Turning cardiac excitation into cell contraction: the importance of sex differences

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IN HEALTHY HUMANS of either sex under normal physiological conditions, the heart works quite well. Cardiac function is adequate to meet all reasonable physiological demands. And yet, it has been known for some time that there are differences in whole organ contractile performance, electrophysiology, cell contractility, and excitation-contraction (E-C) coupling between the sexes in humans and also in a variety of animal model systems (4, 11, 12, 17). In the cardiac myocyte there are numerous possible determinants of calcium transients and contractile function that might differ between the sexes; these have been only partly elucidated. Possible sex-specific control points in E-C coupling include calcium spark amplitude, duration or frequency, sarco(endoplasmic) reticulum (11) calcium stores, L-type calcium channel number or function, or properties of the sodium/calcium exchanger. Additionally, there might be different calcium sensitivity of the contractile proteins or different isoforms of contractile proteins expressed in male and female hearts (16). In healthy, sexually mature humans, there may be subtle differences, on average, in systolic function of the left ventricle between men and women, with some reports showing women’s systolic function, on average, slightly greater than men’s systolic function at rest, but men’s systolic function greater with exercise (1) However, this is of little clinical significance since the difference between the sexes is less than the difference within a population of healthy subjects of a single sex. At the cellular and isolated tissue level, the majority of studies demonstrate similar peak calcium current (I_{Ca}) in both sexes, but smaller calcium transients and smaller cellular contraction or intact tissue contraction for female hearts compared with male hearts (8, 11).

If there is similar peak I_{Ca} in cells from male and female rat hearts, why are there subsequently smaller calcium transients and less cell contraction in the cardiac myocytes from the female heart? In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Farrell et al. (3a) address this problem with a series of carefully designed and executed experiments that provide clear answers at the physiological level and thus beg for more experiments at the cell signaling level.

Farrell et al. (3a) have wisely chosen sexually mature but youthful rats as the model system where there can be little doubt that sex hormones are in full play in cell signaling and in the regulation of gene expression. They find that despite comparable cardiac action potentials, cell contraction is less in cardiac ventricular myocytes from female compared with male hearts. They also find that mean amplitude of peak I_{Ca} is similar in the two groups. This finding is expected and recapitulates findings of most, but not all, other investigators (15). However, the rate of rise is lower and time to peak of the calcium transient is delayed in cells from female hearts relative to that of males. Farrell et al. (3a) have gone on to calculate the “gain” of E-C coupling, measured as calcium flux per unit I_{Ca}. A key finding that is most enlightening is that the gain of E-C coupling in myocytes from female hearts is dramatically less than that for male hearts, with the gain for female cells only 60% of that for the male cells. There is probably no other physiological parameter used to compare female and male hearts that is as dramatically different as the gain in E-C coupling.

What mechanism of calcium entry, uptake, storage, release, or efflux could underlie this critical change in calcium dynamics? Sarcoplasmic reticulum (SR) calcium stores appear to be comparable. When Farrell et al. (3a) studied calcium sparks in quiescent female and male cells, they found no difference in spark frequency, but the mean amplitude of sparks and time to peak were smaller in female cells. Thus Farrell et al. (3a) reasonably conclude that sex differences in unitary calcium release underlie differences in contractile function between male and female myocytes.

It is difficult to design single cell physiological experiments that will model with fidelity the performance of an intact organ or the in vivo circulatory system under conditions of stress. The fundamental observations of Farrell et al. (3a) do permit a conjecture: although at rest, the difference in E-C coupling gain may be of little importance; however, specifically under peak demand such as strenuous exercise, the difference in E-C coupling may, in fact, be important. Under these conditions, SR calcium release may be less in female cardiomyocytes than in that of males. This is consistent with the observation in human physiological studies that females augment their left ventricular ejection fraction less with peak exercise than men (7).

One can reasonably presume that the difference in gain in E-C coupling between cells from male and female hearts is due to sex hormone signaling that is distinctive between the sexes. There is no doubt that sex hormones importantly regulate the expression of proteins that modulate cell contractile performance. We (4) and others (3) have found that gonadectomy of male rats reduces the contractility of isolated myocytes and produces a 50% decline in dihydroxypropride receptor expression and an 80% decline in sodium/calcium exchanger expression. Moreover, testosterone treatment of rats produces a marked increase in transcript abundance for androgen receptors, dihydroxypropride receptors, and the sodium/calcium exchanger (5). Estrogen modulates CaMKII signaling in the heart (10) and thus potentially modulates calcium sparks (6). The work of Farrell et al. (3a) now point to sex hormone modulation of calcium sparks as an important area for focused investigation.

Does it matter that there is a difference in gain of E-C coupling between male and female cardiomyocytes? Yes. It is important that we characterize mammalian physiology accurately. Also, perhaps this is the reason that among the most
elite athletes, the male marathon runner who wins the Boston Marathon is a few minutes ahead of the fastest woman. But does it matter for the rest of the human population of either sex? The findings of Farrell et al. (3a) may in fact be of considerable importance, beyond describing the difference in the heart of the woman and man, a topic of interest, albeit in a different context, in even the very old literature (13, 14). The findings implicating sex hormone-regulated signaling pathways that are determinants of gain in E-C coupling may illuminate avenues for therapeutic strategies to treat cardiac dysfunction and systolic heart failure, problems of immense pathophysiological and clinical importance. In healthy humans of both sexes, cardiac systolic function declines with age (2), although ejection fraction may remain unchanged. However, the ability to increase cardiac output does decline with age. An antecedent of this is menopause in women and andropause in men. It is underappreciated that with advancing age, testosterone levels in men substantially decline. Thus the fundamental observations of Farrell et al. (3a) may have readily apparent therapeutic implications. Perhaps more importantly, these new findings tell us that sex hormone signaling pathways modulate the gain of E-C coupling. The dissection of those pathways and modulation by sex hormones or other perhaps more specific pathway effectors may provide a new approach to boosting E-C coupling and improving the heart failure phenotype of the cardiomyocyte of either sex, and perhaps improving the pathophysiology at the organ and organism level. Estrogens have myriad effects on cell signaling, some leading to alterations in gene expression and others independent of estrogen receptors and gene expression. The promoter for calcium regulatory genes, including the dihydropyridine receptor, includes a hormone response element that positively modulates gene transcription (9). Pursuing sex hormone regulation of additional effectors of SR calcium stores and release may be fruitful and illuminating.

GRANTS

This work was supported by American Heart Association Grant 0755762Z.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES


