THE ROLE OF THE IMMUNE SYSTEM IN CORONARY HEART DISEASE IN WOMEN

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Abstract. The three most important characteristics of CHD in women are: 1) a higher prevalence of angina, 2) a lower burden of obstructive CHD on angiography, and 3) a worse prognosis compared with men. In addition, current risk estimates based on ACS thresholds defined in predominantly male populations do not accurately predict risk in women, suggesting the need for gender-specific biomarker ranges and risk stratification tools to improve diagnosis, treatment, and follow-up in female populations. In a recent prospective cohort study, the highly sensitive troponin I assay markedly increased the diagnosis of MI in women (from 11% to 22%, P<0.001) but had minimal impact in men (19% to 21%, P=0.002). Other biomarkers, such as proneurotensin, were found to be sex-dependent and associated with cardiovascular disease only in women, confirming the need for additional research in this area [132,138].

Keywords: *prevalence of angina, cardioprotection, postmenopausal period, estrogens, risk factors, immune system, minimal impact.*

Often unrecognized and often undiagnosed cardiovascular diseases that are either more common or unique to women include coronary microvascular dysfunction, spontaneous coronary artery dissection, stress-induced cardiomyopathy, and heart failure with preserved ejection fraction. There is still much to be learned, and this requires gender- and sex-specific research approaches with appropriate participation of women in cardiovascular clinical trials. For many decades, CVD research has focused primarily on men, leading to an underestimation of sex differences etiologically, diagnostically, and therapeutically. As long as women are underrepresented in clinical trials, we will continue to lack the data to make accurate clinical decisions for 51% of the world's population. Recent initiatives have raised awareness that cardiovascular disease and its optimal treatment can differ between men and women. We support a new era in research in which cardiovascular research is being designed with sufficient power to analyze it in a gender-specific manner to understand mechanisms and develop optimal treatments for cardiovascular disease in both sexes.

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The adaptive immune response has recently emerged as an important factor in a wide range of cardiovascular diseases, including atherosclerosis, hypertension, cardiac remodeling, and heart failure; however, its role is not fully understood. Because the set of innate sensitive cells, such as neutrophils and monocytes/macrophages, coordinate with adaptive immunity, such as T cells, dendritic cells and B cells, temporal responses and descriptions relating to cellular phenotype and inflammatory processes in general need more research, clarification and consensus, particularly in relation to cardiovascular disease.

Activation as innate and adaptive immune cells and their infiltration into affected tissues has been shown for various cardiovascular diseases: they have been found in atherosclerotic plaques, heart after ischemic and non-ischemic cardiomyopathy and kidney in hypertension [112, 117, 118]. Infiltrated immune cells play an important role in altering the mechanical, structural, and functional characteristics of the mouse/human heart and kidney, often contributing to the progression of these diseases. Cross talk between the leukocyte innate response and the adaptive immune system consisting of lymphocytes, including B- and T-cells, has only recently been the subject of cardiovascular disease research [56, 72].

Monocytes and macrophages are known regulators of atherosclerotic plaque formation and rupture. Xu et al. [142] identified a new mechanism of attraction and retention of CD8+ T-cells in atherosclerotic lesions. The authors determined that costimulation of CD137 on CD8+ T cells is a stimulus for infiltration and, interestingly, occurs independently of atherosclerotic antigen recognition. The main results support a model in which formation of effector CD8+Circulating T cells potentially induced by systemic inflammation induce their infiltration into the atherogenic intima, where they persist, secrete proinflammatory cytokines, and mediate recruitment of other immune cells. Together, these infiltrated cells create a vulnerable plaque and potentially contribute to the process of atherosclerotic plaque development and subsequent thrombovascular events [142].

One of the widely studied and recently recognized topics in the physiology of the immune system is sex differences. Women are protected against cardiovascular disease until the onset of menopause, but the mechanisms of this observation are still unclear. Pollow et al. [119] investigated the contribution of T cells in the development of hypertension in postmenopausal women. For this study, they used a new physiologically relevant mouse model of menopause by giving female mice the chemical 4-vinylcyclohexenediepoxide (VCD). Adaptive T-lymphocyte transfer increased blood pressure after ANH II; however, this effect was absent in Rag-1 menopausal mice. The authors demonstrated that Tregswere decreased in the spleen and kidney of Rag-1 -mice in menopause compared with premenopausal mice. It was concluded that changes in hormonal status during menopause may stimulate pro-inflammatory and T-cell-dependent responses and eliminate protection against hypertension. This study emphasizes that the sex of the animal is an important parameter to consider when interpreting hypertension study results.

