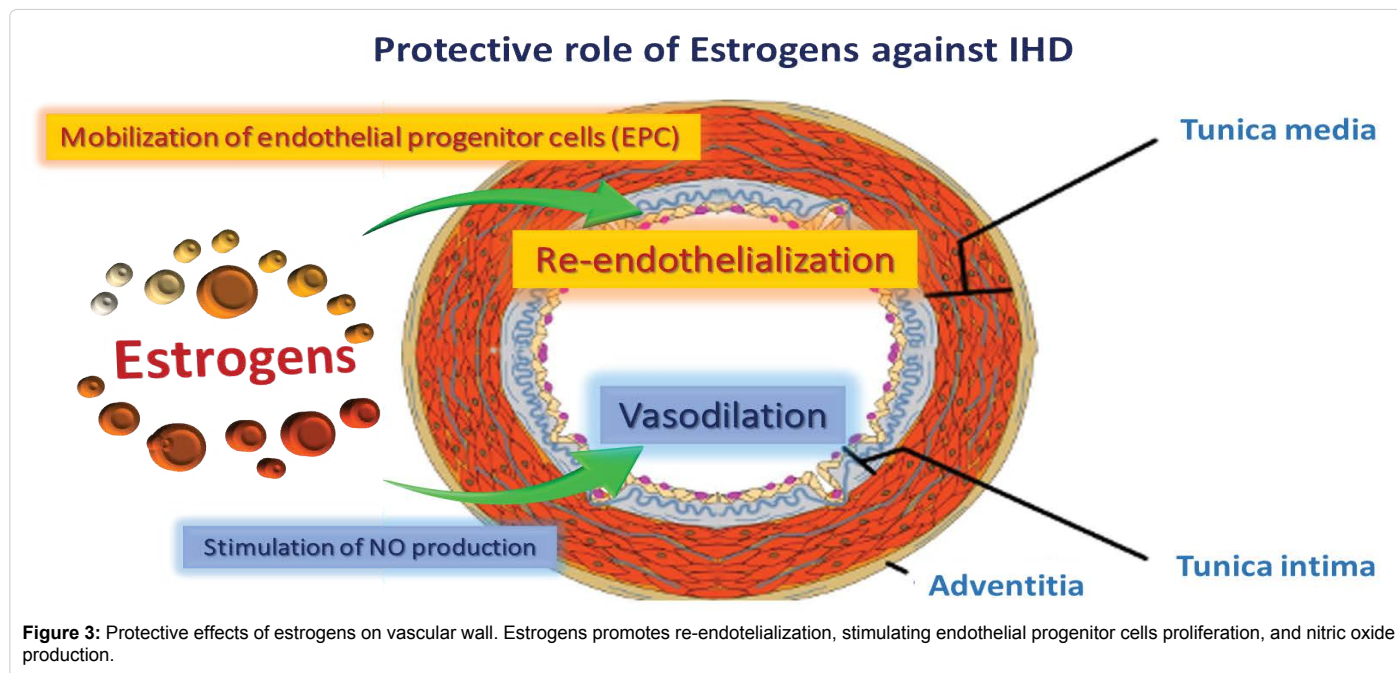


Figure 2: Structure of coronary KATP with the two subunits Kir6.2 and SUR2A.



Classical cardiovascular risk factors in women: Key points
Hypertension is highly prevalent in females over the age of 55, especially in African people.
Females with DM have a double risk for hospitalizations compared to DM males.
Cholesterol levels become higher in females after menopause.
Psychological stress has a great impact in the onset of IHD for females.

Table 1: Main features of CV risk factors in women.

presented more frequently CMD than man and they show a pathological response to intracoronary infusion of acetylcholine at a lower dose than males [53]. Beyond the hormonal motivation, this effect may be due to a worse diastolic function in female, a winding course and smaller diameter of coronary arteries and smaller myocardial mass than males [53-56].

Genetics and ischemic heart disease: Pathophysiological insights and future perspectives

The different pathophysiological pathways in IHD showed in females are probably related to genetic differences between genders. Unfortunately, few studies have addressed the role of genetics in clinical manifestation of IHD [57-60]. The G1733A single nucleotide polymorphism (SNP) of the androgen receptor gene has been related to premature CAD in women, becoming a novel genetic and sex-related marker for CAD [54]. Furthermore, Weng et al. demonstrated that the rs12818945 SNP of the gene encoding for ATP-dependent Ca²⁺ channel (ATP2B1) was associated to a higher risk to develop non-obstructive CAD in women [58].

Previously we reported the association between some SNP in genes encoding coronary ion channels and IHD [3]. In particular, we studied if the SNP rs5215_GG of KCNJ11, the gene encoding for KATP Kir6.2 subunit, represent a protective factor against IHD susceptibility, independently from the other CV risk factors [3,61]. To evaluate our hypothesis about the role of rs5215_GG polymorphisms on female population, we enrolled 460 patients (148 women) with indication to perform coronary angiography and functional intracoronary tests because of suspected myocardial ischemia. The study population was divided in three groups: group 1, 330 patients (72 women) with CAD

without CMD, group 2, 68 patients (40 women) with CMD without CAD and group 3, 62 (36 women) patients with normal coronary arteries both from anatomic and functional point of view. We reported that the SNP rs5215_GG was found more frequently in female than male population [3]. Moreover, we found that the same SNP was more frequent in female population with anatomically and functionally normal coronary arteries (group 3) than that one with CAD (group 1) (9/36- 25% against 7/72- 9,7%; *p*: 0,04) while there were no differences in rs5215_GG frequency between males of the same two groups.

This result suggests that the SNP rs5215_GG of KCNJ11 gene may represent a protective factor, reducing the susceptibility to develop IHD in female gender. From the molecular point of view, rs5215_GG polymorphism consists in a missense SNP at exon 1009 (ATC-GTC) on KCNJ11 gene, which determines a substitution of isoleucine residue with valine one. Considering the protective role of this SNP, we can argue that it is associated with a gain of function of KATP channel leading to membrane hyperpolarization and lowering intracellular Ca levels. Hence, the SNP can lead to increased vasodilation, reduced shear stress and endothelial damage. The protective role of this SNP results in lower CMD reducing the risk of IHD in female.

In consideration of the role of coronary ion channels as final effectors of microvascular function and the more prevalent microvascular involvement in CV pathophysiology in females, our findings legitimate to hypothesize a genetic key role in the susceptibility to CMD. Future studies should clarify the possible causal role of specific SNPs of genes encoding coronary ion channels in the determinism of IHD in females. Considering the possible causal link between CMD and SNPs, the usefulness of genetic tests

to achieve a detailed patient's risk profile should be evaluated in order to optimize prevention and management of IHD.

Discussion and Conclusion

This manuscript provides a revision of literature on the pathophysiological differences in IHD between genders. Although the role of estrogens on CV system is well known, the pathophysiological differences in ischemic profile could be also related to genetic differences in coronary ion channels among genders. Our data strongly confirm this hypothesis, underlining the possible sex-related association between SNPs of ion channels encoding genes and the susceptibility to developing CMD in females. In particular, we found that the SNP rs5215_GG of KCNJ11 gene, encoding for Kir6.2 subunit KATP, could reduce susceptibility to IHD and could be a protective factor against IHD in female gender, independently from the other CV risk factors. These results are encouraging but related to a small simple size. Further large studies are eagerly awaited to confirm our findings and to evaluate the possible role of SNPs in the screening and management of patients at risk of or with IHD.

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