

BRUNO BUCHHOLZ

Sex-specificity in the cellular composition of the heart: beyond hormone regulation of cardiovascular risk

Squiers GT, McLellan MA, Ilinykh A, Branca J, Rosenthal NA, Pinto AR. Cardiac cellularity is dependent upon biological sex and is regulated by gonadal hormones. *Cardiovasc Res.* 2021 Aug 29;117(10):2252-62. <https://doi.org/10.1093/cvr/cvaa265>.

Clinical and epidemiological data point out well-known differences between men and women in the prevalence of cardiovascular diseases. Pre-menopausal women experience less cardiovascular risk compared with men of the same age group. With post-menopausal ageing, the risk of suffering cardiovascular diseases starts becoming equal in both sexes, parallel to a decrease in female sexual hormone levels. Although numerous experimental and epidemiological studies show differences in the functional and pathological characteristics of the heart associated to sexual hormones, the number and diversity of cells forming the myocardium is not well-known. In general, the biological phenomena underlying the incidence of cardiovascular diseases related to gender and gonadal endocrine factors modulating the cellular population have been scarcely analyzed. In addition to cardiomyocytes, the adult mammalian heart is composed of a heterogeneous variety of cells, such as endothelial cells, fibroblasts, inflammation cells and intracardiac nervous tissue.

Using a combination of flow-cytometry techniques in isolated cells and immunofluorescence images, Squiers et al. studied sexual differences in the cellular

composition of the myocardium in an experimental mice model. These authors observed a significant difference in the amount and proportion of non-myocyte gonadal hormone-dependent myocardial cells in young animals, persisting during adult life. Both ovariectomy as castration in male mice resulted in fast changes in the proportion of resident mesenchymal cells, endothelial cells, fibroblasts and the leukocyte population, T-cells, B-cells and monocytes evaluated at two and four weeks. Of note, the exogenous administration of estrogen to female and testosterone to male animals through the implantation of osmotic infusion pumps reversed the constitutional cell changes produced by gonadectomy. These results suggest that not only gonadal hormones regulate the composition of myocardial cells, but that these maintain great plasticity, permanently adapting to endocrine changes and stress

For decades, biological sex has been known to modify cardiac electrical and mechanical properties. Sex differences in the physiology and structure of the heart condition its pathophysiology, marking differences in the diagnosis and treatment of cardiovascular diseases in men and women. In this interesting and well accomplished experimental study, Squiers et al. report new aspects of myocardial cellular composition and its relationship with gonadal hormone function, opening new horizons for the correct interpretation and future treatments of epidemiologically gender-associated cardiovascular diseases. The results of this work promote new interest regarding sex-dependent non-myocyte cell spatial distribution in the heart. Based on the cellular types studied, the data suggest hormone involvement in processes such as cellular chemical attraction and immunomodulation, angiogenesis, cellular differentiation and ventricular remodeling