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Targeted manipulation of T-cell subpopulations may prove to be an effective approach to treating hypertension [119].

During pregnancy, women are closely monitored for hypertension because of the risk of pre-eclampsia for both mother and child. The influence of adaptive and innate immune cells on hypertension caused by placental ischemia is well known; however, the contribution of B1 lymphocytes compared with B2 is unclear. Laule et al. [112] suggested that peritoneal B1 lymphocytes are crucial for the development of hypertension induced by placental ischemia. Using a model of preeclampsia with reduced uterine-placental perfusion pressure (RUPP), they found that classic B2 lymphocytes as well as peritoneal and circulating B1 lymphocytes are not actually required for the development of hypertension after placental ischemia in the third trimester [112].

Taken together, all these studies highlight the complexity of the adaptive immune system in the development of cardiovascular disease. Unfortunately, there is no consensus on the optimal strategy for isolation and characterization of immune cells from the tissue. The study by Covarrubias et al. [83] demonstrated that density-mediated mononuclear cell isolation strategies are less accurate for quantifying tissue-penetrating immune cells because altered cell activation status during tissue transmigration alters their granularity, resulting in loss of mononuclear cells in granules. They suggested that centrifugation of finely ground tissue at very low speed is a viable strategy alternative to labor-intensive approaches with tissue perfusion to remove most intravascular blood cells. In addition, the absolute number of cells isolated is relatively small, and an accurate assessment of flow cytometry data would require a large proportion of the sample to achieve a gold standard of 10,000 events/sample. Additional animal and human studies are needed to fully understand the role of these dynamic cells in cardiovascular disease [83].

The described viewpoint highlights some of the mechanisms of cardiovascular disease driven by adaptive immunity. In the diverse phenotype of cardiovascular disease, the resolution of inflammation and restoration of homeostasis are necessary to improve prognosis. This process depends on the magnitude of the trigger, such as myocardial infarction in ischemic heart failure, and the complex regulation coordinated by the innate and adaptive immune system, highlighting the importance of cellular and molecular inflammation. The role of major risk factors observed in clinical settings, such as sex, aging, obesity, and drug interactions, in the dysregulation of the adaptive immune response should be considered in the future. In addition, the research community should focus on developing a comprehensive range of mechanisms controlled by adaptive immunity in cardiovascular disease as a means of using these cells as therapeutic targets in cardiovascular medicine [83, 141].

Physiological and pathological variations of the adaptive immune response in cardiovascular diseases are not fully understood. The response to a trigger, such as endothelial damage, myocyte death or vascular damage/stress, initiates the activation of the immune response,

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i.e. monocytes/macrophages, T-cells and B-cells. The normal physiologic response would be a weakening/elimination of inflammation after the trigger is triggered. Failure to initiate an adaptive immune response is what leads to a chronic inflammatory state, often leading to cardiovascular pathology such as atherosclerosis, heart failure, and hypertension [43, 63, 118].

Menopause, risk factors for the progression of coronary heart disease

Coronary heart disease is the most important cause of cardiovascular mortality in women worldwide. The regions with the highest age-standardized prevalence of CHD are Eastern Europe, North Africa and the Middle East, and Central Europe, whereas a lower risk of cardiovascular disease is found in Chinese and South Americans. The most recent European data show that CHD and stroke account for 82% of disability-adjusted life years due to CVD in European Society of Cardiology member countries. Despite a slight decrease in age-standardized incidence and prevalence of CHD and stroke over the past 27 years, peripheral vascular disease (PVD) and atrial fibrillation (AF) rates have remained stable. Because most data on CHD are still largely from men, the true incidence of CHD in women may be underestimated. Risk calculations are primarily based on mortality rates rather than overall CHD rates, for which women tend to have higher rates of nonfatal events. In addition, women have lower income and lower socioeconomic status than men, which generally contribute to poorer health outcomes [16, 17, 18].

