THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Sexual Dimorphism in the Heart Failure Population

LETTER TO THE EDITOR

To the Editor,

I read the article titled "Gender-Related Differences in Patients with Acute Heart Failure: Observation from the Journey Heart Failure-Turkish Population Study" by Akyıldız Akçay et al[1] with great interest. In this study, the authors demonstrated that the presentation, treatment options, and in-hospital clinical outcomes in the heart failure population differ between male and female patients. Although the mean LV ejection fraction is higher in the female gender (35.9% vs. 30.3%, $P < .001$), in-hospital mortality is higher than in the male gender (9.3% vs. 6.4%, $P = .022$). Heart Failure with Preserved Ejection Fraction (HFpEF) is also higher in female gender (25.3% vs. 11.4%) ($P < .001$). Another remarkable finding of the study is the data related to the female gender ratio (42.8%). This ratio is higher than that reported in recent large-scale studies.[2] As in many other cardiovascular system pathologies, there are gender-based differences in presentation and clinical outcome in heart failure.[3] Observational and epidemiological studies that are based on differences in demographic data, such as those conducted by Akyıldız Akçay et al[1], help clinicians to speculate about the pathophysiological mechanisms of diseases which are relatively common in the population such as heart failure.

In a recently published study, a conclusion was expressed about the possible factor of higher ratio of HFpEF in female gender compared to male gender.[4] Cao et al[4] hypothesized that mitochondrial gene expressions might play a role in the development of HFpEF and also identified the mitochondrial gene *Acsl6* as a genetic determinant of diastolic dysfunction in mice. Although mitochondria are basically defined as the powerhouse of the cell, they are also involved in many other areas such as steroid hormone synthesis, reactive oxygen radical production, ionic regulation, and cell death.[5] With this large spectrum mitochondria are also considered as the place of marked sexual dimorphism involving mainly oxidative capacity, intracellular calcium handling, and resistance to oxidative stress. Plasma mitochondrial deoxyribonucleic acid (DNA) level was found to be related to inflammatory cytokines in the course of acute myocardial infarction and a significant decrease was also observed after successful percutaneous coronary intervention treatment.[6] In another study based on *in vivo* animal model, the cardioprotective effects of mitochondrial adenosine triphosphate-sensitive potassium channels was demonstrated in the setting of acute myocardial infarction.[7] With its role in the inflammatory cascade, mitochondria may have a crucial place in the development of human heart failure. Sexual differences in the expression of mitochondrial DNA may also explain the female gender frequency, especially in HFpEF. Today, many proven drugs in cardiovascular medicine (β-blockers, renin–angiotensin–aldosterone system blockers) have been shown to have protective effects on mitochondria.[8] As an experimental thought that has been inspired by the mitochondria's endosymbiotic origin, it has been reported that mitochondria transplantation may come to the fore in the treatment of various cardiovascular pathologies such as heart failure.[9] In conclusion, sexual dimorphism in heart failure, especially in HFpEF, may be related to the expression of mitochondrial genes. Considering its role in the inflammatory response, mitochondria-targeted therapies can find a place in the treatment of heart failure in the future.

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Cite this article as: Çoner A. Sexual dimorphism in the heart failure population. *Anatol J Cardiol.* 2024;28(3):173-174.

DOI:10.14744/AnatolJCardiol.2023.4040

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