Taking the Gender Gap to Heart

Barry London

For centuries, poets, philosophers, and writers have described differences between the male and female heart. During the last several decades, many traditional male/female stereotypes have been questioned in the light of our expanding scientific knowledge. Although progress has been made toward a more gender-neutral society, the “gender gap” still exists. At the heart of the complex issues involved, an unanswered fundamental question remains: To what extent are perceived gender differences real, and what are their implications?

Male/female differences in cardiovascular physiology and pathophysiology have long been appreciated. Premenopausal women have a lower incidence of atherosclerotic coronary artery disease, due at least in part to the protective effects of estrogen. Male and female hearts also differ electrophysiologically. Women have a higher incidence of atrioventricular nodal reentrant tachycardias, whereas men account for most symptomatic cases of Brugada syndrome, an autosomal dominant form of idiopathic ventricular fibrillation. Women have longer QT intervals than men and are at greater risks for torsade de pointes from congenital and acquired long-QT syndrome. Surprisingly, women may have a lower overall incidence of sudden cardiac death, even correcting for the difference in coronary artery disease. The molecular basis of these gender differences is largely unknown.

In this issue of Circulation Research, Dr Fiset and colleagues report for the first time on gender differences in the molecular basis of these gender differences is largely unknown. 3 Female mice, rabbits, and humans have longer action potentials than larger mammals. Differences in mice are mediated by the sex hormones. 4 The mechanisms underlying these changes are unknown. In the present study, Trépanier-Boulay et al report higher levels of Kv1.5 expression in the hearts of male mice. Estrogens and androgens affect ion channel expression in the heart. 5 It remains to be seen whether the differences in mice are mediated by the sex hormones.

The electrophysiology of the mouse heart differs markedly from that of larger mammals. Mice have high heart rates (>600 bpm), short action potentials without a significant plateau, and abbreviated QT intervals on their electrocardiograms. At the cellular level, the transient outward currents (Ito,f and Ito,s) and the delayed rectifier currents (IKur and IKr,slow) play a major role in repolarization of the mouse myocyte, whereas IKr and IKs have only minor roles. Thus, it seems unlikely that the mechanisms that underlie the gender-based transcriptional changes of Kv1.5 in the mouse ventricle will be directly applicable to the regulation of the K+ channels important for ventricular repolarization in rabbits or humans.

Female mice, rabbits, and humans have longer action potentials than their male counterparts. This similarity is intriguing, given the marked differences between the species. Is the 8-millisecond “gender gap” in repolarization a side effect caused by the action of gender-specific sex hormones on ion channel regulation in the heart? Does delayed repolarization provide some advantage to the female of the species? The answers to these questions are unknown. It is clear that the male and female hearts differ. For cardiovascular electrophysiology at least, the importance of this sexual diversity remains to be determined.

References


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