Although classic myocardial infarction (MI) type 1 occurs three times more often in men than in (older) women, the number of women under 65 years of age with MI is gradually increasing. In particular, type II MI without obstructive coronary artery disease (IMOCAD) and spontaneous coronary artery dissection (SCAD) are more common in younger women. It is estimated that up to 30% of MIs in women younger than 60 are caused by SCAD. In contrast, the majority of women diagnosed with Takotsubo syndrome (ST) are postmenopausal and over the age of sixty. Altered sex hormone levels, especially estradiol deficiency, have not yet been identified as a risk factor for ST Mental stress is more associated with CHD caused by coronary vascular dysfunction and IMOCAD than with obstructive coronary artery disease, highlighting important gender differences in coping with stress [21, 114, 127].

Obstructive CHD in women occurs 7-10 years later than in men, and focal coronary artery stenoses are less common in women at any age. Women have fewer plaques, less vascular calcifications, more diffuse nature of atherosclerosis and more often soft plaques and erosive lesions compared to men. Coronary vasomotor disorders, such as coronary artery spasm and/or coronary microvascular dysfunction, represent a major cause of CHD in middle-aged women. They may be present with or without nonobstructive CHD. According to a subanalysis of the ISCHEMIA study, women are more likely to have angina with less extensive CHD and less severe ischemia than men. This was also shown in the larger CorMICA trial. These data support important sex differences in the complex relationships between angina, atherosclerosis, and ischemia [121,

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134]. Lower estrogen levels after menopause are associated with altered vascular function, increased inflammation, and upregulation of other hormonal systems such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and reduced nitric oxide-dependent vasodilation. Healthy endothelium is sensitive to the vasodilatory properties of estrogen, but this changes when vascular stiffness and atherosclerotic disease develop over time. Although the risk of cardiovascular disease increases with the onset of menopause, it cannot be distinguished from aging. The Women's Ischemia Syndrome Evaluation Study found that the presence of cardiovascular risk factors caused comparable CHD lesions in premenopausal and postmenopausal women. A validated tool for measuring cardiovascular risk in middle-aged women is the computed tomography (CT) coronary artery calcium (CA) score, which has a higher prognostic value than in men. It is recommended to evaluate the assessment of CA in symptomatic women and in women with an average cardiovascular risk [56, 60, 65].

Decreased endothelial function begins in early menopause even before signs of subclinical atherosclerosis appear. This mechanism may be involved in the pathophysiology of "indeterminate" chest pain and shortness of breath, which are often labeled as "stress" or "menopausal symptoms". However, women with "indeterminate" chest pain syndromes have a doubled risk of developing CHD in the next 5-7 years. Changes in hormonal environment are associated with changes in body composition. Fat mass increases predominantly in central and visceral areas, and muscle mass decreases after menopause. Visceral adipose tissue secretes inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and retinol-binding protein-4. The outflow of free fatty acids into the liver generates reactive oxygen species. Chronic inflammation and oxidative stress respectively increase insulin resistance. Animal studies show that decreased estrogen after gonadectomy is associated with impaired pancreatic β-cell function. In clinical practice, the incidence of metabolic syndrome in postmenopausal women is 2-3 times higher than in premenopausal women of the same age [66, 68, 72].

The transition to menopause leads to changes in the lipid profile with a 10-15% increase in LDL cholesterol and triglycerides and a slightly lower level of HDL cholesterol. The dramatic increase in BP after menopause may be a direct effect of hormonal changes in the vascular network as well as metabolic changes with age. Hypertension is a critical risk factor that affects women in the early years of postmenopause and is often poorly treated. Recent data from Canada show a worsening awareness of hypertension and its treatment over the past decade, especially among women. Overall, 30-50% of women have hypertension (BP>140/90 mmHg), fatigue, and sleep disturbances that are often associated with menopause. Sodium sensitivity increases during the menopausal transition, often resulting in intermittent fluid retention (swelling of the legs, arms, and lower eyelids). Physicians should be more proactive in detecting hypertension in middle-aged women, especially after HPD and preeclampsia. Systolic BP is the most important risk factor in aging and leads to greater vascular and myocardial stiffness in women than in men, which is an important factor in why heart failure with preserved ejection fraction predominates in older

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women. Sex differences in heart failure have recently been described, so we focus on CHF [22, 36, 44].

Immune reactivity is increased in women during and after menopause. Autoimmune rheumatic and endocrine disorders, such as rheumatic arthritis, systemic lupus erythematosus, antiphospholipid syndrome, Sjögren's syndrome and thyroid disorders, are more common in women than in men and are associated with an increased risk of cardiovascular disease. Patients with these disorders also have a higher cluster of traditional risk factors. These risk variables should be taken into account when assessing individual risk during menopause (91, 94, 105).

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