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COMMENTARY

Sex hormones and arrhythmia in myocardial ischemia

T Korte[1] and C Grohé[2]

[1]*Department of Cardiology, Medical School Hannover, Hannover, Germany and* [2]*Department of Cardiology, Medizinische Klinik II, University of Bonn, Bonn, Germany*

The mechanisms by which gender affects cardiac electrophysiological parameters and alters the predisposition to certain arrhythmias are not well understood, although differences in the expression and function of ion channels and in the activation of the autonomic nervous system may contribute. In their study Philp and coworkers address the issue of the effect of 17β-estradiol on ventricular vulnerability in a rat model of ischemia. Their data show that there is a dose-dependent antiarrhythmic activity of 17β-estradiol administration with suppression ventricular premature beats, ventricular tachycardia and ventricular fibrillation during ischemia. Furthermore they show a dose-dependent blockage of I_{CaL} by 17β-estradiol which is again stronger in female than in male mice. They postulate that the shown gender-selective, concentration-dependent inhibition of I_{CaL} is sufficient to account for the reduction in ischaemia-induced arrhythmia. With this data they have added important information on the influence of sex hormones on cardiac electrophysiology under pathophysiological conditions.
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Coronary artery disease, the most common cause of ventricular tachyarrhythmias, is the leading cause of death in both men and women (Cahndra *et al*., 1998; Marrugat *et al*., 1998). However, the incidence of sudden cardiac death at all age groups is significantly lower in women (Kannel *et al*., 1998; Kim *et al*., 2001) and traditional risk factors do not seem to predict sudden death to the same extent in women as they do in men (Lerner and Kannel, 1986; Kannel *et al*., 1998).

The mechanisms by which gender affects cardiac electrophysiological parameters and alters the predisposition to certain arrhythmias are not well understood, although differences in the expression and function of ion channels (Katsube *et al*., 1998; Leblanc *et al*., 1998; Trepanier-Boulay *et al*., 2001) and in the activation of the autonomic nervous system (Burke *et al*., 1997; Airaksinen *et al*., 1998; Cahndler and DiCarlo, 1998; Umetani *et al*., 1998) may contribute. Furthermore, gender has an influence on certain electrophysiological parameters, such as the corrected quantitative transmission (QT) interval, ventricular refractoriness and action potential duration (Burke *et al*., 1997; Trepanier-Boulay *et al*., 2001; Saba *et al*., 2002). However, to date the exact mechanisms that underlie sex hormone-based differences in cardiac electrophysiology after myocardial infarction have not been established. Female sex hormones, in particular estrogen, may play a role in this process. The myocardium contains both functional estrogen receptor α (ERα) and estrogen receptor β (ERβ) (Grohé *et al*., 1998). These transcription factors can activate downstream target genes such as the endothelial/inducible isoforms of the nitric oxide (NO) synthase as well as connexin 43 in the heart (Strehlow *et al*., 2003).

In their study, Philp *et al*. (2006) address the issue of the effect of 17β-estradiol on ventricular vulnerability in a rat model of ischemia. Their data show that there is a dose-dependent antiarrhythmic activity of 17β-estradiol administration with suppression of ventricular premature beats, ventricular tachycardia and ventricular fibrillation during ischemia. Furthermore, they show a dose-dependent blockage of I_{CaL} by 17β-estradiol, which is again stronger in female than in male mice. They postulate that the shown gender-selective, concentration-dependent inhibition of I_{CaL} is sufficient to account for the reduction in ischemia-induced arrhythmia.

These interesting data add to the work on how sex hormones, and estrogen in particular, might influence arrhythmias in myocardial ischemia or myocardial infarction. Few data are available on the influence of 17β-estradiol on cardiac electrophysiology via I_{CaL}. Pham *et al*. (2001) showed that 17β-estradiol treatment in gonadectomized male and female rabbits shifted activation of epicardial I_{CaL} to more negative potentials than in the endocardium and increased epicardial I_{CaL} conductance. The authors also showed that 5α-dihydrotestosterone (DHT) had a similar effect and that progesterone, gonadotropin-releasing hormone,

Correspondence: Dr T Korte, Department of Cardiology, Medical School Hannover, Carl-Neuberg-Str. 1, Hannover 30625, Germany.
E-mail: korte.thomas@mh-hannover.de
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luteinizing hormone or follicle-stimulating hormone may also contribute to I_{CaL} modulation (Pham and Rosen, 2002). In a recent publication, Bupha-Intr and Wattanapermpool (2006) showed that in ovariectomized female rats, estrogen and progesterone play an important role in the regulation of the cardiac sarcoplasmatic reticulum Ca^{2+} uptake. Furthermore, there are data showing that estrogen and DHT influence ventricular repolarization and ischemia or infarct-related arrhythmia via modulation of expression or function of delayed K^+ channels (Trepanier-Boulay *et al*., 2001; Saba *et al*., 2002; Korte *et al*., 2005).

Despite this extension of our knowledge, unsettled claims in this field remain. It is unknown if, in a predominant fashion, I_{CaL} or rectifying K^+ channels influence cardiac electrophysiology via sex hormones. Furthermore, estrogenic hormone levels vary, depending on sex and estrus and the level of concurrent hormones such as androgen derivatives and sex hormone-binding globulin, and therefore might influence cardiac repolarization. It also has to be pointed out that expression and regulation of both calcium and potassium channels are species specific and thus observations are model specific. Taking these points into consideration, it remains to be stated that it is still largely unknown how sex hormones influence ion channel expression or function in the heart. We do not know whether these effects are ER dependent or not. The data of Philp *et al*. (2006) suggest that the shown effect of estrogen on I_{CaL} in acute ischemia is rapid and non-genomic. Therefore, it might be related rather to rapid pathways such as calcium homeostasis or NO generation than to genomic mechanisms. Estrogen also influences cardiac repolarization and arrhythmia occurrence by modulation of the expression of Kv4.3 via ERβ in chronically infarcted female mice (Korte *et al*., 2005), which is thus rather a genomic effect. Finally, Li and co-workers have demonstrated that acute effects of estrogen might also be related to the positive effect on oxidative stress, which appeared to be ER independent and associated with altered Na(+)–K(+) ATPase (Sugishita *et al*., 2003).

Philp *et al*. (2006) have added important information on the influence of sex hormones on cardiac electrophysiology under pathophysiological conditions, but research now has to focus on the mechanisms of how exactly estrogen, progesterone and androgen might change function or expression of cardiac ion channels and influence arrhythmia occurrence in acute ischemia and chronic infarction of the heart.

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